Formal Written Laboratory Report Rubric

	Beginning (0)	Developing (2.6)	Adequate (3)	Accomplished (3.4)	Exemplary (4)
Abstract	Scope of work not sufficiently described or too lengthy. Experimental details included. Results not stated. Written in wrong tense. Many unneeded sentences.	Scope of work not sufficiently described or too lengthy. Experimental details included. Some critical results missing. Written in wrong tense. Few unneeded sentences.	Scope of work not sufficiently described or too lengthy. Not completely in past tense. Some critical results missing.	Between 80 - 200 words. Scope of work incomplete or too detailed. Written in past tense. Describes the work that was done and results found without using experimental details.	Between 80 - 200 words. Written in past tense. Describes the work that was done and results found without using experimental details.
Introduction	Little or no motivation or theoretical background given. Non-technical overview missing in last paragraph.	Motivation/focus miss directed. Theoretical background missing or riddled with errors. Non-technical overview incomplete or too technical.	Describes the motivation and focus of the experiment. Theoretical background incomplete or containing errors. Non-technical overview incomplete or too technical.	Describes the motivation and focus of the experiment. Contains appropriate theoretical background with minor errors. Non-technical overview too technical.	Describes the motivation and focus of the experiment. Contains appropriate theoretical background without errors. Last paragraph is non-technical overview of the experiment.
Methods/ Materials	No citations given. Deviations/ additions/omissions not discussed.	Some materials cited. Citations incorrect or incorrectly formatted. Deviations/additions/ omissions not discussed.	Materials cited. Some citations incorrect or incorrectly formatted. Deviations/additions/ omissions expressed but sometimes vague or unclear.	Lab manual and other materials properly cited. Deviations/ additions/omissions are expressed in paragraph format, but too brief or too lengthy.	Lab manual and other materials properly cited. Deviations/ additions/omissions are clearly expressed in paragraph format.
Results	Result data table not present, but discussed in paragraph format, or the reverse. Critical results missing or incorrect.	Result data presented in table format and discussed in paragraph format. Critical results missing or incorrect. Tables/ graphs incorrectly formatted. Captions missing.	Result data presented in table format, some data missing or incorrect. Data incompletely discussed in paragraph. Tables/graphs incorrectly formatted. Captions could be improved.	Result data presented in table format and discussed in paragraph format. Minor disagreements found between table and text. All data tables, graphs half page with correct captions.	Result data presented in table format and discussed in paragraph format. All data tables, graphs half page with correct captions.
Discussion / Conclusion	Results not analyzed. Experimental difficulties/errors/ questions not discussed. Conclusion not present.	Results analyzed producing some incorrect conclusions. Experimental difficulties/errors discussed incompletely, some questions answered incorrectly. Conclusion not well developed, too lengthy or short and missing the bottom line.	Results analyzed. Experimental difficulties, errors, questions discussed, some answered incorrectly. Conclusion too small or lengthy and missing the bottom line.	Results analyzed to produce sound conclusions. All experimental difficulties/errors/ questions discussed, with some minor error. Last paragraph is conclusion, expressing briefly the bottom line of the experiment.	Results analyzed to produce sound conclusions. All experimental difficulties, errors, questions discussed correctly. Last paragraph is conclusion, expressing briefly the bottom line of the experiment.
Language/ Grammar/ Formatting	First person used throughout. Incomplete sentences. Many grammatical errors. Complete lack of formatting.	Occasional lapses into first person. Sentence structure weak, many grammatical errors. Inconsistent formatting.	Third person used throughout. Sentence structure weak, many grammatical errors. Inconsistent formatting.	Third person used throughout. Well formed sentence structure, few grammatical errors. Few formatting errors.	Third person used throughout. Well formed sentence structure, grammatically correct. Excellent and consistent formatting.

Revised - 2/13/12

Total points = 24

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Aminoborohydrides. 14. Lithium Aminoborohydrides in the Selective Reduction *or* Amination of Alkyl Methanesulfonate Esters

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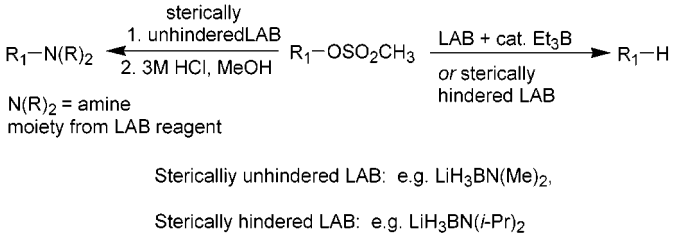
Received September 17, 2001

ABSTRACT



Lithium aminoborohydride (LAB) reagents initiate the amination *or* reduction of alkyl methanesulfonate esters, as dictated by reaction conditions. Alkyl methanesulfonate esters treated with unhindered LABs provide tertiary amines in excellent yield. Reduction to the corresponding alkane is achieved using a hindered LAB reagent or by forming the highly reactive Super-Hydride reagent in situ using LAB and a catalytic amount of triethylborane. The reduction methodology disclosed herein is a safe and convenient alternative to existing synthetic methods.

Introduction

Alkyl and aryl methanesulfonate esters are important reagents in organic synthesis.[1] They have excellent leaving group properties, are readily available, and are common intermediates for the deoxygenation of alcohols to their parent alkanes.[2] Deoxygenation of alcohols to alkanes is a common synthetic transformation that is usually achieved by reducing the sulfonate ester derivatives with lithium aluminum hydride (LAH).[3] LAH reductions of primary alkyl sulfonates generally proceed with satisfactory results, whereas sterically hindered alkyl sulfonates treated with LAH suffer from unfavorable side reactions (elimination and sulfer−oxygen bond cleavage).[3] For reactions where LAH cannot be used, lithium triethylborohydride ($LiEt_3BH$ or Super-Hydride) is an excellent alternative.[4] However, for complete reduction, 2 equiv of the highly reactive $LiEt_3BH$ is required and oxidation of the resulting trialkylborane complicates the workup procedure in a large-scale reaction.

Lithium aminoborohydride (LAB) reagents have recently emerged as a new class of powerful and selective reducing agents[5] that could potentially carry out the deoxygenation of alcohols to their alkanes. However, under certain circumstances, LABs preferentially transfer their amine functionality over a hydride. For example, both unsubstituted and substituted benzyl halides treated with LAB reagents at 0 °C give the corresponding tertiary amine−borane complexes, whereas the same reaction at 65 °C affords toluene products.[6] There is thus a difference in the reactivity of LAB reagents toward

(1) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.
(2) March, J. *Advanced Organic Chemisty*, 4th ed; Wiley and Sons: New York, 1992; pp 441−442.
(3) Gaylord, N. G. *Reduction with Complex Metal Hydrides*; Interscience Publishers: New York, 1956; pp 855−875.
(4) (a) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064. (b) Super-Hydride is a registered trademark of Sigma-Aldrich Chemical Co.
(5) Fisher, G. B.; Harrison, J.; Fuller, J. C.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1992**, *33*, 4533.
(6) Collins, C. J.; Lanz, M.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1999**, *64*, 2574.

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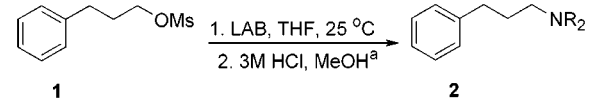
alkyl halides with temperature. Additionally, LAB reagents undergo a unique reaction with 2-halobenzonitriles.[7] During this reaction, reduction of the nitrile is accompanied by amination at the carbon bearing the halogen, and 2-aminobenzylamines are obtained. Clearly, LAB reagents are capable of mediating the transfer of both their amine and hydride functionalities; exploring and ultimately controlling this dual reactivity is desired. Herein we report the controlled reactivity of LABs toward alkyl sulfonates as modulated by temperature, steric bulk, and the in situ generation of Super-Hydride.

Primary alkyl methanesulfonates treated with unhindered LAB reagents at 0 and 25 °C provide only the corresponding tertiary amines; no reduction products are observed by GC analysis. Under these reaction conditions, LABs are exclusively amine transfer agents. For example, 3-phenylpropyl methanesulfonate **1** provides tertiary amines **2** in excellent yield with a variety of LAB reagents after an acidic methanolic workup procedure (Table 1). However, when the same reaction is performed at 65 °C, reduction to the corresponding alkane is a competitive reaction.

Table 1. Amination Reactions of Primary Alkyl Sulfonates with Various Lithium Aminoborohydride Reagents[a]



LiH_3BNR_2[b]	Time	Product	Yield[c]
$LiH_3BN(Me)_2$	30 min.	**2a**	92 %
$LiH_3BN(Et)_2$	30 min.	**2b**	75 %
$LiH_3BPyrr.$	30 min.	**2c**	94 %
$LiH_3BMorph.$	30 min.	**2d**	87 %
$LiH_3BHomopip.$	30 min.	**2e**	99 %

[a] 10 mmol of **1**, 2.5 equiv of LAB, acidic methonolic workup liberates borane from originally formed amine−borane, providing amine products (**CAUTION!** *hydrogen evolution!*). See ref 6 for further experimental details. Compounds identified by proton and carbon NMR. [b] Prepared from corresponding amine−borane, see ref 5 for a detailed procedure. [c] Isolated yield. No other products observed by GC analysis.

^{11}B NMR identifies the boron species that are generated during the reaction, and temperature dependent differences are detected. At 0 °C, only the residual LAB reagent (δ −16, q) and the amine−borane complex of the tertiary amine product (δ −14, q) are evident.[8] At reflux temperature, in addition to these two species, $LiBH_4$ (δ −43, quin.) and H_2BNR_2 (δ 0, t) are present. This difference in boron species with temperature can be accounted for by the more efficient metal hydride transfer reaction at 65 °C between the more Lewis acidic boron of the tertiary amine−borane and the less Lewis acidic boron of the LAB reagent.[9] In this way, $LiBH_4$ is generated along with the amino−borane side product for reactions run at high temperature (Figure 1). Such

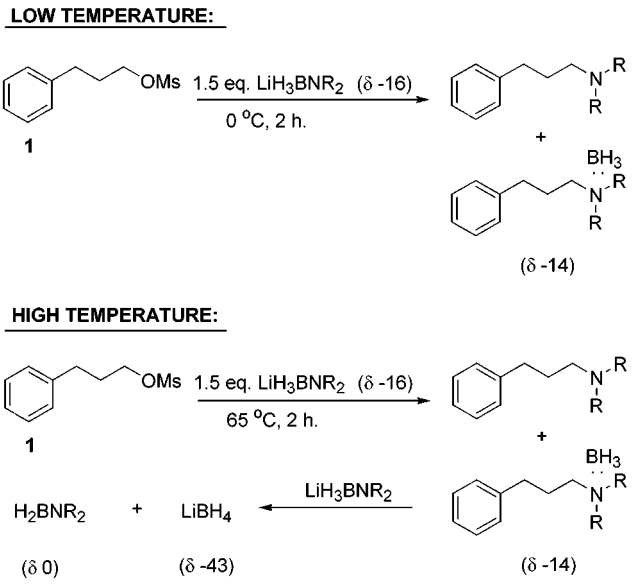


Figure 1. Temperature dependent differences in boron species generated during the reaction of **1** with LAB. Species characterized by coupled and decoupled ^{11}B NMR spectra.

differences in reactivity with temperature have previously been reported for metal hydride transfer reactions.[10]

Controlling the competitive reduction vs amination reactivity of LAB reagents toward alkyl sulfonates is particularly appealing considering the current methods for reducing alkyl sulfonate esters to alkanes. However, to make reduction the dominant reaction, the ability of the LAB reagent to transfer its amine moiety must be suppressed. A sterically hindered LAB reagent (lithium diisopropylaminoborohydride) should be less likely to transfer its amine functionality in an S_N2 fashion, and hydride transfer would thus be expected. Indeed, even at 25 °C, primary alkyl sulfonates undergo only reduction with a sterically hindered LAB reagent.

Although lithium diisopropylaminoborohydride initiates reduction for primary alkyl sulfonates, it is not suitable for secondary alkyl sulfonates, which are recovered unchanged after prolonged exposure at reflux temperature. For example, 3-phenylpropyl methanesulfonate **1** treated with lithium diisopropylaminoborohydride is reduced to 3-phenylpropane **3** in 30 min at 25 °C, but cyclohexylmesylate **4** is not

(7) Thomas, S.; Collins, C. J.; Cuzens, J. R.; Spiciarich, D.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **2001**, *66*, 1999.

(8) Aliquots were removed from the reaction flask via canunula needle, were run neat, and were referenced to BF_3:OEt_2 (δ = 0) for ^{11}B NMR spectra.

(9) Harrison, J.; Alvarez, S. G.; Godjoian, G.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 7193.

(10) Brown, H. C.; Singaram, B.; Singaram, S. *J. Organomet. Chem.* **1982**, *239*, 43.

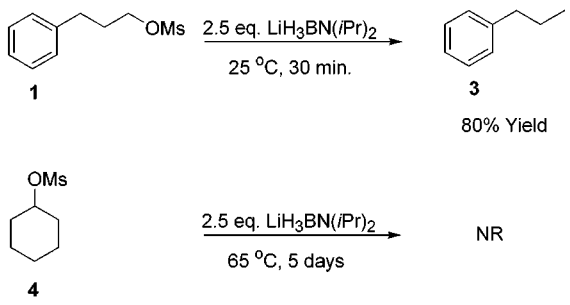


Figure 2. Representative reduction of primary alkyl sulfonates with lithium diisopropylaminoborohydride. Analysis by GC; yield reported was determined using a suitable internal standard and authentic product sample. No other products were detected.

susceptible to reduction (Figure 2). To achieve reduction for secondary mesylates, a more powerful reducing agent is necessary.

$LiEt_3BH$ is an exceptionally powerful nucleophilic reducing agent capable of reducing even hindered alkyl sulfonates.[11] However, it is not without its disadvantages, which are 2-fold: The original procedure requires 2 equiv of $LiEt_3BH$, presumably due to the formation of the unreactive complex $Et_6B_2H^-Li^+$,[12] and an oxidation step in the workup procedure is required.[13] Generating $LiEt_3BH$ in situ eliminates the disadvantages that are associated with this reagent, yet maintains the advantages inherent in using such a powerful, nucleophilic reducing agent.

Since lithium hydride transfer has been reported between LAB reagents and hindered trialkylorganoboranes, producing lithium trialkylborohydrides,[9] conceivably a similar exchange reaction between LAB and Et_3B should generate $LiEt_3BH$. The LAB reagent would act as a lithium hydride transfer reagent with Et_3B, producing $LiEt_3BH$, with aminoborane as a side product. The newly formed $LiEt_3BH$ would then become the reducing species. Since Et_3B is regenerated during reduction of the alkyl sulfonate, theoretically only a catalytic amount of Et_3B is required. In this way, the primary hydride source is from LAB reagent, which is nonpyrophoric.

LAB reagents are an ideal lithium hydride source for the proposed generation of $LiEt_3BH$. They are simple to prepare, are easily handled, and can be stored in an ampule for prolonged periods of time without undergoing decomposition. Unlike LiH, LABs would provide a homogeneous reaction environment, and the reduction product could easily be obtained by performing a simple workup procedure.[14] Additionally, LAH is not suitable for such a metal hydride exchange reaction with Et_3B as it suffers from practical complications resulting from gel formations due to the required addition of triethylenediamine (TED), which precipitates aluminum hydride as TED·AlH_3.[10]

(11) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.

(12) Holder, R. W.; Mattuno, M. G. *J. Org. Chem.* **1977**, *42*, 2166.

(13) CAUTION! Trialkylboranes are known to be extremely pyrophoric. $LiEt_3BH$ generates triethyl borane upon loss of a hydride. Using a catalytic amount of Et_3B for the in situ generation of $LiEt_3BH$ substantially decreases the amount of pyrophoric material for a given reduction.

The in situ generation of $LiEt_3BH$ for the reduction of alkyl methanesulfonates proved to be quite successful. Using 1.5 equiv of LAB and 20 mol % of Et_3B, reduction of both primary and secondary alkyl mesylates is accomplished in very high yield. For example, when 3-phenylpropyl methanesulfonate **1** is treated with 20 mol % of Et_3B and 1.5 equiv of $LiH_3BN(Me)_2$, 3-phenylpropane **3** is the only observable product (Figure 3). After only 15 min at reflux

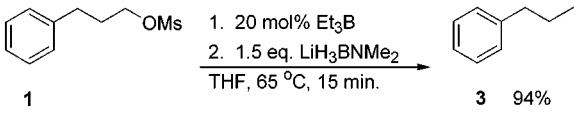
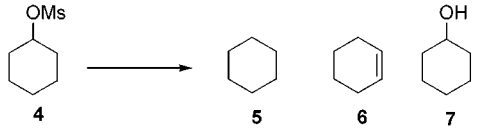


Figure 3. Reduction of primary alkylsulfonic ester with LiH_3BNMe_2 and 20 mol % of Et_3B.

temperature, a 94% yield of the reduction product is obtained, with no other observable products by GC analysis. Not only is the methodology for generating $LiEt_3BH$ in situ using LAB successful, but it is also applicable to secondary and alicyclic methanesulfonate esters. These hindered mesylates are typically more difficult to reduce, as we had experienced with the unsuccessful reduction of cyclohexylmesylate **4** with our hindered LAB reagent. However, after subjecting cyclohexylmesylate **4** to the modified procedure of generating $LiEt_3BH$ via LAB, cyclohexane **5** was generated in 95% yield. This new reduction methodology provides results comparable with those of the original methodology.[4,11] Using our methodology, cyclohexylmesylate **4** is reduced to cyclohexane **5** in 95% yield, with only a trace amount of cylcohexene **6** present in the reaction mixture and no cyclohexanol **7** detected by GC analysis. With the original methodology, a 68% yield of cyclohexane **5** was reported, with a 12% yield of the elimination product cyclohexene **6** (Table 2). Generating $LiEt_3BH$ in situ using LAB and a

Table 2. Reduction of Cyclohexyl Sulfonates with Various Hydride Reducing Agents



Substrate	Reagent	Temp. °C	Products % 5	6	7
4	$LiH_3BN(Me)_2$, cat. Et_3B, THF[a]	65	95	5	0
4	$LiEt_3BH$, THF[b]	60	68	12	0

[a] 1.5 equiv of LAB, 20 mol % of Et_3B. Precent study, solutions were 0.1 M in sulfonate, reaction time 4 h. Analysis by GC using internal standard. [b] 2.1 equiv of $LiEt_3BH$, reaction time 4 h. Reference 12.

catalytic amount of Et_3B is thus a new and useful methodology that is complimentary to existing synthetic methods.

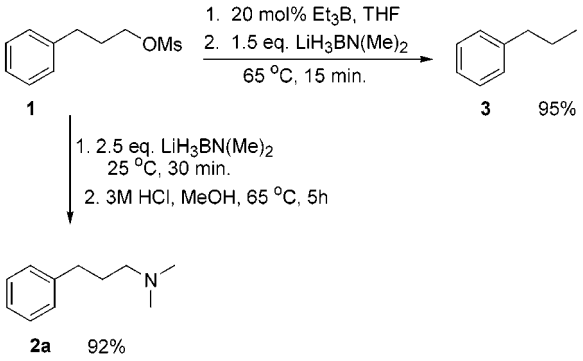


Figure 4. Representative selective reduction *or* amination of alkyl sulfonate 1-mesyl-3-phenylpropane **1** as mediated by lithium dimethylaminoborohydride. Analysis by GC; yield reported was determined using a suitable internal standard and authentic product samples.

The dual properties of LAB reagents are governed by reaction conditions in their reactivity toward alkyl methanesulfonate esters, providing control over reduction vs amination of the title compounds. By treating the alkyl sulfonate **1** with both LAB and a catalytic amount of Et_3B, or by employing a sterically hindered LAB reagent, reduction to the alkane **3** is accomplished. Alternatively, using a sterically unhindered LAB in the absence of Et_3B, LABs mediate the transfer of their amine functionality and tertiary amines **2** are obtained in excellent yield (Figure 4).

The reduction methodology reported herein highlights the synthetic advantages $LiEt_3BH$ offers. Moreover, the controlled reactivity of LAB reagents toward alkyl methanesulfonate esters demonstrates their dual properties as both hydride and amine transfer reagents.

Acknowledgment. We thank the GAANN foundation for a research fellowship for S.T., the Callery Chemical Company for their generous donation of dimethylamine−borane and pyrrolidine−borane, and the donors of the Petroleum Research Fund, administered by the American Chemical Society. We gratefully acknowledge a research grant from the Dow Chemical Co.

Supporting Information Available: Proton and carbon spectra for compounds **2a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0167659

(14) **Procedure for the preparation of 3-phenylpropane 3 from 3-phenylpropyl methanesulfonate 1 is representative.** An oven-dried 50 mL round-bottom flask with a sidearm is equipped with a magnetic stir bar and reflux condenser. The apparatus is assembled while hot and cooled under a stream of nitrogen. The sidearm and reflux condenser are fitted with rubber septum and secured with copper wire. The apparatus is kept under a stream of nitrogen run through an oil bubbler. The flask is charged with 10 mL of dry THF (distilled from sodium−benzophenone), followed by 1 mmol of 3-phenylpropyl methanesulfonate **1**, 1 mmol of internal standard (mesitylene), and 0.2 mmol of Et_3B. The solution is allowed to reach reflux temperature, at which time 1.5 mmol of 1 M LiH_3BNMe_2 is added *dropwise*. See refs 5, 6, or 7 for a more detailed description of LAB handling and quenching. (CAUTION!, if quenched with 3 M HCl, *hydrogen evolution!*) After 15 min, a 0.1 mL aliquot is removed from the reaction mixture and placed in 1 mL of pentane (LAB and amine−boranes are insoluble in pentane). The sample is filtered through a syringe filter and analyzed by GC. Yields reported are GC yields, utilizing an internal standard and corrected for detector response.

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Aminoborohydrides. 12. Novel Tandem S_NAr Amination−Reduction Reactions of 2-Halobenzonitriles with Lithium *N,N*-Dialkylaminoborohydrides

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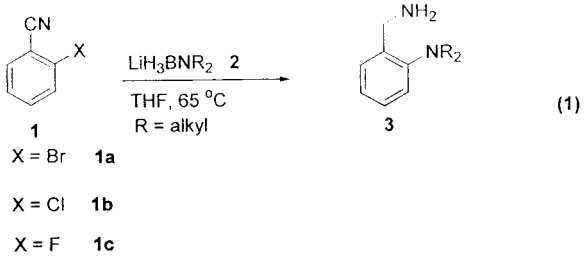
A novel tandem amination−reduction reaction has been developed in which 2-(*N,N*-dialkylamino)-benzylamines are generated from 2-halobenzonitriles and lithium *N,N*-dialkylaminoborohydride (LAB) reagents. These reactions are believed to occur through a tandem S_NAr amination−reduction mechanism wherein the LAB reagent promotes halide displacement by the *N,N*-dialkylamino group, and the nitrile is subsequently reduced. This one-pot procedure is complimentary to existing synthetic methods and is an attractive synthetic tool for the nucleophilic aromatic substitution of halobenzenes with less nucleophilic amines. The (*N,N*-dialkylamino)benzylamine products of this reaction are easily isolated after a simple aqueous workup procedure in very good to excellent yields.

Introduction

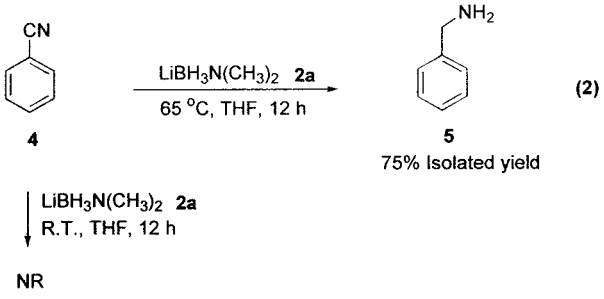
Tandem reactions are a unique class of reactions in organic chemistry in which two or more chemical transformations are carried out in one synthetic step. A new addition to this class of reactions has been discovered that is complementary to existing synthetic methods.[1] In particular, lithium aminoborohydride (LAB) reagents (**2**) have been found to promote a unique tandem S_NAr amination−nitrile reduction reaction with 2-halobenzonitriles (**1**) to produce 2-(*N,N*-dialkylamino)benzylamine (**3**) products in very good to excellent yields after a simple aqueous workup procedure (eq 1).



(1)

Nucleophilic aromatic substitution (S_NAr) reactions of amines with halobenzenes containing strong electron-withdrawing groups, such as nitrohalobenzenes, are well-known.[1] Halobenzonitriles do not generally undergo S_NAr reactions with amines due to lack of activating strength of the nitrile group.[1] A unique and synthetically useful exception to this generality has been found in the reaction of various LAB reagents with halobenzonitriles. Notably, the lithium *N,N*-dialkylaminoborohydride reagent apparently activates the halobenzonitrile toward nucleophilic attack by the amine contained within the reagent.

Lithium aminoborohydrides are a new class of powerful and chemoselective reducing agents which are easy to prepare and handle and can be stored under nitrogen in an ampule for prolonged periods of time without undergoing decomposition.[2] While investigating their reduction capabilities, it was found that LABs reduce aromatic nitriles, but the reduction requires extended refluxing in THF.[2] For example, lithium dimethylaminoborohydride (**2a**) reduces benzonitrile (**4**) to benzylamine (**5**) in 75% isolated yield after refluxing for 12 h in THF. Recovery of starting material is observed if the reaction is carried out at room temperature (eq 2).



(2)

Transfer of the aminoborohydride group from lithium aminoborohydrides to alkyl halides has also been observed, producing the corresponding amine−borane complex.[3] For instance, 4-cyanobenzyl bromide (**6**) is con-

‡ The Dow Chemical Company.

(1) (a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley and Sons: New York, 1989; pp 641−653. (b) Miller, J. *Aromatic Nucleophilic Substitution*; Elsevier Publishing Co.: New York, 1968.

(2) Collins, C. J.; Fisher, G. B.; Reem, A.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1997**, *38*, 529.

(3) Collins, C. J.; Lanz, M.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1999**, *64*, 2574.

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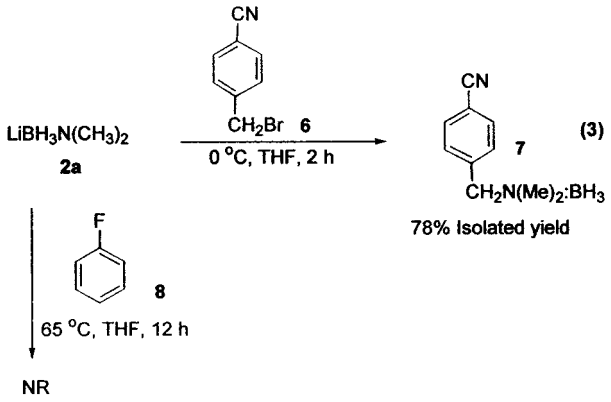
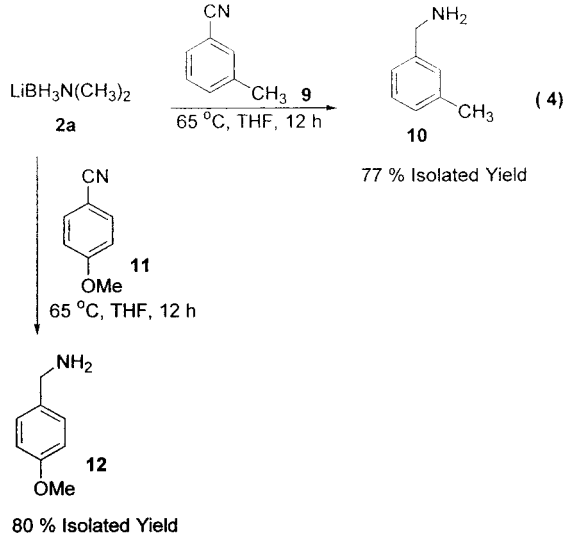
verted to the 4-cyanobenzylamine borane complex (7) in 78% isolated yield when treated with LAB 2a (eq 3).



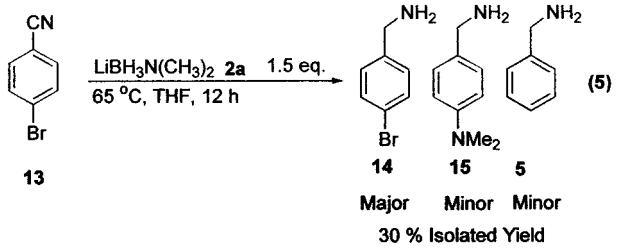
Additionally, LAB reagents had not been found to react with aryl halides, such as bromobenzene, chlorobenzene, or fluorobenzene (8). However, aryl halides containing a cyano group behaved differently with LAB reagents and gave a uniquely novel reaction. In this paper the results of this new reaction between LAB reagents and 2-halobenzonitriles is disclosed.

Results and Discussion

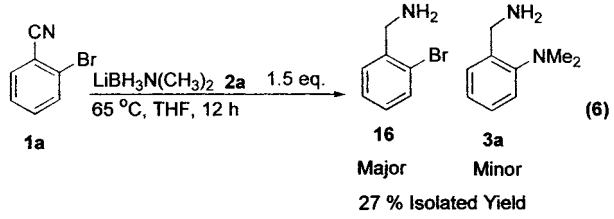
Initially, our interests were in the reduction of substituted benzonitriles with LAB reagents. Benzonitriles containing electron-donating substituents gave benzylamine products in very good yields after refluxing in THF (65 °C) with 1.5 equiv of lithium dimethylaminoborohydride (2a) for 12 h. For instance, reduction of 3-methylbenzonitrile (**9**) and 4-methoxybenzonitrile (**11**) gave 3-methylbenzylamine (**10**) and 4-methoxybenzylamine (**12**) in 77% and 80% yield, respectively (eq 4).



However, when reduction of benzonitriles containing electron-withdrawing groups such as halogens were attempted in the same reaction, instead of obtaining just halobenzylamines as the simple reduction product, (*N,N*-dialkylamino)benzylamines were also detected in the product mixture by ^{1}H NMR analysis. When 4-bromobenzonitrile (**13**) was treated with 1.5 equiv of LAB reagent, rather than recovering the simple nitrile reduction product in good yield as expected, a mixture of products was obtained in low yield (eq 5).

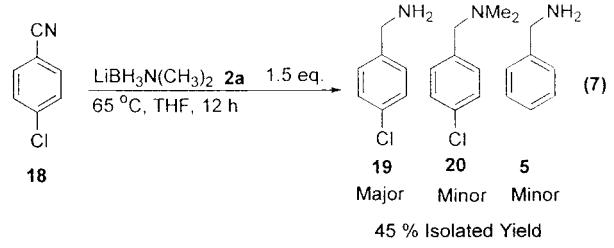


The major product of this mixture was 4-bromobenzylamine (**14**), the expected reduction product. However, minor products were both 4-(*N,N*-dimethylamino)benzylamine (**15**) and the dehalogenated product, benzylamine (**5**). A similar result was observed when the *o*-bromobenzonitrile was used in this reaction. When 2-bromobenzonitrile (**1a**) was treated with 2a, a mixture of products was again obtained in low yield (eq 6).

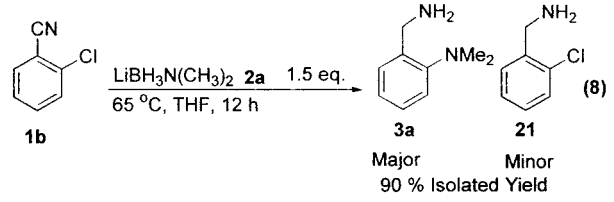


The simple reduction product (**16**) was the major product, and 2-(*N,N*-dimethylamino)benzylamine (**3a**) was observed as a minor product. The expected result of isolating bromobenzylamine as the sole product of these reactions, arising from nitrile reduction, was not achieved. The results obtained seemed uncharacteristic and called for further investigation.

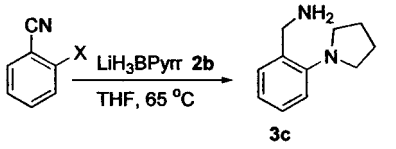
When 4-chlorobenzonitrile (**18**) was treated with 1.5 equiv of LAB reagent 2a, as with the bromo-substituted counterpart, a mixture of products was obtained (eq 7).



The expected reduction product (**19**) was obtained as the major component, and 4-chloro-*N,N*-dimethylbenzylamine (**20**) and benzylamine (**5**) were obtained as minor products. Similar results were expected when 2-chlorobenzonitrile (**1b**) was refluxed with 1.5 equiv of lithium *N,N*-dimethylaminoborohydride (2a). However, unlike the reaction of 2-bromobenzonitrile (**1a**), when 2-chlorobenzonitrile (**1b**) was used as the substrate, 2-(*N,N*-dimethylamino)benzylamine (**3a**) was recovered as the major product in good yield (eq 8).



Scheme 1

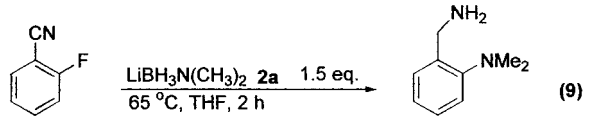


X = Br **1a** 10 % GC yield

X = Cl **1b** 70 % GC yield

X = F **1c** 100 % GC yield

This result indicated that a novel reaction was taking place. In particular, a one-pot tandem reaction seemed to occur, wherein amination at the carbon bearing the halogen was accompanied by reduction of the nitrile. Furthermore, it was found that 2a similarly reacts with 2-fluorobenzonitrile (**1c**) to give exclusively the *tandem amination−reduction* reaction product, 2-(*N,N*-dimethylamino)benzylamine (**3a**) (eq 9).



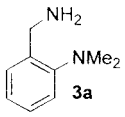
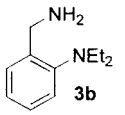
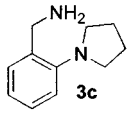
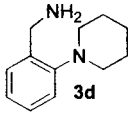
1c **3a** 81% Yield (9)

In addition, rather than requiring extended reaction times at reflux temperature, this reaction was complete in 2 h. This reaction was termed the tandem amination−reduction reaction.

The results obtained for the tandem reactions of *ortho* bromo-, chloro-, and fluorobenzonitriles, summarized in Scheme 1 for lithium pyrrolidinoborohydride, led toward a proposed mechanism to explain the results. It is well-known that in nucleophilic aromatic substitution reactions, the leaving group order of reactivity is F > Cl ≫ Br. The product ratios for bromo-, chloro- and fluorobenzonitrile are in good agreement with the involvement of a S_NAr mechanism, as fluoride is a better leaving group than chloride and bromide in the S_NAr reaction. In contrast, the leaving group order of reactivity is I > Br > Cl >F for the benzyne mechanism[4] and $S_{RN}1$ mechanism.[5] In addition, *cine* substitution would be expected for a benzyne mechanism.

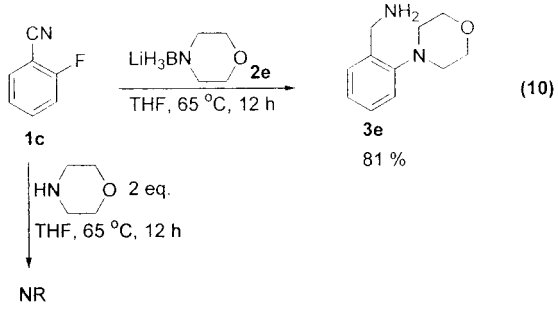
Encouraged by the initial results, the generality of this reaction was investigated with the use of various lithium *N,N*-dialkylaminoborohydrides with fluorobenzonitriles, since the fluoride ion is a much better leaving group than chloride or bromide in nucleophilic aromatic substitution reactions.[6] Through this screening a particularly appealing aspect of the LAB-induced tandem amination−reduction reaction of halobenzonitriles is illustrated. In particular, LAB reagents containing a less nucleophilic amine were able to undergo amine substitution as well as reduction of the nitrile. In contrast, the free amine failed to induce amine substitution. In this case, the nitrile moiety does not activate the aromatic ring for nucleophilic attack by the free amine, and the starting material is recovered unchanged. For example, lithium morpholinoborohydride (2e) reacts with 2-fluorobenzonitrile **1c** via the tandem amination−reduction reaction

Table 1. Tandem S_NAr Amination−Reduction Products from the Reaction of 2-Fluorobenzonitrile with Various Lithium Aminoborohydrides

entry	LiH_3BNR_2	product[a, b]	yield (%)[c]
1	LiH_3BNMe_2 **2a**	 **3a**	81
2	LiH_3BNEt_2 **2b**	 **3b**	70
3	LiH_3BN **2c**	 **3c**	84
4	LiH_3BN **2d**	 **3d**	94
5	LiH_3BN O **2e**	 **3e**	81
6	LiH_3BN **2f**	 **3f**	75

[a] All reactions were carried out on a 10 mmol scale with 1.5 equiv of LiH_3BNR_2 for 2 h at 65 °C in THF, unless otherwise noted. [b] All products characterized by ^1H and ^{13}C NMR spectroscopy. [c] Crude, isolated yields.

pathway to provide 2-(4-morpholino)benzylamine (**3e**) in 81% yield. In comparison, free morpholine does not give any S_NAr reaction with the same substrate under reflux conditions, and the starting material is recovered unchanged (eq 10).



1c **3e** 81 % (10)

The reaction of 2-fluorobenzonitrile (**1c**) with various lithium *N,N*-dialkylaminoborohydrides is fairly general and gives the corresponding 2-(*N,N*-dialkylamino)benzylamines in very good yield (Table 1).

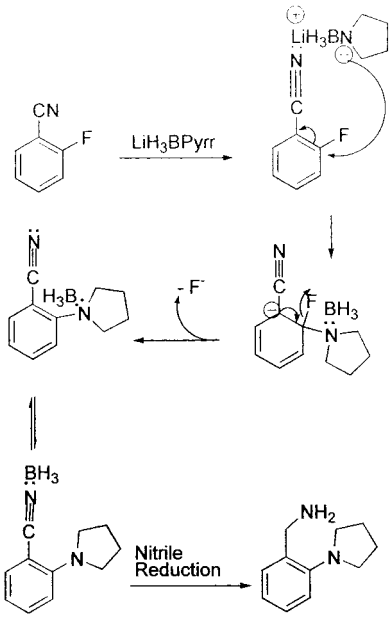
Thus, a wide variety of amines, from the very nucleophilic, such as pyrrolidine, to the less nucleophilic, such as morpholine, are able to undergo substitution with 2-fluorobenzonitriles via LAB reagents. However, aminoborohydrides containing a sterically demanding amine,

(4) March, J. *Advanced Organic Chemistry*; 4th ed.; John Wiley and Sons: New York, 1992; p 646.

(5) Kim, J. K.; Bunnett, J. *J. Am. Chem. Soc.* **1970**, *92*, 7463.

(6) Vlaov, V. M. *J. Fluorine Chem.* **1993**, 193.

Scheme 2



such as lithium diisopropylaminoborohydride, gives primarily reduction of the nitrile moiety in 2-fluorobenzonitrile.

The one-pot tandem amination−reduction reactions of various LAB reagents are complementary to existing synthetic methods. A similar transformation could be carried out in two steps by palladium-catalyzed amination[7] of 2-chloro- or 2-bromobenzonitrile followed by reduction of the nitrile with lithium aluminum hydride[8] or borane.[9] However, lithium *N,N*-dialkylaminoborohydrides offer the convenience of a one-pot procedure, as well as the ability to induce substitution of less nucleophilic amines.

The proposed mechanism for these tandem reactions is depicted in Scheme 2.[10]

Initial coordination of the lithium ion to the nitrogen lone pair on the nitrile activates the aromatic ring for nucleophilic attack. The *N,N*-dialkylaminoborane moiety attacks the carbon containing the halide on the benzene ring, forming a Meisenhiemer complex. The fluoride ion then leaves to give a 2-(*N,N*-dialkylamino)benzonitrile−borane. The borane moiety of the 2-(*N,N*-dialkylamino)-benzonitrile−borane is quite labile and dissociates from the amine. The short reaction times for these reactions imply the presence of a Lewis acidic reducing agent, such as borane, which tend to rapidly reduce nitriles when compared to nucleophilic hydride reagents. ^{11}B NMR displayed a quartet at δ −1.1 ppm, attributable to a borane−THF complex. The availability of free borane was investigated by the addition of 1-hexene to the reaction flask. However, ^{11}B NMR analysis did not detect the expected trihexylborane. Rapid association of the borane with the lone pair of electrons of the nitrile and subsequent reduction is thus suspected.

It was speculated that if the lithium ion of the LAB reagent was indeed promoting the S_NAr reaction, then the simple addition of a lithium salt to a refluxing mixture of 2-fluorobenzonitrile and a less nucleophilic amine could promote amination in a similar manner. However, only a trace amount of the aminated product was observed with the addition of LiCl to a refluxing mixture of 2-fluorobenzonitrile and piperidine. Though the addition of a lithium salt was not sufficient to promote a S_NAr reaction, the corresponding LAB reagent, lithium piperidinoborohydride, provided 81% of the tandem amination−reduction reaction product **3e**.

Conclusions

In summary, a novel tandem amination−reduction reaction of 2-halobenzonitriles with lithium *N,N*-dialklaminoborohydride reagents has been discovered. LAB reagents react with 2-halobenzonitriles via a unique tandem reaction mechanism, promoting nucleophilic aromatic substitution on substrates that are otherwise unreactive toward amine substitution. The reaction of 2-bromobenzonitrile (**1a**) with various LAB reagents gives primarily the reduction product, 2-bromobenzylamine (**16**), while the reaction of 2-chlorobenzonitrile (**1b**) with various LAB reagents gives primarily the tandem reaction product, 2-(*N,N*-dialkylamino)benzylamine **2**. Last, when 2-fluorobenzonitrile is treated with LAB reagent, the tandem reaction product is exclusively obtained. The S_NAr tandem amination−reduction reaction of 2-halobenzonitriles with lithium aminoborohydrides is a one-pot procedure and an attractive synthetic tool for the aromatic substitution of less nucleophilic amines.

Experimental Section

General Methods. All reactions were performed in oven-dried, nitrogen-cooled apparatus. All air- and moisture-sensitive compounds were introduced via syringes or cannula through a rubber septum. THF was distilled from sodium−benzophenone. NMR spectra were recorded in $CDCl_3$. Chemical shifts are reported relative to TMS ($\delta = 0$) for ^{1}H NMR and are referred to the $CDCl_3$ resonance ($\delta = 77$) for ^{13}C NMR spectra. Boron NMR samples were run neat and referenced to BF_3:OEt_2 ($\delta = 0$) for ^{11}B NMR spectra. Mass spectra were obtained on a mass spectrometer in TIS (turbo ion spray) mode. The 2-bromobenzonitrile, 2-chlorobenzonitrile, and 2-fluorobenzonitrile were purchased from the Acros chemical company and used without further purification. The 4-methoxybenzonitrile, 3-methylbenzonitrile, benzonitrile, and 4-cyanobenzyl bromide were purchased from Aldrich Chemical Co. and were used without further purification. The *N,N*-dimethylamine−borane was donated from the Callery Chemical Company.

General Procedure for the Preparation of LAB Reagent 1 M Solution in THF. The following procedure for the preparation of LiH_3Bpyrr (**2c**) is representative. A dry 125-mL serum vial equipped with a magnetic stirring bar and fitted with a rubber septum was charged with pyrrolidine (7.11 g, 100 mmol) and anhydrous THF (43 mL) via syringe. At 0 °C,

(7) (a) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.

(8) Brown, H. C.; Weissman, J.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *58*, 1458.

(9) Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1960**, *82*, 681.

(10) Lithium aminoborohydrides can act as hydride or nitrogen transfer agents. This *proposed* mechanism is based on the dual properties of LABs, both of which are moderated by boron. X-ray crystal data obtained by Heinrich Noth (*Chem. Ber.* **1996**, *129*, 451−458) confirms that LABs are a mixed aggregate, with Li situated between boron and nitrogen. The amino group is thus a strong base, as it initiates Li−N bonding. However, the addition of Li salts to the reaction of a free amine did not enhance the S_NAr reaction with halobenzonitrile, indicating that the LAB reagent does not behave as a lithium amide. A referee suggested as a possible mechanism the transfer of the B−N bond via intermolecular transfer analogous to a tetravalent "ate" complex. However, this type of transfer would only be possible if boron was on the migrating terminus. It is thus suggested that the amine of the LAB reagent acts as the nucleophile attacking the carbon bearing the leaving group.

borane−dimethyl sulfide (10 mL, 10 M, 100 mmol) was added dropwise via syringe. After stirring at 0 °C for 1 h, an aliquot was taken and analyzed by ^{11}B NMR spectroscopy. ^{11}B NMR analysis (80.25 MHz, THF) showed the solution to be pyrrolidine−borane $\delta = -18.0$ ppm (q, $J = 96$ Hz). If commercial amine−borane is used, the previous step is modified so as to dissolve the complex in the appropriate volume of dry THF. At 0 °C, *n*-butyllithium in hexanes (40 mL, 2.5 M, 100 mmol) was added dropwise via syringe. After stirring at 0 °C for 1 h, an aliquot was taken and analyzed by ^{11}B NMR spectroscopy. ^{11}B NMR analysis (80.25 MHz, THF) showed the solution to be lithium pyrrolidinoborohydride (**2c**) $\delta = -20.6$ ppm (q, $J =$ 85 Hz). LAB reagents may be transferred to an oven-dried, nitrogen-cooled ampule via a cannula and stored under nitrogen for up to six months without undergoing decomposition.

General Procedure for the Tandem Amination−Reduction Reaction of Halobenzonitriles. The following procedure for the reduction of 2-fluorobenzonitrile (**1c**) with LiH_3Bpyrr (**2c**) is representative. A dry 50-mL round-bottom flask equipped with a magnetic stirring bar was sealed with a rubber septum and was charged with 2-fluorobenzonitrile (10 mmol, 1.21 g). At 0 °C, 1 M lithium pyrrolidinoborohydride (15 mmol) was added dropwise via syringe. The flask was fitted with a water-cooled reflux condenser and the reaction mixture heated to reflux under nitrogen. After 2 h, the reaction was cooled under N_2 gas. At 0 °C, the reaction was quenched by the slow addition of 25 mL of 3 M HCl [*Caution: Hydrogen evolution!*]. The aqueous fraction was extracted with diethyl ether (4 × 20 mL). Solid sodium hydroxide was added to the aqueous fraction until strongly basic to litmus. The aqueous layer was extracted with diethyl ether/THF 1:1 (4 × 20 mL). The combined ethereal fractions were dried over $MgSO_4$ and filtered. The solvents were removed in vacuo (25 °C, 1 Torr) to yield 2-(1-pyrrolidino)benzylamine (**3c**) as a light yellow oil (1.48 g, 84%). ^1H NMR (500 MHz, $CDCl_3$) δ 1.87−1.97 (m, 4H), 2.29 (s, 2H), 3.18−3.21 (t, $J = 7$ Hz, 4H), 3.92 (s, 2H), 6.92−6.95 (t, $J = 8$ Hz, 1H), 6.98−6.99 (d, $J = 8$ Hz, 1H), 7.17−7.20 (td, $J = 1$ Hz, $J = 8$ Hz, 1H), 7.26−7.28 (dd, $J = 1$ Hz, $J = 8$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.06, 29.81, 54.38, 117.21. 121.30, 127.88, 129.54, 130.68, 148.66; HRMS (70 eV) *m*/*z* ($M^+ + 1$), calcd 177.1386, found 177.1363.

2-(*N,N*-Dimethylamino)benzylamine (3a). Reaction of 2-fluorobenzonitrile (**1c**) (0.606 g, 5 mmol) and lithium dimethylaminoborohydride (7.5 mmol, 7.5 mL, 1 M) produced **3a** as a light yellow oil (0.61 g, 81%); ^1H NMR (500 MHz, $CDCl_3$) δ 2.71 (s, 6H), 3.93 (s, 2H), 7.05−7.08 (td, $J = 1$ Hz, $J = 7$ Hz, 3H), 7.12−7.14 (d, $J = 8$ Hz, 1H), 7.21−7.25 (td, $J = 2$ Hz, $J = 8$ Hz, 1H), 7.31−7.32 (d, $J = 8$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 43.45, 45.10, 119.57, 123.65, 127.63, 128.66, 138.07, 152.47; HRMS (70 eV) *m*/*z* ($M^+ + 1$), calcd 151.1230, found 151.1182.

2-(*N,N*-Diethylamino)benzylamine (3b). Reaction of 2-fluorobenzonitrile (**1c**), (1.21 g, 10 mmol) and lithium diethylaminoborohydride (15 mmol, 15 mL, 1 M) produced **3b** as a light yellow oil (1.24 g, 70%); ^1H NMR (500 MHz, $CDCl_3$) δ 0.98−1.02 (td, $J = 2$ Hz, $J = 8$ Hz, 6H), 1.76 (bs, 2H), 2.95−3.00 (qd, $J = 2$ Hz, $J = 8$ Hz, 4H), 3.88 (s, 2H), 7.05−7.09 (tt, $J = 1$ Hz, $J = 7$ Hz, 1H), 7.13−7.15 (d, $J = 8$ Hz, 1H), 7.19−7.22 (tt, $J = 2$ Hz, $J = 8$ Hz, 1H), 7.27−7.29 (d, $J = 8$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.84, 43.74, 48.35, 122.93, 124.30, 140.83, 149.59; HRMS (70 eV) *m*/*z* ($M^+ + 1$), calcd 179.1519, found 179.1543.

2-(1-Piperidino)benzylamine (3d). Reaction of 2-fluorobenzonitrile (**1c**), (0.606 g, 5 mmol) and lithium piperidinoborohydride (7.5 mmol, 7.5 mL, 1 M) produced **3d** as a light yellow oil (0.89 g, 94%); ^1H NMR (500 MHz, $CDCl_3$) δ 1.57−1.60 (quint. $J = 6$ Hz, 4H), 2.85−2.87 (t, $J = 5$ Hz, 4H), 3.90 (s, 2H), 7.04−7.07 (t, $J = 7$ Hz, 1H), 7.10−7.12 (d, $J = 8$ Hz, 1H), 7.20−7.23 (t, $J = 8$ Hz, 1H), 7.27−7.29 (d, $J = 8$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.40, 26.90, 43.61, 54.40, 120.41, 123.90, 127.68, 128.55, 138.81, 152.69; HRMS (70 eV) *m*/*z* ($M^+ + 1$), calcd 191.1543, found 191.1526.

2-(4-Morpholino)benzylamine (3e). Reaction of 2-fluorobenzonitrile (**1c**), (0.606 g, 5 mmol) and lithium morpholinoborohydride (7.5 mmol, 15 mL, 0.5 M) produced **3e** as a light yellow oil (0.77 g, 81%); ^1H NMR (500 MHz, $CDCl_3$) δ 2.92−2.94 (t, $J = 5$ Hz, 4H), 3.84−3.86 (t, $J = 5$ Hz, 4H), 3.91 (s, 2H), 7.10−7.14 (m, 2H), 7.24−7.27 (m, $J = 2$ Hz, $J = 9$ Hz, 1H), 7.31−7.32 (d, $J = 7$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 43.09, 53.26, 67.20, 120.33, 124.63, 127.89, 128.78, 138.78, 138.63, 150.98; HRMS (70 eV) *m*/*z* ($M^+ + 1$), calcd 193.1335, found 193.1345.

2-(1-Hexamethyleneimino)benzylamine (3f). Reaction of 2-fluorobenzonitrile (**1c**), (1.21 g, 10 mmol) and lithium homopiperidinoborohydride (15 mmol, 15 mL, 1 M) produced **3f** as a light yellow oil (1.53 g, 75%); ^1H NMR (500 MHz, $CDCl_3$) δ 1.69 (bs, 4H), 3.03−3.06 (t, $J = 6$ Hz, 4H), 3.86 (s, 2H), 6.98−7.01 (t, $J = 8$ Hz, 1H), 7.10−7.11 (d, $J = 8$ Hz, 1H), 7.15−7.18 (t, $J = 8$ Hz, 1H), 7.21−7.22 (d, $J = 8$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.16, 29.85, 44.22, 57.26, 122.28, 123.69, 127.80, 128.56, 138.78, 154.85; HRMS (70 eV) *m*/*z* ($M^+ + 1$), calcd 205.1699, found 205.1699.

3-Methylbenzylamine (10).[11] A 100 mL, round-bottom flask equipped with a magnetic stirring bar and fitted with a rubber septa was charged with lithium dimethylaminoborohydride (30 mmol, 30 mL, 1 M) and cooled under nitrogen to 0 °C. At °C, *m*-tolunitrile (0.58 g, 5 mmol) was added via syringe. The reaction was heated to reflux (65 °C) under nitrogen and quickly became blood red in color. After 12 h, TLC analysis indicated the absence of starting material. The reaction mixture was then cooled under nitrogen to 0 °C. At °C, deionized water (4 mL) and then 12 M HCl (10 mL, 120 mmol) were added [*Caution: Hydrogen evolution!*]. The aqueous layer was extracted with 2 × 50 mL portions of diethyl ether/THF. At 0 °C, the aqueous layer was made strongly basic to litmus (pH = 12 with solid NaOH. The aqueous layer was extracted with 2 × 50 mL portions of diethyl ether/THF. The organic layers were combined, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under vacuum (35 °C, 30 Torr and then 25 °C, 1 Torr). The 3-methylbenzylamine product was obtained as (1.87 g, 77% yield) a light yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (brd. S, 2H), 2.37 (s, 3H), 3.84 (s, 2H), 7.07−7.27 (mult., 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.42, 46.58, 1247.14, 127.54, 127.90, 128.50, 138.18, 143.45.

4-Methoxybenzylamine (11).[12] 80% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 2H), 3.78 (s, 5H), 6.68 (d, 2H), 7.22 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.98, 55.32, 114.0, 128.26, 135.74, 158.60.

Attempted Borane Scavenging Using 1-Hexene. A dry 100-mL round-bottom flask equipped with a magnetic stirring bar was sealed with a rubber septum and was charged with 2-fluorobenzonitrile (5 mmol, 0.545 mL) and 1-hexene (22.5 mmol, 5.66 mL). At 0 °C, lithium dimethylaminoborohydride (7.5 mmol, 7.5 mL, 1 M) was added dropwise via syringe. The flask was fitted with a water-cooled reflux condenser, and the reaction mixture heated to reflux under nitrogen. After 2 h, the reaction was monitored by ^{11}B NMR, and no peaks indicating an alkylborane were present. A TLC analysis at this time showed no indication of starting material. The reaction was cooled under N_2 gas. At 0 °C, the reaction was quenched by the slow addition of 25 mL of 3 M HCl [*Caution: Hydrogen evolution!*]. The aqueous fraction was extracted with diethyl ether (4 × 20 mL). Solid sodium hydroxide was added to the aqueous fraction until strongly basic to litmus. The aqueous layer was extracted with diethyl ether/THF 1:1 (4 × 20 mL). The combined ethereal fractions were dried over $MgSO_4$ and filtered. The solvents were removed in vacuo (25 °C, 1 Torr) to yield 2-(*N,N*-dimethylamino)benzylamine **3c** as a light yellow oil in 71% yield.

Attempted Activation of 2-Fluorobenzonitrile with LiCl. A dry 100-mL, round-bottom flask equipped with a sidearm and a magnetic stirring bar was charged with LiCl (15 mmol, 0.63 g) and sealed with a rubber septum. Dry THF (7.5 mL), 2-fluorobenzonitrile (10 mmol, 1.09 mL), and piperdine (15 mmol, 1.49 mL) were introduced to the flask via the

(11) Harada, H.; Marie, T.; Suzuki, T.; Yoshida, T.; Kato, S. *Tetrahedron* **1998**, *54*, 10671.

(12) LopeZ, F. J.; Nitzan, D. *Tetrahedron Lett.* **1999**, *40*, 2071.

sidearm, and the flask was fitted with a nitrogen-filled reflux condenser. The reaction mixture was heated to reflux under nitrogen. The reaction was monitored by TLC analysis at 2 h, 4 h, 6 h, and 24 h. After 24 h at reflux temperature (65 °C), a TLC analysis showed the strong presence of starting material, with a faint indication of another compound. At this time, the reaction was cooled under N_2 gas, and at 0 °C, the reaction was quenched by the slow addition of 25 mL of 3 M HCl [*Caution: Hydrogen evolution!*]. The aqueous fraction was extracted with diethyl ether (4 × 20 mL). Solid sodium hydroxide was added to the aqueous fraction until strongly basic to litmus. The aqueous layer was extracted with diethyl ether/THF 1:1 (4 × 20 mL). The combined ethereal fractions were dried over $MgSO_4$ and filtered. The solvents were removed in vacuo (25 °C, 1 Torr) to yield only a trace amount of 2-(1-piperidino)benzylamine. The starting material was recovered unchanged in the neutral ether fraction.

Acknowledgment. The authors thank the Callery Chemical Co., for supplying the *N,N*-dimethylamine−borane used in this research, and the donors of the Petroleum Research Fund. We also thank Dr. RuAngelie Edrada for help in obtaining the HRMS data.

Supporting Information Available: Proton and carbon spectra and HRMS data for representative compounds. This material is free of charge via the Internet at http://pubs.acs.org.

JO001388J

The Small Scale Synthesis of Acetylsalicylic Acid (Aspirin)

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Abstract

Salicylic acid was reacted with concentrated phosphoric acid and acetic anhydride to create acetylsalicylic acid ~~at~~ in 74.1% yield. The negative ferric chloride test and the melting point of 132.4-135.7°C were consistent with ~~a pure result,~~ literature values but the infrared spectrum showed a peak ~~as~~ at 3427.89 cm^{-1}, ~~inconsistent with literature value~~. That was inconsistent with the product.

Introduction

Missing References

The discovery of salicylic acid as a great new pain reliever, fever reducer and swelling reducer was marred by how acidic it was. Trying to take the new medicine would lead to irritation of the mucous lining from mouth to stomach. Organic chemists were interested in finding away to use this compound but decrease its acidic properties. Success came to Felix Hofmann, a German chemist with Bayer, when he synthesized acetylsalicylic acid, known commonly as aspirin, by adding an acetyl group to the salicylic acid. The new compound still kept the medicinal properties of salicylic acid but is less acidic.

Hofmann added acetyl group by reacting the hydroxyl group on the ring system in salicylic acid with the acetic anhydride to form an ester. The reaction is an esterification that requires an acid catalyst as indicated in

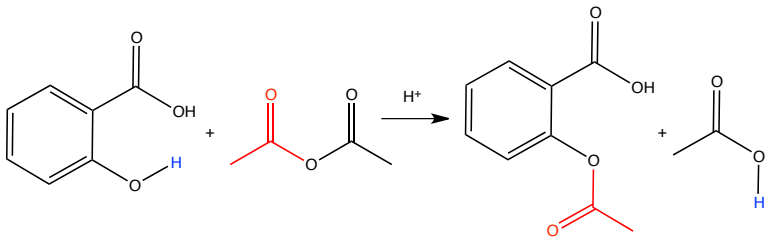


Figure 1. Esterification of Salicylic Acid

Figure 1. To help the reaction moved forward, acetic anhydride was used in excess. The excess reactant pushes the reaction to the product.

Although the exact mode of action of aspirin is still unknown, synthesizing it in the lab is straightforward. The reaction between salicylic acid and acetic anhydride, used as solvent, with an acid catalyst, concentrated phosphoric acid, at 50ºC for eight to ten minutes produces acetylsalicylic

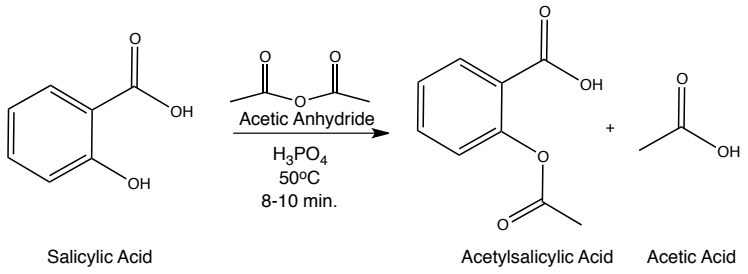


Figure 2. Reaction of salicylic acid in acetic anhydride with phosphoric acid to form acetylsalicylic acid and acetic acid.

acid and acetic acid (Figure 2).

Methods and Materials

The procedure in Pavia was followed with only the following modifications[1]. A sand bath was used to control heat instead of a hot water bath.

Salicylic acid, acetic anhydride, phosphoric acid, 5% aqueous sodium bicarbonate solution, and magnesium phosphate were obtained from the Cabrillo College chemistry stockroom and used without modification.

FT-IR spectrum were obtained on a Nicolet Avatar 360 FT-IR ESP using Omnic 8.1.210 FTIR Software by Thermo Fisher Scientific Inc., 2009. Solid FT-IR spectrum were taken in a solid potassium bromide pellet, pressed to ten tons in an International Crystal Laboratories FTIR 20 ton press. Melting points were obtained in a Laboratory Devices, Inc. Meltemp II equipped with a Fluke Corporation 51 K/J Thermometer thermocouple.

Results

Table 1. Properties of Aspirin Sample

Yield (mg)	207.5 mg
Percentage Yield	74.1%
Melting Point Trial 1	132.6 - 136.4 °C
Melting Point Trial 2	132.1 - 134.6 °C

Average?

Acetylsalicylic acid was obtained as white crystals in 74.1% yield following recrystallization out of acetic acid and water. The average melting point of the acetylsalicylic acid was 132.3-135.5°C.

Table 2. Ferric Chloride Test

Salicylic Acid (Positive)	Water (Negative)	Sample
Violet	Slight Yellow	Clear with light yellow

A ferric chloride test of the sample was negative for phenols.

The infrared spectrum of the sample, figure 12, showed that the sample of acetylsalicylic acid was not a pure sample of acetylsalicylic acid.

Discussion

The Mechanism

The esterification of salicylic acid and acetic anhydride has a six step mechanism. The first step is protonation of a primary oxygen on the acetic

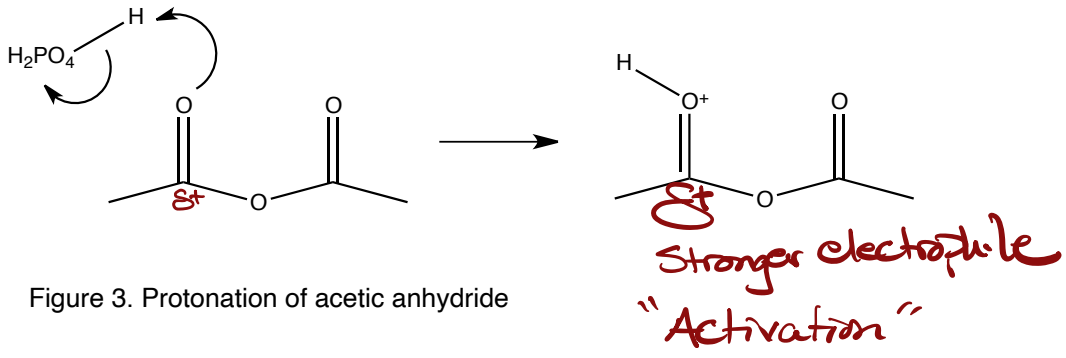


Figure 3. Protonation of acetic anhydride

anhydride by the phosphoric acid, leaving an oxonium ion(Figure 3).The concentrated phosphoric acid is used as a catalyst to start and help the reaction along, and without the phosphoric acid, the reaction would not run because there would be no free protons to start the mechanism.The positive charge sits on the oxygen but this increases the partial positive on the double bonded carbon. The salicylic acid is now able to act as a nucleophile and attack that carbon, forming a bond between the acetic

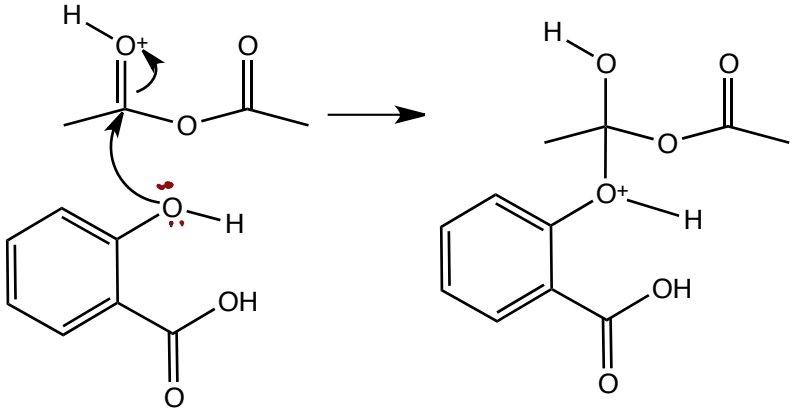


Figure 4. Nucleophilic attack by salicylic acid

anhydride and salicylic acid(Figure 4). Now the conjugate base comes back and deprotonates the new positively charged oxygen returning the

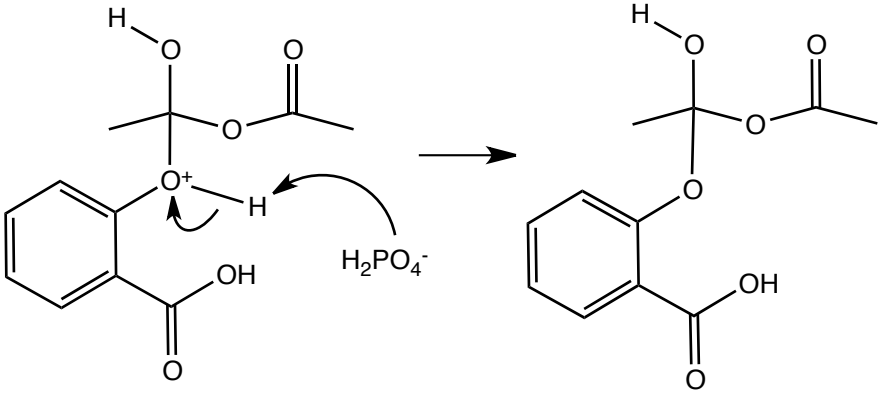


Figure 5. Deprotonation of positively charged oxygen

molecule to a neutral state (Figure 5). Another acid molecules then protonates the other double bonded oxygen from the acetic anhydride

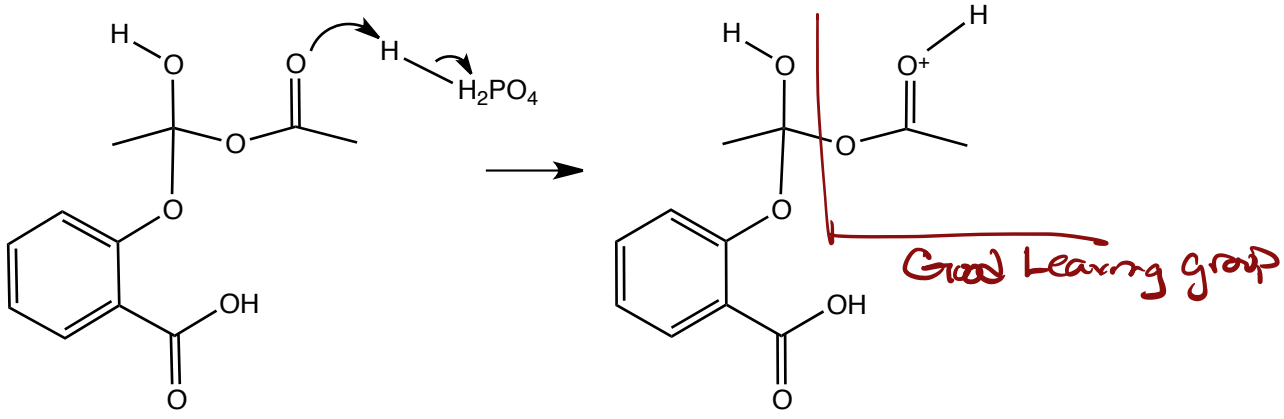


Figure 6. Protonation of second double bonded oxygen of acetic anhydride

forming a leaving group (Figure 6). The sigma bond between *carbon and oxygen breaks. The electrons form a pi bond with the tertiary carbon and push out the other pi bond electrons to the positively charged oxygen

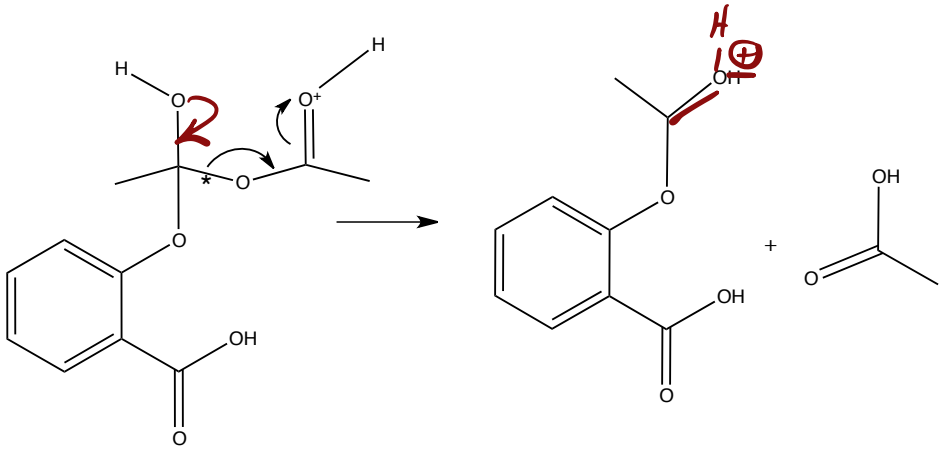


Figure 7. Bond breaking and electron transfer.

(Figure 7). A final deprotonation of the new oxygen completes the mechanism (Figure 8).

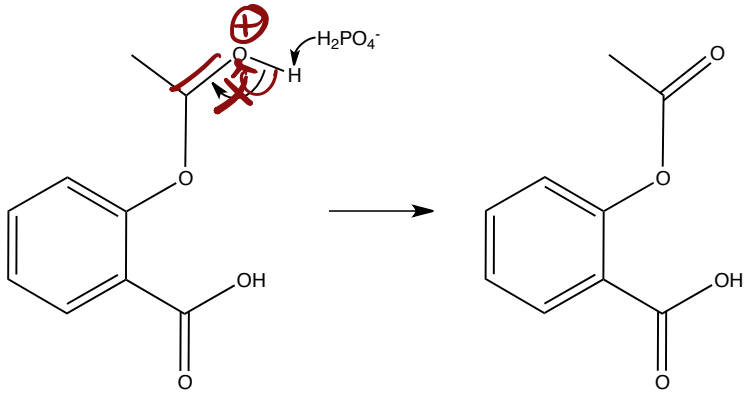


Figure 8. Final deprotonation to acetylsalicylic acid.

The Product

The experiment produced 207.5 mg of acetylsalicylic acid at a 74.1% yield. The percentage yield was moderate. Loss may have been due to the experiment not have running to completion or occurred during the separation the acetylsalicylic acid. To separate the acetylsalicylic acid from the acetic acid and other impurities, the solution was cooled and the acetylsalicylic acid crystallized within the solution. Water was added to decrease the solubility of the acetylsalicylic acid (Figure 13). Unreacted salicylic acid is the most likely impurity.

Acetylsalicylic acid also reacts with water to undo the desired reaction

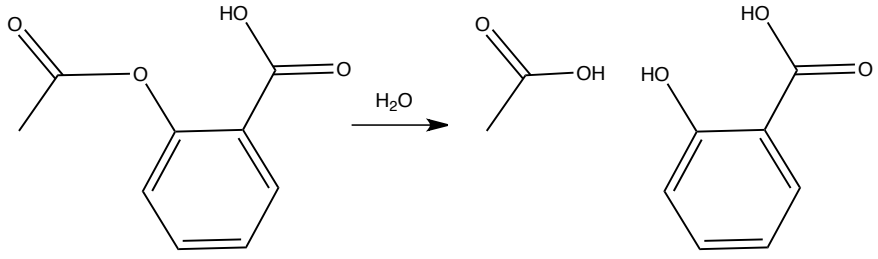


Figure 9. Reaction of acetylsalicylic acid and water

(Figure 9) The water is useful in separating the acetylsalicylic acid, but it

cleaves the bond made in the first reaction and some product is lost to this competing reaction.

The purity of the product was tested using a ferric chloride test, melting point determination and infrared spectroscopy. Ferric chloride reacts with phenols, the most likely impurity salicylic acid, to produce a vivid violet solution. When acetylsalicylic acid is added to the ferric chloride solution, it doesn't react because it's hydroxyl group isn't located on the ring system. The test showed up similar to the negative control, water, but was slightly less yellow, showing that there my have been slight impurities, but not enough to produce the violet that pure salicylic acid produces (Table 2).

Melting point shows that a product is pure. Impurities make overcoming intermolecular forces easier and decrease the melting point. If a material isn't completely dry, the melting point will decrease and the range will be wider. The melting point of the acetylsalicylic acid was within a 3 degree range of literature values, but the range was larger. The product may not have dried completely, or there may have been impurities.

Infrared spectroscopy shows the composition of a product and is the clearest way to test for impurities. Pure acetylsalicylic acid doesn't have a phenol group, and doesn't show the peak at 3237.36 cm^{-1} that salicylic acid does (Figures 10-11). The sample of acetylsalicylic acid shows a

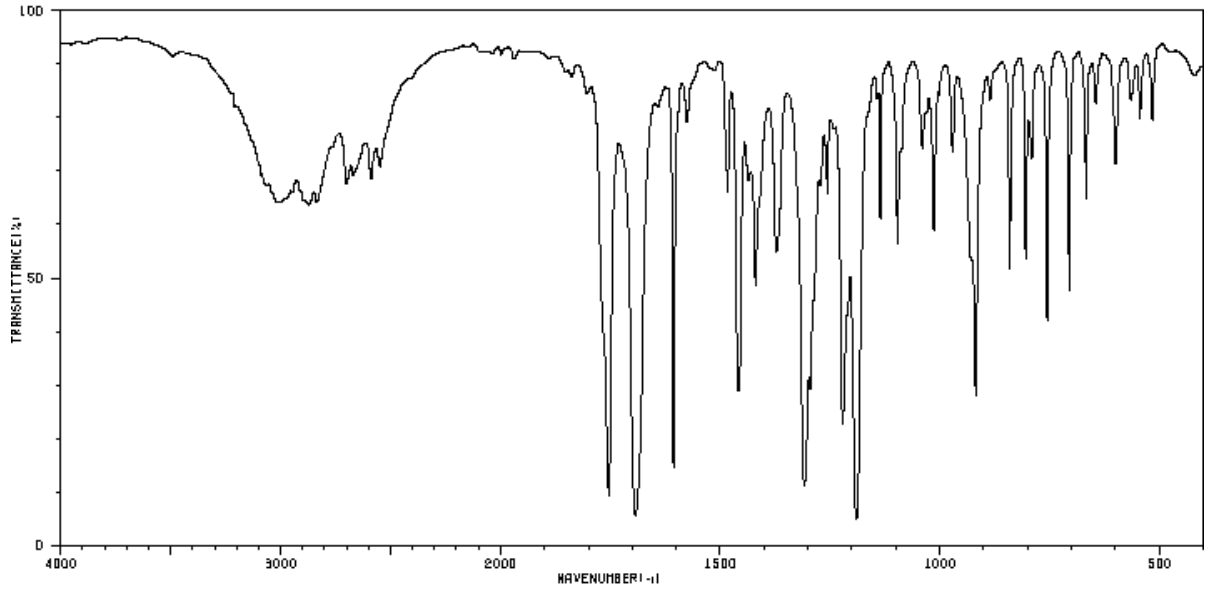
peak at 3427.89 cm^{-1} that pure acetylsalicylic acid does not (Figure 12). This shows that there are some phenol impurities in the sample.

Conclusion

The synthesis of acetylsalicylic acid using salicylic acid, acetic anhydride and concentrated phosphoric acid and was completed at 74.1% yield. The ferric chloride test and melting point of 132.4-135.7°C showed a slight impurity, and the IR spectrum confirmed.

References

1. Pavia, Donald L., Gary M. Lampman, George S. Kriz, and Randell G. Engel. *Introduction to Organic Laboratory Techniques: a Small Scale Approach*. Fourth ed. Belmont, CA: Thomson Brooks/ Cole, 2007. Print.
2. *AIST:RIO-DB Spectral Database for Organic Compounds,SDBS*. Web. 30 Nov. 2011. <http://riodb01.ibase.aist.go.jp/sdbs/cgi-bin/direct_frame_top.cgi>.



3006	62	2589	66	1436	66	1222	21	918	26
2983	62	2548	68	1420	47	1190	4	841	50
2891	82	1754	9	1372	53	1136	58	805	52
2872	62	1693	5	1308	10	1096	55	756	41
2834	62	1606	14	1295	28	1014	57	706	46
2701	66	1483	64	1272	64	971	70	667	62
2670	66	1459	27	1257	64	928	52	600	68

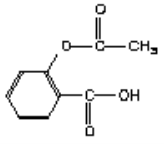


Figure 10. Infrared spectrum for acetylsalicylic acid[2].

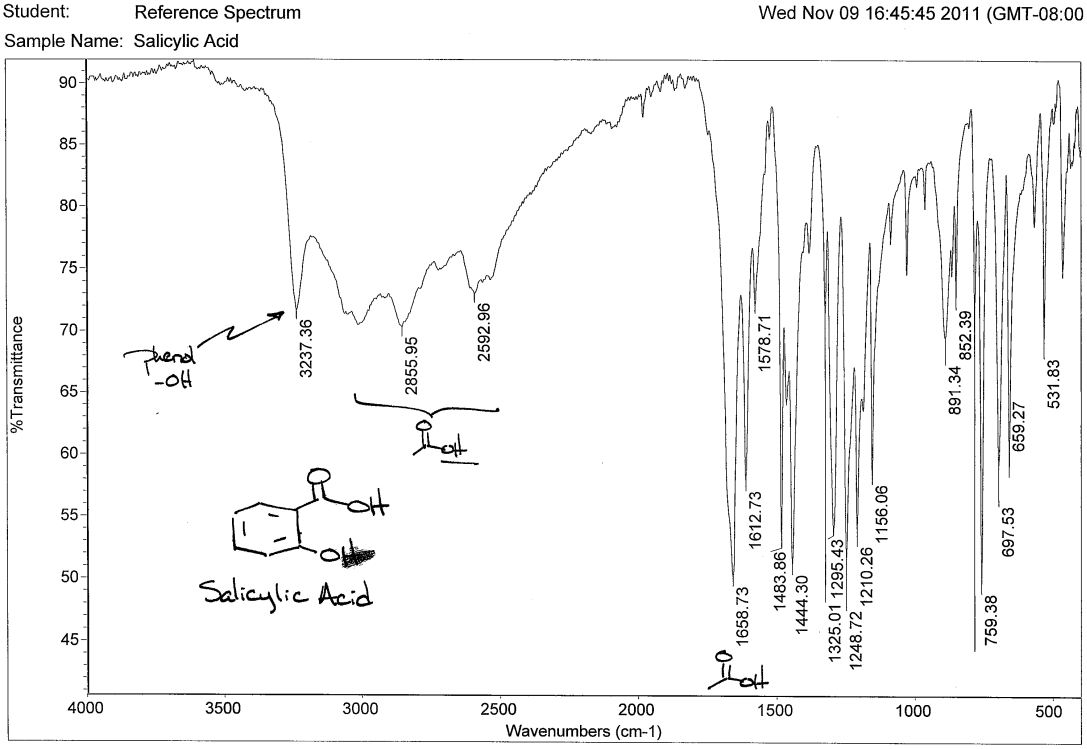


Figure 11. Infrared spectrum of salicylic acid.

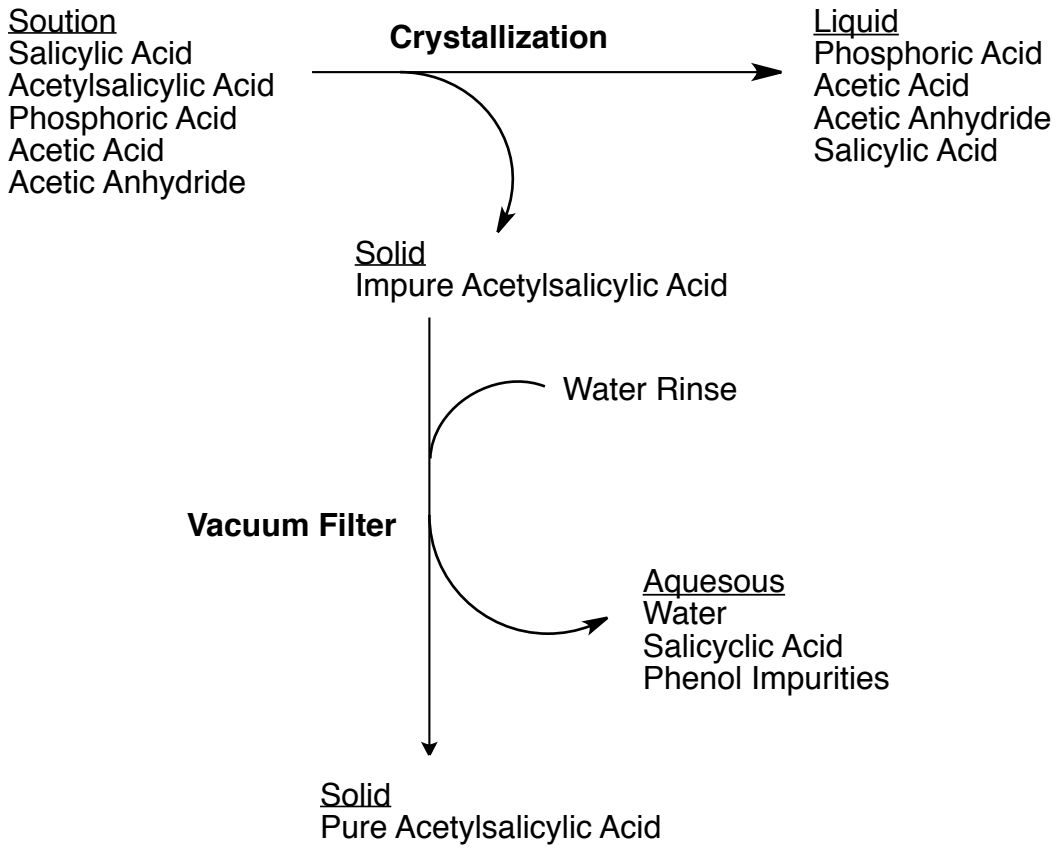


Figure 13. Separation Scheme After Reaction

Formal Written Laboratory Report Rubric

	Beginning (0)	Developing (2.6)	Adequate (3)	Accomplished (3.4)	Exemplary (4)
Abstract	Scope of work not sufficiently described or too lengthy. Experimental details included. Results not stated. Written in wrong tense. Many unneeded sentences.	Scope of work not sufficiently described or too lengthy. Experimental details included. Some critical results missing. Written in wrong tense. Few unneeded sentences.	Scope of work not sufficiently described or too lengthy. Not completely in past tense. Some critical results missing.	Between 80 - 200 words. Scope of work incomplete or too detailed. Written in past tense. Describes the work that was done and results found without using experimental details.	Between 80 - 200 words. Written in past tense. Describes the work that was done and results found without using experimental details.
Introduction	Little or no motivation or theoretical background given. Non-technical overview missing in last paragraph.	Motivation/focus miss directed. Theoretical background missing or riddled with errors. Non-technical overview incomplete or too technical.	Describes the motivation and focus of the experiment. Theoretical background incomplete or containing errors. Non-technical overview incomplete or too technical.	Describes the motivation and focus of the experiment. Contains appropriate theoretical background with minor errors. Non-technical overview too technical.	Describes the motivation and focus of the experiment. Contains appropriate theoretical background without errors. Last paragraph is non-technical overview of the experiment.
Methods/ Materials	No citations given. Deviations/ additions/omissions not discussed.	Some materials cited. Citations incorrect or incorrectly formatted. Deviations/additions/ omissions not discussed.	Materials cited. Some citations incorrect or incorrectly formatted. Deviations/additions/ omissions expressed but sometimes vague or unclear.	Lab manual and other materials properly cited. Deviations/ additions/omissions are expressed in paragraph format, but too brief or too lengthy.	Lab manual and other materials properly cited. Deviations/ additions/omissions are clearly expressed in paragraph format.
Results	Result data table not present, but discussed in paragraph format, or the reverse. Critical results missing or incorrect.	Result data presented in table format and discussed in paragraph format. Critical results missing or incorrect. Tables/ graphs incorrectly formatted. Captions missing.	Result data presented in table format, some data missing or incorrect. Data incompletely discussed in paragraph. Tables/graphs incorrectly formatted. Captions could be improved.	Result data presented in table format and discussed in paragraph format. Minor disagreements found between table and text. All data tables, graphs half page with correct captions.	Result data presented in table format and discussed in paragraph format. All data tables, graphs half page with correct captions.
Discussion / Conclusion	Results not analyzed. Experimental difficulties/errors/ questions not discussed. Conclusion not present.	Results analyzed producing some incorrect conclusions. Experimental difficulties/errors discussed incompletely, some questions answered incorrectly. Conclusion not well developed, too lengthy or short and missing the bottom line.	Results analyzed. Experimental difficulties, errors, questions discussed, some answered incorrectly. Conclusion too small or lengthy and missing the bottom line.	Results analyzed to produce sound conclusions. All experimental difficulties/errors/ questions discussed, with some minor error. Last paragraph is conclusion, expressing briefly the bottom line of the experiment.	Results analyzed to produce sound conclusions. All experimental difficulties, errors, questions discussed correctly. Last paragraph is conclusion, expressing briefly the bottom line of the experiment.
Language/ Grammar/ Formatting	First person used throughout. Incomplete sentences. Many grammatical errors. Complete lack of formatting.	Occasional lapses into first person. Sentence structure weak, many grammatical errors. Inconsistent formatting.	Third person used throughout. Sentence structure weak, many grammatical errors. Inconsistent formatting.	Third person used throughout. Well formed sentence structure, few grammatical errors. Few formatting errors.	Third person used throughout. Well formed sentence structure, grammatically correct. Excellent and consistent formatting.

Revised - 2/13/12

Total points = 24

$4 \times 2 = 8$

$3.4 \times 3 = 10.2$

$1 \times 3 = 3$

21.2

88.3%