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Microwave-assisted synthesis of primary amine HX salts from halides and 7 M ammonia in methanol

Mark G. Saulnier,* Kurt Zimmermann,* Charles P. Struzynski, Xiaopeng Sang, Upender Velaparthi, Mark Wittman and David B. Frennesson

Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA

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Abstract—The atom economical synthesis of hydrogen halide salts of primary amines, directly from the corresponding halides, avoids the production of significant amounts of secondary amine side products, and requires only evaporation of the solvent to access the products in yields generally greater than 90%. The procedure uses microwave irradiation in 7 M ammonia in methanol (Aldrich) at 130 °C from 0.5 to 2.5 h and works on a variety of alkyl halides, as well as mesylates and tosylates. Benzylamines are obtained from benzyl halides without significant amounts of the secondary amine side products that result without microwave heating. Direct isolation of even highly volatile primary amines as their hydrogen halide salts makes the method ideal for use in parallel synthesis.

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There are numerous methods for the synthesis of primary amines from halides.[1] While the use of ammonia for this purpose has certainly been described,[2] its rather poor nucleophilicity tends to demand long reaction times and can often give significant amounts of symmetrical secondary amine side products. For example, a recent patent[3] describes the conversion of (3-chloropropyl)triethoxysilane to the corresponding primary amine using 100 equiv of ammonia in a continuous flow reactor at 100–120 °C at 50 bar. This method gives 30–35% secondary amine and a small amount of tertiary amine in addition to the desired primary amine. A recent disclosure of the synthesis of tertiary trialkanolamines by opening of epoxides with ammonia in a microwave reactor[4] prompted our reasoning that similar use of ammonia might be ideally suited for the synthesis of primary amines from alkyl halides. Herein we now report a simple, atom economical synthesis of the hydrogen halide salts of primary amines, directly from the corresponding halides, that avoids the production of significant amounts of secondary amine side products and requires only evaporation of the solvent to access the products in yields generally greater than 90%.

Our procedure[5] uses microwave irradiation at 100–130 °C from 0.25 to 2.5 h and works on a variety of alkyl halides, as well as tosylates and mesylates, as shown in Table 1. The use of 2 M ammonia in methanol tends to give substantially more recovered starting halide and secondary amine side products than 7 M ammonia in methanol. The preferred reaction concentration is 0.04 M, using 0.25 mmol of substrate in 6.25 mL of 7 M ammonia in methanol (Aldrich) in a 10 mL microwave vial, as shown in Scheme 1, for example, **1a** to **2a**. Using 1 mmol of substrate **1a** in 5 mL of 7 M ammonia in methanol gives somewhat more secondary amine (7%) and recovered starting material (5%). Several other alkyl halides also serve as suitable substrates, including those containing nitro, alkoxy, and halogen substituents.

Table 1 summarizes the range of alkyl halides that were converted to the corresponding primary amines using this protocol. All reactions gave 2–4% or less of the symmetrical secondary amine side product. The scope of the reaction includes less reactive halides (**1h**–**i**) and branching adjacent to (**1g**), and at (**1o**), the reaction center. Direct isolation of the primary amine products as

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Keywords: primary amines; ammonia; microwave-assisted synthesis.

* Corresponding authors. Tel.: +1-203-677-6325; fax: +1-203-677-7702 (M.G.S.), Tel.: +1-203-677-7236; fax: +1-203-677-7702 (K.Z.); e-mail: mark.saulnier@bms.com; kurt.zimmermann@bms.com

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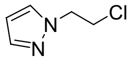
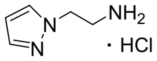
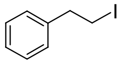
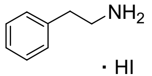
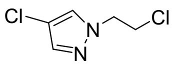
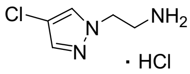
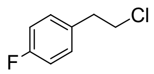
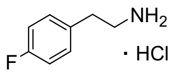
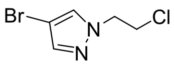
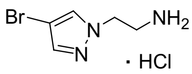
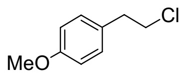
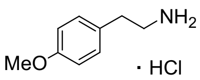
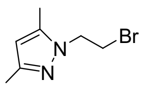
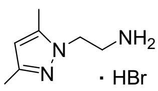
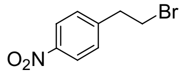
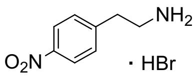
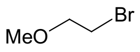
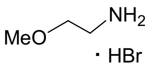
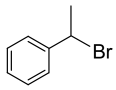
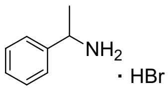
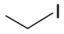
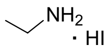
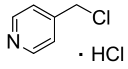
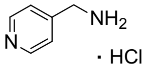
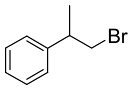
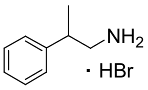
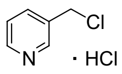
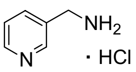
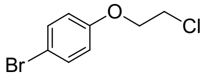
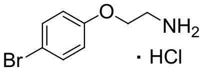
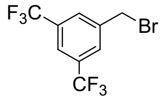
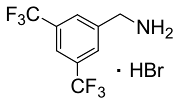
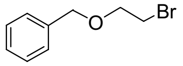
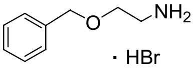
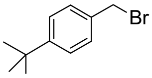
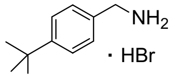
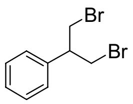
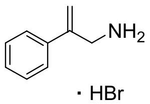
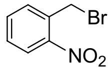
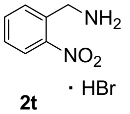
Table 1. Microwave-assisted synthesis of primary amine HX salts from halides and 7 M ammonia in methanol[a]

Halide	Product[b]	Yield (%)[c]	Halide	Product[b]	Yield (%)[c]
 **1a**	 **2a**	95	 **1k**	 **2k**	93
 **1b**	 **2b**	95	 **1l**	 **2l**	96
 **1c**	 **2c**	95	 **1m**	 **2m**	96
 **1d**	 **2d**	94	 **1n**	 **2n**	75[d]
 **1e**	 **2e**	95	 **1o**	 **2o**	98
 **1f**	 **2f**	70	 **1p**	 **2p**	95
 **1g**	 **2g**	90	 **1q**	 **2q**	95
 **1h**	 **2h**	97	 **1r**	 **2r**	95
 **1i**	 **2i**	95	 **1s**	 **2s**	95
 **1j**	 **2j**	88	 **1t**	 **2t**	94

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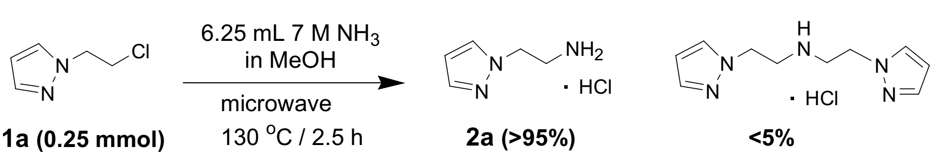
[a] All reactions gave 2–4% or less of the symmetrical secondary amine side product.

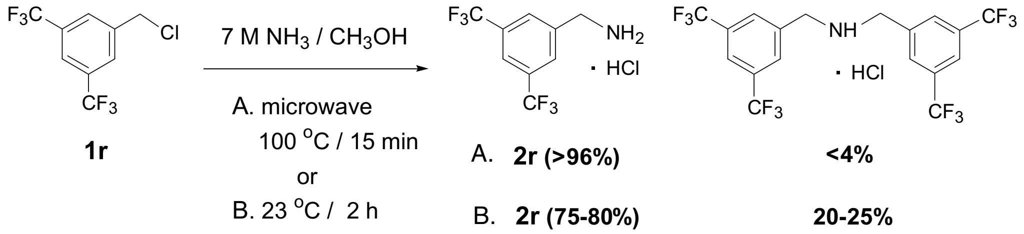
[b] Reaction conditions: 130 °C for 2.5 h, for example, **2a**–**e**, **2g**–**j**, **2l**–**n**; 130 °C for 0.5 h, for example, **2f**, **2k**, **2o**–**q**; 100 °C for 0.25 h, for example, **2r**–**t**. All reactions used 0.25 mmol substrate in 6.25 mL of 7 M ammonia in methanol in a 10 mL microwave vial.

[c] Yields refer to weight of product obtained after evaporation of the solvent. All of the examples in the table were >95% pure as determined by ^{1}H NMR (except example **2n**).

[d] For **2n**, the *p*-nitrostyrene elimination side product (20%) was present as indicated by ^{1}H NMR.



Scheme 1. Optimal conditions for microwave-assisted synthesis of **2a** using 7 M ammonia in methanol.



Scheme 2. Dramatic improvement in the synthesis of benzyl amines from benzyl halides using microwave irradiation.

their hydrogen halide or sulfonate[6] salts by simple evaporation allows very volatile primary amines (**1e–f**) to be obtained in good yield as well.[7]

The results with benzyl halides (**1r–t**) are noteworthy since reaction of these substrates with 7 M ammonia in methanol proceeds to completion in 2 h at room temperature. However, 20–25% of the bisalkylated secondary amine is produced as side product. We were surprised to discover that under conditions of microwave irradiation at 100 °C for 15 min, there was less than 4% of secondary amine formed as shown in Scheme 2.

In summary, we have described a practical and atom economical synthesis of hydrogen halide salts of primary amines, directly from the corresponding halides, using microwave irradiation in 7 M ammonia in methanol, commercially available from Aldrich. This procedure avoids the production of significant amounts of secondary amine side products, and requires only evaporation of the solvent to access the products in yields generally greater than 90%. Benzylamines are obtained from benzyl halides, avoiding significant amounts of the secondary amine side products that result without microwave heating. Direct isolation of the primary amine products as their hydrogen halide salts by simple evaporation is ideal for their subsequent use in parallel synthesis. The fact that hydrogen halide salts of the primary amine products are obtained directly, allows even very volatile primary amines to be accessed in good yield as well.

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5. *General experimental procedure:* A solution of 7 M ammonia in methanol (Aldrich; 6.25 mL) was added to 0.25 mmol of the alkyl halide (or sulfonate) in a 10 mL microwave vial. The reaction mixture was heated with stirring at 100–130 °C in a Smith synthesizer auto-sampling microwave from 0.25 to 2.5 h as indicated in Table 1. The solvent was evaporated under a stream of dry nitrogen to give the primary amine HX salts as solids. All of the examples in the table were >95% pure as determined by ^{1}H NMR and LC/MS and were used directly as obtained in a parallel synthesis fashion.
6. Both ethyl methanesulfonate and 3-butynyl *p*-toluenesulfonate are similarly converted to their corresponding primary amine sulfonate salts in high yield.
7. The yield for ethyl iodide **1f** is only 70% due to the high volatility of ethylamine. In fact, if the product of this reaction (ethylamine HI salt, obtained after evaporation) is redissolved in 7 M ammonia in methanol and evaporated under nitrogen again, further loss occurs. Presumably ammonium iodide is formed as ethylamine is lost. Using ethyl methanesulfonate instead of ethyl iodide gives an identical result with the caveat that the anion, methanesulfonate, can be identified by ^{1}H NMR (CD_3OD). The integration of the methanesulfonate signal at 2.70 ppm is almost 50% greater than the methyl triplet for the ethylamine, indicating about a 2:1 mixture of ethylamine methanesulfonate to ammonium methanesulfonate. Redissolving this material in 7 M ammonia in methanol followed by evaporation under a stream of nitrogen leads to the integration of the methanesulfonate signal at 2.70 ppm being 100% greater than the methyl triplet for the ethylamine. This result confirms some loss of ethyl amine due to equilibration with ammonia.