

**A CONVENIENT SYNTHESIS OF HINDERED AMINES AND  
 $\alpha$ -TRIFLUOROMETHYLAMINES FROM KETONES**

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**Abstract:** Ketones and  $\alpha$ -trifluoromethylketones were converted to primary, secondary, and tertiary amines in good to excellent yields by a reductive amination procedure utilizing  $\text{TiCl}_4/\text{NaCNBH}_3$ . The method provides the first direct route to  $\alpha$ -trifluoromethylamines from ketones, and access to hindered amines from ketones which are unobtainable by Borch reductive amination.

Since the biological activity of many classes of pharmaceutical agents depends on the amino functionality, considerable effort continues to be focused on new methods for the synthesis of amines. Although several methods exist for the synthesis of amines from aldehydes and ketones<sup>1</sup>, a general method to hindered amines from these starting materials is lacking.<sup>2</sup> The method of choice for the one-pot conversion of aldehydes and ketones to amines is the Borch reduction.<sup>3</sup> However, the reductive amination of ketones with aromatic amines proceeds sluggishly and hindered ketones, such as isobutyrophenone, are reductively aminated with dimethylamine in <5% yield. The low yields are presumably the result of poor enamine/imine formation. In addition, the reaction usually requires excess starting amine to prevent product amine from reacting further with starting ketone. Azeotropic methods<sup>4</sup> for forming enamines from aldehydes and ketones which use either acid catalysts or molecular sieves are unsatisfactory for hindered ketones.

We report a new procedure which provides the first direct synthesis of  $\alpha$ -trifluoromethylamines and a convenient route to hindered amines in good to excellent yield from ketones. We reasoned that a modified Borch reduction in which complete enamine/imine formation was possible should provide a useful synthesis of aromatic amines, hindered amines, and  $\alpha$ -trifluoromethylamines. Titanium tetrachloride, a good Lewis acid as well as an excellent water scavenger, catalyzes enamine/imine formation with hindered ketones<sup>5</sup>, although three equivalents of amines are required.

Treatment of a ketone with stoichiometric amounts of amine and  $\text{TiCl}_4$  in  $\text{CH}_2\text{Cl}_2$  or benzene forms the imine/enamine when Hunig's base (diisopropylethylamine) or triethylamine was

TABLE 1<sup>7</sup>

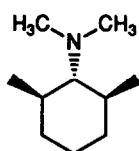
PRODUCT 3	STRUCTURE	YIELD, % (Free Base)	mp, °C (HCl Salt)
<b>3a</b> <sup>10</sup>		94	188-90 (i-PrOH)
<b>3b</b> <sup>11</sup>		54	194-6 (Toluene)
<b>3c</b> <sup>a</sup> , <b>3d</b> <sup>b</sup>		50	75 (0.5mm) (free base)
<b>3e</b>		71	— (free base)
<b>3f</b> <sup>12</sup>		52	>240 (i-PrOH)
<b>3g</b>		65	— (free base)
<b>3h</b>		65	124-5 (EtOAc/i-PrOH)
<b>3i</b>		60	180-1 (EtOAc/EtOH)
<b>3j</b> <sup>13</sup>		66 (HCl Salt)	293-6 (i-PrOH)
<b>3k</b> <sup>14</sup>		82 (HCl Salt)	>250 (CH <sub>2</sub> ClN)

(a) Isolated as the hydrochloride salt in >95% purity from the filtrate of **3d**

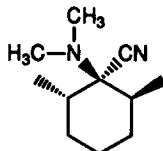
(b) Isolated as the hydrochloride salt; mp 222-5°C (dec) (EtOAc)

substituted for excess amine. It was significant that enamine/imine formation of  $\alpha$ -trifluoromethylketones also readily proceeded, since  $\alpha$ -trifluoromethylketones prefer to form enamines.<sup>6</sup> Direct addition of  $\text{NaCNBH}_3$  in methanol to the reaction mixture provides the desired amines in good to excellent yields (see Table 1).<sup>7</sup> For products 3a and 3b, direct comparison of yields with the Borch reduction was made. Borch reported<sup>3</sup> a 55% yield for amine 3a and <5% for 3b versus 94% and 54%, respectively, by our procedure. For the preparation of primary amines 3j and 3k, hexamethyldisilazane (HMDS) was effectively used as a source of ammonia even though HMDS is a bulky amine and a poor nucleophile.<sup>8</sup> Since there is no direct route to  $\alpha$ -trifluoromethylamines from aldehydes or ketones, products 3h, 3i, and 3k are of particular interest.

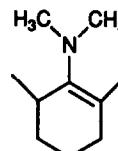
The synthesis of 2,6,N,N-tetramethylcyclohexylamine (3c and 3d) deserves special comment. The desired product was readily isolated by Kugelrohr distillation. A total of 15 peaks were observed by  $^{13}\text{C}$  NMR indicating the presence of diastereomer 3c (9 peaks) and one of the two remaining diastereomers, 3d or 4 (plane of symmetry, 6  $^{13}\text{C}$  NMR peaks for either diastereomer).



4



5



6

Treatment of the mixture with methanolic  $\text{HCl}$  provided crystalline 3d as the hydrochloride salt and 3c hydrochloride from the filtrate as a foam of >95% purity. The stereochemistry of 3d hydrochloride was established based on  $^{13}\text{C}$  NMR (6 peaks), proton coupling constants ( $N$ -methine,  $\delta$  3.32, t,  $J = 5.2$ ), and NOE spectroscopy (NOE observed between the  $N$ -methine, and the 3- and 5-axial protons establishing the 1,3-diaxial configuration of these protons). The stereochemistry of 3c hydrochloride was established based on  $^{13}\text{C}$  NMR (9 peaks) and proton coupling constants ( $N$ -methine,  $\delta$  3.09, dd,  $J = 11.2$  and  $4.1$  Hz). The hindered environment of the amine is exemplified by severely broadened signals at ambient temperature in both the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for the  $N$ -methyl signals indicative of hindered rotation. In addition to 3c and 3d, the  $\alpha$ -cyanoamine 5 was isolated as a higher boiling fraction (bp  $150^\circ\text{C}$ , 0.5 mm) in 14% yield. Attempts to avoid formation of 5 by quenching the reaction with  $\text{NaBH}_4$  in methanol or ethanol resulted in the isolation of unreduced enamine 6.<sup>5</sup>

An illustrative example is as follows:

To a dry 100 ml flask with septum and nitrogen bubbler was added piperidine hydrochloride (1.0 g, 8.2 mmole), triethylamine (2.5 g, 25 mmole), trifluoroacetophenone (1.4 g, 8.2 mmole), and  $\text{CH}_2\text{Cl}_2$  (50 mL). Titanium tetrachloride (4.1 mL of a 1 M solution in  $\text{CH}_2\text{Cl}_2$ , 4.1 mmole) was added via syringe. The reaction was stirred for 18 hrs, carefully quenched with a methanolic solution of  $\text{NaCNBH}_3$  (1.5 g, 25 mmole in 20 mL of MeOH) and stirred for 15 min. The reaction was basified to pH 13 with 5N NaOH, extracted with EtOAc (2 x 100 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to a yellow oil. Flash chromatography (100:10:1/ $\text{CHCl}_3$ :MeOH: $\text{NH}_4\text{OH}$ ) provided the desired product as a yellow oil (1.2 g, 60%). The oil was dissolved in ether (20 mL), treated with saturated MeOH/HCl, the solid collected and recrystallized (EtOAc/EtOH) to give **3i** as the HCl salt, mp 180-181°C.  $^1\text{H-NMR}$  (300 MHz,  $\text{DMSO-d}_6$ )  $\delta$  1.35 (m, 2H), 1.6 (m, 4H), 2.7 (m, 4H), 4.7 (q, 1H), 5.6 (br s, 1H), 7.5 (m, 5H);  $^{19}\text{F-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$  -64.6 vs  $\text{CFCl}_3$ ; MS (EI/70eV) 243 ( $\text{M}^+$ ), 174 ( $\text{M}^+ - \text{CF}_3$ ). Anal. Calcd for  $\text{C}_{13}\text{H}_{16}\text{F}_3\text{N}\cdot\text{HCl}$ : C, 55.81; H, 6.12; N, 5.01; Found: C, 55.76; H, 6.11; N, 4.85.

In summary, a convenient one-pot procedure to aromatic amines, hindered amines, and  $\alpha$ -trifluoromethylamines from ketones and one equivalent of starting amine was developed using  $\text{TiCl}_4/\text{NaCNBH}_3$ .

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- All compounds in Table I were characterized by NMR, MS and except for **3d** gave satisfactory elemental analyses. Amines **3c**, **3d**, **3e**, **3g**, **3h**, and **3i** are new. Literature references to the other amines are cited in Table I.
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- The positional and stereochemical configuration of **5** was established using an attached proton test (APT) $^{13}\text{C}$  NMR spectrum (10 peaks total, C-1 observed at  $\delta$  69.1 as a quaternary carbon).
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