One-Pot Synthesis of Primary *tert*-Alkylamines by the Addition of Organometallic Reagents to Nitriles Mediated by Ti(O*i*-Pr)$_4$

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Abstract: A number of primary *tert*-alkylamines (18 examples, 25–72% yields) have been prepared according to a simple one-pot procedure by the addition of organometallic reagents such as Grignard reagents and organolithium compounds to nitriles in the presence of Ti(O*i*-Pr)$_4$.

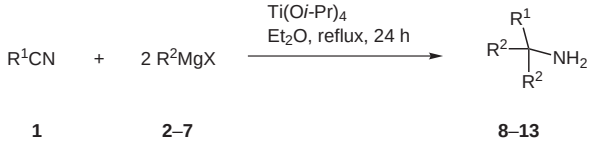
Key words: amines, nitriles, nucleophilic addition, organometallic reagents, titanium tetraisopropoxide

Primary *tert*-alkylamines are not easily available. The Ritter reaction, by which these amines are obtained from tertiary alcohols or from certain alkenes in two steps is one of the most general and widely used approaches to these compounds.[1] Some considerable disadvantages of this method are the moderate overall yields along with the drastic conditions required for the cleavage of the intermediates. A similar approach to primary *tert*-alkylamines is by reduction of *tert*-alkyl azides, which are usually prepared from the corresponding halides[2] or alcohols.[3]

The addition of organometallic reagents to certain N-protected ketimines and subsequent deprotection can also provide *tert*-alkylamines.[4] However, addition of organolithium compounds and Grignard reagents to N-metalated ketimines fails, and this renders the direct synthesis of primary *tert*-alkylamines from nitriles and an excess of the corresponding organometallic reagents impossible. Exceptions are, on the one hand, reactions of certain α-substituted nitriles,[5] and, on the other hand, reactions with allylmagnesium bromide[6] for which the second step appears to be concerted. Only organocerium reagents of the formal composition RCeCl$_2$, obtained in situ from organolithium compounds and CeCl$_3$, are known to undergo twofold addition to different nitriles.[7] In view of the price of CeCl$_3$, however, this method is quite expensive.

The recently developed synthesis of primary cyclopropylamines by reaction of nitriles with Grignard reagents in the presence of Ti(O*i*-Pr)$_4$[8] has certain peculiarities. At least with the use of ethylmagnesium bromide, the corresponding α,α-diethylalkylamines have been observed as byproducts (3–5 mol%).[9] Their formation was supposed to be connected with the complex role of Ti(O*i*-Pr)$_4$: on one side it serves as the precursor to the titanacyclopropane intermediates and on the other side it also acts as a mild Lewis acid and enhances the electrophilicity of the carbon atom in an imino group.

Since the formation of a titanacyclopropane en route to cyclopropylamines can only occur with alkylmagnesium halides that contain a β-hydrogen atom, Grignard reagents without β-hydrogens appeared to be the most promising reagents for the synthesis of primary *tert*-alkylamines from nitriles (Scheme 1). Thus propionitrile (**1a**), phenylmagnesium bromide (**2**) and Ti(O*i*-Pr)$_4$ were chosen to optimize the reaction conditions. In the protocol for the synthesis of cyclopropylamines,[10] Ti(O*i*-Pr)$_4$ is already present in the diethyl ether solution of a nitrile, before two equivalents of the Grignard reagent are added. As this did not appear to be optimal for the synthesis of primary *tert*-alkylamines, the Grignard reagent was added before Ti(O*i*-Pr)$_4$. With 2 equivalents of PhMgBr, 0.1 equivalent of Ti(O*i*-Pr)$_4$, and 1 equivalent of propionitrile (**1a**), the primary *tert*-alkylamine **8a** was not formed at all. With an equimolar quantity of Ti(O*i*-Pr)$_4$, the amine **8a** was produced in a low yield (11%) but with 1 equivalent of Ti(O*i*-Pr)$_4$ and 3 equivalents of the Grignard reagent **2**, a 60% yield of **8a** was obtained. Monitoring of the reaction by workup of aliquots of the reaction mixture showed that the first addition of **2** to form the *N*-magnesio derivative of the corresponding imine was rapid, whereas the subsequent second addition of the Grignard reagent **2** required heating under reflux for up to 24 hours. In tetrahydrofuran instead of diethyl ether, the amine **8a** was formed in a very low yield, if at all.



Scheme 1

A variety of nitriles **1a**–**f** and Grignard reagents **2**–**7** were employed to test the scope and limitations of this transformation. Aliphatic and aromatic nitriles which do not possess highly CH-acidic α-protons, with phenylmagnesium bromide (**2**) and its substituted derivatives **3**, **4** gave the corresponding primary *tert*-alkylamines **8**–**10** in 25–60% yields (Table 1). Unexpectedly, in view of an earlier report,[6] even benzylmagnesium chloride (**5**) gave accept-

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Table 1 Primary *tert*-Alkylamines $R^1R^2{}_2CNH_2$ from Nitriles and Grignard Reagents[11]

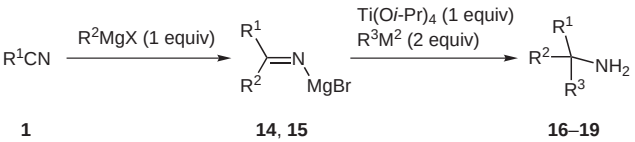
Nitrile, R^1	R^2MgX	Product	Yield (%)
1a, Et	**2**, PhMgBr	**8a**	60
1b, Me	**2**, PhMgBr	**8b**	57
1c, $MeO(CH_2)_2$	**2**, PhMgBr	**8c**	40
1d, *i*-Pr	**2**, PhMgBr	**8d**	55
1e, Ph	**2**, PhMgBr	**8e**	55
1a, Et	**3**, 4-MeC_6H_4MgBr	**9a**	65
1e, Ph	**4**, 3-$CF_3C_6H_4MgBr$	**10e**	25
1b, Me	**5**, BnMgCl	**11b**	40
1a, Et	**5**, BnMgCl	**11a**	72
1f, *n*-Pr	**5**, BnMgCl	**11f**	67
1d, *i*-Pr	**5**, BnMgCl	**11d**	28
1c, $MeO(CH_2)_2$	**5**, BnMgCl	**11c**	35
1e, Ph	**5**, BnMgCl	**11e**	64
1e, Ph	**6**, MeMgCl	**12e**	44
1d, *i*-Pr	**6**, MeMgCl	**12d**	27
1e, Ph	**7**, EtMgBr	**13e**	60

able yields (28–72%) of the corresponding primary *tert*-alkylamines **11** (Table 1). Methylmagnesium chloride (**6**) with benzonitrile (**1e**) and isobutyronitrile (**1d**) also gave the corresponding amines **12e** and **12d** in moderate yields (Table 1).

However, benzyl cyanide and phenylmagnesium bromide (**2**) did not provide the corresponding primary amine, probably due to the high CH acidity of benzyl cyanide. Vinylmagnesium chloride and ethynylmagnesium chloride also did not yield any primary *tert*-alkylamines.

The successive additions of two different organometallic reagents to nitriles is also possible and allows one to obtain amines with three different substituents at the tertiary carbon atom (Scheme 2 and Table 2). Thus from propionitrile (**1a**), phenylmagnesium bromide (**2**) and methylmagnesium chloride (**6**), 1-methyl-1-phenyl-*n*-propylamine (**16a**) was obtained in 30% yield along with the byproduct **8a**. The second organometallic can be an organolithium compound as was demonstrated with 2-furyl-, 2-pyridylmethyl- and 2-thienyllithium to provide the amines **17f**, **18f** and **19d** in 25%, 55% and 30% yields, respectively, (Table 2).

The role of Ti(O*i*-Pr)$_4$ in the successive additions of the two equivalents of an organometallic reagent to a nitrile is not clear. If Ti(O*i*-Pr)$_4$ would only coordinate with the imino nitrogen and increase the electrophilicity of the imino carbon atom, Ti(O*i*-Pr)$_4$ could be replaced by other



Scheme 2

Table 2 Primary *tert*-Alkylamines $R^1R^2R^3CNH_2$ from Nitriles and Two Different Organometallic Reagents[12]

Nitrile, R^1	R^2MgX	R^3M^2	Product	Yield (%)
1a, Et	**6**, MeMgCl	**2**, PhMgBr	**16a**	30
1f, *n*-Pr	**2**, PhMgBr	2-FurylLi	**17f**	25
1f, *n*-Pr	**2**, PhMgBr	2-$PyCH_2Li$	**18f**	55
1d, *i*-Pr	**2**, PhMgBr	2-ThienylLi	**19d**	30

Lewis acids. But an attempt to use Al(O*i*-Pr)$_3$ instead of Ti(O*i*-Pr)$_4$ in this transformation failed. This emphasizes the unique role of Ti(O*i*-Pr)$_4$ in this reaction.

References and Notes

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(11) **General Experimental Procedure for the Synthesis of Primary *tert*-Alkylamines 8–13**: To a solution of the nitrile (10 mmol) in Et_2O (30–50 mL) was added the respective Grignard reagent as a 1–3 M Et_2O solution (3 equiv), and after stirring for 30 min Ti(O*i*-Pr)$_4$ (1 equiv) was added successively at r.t. After the mixture had been heated under reflux for 10 h, a 10% aq solution of NaOH (40 mL) was added. Stirring was continued for 15–30 min. The solution was filtered and the filtrate was extracted with Et_2O (3 × 30 mL). The combined Et_2O layers were concentrated under reduced pressure and the residue was extracted with dilute aq 5% HCl. The combined aqueous layers were washed with Et_2O (2 × 30 mL), made basic by addition of aq 10% NaOH and extracted with Et_2O (3 × 30 mL). A few drops of concd HCl were added to the combined Et_2O phases and Et_2O was evaporated to dryness to leave the respective amine hydrochloride. In some cases it was necessary to purify the amine hydrochloride by recrystallization (EtOH–Et_2O).

1,1-Dibenzyl-*n*-propylamine Hydrochloride (11a): ^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.06 (t, *J* = 7.3 Hz, 3 H), 1.49 (q, *J* = 7.3 Hz, 2 H), 2.84 (d, *J* = 13.8 Hz, 2 H), 3.18 (d, *J* = 13.8 Hz, 2 H), 7.24–7.34 (m, 10 H), 8.32 (br s, 3 H). ^{13}C NMR (250 MHz, DMSO-d_6): δ = 7.6 (CH_3), 26.8 (CH_2), 41.2 (CH_2), 58.7 (C), 126.9 (CH), 128.4 (CH), 130.9 (CH), 134.9 (C). MS (ESI): *m*/*z* = 1067 (46) $[4 \times M - Cl]^+$, 515 (18) $[2 \times M - Cl]^+$, 479 (10) $[2 \times M - HCl - Cl]^+$, 240 (100) $[M - Cl]^+$. Anal. Calcd for $C_{17}H_{21}N{\cdot}HCl$ (275.8): C, 74.03; H, 8.04; N, 5.08. Found: C, 74.23; H, 8.14; N, 5.19.

(12) **Experimental Procedure for the Synthesis of 1-(2-Furyl)-1-phenyl-*n*-butylamine Hydrochloride (17f)**: To the solution of furan (1.7 g, 25 mmol) in THF (10 mL) was added *n*-BuLi (2.9 M in hexane, 25 mmol) keeping the temperature below –10 °C, and the mixture was stirred at r.t. for 4 h to provide a solution of 2-furyllithium.
To a solution of butyronitrile (0.69 g, 10 mmol) in Et_2O (30 mL) were added successively at ambient temperature PhMgBr (1.1 M in Et_2O, 10 mmol) then, after stirring for 30 min, Ti(O*i*-Pr)$_4$ (2.84 g, 10 mmol) and finally the solution of 2-furyllithium. After heating under reflux for 10 h, the reaction mixture was worked up as described in the general procedure above. The product **17f** was purified by column chromatography on silica gel (50 g), eluting with $CHCl_3$–MeOH (30:1). ^{1}H NMR (250 MHz, DMSO-d_6): δ = 0.93 (t, *J* = 7.2 Hz, 3 H), 1.15–1.45 (m, 2 H), 2.25–2.42 (m, 2 H), 6.46 (m, 1 H), 6.57–6.58 (m, 1 H), 7.29–7.37 (m, 5 H), 7.55 (m, 1 H), 9.47 (br s, 3 H). ^{13}C NMR (250 MHz, DMSO-d_6): δ = 14.7 (CH_3), 17.7 (CH_2), 41.1 (CH_2), 61.6 (C), 109.9 (CH), 111.2 (CH), 127.2 (CH), 128.6 (CH), 128.9 (CH), 130.5 (C), 143.4 (CH), 153.7 (C). MS (ESI): *m*/*z* = 970 (16) $[4 \times M - Cl]^+$, 199 (100) $[M - Cl - NH_3]^+$, 157 (18). Anal. Calcd for $C_{14}H_{17}NO{\cdot}HCl$ (251.8): C, 66.79; H, 7.21; N, 5.56. Found: C, 66.69; H, 7.31; N, 5.26.