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An efficient sequence for the preparation of small secondary amine hydrochloride salts for focused library generation without need for distillation or chromatographic purification

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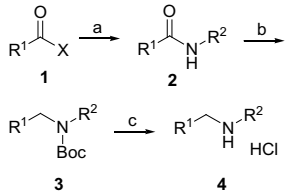
Abstract—Collections of small secondary amines for compound library generation can be efficiently prepared by amide reduction using BH_3–THF or Red-Al followed by brief methanolysis, trapping with di-*tert*-butyl dicarbonate, and deprotection with 4 M HCl in dioxane. The sequence requires no chromatography or distillation and provides multi-gram quantities of pure HCl salts in a short time.

Medicinal chemistry depends to an ever greater extent on the generation of compound libraries for the discovery of leads, exploration of SAR, and optimization of physical properties.[1] The expansion of synthetic methodologies that can now be carried out on solid support or in parallel solution phase have increased the demand for diverse components that can be used as in-house collections for library generation.[2] In terms of both gross and fine structural diversity, some chemical classes such as carboxylic acids and primary amines are already well-represented commercially. However, the scope of a particular library, especially one whose purpose is lead optimization, can be limited by commercial scarcity of desired components.[3] We found this to be true in a recent program in which tertiary amines were most easily made by amination of a halomethyl core structure with secondary amines. When it became clear that nearly all of the amines that we wanted to use could not be purchased we sought an efficient way to prepare them with minimum effort. Secondary amines have been synthesized on solid support[4] and using automated solution phase synthesis[5] for immediate derivatization. However, since we intended to prepare libraries of numerous core structures we desired multi-gram quantities. In addition, because many secondary amines form carbamic acids or otherwise age badly, it was desirable that they be generated in protonated form. Herein we report a simple method to prepare HCl salts of secondary amines containing functionality stable to BH_3–THF or Red-Al in multi-gram quantities and in pure form without need for chromatography or distillation.

Scheme 1 shows the synthetic sequence used to prepare amine HCl salts **4**. Amides **2** were generated from standard coupling of activated carboxylic acids **1** (acid chlorides, anhydrides, or 3,3,3-trifluoropropionyl compounds, the *N*-hydroxysuccinimide activated ester **1a** (Scheme 2)) with primary amines. Reaction workups simply involved evaporation of solvent, partitioning of the residue between ethyl acetate and saturated $NaHCO_3$, extraction of the aqueous phase with more ethyl acetate, and washing of the organic phases with 2% H_3PO_4.



Scheme 1. Reagents and conditions: (a) R^2NH_2, Et_3N, CH_2Cl_2, 0 °C to rt; (b) (i) BH_3–THF (3 equiv), reflux, 14 h; (ii) MeOH, reflux, 2 h; (iii) Boc_2O (1.4 equiv), CH_2Cl_2, rt, 14 h; (c) 4 M HCl/dioxane (1.2 equiv), CH_2Cl_2, rt, 14 h.

Keywords: Amide reduction; Combinatorial.
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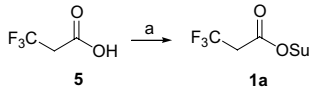


5 1a

Scheme 2. Reagents and conditions: (a) HOSu, EDC–HCl (1.1 equiv), CH_2Cl_2, 0 °C to rt (92%).

Initial attempts were made to prepare amines **4b**, **4m**, and **4n** (Table 1) by reduction of the corresponding amides **2** with 1 M BH_3–THF[6] followed by methanolysis and fractional distillation. For **4b** this resulted in no isolated product, probably because of excessive volatility, which caused it to co-distill with the solvents. Amines **4m**,**n** remained in the distillation flask in 39% and 62% crude yields after solvent removal, but in very impure form, as determined by ^{1}H NMR.

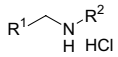
In order to facilitate isolation of the amines following reduction, di-*tert*-butyl dicarbonate (1.4 equiv) was added as a concentrated CH_2Cl_2 solution directly to the reaction mixture after brief methanolysis. The resulting *N*-Boc derivatives **3** were easily formed in the presence of the borate methyl esters and were isolated by simple extractive aqueous workups. By ^{1}H NMR, the only detectable impurities in crude mixtures were *tert*-butanol and di-*tert*-butyl dicarbonate. Treatment with 4 M HCl in dioxane liberated the amines **4** as their HCl salts, most of which gradually precipitated out of solution. Because of the presence of *tert*-butanol, a by-product that might attenuate the acidity of HCl, deblocking reactions were allowed to proceed overnight. Concentration in vacuo, followed by trituration with ether, filtration, and drying gave the amine–HCl salts **4** as pure white solids.[7] Overall yields given in Table 1 are unoptimized and most compounds were made only once. In cases where overall yields were low, additional product precipitated from the cold filtrate suggesting that either the HCl salts had significant ether solubility or that a polar impurity, perhaps *tert*-butanol, was aiding solubility. In the latter case, concentration of the crude mixture after *N*-Boc removal under higher vacuum and/or for longer periods might increase yields.

When *N*-Boc trapping was not used, amine–HCl salts of satisfactory purity could sometimes be obtained. But just as often, this shortcut led to intractable mixtures. For example, direct quenching of the borane–amine complex of **4vv** with 4 M HCl in dioxane after methanolysis, followed by evaporation of the solvent to dryness, afforded the product as a viscous semisolid, which was quite impure by ^{1}H NMR. In contrast, a chemically pure white solid HCl salt of **4vv** was obtained as a result of trapping the amine with di-*tert*-butyl dicarbonate, followed by acidic deprotection.

We prepared one example, an allyl substrate (**4tt**), that would not be compatible with borane (Scheme 3). In this case, Red-Al was used for amide reduction,[8] which proceeded at rt. After initial quenching with acetone and brief methanolysis, di-*tert*-butyl dicarbonate was added as before to the crude mixture that included precipitated aluminum salts. These were subsequently dissolved by using 10% citric acid in the initial workup of the crude *N*-Boc derivative **3tt**. Deblocking as described above gave **4tt** in 60% overall yield.

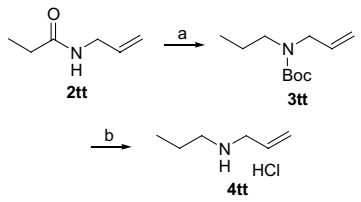
Compounds **4h**–**k** were synthesized using 2-cyclopropylethylamine **11**, which was not commercially available. This was prepared in good yield as shown in Scheme 4

Table 1

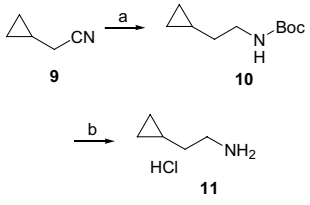


Compd	R^1	R^2	Overall yield, %[a]
4a	Me	*c*-$PrCH_2$	71
4b	*c*-Pr	CF_3CH_2	85
4c	CF_3CH_2	*c*-$PrCH_2$	86
4d	*c*-Pr	*c*-$PrCH_2$	45
4e	*c*-Bu	*n*-Pr	62
4f	*c*-Bu	Et	41
4g	*c*-Bu	CF_3CH_2	75
4h	Me	*c*-$PrCH_2CH_2$	25
4i	Et	*c*-$PrCH_2CH_2$	42
4j	CF_3	*c*-$PrCH_2CH_2$	76
4k	CF_3CH_2	*c*-$PrCH_2CH_2$	51
4l	CF_3	*n*-Pr	64
4m	CF_3CH_2	*n*-Pr	62
4n	CF_3CF_2	*n*-Pr	65
4o	CF_3CF_2	*c*-$PrCH_2$	59
4p	Et	$PhCH_2$	47
4q	CF_3	$PhCH_2$	90
4r	CF_3CH_2	$PhCH_2$	75
4s	Et	*m*-F–$PhCH_2$	50
4t	CF_3	*m*-F–$PhCH_2$	87
4u	CF_3CH_2	*m*-F–$PhCH_2$	83
4v	Et	*p*-F–$PhCH_2$	60
4w	CF_3	*p*-F–$PhCH_2$	88
4x	CF_3CH_2	*p*-F–$PhCH_2$	78
4y	Et	*p*-Cl–$PhCH_2$	64
4z	CF_3	*p*-Cl–$PhCH_2$	90
4aa	CF_3CH_2	*p*-Cl–$PhCH_2$	84
4bb	Et	2-Pyr	55[b]
4cc	Et	3-Pyr	67[b]
4dd	Et	4-Pyr	63[b]
4ee	Et	$PhCH_2CH_2$	43
4ff	Me	$PhCH_2CH_2$	60
4gg	CF_3	$PhCH_2CH_2$	90
4hh	CF_3CH_2	$PhCH_2CH_2$	78
4ii	Et	*p*-F–$PhCH_2CH_2$	26
4jj	Me	*p*-F–$PhCH_2CH_2$	28
4kk	Et	*o*-F–$PhCH_2CH_2$	32
4ll	Me	*o*-F–$PhCH_2CH_2$	31
4mm	Me	*m*-F–$PhCH_2CH_2$	46
4nn	Et	*p*-MeO–$PhCH_2CH_2$	55
4oo	Me	*p*-MeO–$PhCH_2CH_2$	32
4pp	Et	*o*-MeO–$PhCH_2CH_2$	53
4qq	Me	*o*-MeO–$PhCH_2CH_2$	34
4rr	Et	*m*-MeO–$PhCH_2CH_2$	34
4ss	Me	*m*-MeO–$PhCH_2CH_2$	52
4tt	Et	Allyl	60
4uu	CH_2FCH_2	Et	75
4vv	CH_2FCH_2	$CH_3OCH_2CH_2$	70

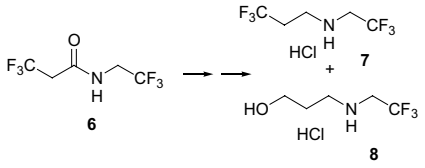
[a] All products gave satisfactory microanalytical results (C,H,N within 0.4%); and ^{1}H NMRs in D_2O showed no discernable impurities.
[b] Prepared as bis-hydrochloride salts.



Scheme 3. Reagents and conditions: (a) (i) Red-Al (2.5 equiv), toluene, 0 °C to rt, 14 h; (ii) acetone, 0 °C then MeOH, rt, 1 h; (iii) Boc_2O (1.4 equiv), CH_2Cl_2, rt, 14 h; (b) 4 M HCl in dioxane (1.2 equiv), CH_2Cl_2, rt, 14 h (60% for three steps).



Scheme 4. Reagents and conditions: (a) (i) BH_3–THF (3 equiv), reflux, 14 h; (ii) MeOH, reflux, 2 h; (iii) Boc_2O (1.4 equiv), CH_2Cl_2, rt, 14 h; (b) 4 M HCl in dioxane (1.2 equiv), CH_2Cl_2, rt, 14 h (85% for three steps).



Scheme 5.

from cyclopropylacetonitrile **9** using a modification of the general procedure reported herein.

In only one case was a significant impurity formed that co-precipitated with the desired product (Scheme 5). In this instance, reduction of amide **6** with borane followed by further treatment as described above gave the expected HCl salt **7** as well as the 3-hydroxypropylamine **8** in a roughly 2:1 ratio by an unknown mechanism.[9] Conversion of 3,3,3-trifluoropropionyl to 3-hydroxypropyl under these conditions is apparently specific to this substrate since clean reduction to 3,3,3-trifluoropropyl occurs in all other cases.

In this way, a diverse set of secondary amine hydrochloride salts was generated on a multi-gram-scale in a relatively short time with a minimum of effort. In general, two or three amine preparations could be carried on at one time by a chemist who was also working on other tasks. Some of the HCl salts, especially pyridyls **4bb–dd** and small, nonhalogen-containing compounds such as **4a**, **4d–f**, and **4tt** were moderately-to-strongly hygroscopic, and were routinely stored in a dessicator. These compounds were successfully used for the rapid optimization of binding affinities for several chemical classes through parallel, solution-phase synthesis. These results will be reported in due course.

References and notes

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7. All products gave satisfactory ^1H NMR and microanalytical results. Representative synthetic procedure for **4c**: A stirred solution of 3,3,3-trifluoroacetic acid *N*-hydroxysuccinimide ester (12.98 g, 57.65 mmol) in CH_2Cl_2 (80 mL) at 0 °C was treated with cyclopropylmethylamine (5.0 mL, 1 equiv). The mixture was stirred at rt for 14 h and then concentrated in vacuo. The residue was partitioned between ethyl acetate and water. The organic phase was washed with water, brine, dried over $MgSO_4$, and evaporated to give the crude amide. This was dried under high vacuum for several hours and then, under nitrogen at 0 °C, it was carefully treated with 1 M BH_3 in THF (173 mL, 3 equiv). The mixture was heated at reflux for 14 h and then re-cooled to 0 °C. MeOH (50 mL) was added carefully to avoid excess foaming, and the mixture was heated at reflux for 5 h. Upon re-cooling to 0 °C, a solution of Boc_2O (17.62 g, 1.4 equiv) in CH_2Cl_2 (25 mL) was added. The resulting mixture was stirred at rt overnight and then concentrated in vacuo. The residue was partitioned between ethyl acetate and water. The organic was washed with water, brine, dried over $MgSO_4$, and evaporated to give the crude Boc-protected amine. This was dissolved in CH_2Cl_2 (25 mL) and treated with 4 M HCl in dioxane (17 mL, 1.2 equiv), carefully to avoid uncontrolled bubbling. The mixture was stirred at rt overnight and then evaporated. The resulting white solid was triturated with ether and the product was collected by filtration, washed with ether, and dried in vacuo (10.10 g, 86%). ^1H NMR δ (D_2O) 0.36 (m, 2H), 0.67 (m, 2H), 1.07 (m, 1H), 2.72 (m, 2H), 2.99 (d, 2H), 3.89 (t, 2H). Anal. Calcd for $C_7H_{12}NF_3$–HCl: C 41.29; H 6.43; N 6.88. Found: C 41.11, H 6.48, N 6.77.
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