Preparation of Sterically Hindered Secondary Amines

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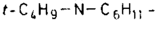
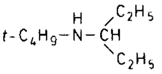
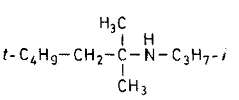
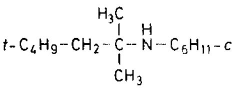
The metal amides from sterically hindered secondary amines have found widespread application in synthesis where a strong base with low nucleophilicity is required[1]. Lithium diethylamide, diisopropylamide and cyclohexylisopropylamide are most frequently used. In some applications even more hindrance is valuable, for example lithium 2,2,6,6-tetramethylpiperidide gives higher yields of cyclopropanes from benzyl chloride and olefins[2]. It would be interesting to examine the anions from the intermediate class of secondary amines, those with one secondary and one tertiary alkyl group. Amines of this class have rarely been made, and then by an inconvenient high pressure, high temperature displacement of secondary halides or tosylates with *t*-butylamine[3], or in lower yield with 2,2,4-trimethyl-2-pentylamine[4]. One example was prepared via the formamide using the Leuckart procedure[5].

Secondary amines with two secondary alkyl groups are readily prepared by hydrogenation of a solution of a primary amine and a ketone via the intermediate ketimine[6,7]. However, attempts to do this with *t*-butylamine fail since steric hindrance makes ketimine formation unfavorable[8]. A similar problem, the formation of ketimines from unhindered primary amines and highly hindered cyclohexanones, was solved by use of titanium(IV) chloride as catalyst and water scavenger[9,10]. We have found that titanium(IV) chloride is effective for preparation of the rare[11] *N*-*t*-alkylketimines as well. Combining this with *in situ* hydrogenation provides a quick and simple preparation of the desired secondary amines in 50–78% yield.

Table. Preparation of Secondary Amines

Amine	Yield (%)	B. p.
 $t\text{-}C_4H_9\text{-}\overset{H}{N}\text{-}C_3H_7\text{-}i$	50	99–99.5° (Lit.[3] 98–99°)
 $t\text{-}C_4H_9\text{-}\overset{H}{N}\text{-}C_6H_{11}\text{-}c$	78	81–82°/23 torr (Lit.[11] 87°/37 torr)
 $t\text{-}C_4H_9\text{-}\overset{H}{N}\text{-}CH(C_2H_5)_2$	53	149–149.5° (Lit.[3] 145°)
 $t\text{-}C_4H_9\text{-}CH_2\text{-}C(CH_3)_2\text{-}\overset{H}{N}\text{-}C_3H_7\text{-}i$	65	88–89°/37 torr (Lit.[4] 174–176°)
 $t\text{-}C_4H_9\text{-}CH_2\text{-}C(CH_3)_2\text{-}\overset{H}{N}\text{-}C_6H_{11}\text{-}c$	57	120°/11 torr

General procedure:

A 500 ml hydrogenation bottle was equipped with magnetic stirring, an ice bath, and a nitrogen atmosphere. In it was placed the ketone (0.05 mol), the primary amine (0.20 mol), and benzene (100 ml). A solution of titanium(IV) chloride (3.3 ml, 0.03 mol) in benzene (15 ml) was added dropwise over 30 min at about 15°. The resulting dark mixture was stirred at room temperature for 2 or 3 hours, and then platinum oxide (25 mg) was added. This was hydrogenated on a Parr shaker at 4 atm initial pressure. Absorption was complete in 30 min to 1 hr. A solution of sodium hydroxide (5 g) in water (50 ml) was added, giving a clear benzene layer and a water layer containing the suspended white precipitate of titanium dioxide. The benzene layer was separated and distilled.

***t*-Butylisopropylamine:**

From acetone and *t*-butylamine. In the case of this low boiling product, the benzene layer was extracted with aqueous hydrochloric acid and the extract made basic with sodium hydroxide. The resulting organic layer was taken up in ether and distilled. ^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.92$ (septuplet, 1H), 1.08 (s), 1.04 (d, half obscured by *t*-butyl), 0.57 ppm (b, 1H, D_2O exchanged).

***t*-Butylcyclohexylamine**:
From cyclohexanone and *t*-butylamine.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.2$–2.6 (m, 1H), 0.9–2.0 (m), 1.07 (s), 0.67 ppm (b, 1H).

***t*-Butyl-3-pentylamine**:
From 3-pentanone and *t*-butylamine.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.38$ (pentuplet, 1H), 0.70–1.6 (m), 1.06 (s), 0.55 ppm (b, 1H, D_2O exchanged).

2,4,4-Trimethyl-2-pentylisopropylamine:
From acetone and 2,4,4-trimethyl-2-pentylamine.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.95$ (septuplet, 1H), 1.41 (s, 2H), 1.13 (s, 6H), 1.05 (d), 1.00 (s), 0.76 ppm (b, 1H).

2,4,4-Trimethyl-2-pentylcyclohexylamine:
From cyclohexanone and 2,4,4-trimethyl-2-pentylamine.

$C_{14}H_{29}N$	calc.	C 79.54	H 13.83	N 6.62
(211.4)	found	79.48	13.97	6.49

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.2$–2.6 (m), 0.9–2.0 (m), 1.39 (s), 1.12 (s), 0.99 (s), 0.71 ppm (b).

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