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Synthesis of Hindered Secondary Amines via Grignard Reagent Addition to Ketonitrones

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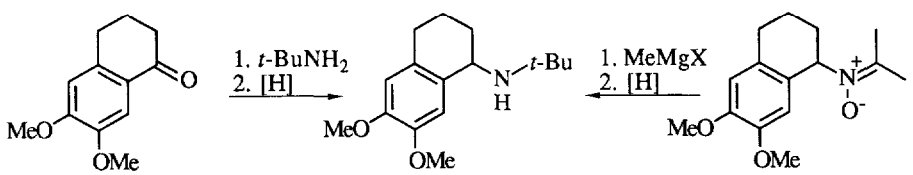
Abstract: *Grignard reagents add to ketonitrones in a nonpolar solvent to afford N,N-dialkylhydroxylamines in good yields and with little competing proton transfer. Deoxygenation of the crude hydroxylamines with carbon disulfide then completes an efficient general synthetic route to hindered sec-alkyl-tert-alkylamines and to di-tert-alkylamines.*

We recently described a new synthetic route to 1-substituted-1,4-dihydro-3(2*H*)-isoquinolinones and related compounds that required *N*-α-aralkyl-*N*-*tert*-butyl-substituted secondary amines as starting materials.[1,2] While many of the latter amines proved to be readily available by reductive amination of ketones[3-5] with *tert*-butylamine, that method gave very poor results in our hands (8-13% yields) when applied to the preparation of secondary amines such as **1** from the corresponding α-tetralones (Scheme 1).[2] Secondary *N*-*sec*-alkyl-*N*-*tert*-alkylamines, which are additionally of considerable interest as precursors to potentially useful metal amide bases, have also been prepared by the addition of organolithium reagents to *N*-*tert*-alkylaldimines.[6] However, the analogous organometallic addition to an *N*-*sec*-alkylketimine is precluded by the sluggish reactivity of ketimines and the concomitant propensity for competing proton transfer reaction.



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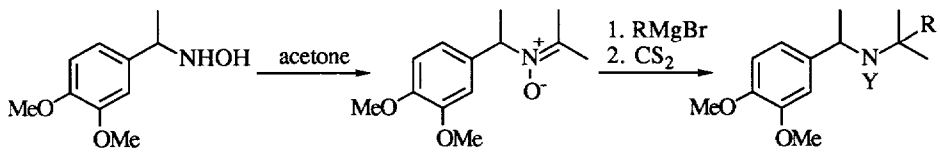
Scheme 1

The addition of Grignard and organolithium reagents to aldonitrones to give α-substituted *N,N*-dialkylhydroxylamines occurs readily and often in good yield.[7-9] Examples of organometallic additions to ketonitrones have also been reported, albeit in cases limited to cyclic nitrones (substituted pyrroline- and 2,3,4,5-tetrahydropyridine-1-oxides).[8,10,11] The modest yields (22-47%) realized in these latter cases could again be ascribed to the competing proton transfer reaction.[11] We decided to explore the reaction of Grignard reagents with ketonitrones as a route to *tert*-alkyl-substituted secondary amines such as **1** (Scheme 1). We can now report that good selectivity for Grignard reagent addition versus proton transfer can be realized, and that the reactivity is sufficient to allow even di-*tert*-alkylamines to be prepared by this method.

Initial studies were carried out with nitrone **2** derived from condensation of *N*-(α-(3,4-dimethoxyphenyl)ethyl)hydroxylamine (from 3,4-dimethoxyacetophenone via $NaBH_3CN$ reduction[12] of its oxime, 94% yield) with acetone (quantitative yield). After considerable experimentation with solvents and reaction temperature, optimum conditions for the desired reaction were found to be addition of the Grignard reagent (3-4 eq) in diethyl ether to a benzene solution of the nitrone at 0 °C followed by warming to room temperature for 0.5 h. Since the *N*-*tert*-alkylhydroxylamines **3** usually were unstable, the crude reaction mixtures were analyzed by ^1H NMR and then were immediately subjected to deoxygenation with CS_2[13] to give the corresponding amines which were purified by flash chromatography. The results are summarized in the table below.



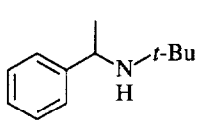
2 **3**, Y = OH; **4**, Y = H

R	3:2 [a]	4 (%) [b]
Me	13:1	91
Et	7:1	84
n-Bu	9:1	86
Ph	7:1	69
allyl	100:0	82
Me [c]	1:4	---

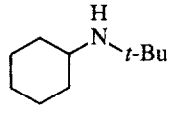
[a] Determined by ^1H NMR. [b] Overall isolated yield. [c] Using MeLi.

Omission of THF from the reaction medium proved to be critical to minimizing proton transfer with Grignard reagents other than MeMgBr. While the latter reagent gave essentially the same results either in benzene or in THF, the addition of a THF solution of EtMgBr, instead of ethereal EtMgBr, to a benzene solution of **2** under the otherwise optimum reaction conditions afforded a 1:1 mixture of **2** and **3**; that the recovered **2** arose from its anion was demonstrated by a D_2O quench of the reaction mixture. Organolithium reagents were completely unsuitable for the addition reaction, affording complex mixtures of products under all conditions.

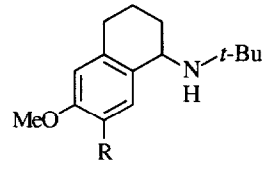
The *N*-*tert*-butylamines **5** - **7** and the original target amine **1** could be synthesized from the corresponding hydroxylamines in the overall yields shown below by application of the same three-step sequence: condensation of the hydroxylamine with acetone, reaction of the resulting nitrone in benzene with ethereal methylmagnesium bromide, and deoxygenation of the crude *N*,*N*-disubstituted hydroxylamine with carbon disulfide. Amine **8** was prepared by substitution of 3-pentanone for acetone in the reaction sequence; in this case proton transfer and subsequent side reactions could not be suppressed completely, thus accounting for the somewhat diminished yield of the amine.



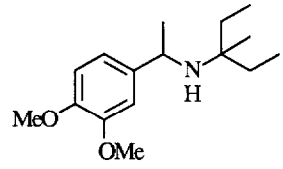
5 [6] (82%)



6 [3] (75%)

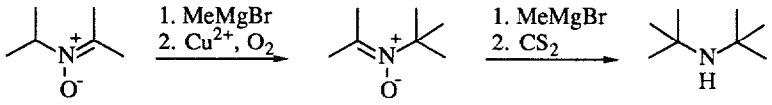


7, R = H (80%)
1, R = OMe (86%)



8 (60%)

Since methods for the preparation of di-*tert*-alkylamines are quite limited,[14,15] we were interested in investigating the Grignard reagent addition to an *N*-*tert*-alkyl ketonitrone as a new route to compounds of that class. All efforts to synthesize the *N*-*tert*-butyl nitrone **9** by direct condensation of acetone with *N*-*tert*-butylhydroxylamine were unsuccessful, so the Grignard reagent alkylation approach was applied to its preparation as well. *N*-Isopropyl nitrone **10**,[8] upon reaction with ethereal methylmagnesium bromide in benzene followed by copper(II)-catalyzed air oxidation[11] of the resulting hydroxylamine and purification by flash chromatography, gave nitrone **9** in 66% overall yield. Alkylation of **9** with MeMgBr and immediate deoxygenation of the crude hydroxylamine product with CS_2 smoothly afforded di-*tert*-butylamine in 78% yield.



10 **9**

In summary, Grignard reagent additions to ketonitrones proceed in good yields with little competition from proton transfer, when they are carried out in benzene solvent with the exclusion of THF as a cosolvent. The reaction, when combined with a simple procedure for the deoxygenation of hydroxylamines,[13] provides an easy and quite general approach to hindered *sec*-alkyl-*tert*-alkyl- and di-*tert*-alkylamines. Representative experimental procedures follow.

***N*-(1,1-Dimethylethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-naphthalenamine (1).** To a solution of 4.63 g (21.1 mmol) of 6,7-dimethoxy-1-tetralone[16] oxime and 2.66 g (42.2 mmol) of $NaBH_3CN$ in 50 mL of MeOH was added a trace of bromocresol green as an indicator. A solution of 3 *N* HCl in MeOH was then added dropwise with stirring to maintain a yellow color (pH ~4). The reaction mixture was stirred at room temperature for 24 h with maintenance of pH ~4 by periodic addition of the 3 *N* methanolic HCl. The mixture was then made basic with 10% NaOH and it was extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, the solvent was evaporated, and the solid residue was recrystallized from ethyl acetate/hexane to give 4.57 g (20.5 mmol, 97%) of the hydroxylamine, mp 116-118 °C.

A solution of 3.00 g (13.6 mmol) of the hydroxylamine in 200 mL of distilled acetone was stirred at room temperature for 10 h. The solvent was evaporated at room temperature under reduced pressure to give 3.52 g (13.4 mmol, 98%) of the nitrone as a thick yellow oil which was used without further purification. Crystallization of a sample of the crude product from ethyl acetate/hexane afforded pale yellow needles: mp 134-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (s, 1H), 6.44 (s, 1H), 5.43 (t, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 2.25 (s, 3H), 2.24 (s, 3H).

A solution of 3.23 g (12.3 mmol) of the nitrone in 150 mL of anhydrous benzene under N_2 was cooled to 0 °C in an ice bath, then 10.0 mL of 3.65 *M* CH_3MgBr in ether (36.5 mmol, 3 eq) was added via syringe. The ice bath was removed and the mixture was allowed to warm to room temperature with stirring for 30 min. The excess Grignard reagent was decomposed by the addition of H_2O and the mixture was extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and evaporated, and the crude product was crystallized from ethyl acetate/hexane to afford 3.15 g (11.3 mmol, 92%) of the *N*-*tert*-butylhydroxylamine: mp 115-116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.54 (s, 1H), 4.21-4.16 (br, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 1.26 (s, 9H).

A solution of 1.33 g (4.76 mmol) of the hydroxylamine in 5 mL of carbon disulfide was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure, the residue was dissolved in 5 mL of acetone, and the precipitated sulfur (0.138 g, 91%) was removed by filtration. The filtrate was evaporated and the residue was purified by flash chromatography on silica gel (4:1 hexane:ethyl acetate) to give 1.20 g (4.56 mmol, 96%) of the *tert*-butylamine **1** as a viscous oil which solidified upon standing: mp 50-51 °C; ^{1}H NMR

(300 MHz, $CDCl_3$) δ 6.95 (s, 1H, H-8), 6.53 (s, 1H, H-5), 3.85 (s, 3H, CH_3O), 3.84 (s, 3H, CH_3O), 3.81-3.77 (m, 1H, H-1), 2.78- 2.57 (m, 2H), 2.02-1.83 (m, 2H), 1.78-1.66 (m, 2H), 1.23 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6 (C-Ar), 146.8 (C-Ar), 133.5 (C-Ar), 129.9 (C-Ar), 112.2 (CH-Ar), 111.6 (CH-Ar), 55.8 (2 CH_3O), 51.4 (CH-N), 49.7 (C-N), 33.1 (CH_2), 30.2 (3 CH_3), 28.9 (CH_2), 19.6 (CH_2). The HCl salt (subl. from 170 °C) was prepared for combustion analysis. Anal. Calcd for $C_{16}H_{26}ClNO_2$: C, 64.09; H, 8.74; Cl, 11.82; N, 4.67. Found: C, 64.19; H, 8.78; Cl, 11.89; N, 4.63.

Di-*tert*-butylamine. A solution of 4.00 g (34.8 mmol) of nitrone **10**[8] in 100 mL of anhydrous benzene was treated with 32 mL of 1.36 *M* ethereal CH_3MgBr (43.5 mmol, 1.25 eq) as described for **1** above, to afford 3.50 g of the hydroxylamine as a colorless liquid (no starting nitrone by ^1H NMR). A solution of the crude hydroxylamine, 0.53 g (2.65 mmol) of $Cu(OAc)_2$ and 1.3 mL of concentrated NH_4OH in 16 mL of methanol was stirred at room temperature with an air stream bubbled through via a gas dispersion tube until a deep blue color developed (about 2 min).[11] The mixture was partitioned between CH_2Cl_2 and water. The organic layer was evaporated on a rotary evaporator with little heating and the residue was subjected to flash chromatography on silica gel (ethyl acetate-methanol 2/1) to afford 2.98 g (23.1 mmol, 66% overall) of nitrone **9** as a pale yellow liquid: bp 55 °C, 1 mm Hg; ^1H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.12 (s, 3H), 1.60 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 69.8, 28.8, 22.9, 21.6.

A solution of 1.00 g (7.75 mmol) of nitrone **9** in 40 mL of anhydrous benzene was treated with 11.4 mL of 1.36 *M* CH_3MgBr in ether (15.5 mmol, 2 eq) as described for **1** above, to give 1.05 g of crude *N,N*-di-*tert*-butylhydroxylamine as a 40:1 (^1H NMR) product:starting material mixture: ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 64.8, 25.5. The crude hydroxylamine was dissolved in 2 mL of carbon disulfide and the solution was stirred at room temperature for 2 min. The solvent was evaporated on a rotary evaporator without heating and the amine was distilled from the residue at 130 mm Hg into a cooled flask (-25 °C) to give 0.778 g (6.03 mmol, 78%) of di-*tert*-butylamine: ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.3, 32.6; hydrochloride mp 258-260 °C (subl. from 180 °C) (lit[14] hydrochloride mp 250-260 °C (subl. from 220 °C)).

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