Facile preparation of *N*-methyl secondary amines by titanium(IV) isopropoxide-mediated reductive amination of carbonyl compounds

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A simple, mild and efficient procedure for obtaining *N*-methyl secondary amines from aldehydes and ketones is reported. Treatment of carbonyl compounds with methylamine hydrochloride, triethylamine and titanium(IV) isopropoxide, followed by *in situ* sodium borohydride reduction and straightforward aqueous work-up, affords clean products in good to excellent yields.

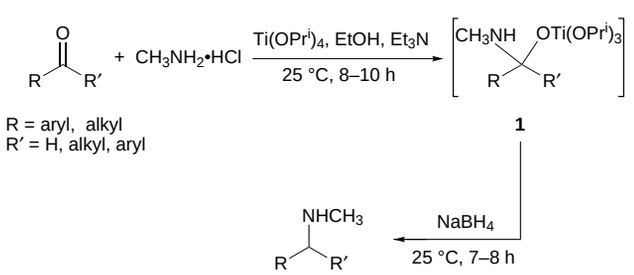
Introduction

Amines are important synthetic targets as well as valuable synthons for a wide variety of medicinal agents and agrochemicals.[1] More recently, interest has turned to their use in solid-phase combinatorial chemistry for the generation of small molecule libraries.[2,3] *N*-Methyl secondary amines are particularly important for the syntheses of various tertiary amines, as versatile ligands[4] in homogeneous asymmetric transformations, as fluorescence probes[5] in HPLC, and as a modifier[6] in reversed-phase chromatography, among other applications.[7] The traditional methods[8] for the preparation of *N*-methyl secondary amines have often resulted in the formation of complex mixtures of unmethylated, partially methylated and permethylated products. Consequently, development of new, general and efficient protocols for the preparation of this class of amines is a current theme in chemical research. Particularly important is the development of novel methods than can produce amines with reagent sensitive functional groups.

The reductive amination of aldehydes and ketones is one of the most used reactions for the syntheses of different types of amines.[9,10] Catalytic hydrogenation[9] is one of the classical methods for carrying out this transformation. However, these reaction conditions are not compatible with a number of otherwise reducible functional groups such as nitro, cyano, double and triple bonds. Among the hydride reagents utilized to effect this transformation, sodium cyanoborohydride[11] (Borch reduction) has found considerable application. Unfortunately, the use of this reagent is compromised by its cost and toxicity,[12] which risks the presence of residual cyanide[13] in the product as well as in the work-up system. Alternative reducing systems currently include sodium triacetoxyborohydride (Gribble reduction) in neutral or acidic media,[14] sodium borohydride in aqueous sulfuric acid[15] and pyridine–borane.[16]

Results and discussion

As a part of our interest in the development of mild and inexpensive reagent systems for reductive amination reactions, we have recently reported an efficient method for the reductive amination of formaldehyde with primary and secondary amines,[17] as well as the general reductive amination of aldehydes and ketones with secondary amines,[18] using a combination of titanium(IV) isopropoxide and sodium borohydride. We now wish to report the results for our expanded application of this mild, safe and efficient one-pot reagent system to the conversion of various aldehydes and ketones to *N*-methyl secondary amines. Titanium(IV) isopropoxide has been utilized[11d,17,18,19] as a mild Lewis acid compatible with a variety of potentially acid-sensitive functional groups such as acetals, acetonides, silyl ethers and Boc derivatives. An equimolar mixture of methylamine hydrochloride and triethylamine has been employed as the methylamine equivalent; this requires no special handling techniques and alleviates the use of excess gaseous methylamine. One of the classical problems encountered with the reductive alkylation of primary amines is the formation of tertiary amines[11b] along with the desired *N*-monoalkylated products. Alkylation of primary amines with various alkyl halides[8] often leads to the generation of tertiary amines and quaternary ammonium salts. The present reaction conditions, however, offer very clean conversions affording only the desired *N*-methyl secondary amines in good to excellent yields; no over-alkylation of the product amines is observed. The reaction may proceed through an intermediate[11d,20] methylaminoalcoholatotitanium(IV) complex **1** (Scheme 1) which

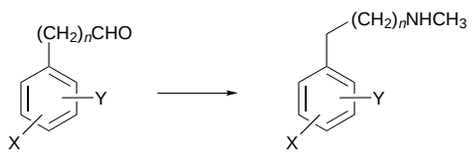


Scheme 1

is either reduced directly or *via* equilibration of **1** to form a transient imine species. Similar intermediates have been proposed[21] in the synthesis of phenethylamines through titanate–amide complexes.

The scope of the method proved to be quite general for a variety of aldehydes and ketones. The molar ratio of the reactants and the results obtained for a representative group of aldehydes and ketones are summarized in Table 1 and Table 2, respectively. Typically, the intermediate methylaminoalcoholatotitanium(IV) complex **1** was first allowed to form by stirring a mixture of the carbonyl compound, methylamine hydrochloride, triethylamine and titanium(IV) isopropoxide in absolute ethanol at ambient temperature for 8–10 h. The reducing agent, sodium borohydride was then added and the resulting mixture was further stirred for 7–8 h at ambient

Table 1 Conversion of aldehydes to secondary amines by $Ti(OPr^i)_4$, $MeNH_2 \cdot HCl$, Et_3N and $NaBH_4$[a,b]



Entry	*n*	X	Y	Reaction time/h[c]	Yield (%)[d]
1	0	4-F	H	8(7)	73
2	0	2-F	H	8(7)	75
3	0	3-Br	H	8(7)	84
4	0	3-CN	H	8(7)	81
5	0	4-CH_3O	H	10(8)	91
6	0	3-CH_3O	H	9(8)	72
7	0	3-CH_3O	4-CH_3O	9(8)	81
8	0	3-$PhCH_2O$	H	9(8)	72
9	0	3-$PhCH_2O$	4-$PhCH_2O$	9(8)	64
10	0	3,4-OCH_2O		8(7)	88
11	0	3-NO_2	H	8(8)	71
12	0	4-NHAc	H	8(8)	79
13	0	4-$CH(OEt)_2$	H	8(8)	76
14	1	H	H	8(7)	81

[a] Molar ratio of aldehyde : methylamine hydrochloride : triethylamine : titanium(IV) isopropoxide : sodium borohydride = 1 : 2 : 2 : 2 : 1.5. [b] All products were characterized by their ^1H and ^{13}C NMR, and GC–mass spectral data. [c] The numbers on the left denote duration of intermediate formation and those in parentheses denote duration of reaction after sodium borohydride addition. [d] Yields are of isolated and purified products.

temperature. Finally, the reaction mixture was quenched with aqueous ammonia (2 mol dm^{-3}), the resulting inorganic precipitate was filtered and the filtrate was extracted with dichloromethane. The product *N*-methyl secondary amines were isolated in their pure forms by simple extraction of the dichloromethane solution with hydrochloric acid (1 mol dm^{-3}), basification of the aqueous layer and subsequent dichloromethane extraction. The acid-sensitive acetal amines (Table 1, entry 10 and 13; Table 2, entry 4) were purified *via* flash chromatography on silica gel.

As shown in Tables 1 and 2, both aldehydes and ketones were converted to the corresponding *N*-methyl secondary amines in good to excellent yields. A comparison of the data between Tables 1 and 2 show little difference in the reactivities of the carbonyl compounds toward reductive amination under the reaction conditions employed. Steric hindrance posed no problem within the aldehyde series (Table 1) and appeared to play only a limited role in dictating the outcome of the reactions in the ketone series, with the only notable exceptions being entries 5 and 10 (Table 2). The reaction conditions have been successfully applied to carbonyl compounds containing acid sensitive groups such as acetals (Table 1, entry 10 and 13; Table 2, entry 4), and carbamate (Table 2, entry 11) or to the nucleophile/base-sensitive amide (Table 1, entry 12). The reagent system is also found to be tolerant to a number of other functional groups such as benzyloxy, methoxy, nitro, cyano, bromo and fluoro. In contrast to the existing acid-mediated reductive amination methods, the present method is equally applicable to enolizable carbonyl compounds.

Notable advantages of the present method include: the mild reaction conditions, the simple work-up procedure, no need for any chromatographic separations, as well as the use of relatively safe and inexpensive reagents that require no special handling techniques. Under these reaction conditions, only the *N*-monomethylated secondary amines are formed—the classical problem of overalkylation of the product amines has been eliminated. Moreover, due to the compatibility of titanium(IV) isopropoxide with a variety of acid- or base-sensitive groups, this method should find particular application in the preparation of functionalized secondary amines, required for further synthetic elaboration.

In conclusion, a simple and efficient one-pot method has been developed for the synthesis of *N*-methyl secondary amines by reductive amination of aldehydes and ketones with methylamine using titanium(IV) isopropoxide and sodium borohydride. A mixture of methylamine hydrochloride and triethylamine has been used as the source of nucleophilic methylamine. Because this method allows easy, direct access to a variety of *N*-methylated secondary amines, it should find widespread application. Further studies addressing the possibility of asymmetric induction in the reductive aminations of unsymmetrical ketones, as well as the application of this methodology to solid-phase chemistry, are currently underway.

Experimental

Starting materials were used as received form their respective suppliers. The 300 MHz ^1H NMR and 75.5 MHz ^{13}C NMR spectra were determined on a Bruker AM 300 spectrometer using $CDCl_3$ with $SiMe_4$ as the internal reference (*J* values are given in Hz). GC–MS Analyses were performed at an ionizing voltage of 70 eV (EI) on a Hewlett Packard 5989B GC–MS instrument equipped with a DB-5 column (diameter: 30 m; inner diameter: 30 mm; film thickness: 0.1 mm). Analytical thin layer chromatography was performed on pre-coated silica gel plates with fluorescent indicators using purified solvents, followed by I_2 visualization, as necessary. Products were typically >95% pure by NMR spectroscopy and TLC analyses after simple work-up, but preparative TLC or column chromatography (CH_2Cl_2–MeOH, 9 : 1) was occasionally employed for the preparation of analytically pure samples. All products were characterized by their ^1H and ^{13}C NMR spectra and GC–MS data; identities of known compounds were established by comparison of their NMR data with reported values.

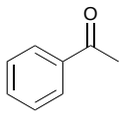
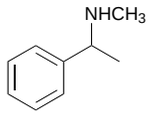
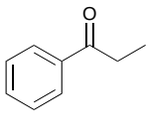
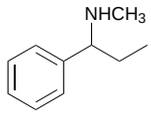
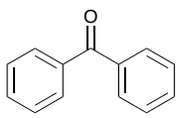
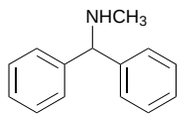
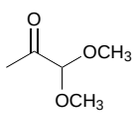
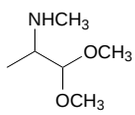
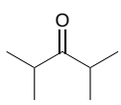
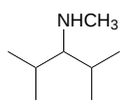
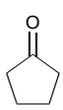
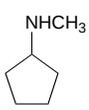
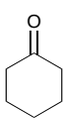
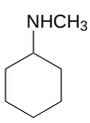
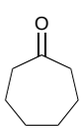
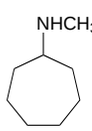
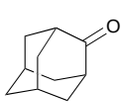
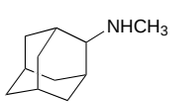
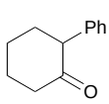
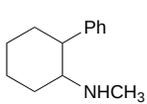
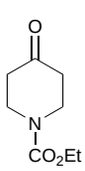
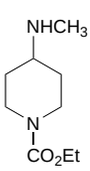
General procedure for the reductive alkylation of methylamine

A mixture of the carbonyl compound (10 mmol), titanium(IV) isopropoxide (5.9 cm^3, 20 mmol), methylamine hydrochloride (1.35 g, 20 mmol) and triethylamine (2.79 cm^3, 20 mmol) in absolute ethanol (15 cm^3) was stirred under Ar at ambient temperature for 8–10 h. Sodium borohydride (0.57 g, 15 mmol) was then added and the resulting mixture was stirred for an additional 7–8 h at ambient temperature. The reaction was then quenched by pouring into aqueous ammonia (2 mol dm^{-3}, 30 cm^3), the resulting inorganic precipitate was filtered off, and washed with dichloromethane (50 cm^3). The organic layer was separated and the remaining aqueous layer was extracted once with dichloromethane (50 cm^3). The combined organic extracts were next extracted once with hydrochloric acid (1 mol dm^{-3}, 25 cm^3) to separate the neutral materials. The acidic aqueous extracts were washed once with dichloromethane (50 cm^3), then treated with aqueous sodium hydroxide (2 mol dm^{-3}) to pH 10–12, and extracted with dichloromethane (50 $cm^3 \times 3$). The combined organic extracts were washed with brine (50 cm^3), dried (Na_2CO_3) and concentrated *in vacuo* to afford *N*-methyl secondary amines in good to excellent yield.

In the case of the acid-sensitive acetals (Table 1, entry 10 and 13; Table 2, entry 4), the same work-up procedure was used, except that the combined dichloromethane layers of each product were not treated with hydrochloric acid. Instead, the solutions were washed with brine (50 $cm^3 \times 2$), dried with Na_2CO_3, and concentrated *in vacuo* to afford the product acetal amines as oils. Each sample was purified by preparative TLC (CH_2Cl_2–MeOH, 9 : 1) on silica gel, to afford pure products in good yields.

The data below correspond to the entries in Table 1.

Table 2 Reductive aminations of ketones using $Ti(OPr^i)_4$, $MeNH_2 \cdot HCl$, Et_3N and $NaBH_4$ [a,b]

Entry	Starting ketone	Product	Reaction time/h [c]	Yield (%) [d]
1			9(7)	86
2			10(8)	85
3			10(8)	79
4			9(7)	77
5			10(8)	64
6			10(8)	71
7			10(8)	73
8			10(8)	72
9			10(8)	75
10			10(8)	70
11			10(8)	91

[a] Molar ratio of ketone : methylamine hydrochloride : triethylamine : titanium(IV) isopropoxide : sodium borohydride = 1 : 2 : 2 : 2 : 1.5. [b] All products were characterized by their ^1H and ^{13}C NMR, and GC–mass spectral data, and physical constant data. [c] The numbers on the left denote duration of reaction for intermediate formation and those in parentheses denote duration of reaction after sodium borohydride addition. [d] Yields are of isolated and purified products.

Entry 1: δ_H 7.19 (2H, dd, *J* 5.6 and 8.4), 6.90 (2H, m), 3.59 (2H, s), 2.32 (3H, s) and 1.93 (1H, s, NH).

Entry 2: δ_H 7.76 (1H, t, *J* 8.2), 7.45–6.95 (3H, m), 4.14 (2H, s), 2.56 (3H, s) and 2.27 (1H, s, NH).

Entry 3: δ_H 7.49 (1H, s), 7.38 (1H, d, *J* 7.4), 7.29–7.16 (2H, m), 3.73 (2H, s), 2.45 (3H, s) and 1.42 (1H, s, NH); δ_C 142.0, 131.6, 130.4, 130.3, 127.1, 122.9, 55.2 and 36.0; GC–MS: *m*/*z* (EI) 201 ($M^+ + 1$, 10%), 200 (M^+, 17), 120 (46), 89 (14), 63 (11) and 44 (100).

Entry 4: δ_H 7.54 (1H, s), 7.48 (1H, d, *J* 7.2), 7.41 (1H, d, *J* 7.7), 7.32 (1H, t, *J* 7.8), 3.69 (2H, s), 2.35 (3H, s) and 1.72 (1H, s, NH); δ_C 141.2, 132.9, 132.0, 131.3, 129.5, 119.3, 112.8,

55.5 and 36.0; GC–MS: *m*/*z* (EI) 146 (M^+, 17%), 145 ($M^+ - 1$, 38), 116 (18), 89 (13) and 44 (100).

Entry 5: δ_H 7.19 (2H, d, *J* 6.7), 6.84 (2H, d, *J* 6.6), 3.73 (3H, s), 3.63 (2H, s), 2.39 (3H, s) and 1.33 (1H, s, NH).

Entry 6: δ_H 7.06 (1H, t, *J* 8.0), 6.73–6.60 (2H, m), 6.71 (1H, s), 3.65 (3H, s), 3.54 (2H, s), 2.28 (3H, s) and 1.30 (1H, s, NH).

Entry 7: δ_H 6.65 (1H, s), 6.59–6.52 (2H, m), 3.60 (3H, s), 3.57 (3H, s), 3.41 (2H, s), 2.18 (3H, s) and 1.23 (1H, s, NH); GC–MS: *m*/*z* (EI) 181 (M^+, 58%), 180 ($M^+ - 1$, 52), 151 (100), 150 (87), 135 (10), 107 (19), 91 (10), 77 (13), 65 (15) and 44 (47).

Entry 8: δ_H 7.49–7.29 (6H, m), 7.07–6.92 (3H, m), 5.10 (2H, s), 3.78 (2H, s), 3.05 (1H, s, NH) and 2.47 (3H, s); δ_C 159.5, 141.8, 138.0, 137.3, 130.2, 129.0, 128.4, 128.0, 121.9, 115.6, 115.1, 70.4, 54.7 and 34.4; GC–MS: *m*/*z* (EI) 227 (M^+, 5%), 198 (22), 91 (100), 65 (10) and 44 (12).

Entry 9: δ_H 7.28–7.41 (11H, m), 7.01 (1H, m), 6.80 (1H, m), 5.25 (2H, s), 5.12 (2H, s), 3.93 (2H, s), 2.47 (3H, s) and 2.20 (1H, s, NH).

Entry 10: δ_H 6.77 (1H, s), 6.69 (2H, s), 5.86 (2H, s), 3.58 (2H, s), 2.36 (3H, s) and 1.36 (1H, s, NH); δ_C 148.0, 147.0, 133.0, 122.0, 109.2, 108.3, 101.2, 55.4 and 35.2.

Entry 11: δ_H 8.21 (1H, s), 8.12 (1H, d, *J* 8.2), 7.68 (1H, d, *J* 7.6), 7.50 (1H, t, *J* 7.9), 3.87 (2H, s), 2.47 (3H, s) and 1.42 (1H, s, NH); δ_C 148.6, 142.4, 134.6, 129.6, 123.3, 122.4, 55.0 and 36.0; GC–MS: *m*/*z* (EI) 166 (M^+, 13%), 165 ($M^+ - 1$, 19), 136 (8), 119 (16), 107 (17), 77 (9) and 44 (100).

Entry 13: δ_H 7.40 (2H, d, *J* 8.1), 7.27 (2H, d, *J* 8.1), 5.45 (1H, s), 3.69 (2H, s), 3.60–3.46 (4H, m), 2.39 (3H, s), 1.43 (1H, s, NH) and 1.21–1.17 (6H, m); δ_C 140.5, 138.2, 128.3, 127.0, 101.8, 61.2, 56.1, 36.3 and 15.5; GC–MS: *m*/*z* (EI) 223 (M^+, 10%), 178 (100), 150 (55), 132 (36), 119 (35), 107 (9), 91 (34), 75 (12) and 44 (56).

The data below corresponds to the entries in Table 2.

Entry 2: δ_H 7.50–7.15 (5H, m), 3.39 (1H, t, *J* 6.3), 2.29 (3H, s), 1.90–1.60 (3H, m) and 0.82 (3H, t, *J* 7.2).

Entry 3: δ_H 7.38–7.15 (10H, m), 4.66 (1H, s), 2.37 (3H, s) and 1.78 (1H, s, NH); δ_C 143.8, 128.4, 127.2, 127.0, 69.5 and 35.0; GC–MS: *m*/*z* (EI) 197 (M^+, 6%), 196 ($M^+ - 1$, 5), 167 (16), 152 (8), 120 (100), 104 (13), 77 (12) and 42 (36).

Entry 4: δ_H 4.25 (1H, d, *J* 6.0), 3.45 (3H, s), 3.43 (3H, s), 2.83 (1H, quintet, *J* 6.2), 2.51 (3H, s), 2.25 (1H, br s, NH) and 1.15 (3H, d, *J* 6.5) (Found: C, 54.25; H, 11.12; N, 10.82. $C_6H_{15}NO_2$ requires C, 54.10; H, 11.35; N, 10.51%).

Entry 5: δ_H 2.81 (3H, s), 2.52 (1H, br s), 2.25–2.10 (2H, m), 1.30 (1H, br s), 1.16 (6H, d, *J* 9.0) and 1.13 (6H, d, *J* 7.0) (Found: C, 74.13; H, 14.98; N, 10.56. $C_8H_{19}N$ requires C, 74.34; H, 14.82; N, 10.83%).

Entry 7: δ_H 3.0–2.71 (1H, m), 2.65 (3H, s), 2.20 (2H, d, *J* 11.0) and 1.95–1.10 (9H, m); δ_C 58.7, 30.4, 29.6, 25.3 and 24.8.

Entry 8: δ_H 3.08–3.04 (1H, m), 2.64 (3H, s), 2.21–2.18 (2H, m), 1.90–1.72 (4H, m) and 1.65–1.40 (7H, m); δ_C 60.7, 30.7, 30.2, 27.6 and 23.8.

Entry 9: δ_H 2.62 (1H, s), 2.42 (3H, s), 1.96–1.60 (12H, m) and 1.55–1.42 (3H, m); δ_C 64.2, 38.4, 38.0, 34.2, 32.0, 31.7, 28.3 and 28.0; GC–MS: *m*/*z* (EI) 165 (M^+, 42%), 164 ($M^+ - 1$, 90), 134 (9), 122 (12), 92 (17), 79 (18), 70 (24) and 44 (100).

Entry 10: δ_H(diastereomeric mixture) 7.36–7.10 (5H, m), 2.90–2.80 (1H, m), 2.60–2.30 (1H, m), 2.20, 2.19 (3H, 2s) and 2.10–1.15 (9H, m); δ_C(diastereomeric mixture) 144.7, 129.0, 128.7, 128.0, 127.9, 126.9, 126.5, 63.4, 60.5, 51.4, 47.6, 35.1, 34.9, 33.9, 31.9, 29.5, 26.9, 25.6, 25.1 and 19.8; GC–MS: *m*/*z* (EI) 189 (M^+, 24%), 146 (15), 91 (10), 70 (100), 57 (31) and 44 (12).

Entry 11: δ_H 3.78 (2H, q, *J* 7.1), 3.79–3.70 (2H, m), 2.57 (2H, t, *J* 11.7), 2.22–2.20 (1H, m), 2.11 (3H, s), 1.54 (2H, dd, *J* 2.8 and 12.7), 1.22 (1H, br s), 0.98–0.91 (2H, m) and 0.93 (3H, t, *J* 7.1); δ_C 155.1, 60.8, 56.3, 42.3, 33.2, 31.8 and 14.5; GC–MS: *m*/*z* (EI) 186 (M^+, 34%), 171 (6), 157 (28), 155 (34), 113 (37), 70 (100), 56 (62) and 42 (63).

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