Convenient synthesis of protected primary amines from nitriles

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Abstract

Investigations into the use of nickel chloride and sodium borohydride for the reduction of nitriles showed the secondary amine dimers to be the major products under normal conditions. The addition of a suitable trapping agent, such as di-*tert*-butyl dicarbonate, allowed the isolation of the protected primary amines. © 2000 Published by Elsevier Science Ltd. All rights reserved.
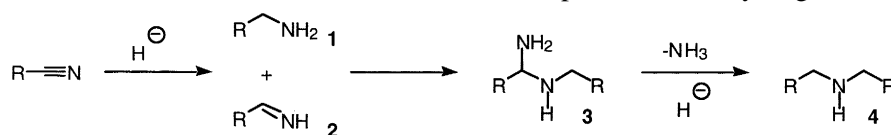
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During ongoing investigations it became necessary for us to uncover a selective and, more importantly, a generally applicable procedure for the reduction of nitriles. Due to its chemical robustness the cyano group is ordinarily reduced using either catalytic hydrogenation or a strong hydride donor, such as lithium aluminium hydride, which leaves little scope for selectivity.[1] Sodium borohydride is generally not strong enough to bring about reduction,[2] although exceptions do exist.[3] However, the addition of various transition metal salts to reaction mixtures has long been known to dramatically improve the reactivity of hydride donors.[4] Cobalt(II) salts have found repeated application in the reduction of nitriles and of particular note is the use of cobalt chloride in conjunction with sodium borohydride.[5,6] Mechanistically, this reaction is thought to occur with initial formation of cobalt boride[7] through the reaction of cobalt chloride and sodium borohydride.[5,8] Subsequent coordination of the nitrile group to the boride surface then leaves it open to hydride attack from excess borohydride. Related reactions using nickel boride and hydrogen have also appeared in the literature with excellent chemo-selectivities being recorded in some cases.[9,10] Confusion as to the exact nature of these reagents[11] has meant that no generally applicable procedure has been developed. In this paper we describe a new procedure for the transformation of nitriles to protected primary amines as a single-step operation using sodium borohydride and nickel chloride.

We began our investigations by treating benzyl cyanide with nickel chloride and an excess of sodium borohydride in methanol. We were pleased to find complete reduction of the nitrile triple bond.[12]

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However, close scrutiny of the reaction product revealed that we had in fact isolated the symmetrical secondary amine **4** as a result of dimerisation, a common side product in the hydrogenation of nitriles.[1,13]

$$R-\!\!\equiv\!\!N \xrightarrow{H^\ominus} \begin{array}{c} R\text{-}CH_2NH_2 \;\; \mathbf{1} \\ + \\ R\text{-}CH=NH \;\; \mathbf{2} \end{array} \longrightarrow R\underset{\underset{H}{|}}{\overset{NH_2}{C}}N\!\!-\!\!CH_2R \;\; \mathbf{3} \xrightarrow[\ominus]{-NH_3} R\,CH_2\!-\!\underset{H}{N}\!-\!CH_2R \;\; \mathbf{4}$$

It seems that addition of the primary amine **1** to the intermediate imine species **2** is faster than hydride attack. The resulting hemiaminal **3** can then extrude an equivalent of ammonia to give an imine which is further reduced to deliver the final product **4**. Varying degrees of this type of coupling have previously been noted in other metal boride mediated reductions of nitriles.[9,14] The stoichiometry of the reagents obviously plays a critical role in the determination of the reaction products. In our hands only the secondary amines were formed (Table 1)[15] and longer reaction times (up to 24 h) seemed to give the best conversions. A large excess of reducing agent was also found to be necessary to bring about complete transformation, presumably due to the instability of sodium borohydride in methanol. Although quantitative conversions of secondary amines were achieved in some cases, yields did vary considerably. Simple alkyl nitriles, in particular, gave poor yields possibly as a result of stronger complexation of these products to the nickel boride catalyst (Table 1).

Table 1

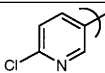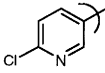| R	Starting Material	Reaction time	Yield of 2°-amine **4**[c]
PhCH₂-	Benzyl cyanide	20h	99
PhCH₂-	Benzyl cyanide	1h	86
Ph-	Benzonitrile	4h	96
p-Br-C₆H₄CH₂-	Bromophenylacetonitrile	24h	42
C₅H₁₁-	Hexanenitrile	20h	23

[c]Yields of 2°-amine are quoted as a percentage of the theoretical maximum conversion of 50%.

To circumvent the problem of dimerisation we reasoned that if we were able to trap the initially formed primary amine in situ, by acylation for example, then the reduced nucleophilicity of the resultant amide would prevent further reaction with the intermediate imine. Such a strategy should then provide a direct route from the starting nitrile to a protected primary amine. Indeed, the addition of acetic anhydride (Ac₂O) to the reaction mixtures resulted in formation of the *N*-acetylamines (Table 2, entries 1–6). By extension, the use of di-*tert*-butyl dicarbonate (BOC₂O) delivers the *tert*-butyl-carbamates,[16] which obviously offer greater synthetic versatility due to their facile deprotection (Table 2, entries 7–18). Yields of the protected amines were generally found to be greater than the corresponding secondary amine products above, although very good conversions still proved elusive for some alkyl nitriles (entry 5, Table 2). Similarly, nitriles containing pyridines gave poor conversions (entries 6 and 14, Table 2). Again, we can only speculate that this is either due to chelation of the pyridine nitrogen to nickel reducing the efficiency of product extraction or as a result of the formation and reduction of a pyridinium species. Nitro groups were also found to reduce under the reaction conditions (entries 17, 18, Table 2) as was the double bond of acrylonitrile (entry 16, Table 2).

In conclusion we have found that a combination of nickel chloride and sodium borohydride efficiently reduces nitrile groups. The procedure seems to offer reasonable selectivity with esters, acetals, amides and carbamates apparently remaining unchanged under the reaction conditions. Furthermore, the addition of a suitable trapping agent such as Ac₂O or BOC₂O allows the isolation of the protected primary amine thus avoiding the formation of the secondary amine dimers.

Table 2
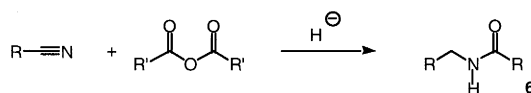
Entry	R	Additive[d]	R'	Yield of 6 (%)
1	PhCH$_2$-	Ac$_2$O (1.5eq)	CH$_3$-	94
2	Ph-	Ac$_2$O (1.5eq)	CH$_3$-	87
3	PhC$_3$H$_6$-	Ac$_2$O (1.5eq)	CH$_3$-	71
4	n-C$_3$H$_7$-	Ac$_2$O (1.5eq)	CH$_3$-	99
5	n-C$_5$H$_{11}$-	Ac$_2$O (1.5eq)	CH$_3$-	53
6		Ac$_2$O (1.5eq)	CH$_3$-	27
7	PhCH$_2$-	BOC$_2$O (2eq)	^{t}BuO-	99
8	n-C$_7$H$_{15}$-	BOC$_2$O (2eq)	^{t}BuO-	61
9	n-C$_3$H$_7$-	BOC$_2$O (2eq)	^{t}BuO-	80
10	p-F-C$_6$H$_4$-	BOC$_2$O (2eq)	^{t}BuO-	76
11	PhC$_3$H$_6$-	BOC$_2$O (2eq)	^{t}BuO-	71
12	CH$_3$OCH$_2$-	BOC$_2$O (2eq)	^{t}BuO-	60
13	p-Br-C$_6$H$_4$CH$_2$-	BOC$_2$O (2eq)	^{t}BuO-	62
14		BOC$_2$O (2eq)	^{t}BuO-	25
15	p-HO-C$_6$H$_4$-	BOC$_2$O (2eq)	^{t}BuO-	46[e]
16	CH$_2$=CH-	BOC$_2$O (2eq)	^{t}BuO-	59[f]
17	m-NO$_2$-C$_6$H$_4$-	BOC$_2$O (2eq)	^{t}BuO-	59[g]
18	p-NO$_2$-C$_6$H$_4$-	BOC$_2$O (2eq)	^{t}BuO-	40[g]

[d]The quenching agent was added to the reaction mixture prior to the addition of sodium borohydride.
[e]Product is N,O-bis-BOC-hydroxyphenylmethylamine
[f]N-BOC-propylamine was isolated as a result of the reduction of both the nitrile group and the double bond.
[g] The bis-BOC-diamine was isolated as a result of both the nitro and nitrile groups being reduced.

Acknowledgements

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12. Preparation of diphenethylamine: $NiCl_2$ (1 equiv., 1.19 g, 5 mmol), MeOH (50 ml) and benzyl cyanide (1 equiv., 0.53 ml, 5 mmol) were added to a round bottom flask. $NaBH_4$ (7 equiv., 1.32 g, 35 mmol) was cautiously added to this solution at 0°C, vigorous effervescence was accompanied by the formation of a black solid. The reaction mixture was left to stir at room temperature for 20 h. The methanol was then removed under reduced pressure, leaving a black precipitate. The precipitate was then dissolved in EtOAc and $NaHCO_3$, filtered and repeatedly washed with EtOAc. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to yield diphenethylamine (99%, 0.56 g, 2.49 mmol).

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16. Preparation of *N*-BOC-phenethylamine: $NaBH_4$ (0.79 g, 21 mmol) was cautiously added to a solution of $NiCl_2$ (0.71 g, 3 mmol), BOC_2O (1.31 g, 6 mmol) and benzyl cyanide (0.32 ml, 3 mmol) in MeOH (25 ml) at 0°C (vigorous reaction with the formation of a black precipitate). Once the reaction had subsided the mixture was left to stir, at room temperature, for 24 h. Methanol was removed under reduced pressure and the precipitate dissolved in EtOAc and $NaHCO_3$, filtered and repeatedly washed with EtOAc. The combined organic phases were dried (Na_2SO_4) and concentrated to yield *N*-BOC-phenethylamine (99%) Mp: 59.1°C. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.22–7.08 (5H, m, Ar**H**), 4.64 (1H, br, s, N**H**), 3.30 (2H, q, *J*=7.0 Hz, **CH$_2$**NH), 2.69 (2H, t, *J*=7.0 Hz, **CH$_2$**Ar), 1.34 (9H, s, *t*-Bu). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.36, 139.47, 129.24, 128.98, 126.80, 42.25, 36.64, 28.85. MS(EI) *m/z* 165, 104, 91, 77. IR ν_{max}/cm^{-1} 3447, 3055, 2985, 1708, 1506.