Titanium(IV) mediated reductive aminations of 1-adamantyl methyl ketone: facile preparation of potential antiviral agents rimantadine and its analogues

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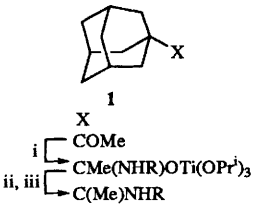
A preparatively efficient, mild method for the synthesis of rimantadine and its analogues *via* novel reductive aminations of 1-adamantyl methyl ketone using titanium(IV) isopropoxide and sodium borohydride is reported.

The synthesis of adamantane and its derivatives, compounds long of interest because of their unique physical and chemical behaviour,[1] has been stimulated by their medicinal properties.[2] Thus, the potent antiviral activity of rimantadine (1-adamantylethylamine) and amantadine (1-aminoadamantane)[3] and the significant neuroprotective properties of memantine (1-amino-3,5-dimethyladamantane) make aminoadamantanes of particular interest in this respect.[4] The procedures reported[5] for the preparation of rimantadine and its analogues together with the corresponding patent literature, however, suffer from either low overall product yields or lack of experimental detail.

Reductive aminations[6] of an appropriate carbonyl compound is the most direct approach to the preparation of amines. While for acyladamantanes this is effected indirectly with amides[5a] (refluxing formic acid) and also with nitriles[5e] (hydrogen at elevated temperature and pressure over Cu–LiOH–Al_2O_3), surprisingly, there is no literature precedent for direct reductive alkylation of amines with acyladamantanes. We have recently reported[7] a mild, safe and efficient method for the reductive amination of formaldehyde with a combination of titanium(IV) isopropoxide and sodium borohydride. Here, we report the use of this reagent system for the reductive amination of commercially available 1-adamantyl methyl ketone with a variety of amines and ammonia at room temperature, an effective single-step synthesis of the antiviral agent rimantadine and its potentially useful analogues. It seems likely that the reaction proceeds *via* the aminoethanolatotitanium(IV) complex **1** (Scheme 1) which is reduced either directly



Scheme 1 *Reagents and conditions:* i, $Ti(OPr^i)_4$, H_2NR, 25 °C; ii, abs. EtOH, $NaBH_4$, 25 °C; iii, aqueous NH_3

or *via* a transient iminium species. Similar intermediates have recently been proposed[8] in the synthesis of phenethylamines *via* titanium amide complexes.

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The utility of this method was evaluated by treating a mixture of 1-acetyladamantane and various amines with titanium(IV) isopropoxide and sodium borohydride at room temperature. The molar ratio of the reactants and the results obtained for a representative group of amines are collated in Table 1. The intermediate complex **1** was first formed by stirring a mixture of 1-acetyladamantane, titanium(IV) isopropoxide and amine at room temperature for 5–6 h after which sodium borohydride and absolute ethanol were added to it. The resulting mixture was further stirred for 12–13 h at room temperature after which the reaction was quenched with aqueous ammonia (2 mol dm^{-3}) and the pure amines were isolated by simple extraction with hydrochloric acid (1 mol dm^{-3}). For the preparation of the primary amine, rimantadine (entry 1) a mixture of ammonium chloride and triethylamine in absolute ethanol was employed as the convenient source of nucleophilic ammonia. In the presence of triethylamine, ammonia was liberated from its hydrochloride and treated with 1-acetyladamantane and titanium(IV) isopropoxide in absolute ethanol during 12 h to form the intermediate adduct **1** which was then reduced with sodium borohydride. Similarly, the preparation of *N*-methylrimantadine (entry 2) entailed the use of a mixture of methylamine hydrochloride and triethylamine as the source of nucleophilic methylamine.

The neutral non-aqueous reaction conditions, simple work-up, isolation of pure products without chromatographic separation, high yields and the use of safe and cheap reagents with no special handling techniques are the notable advantages of the present method. Moreover, because of the compatibility[7,9] of titanium(IV) isopropoxide with a variety of acid-sensitive functional groups including acetonide, *tert*-butyldimethylsilyl ether and acetals this method provides easy access to analogous aminoadamantanes bearing functionalised pendant chains.

Further studies addressing the possibility of asymmetric induction in the reductive aminations of acyladamantanes using chirally modified titanium(IV) isopropoxide as well as optimisation and refinement of this methodology are currently underway.

Experimental

^1H NMR spectra were recorded at 60 MHz on an EM 360 spectrometer of Varian Associates and at 300 MHz on a Bruker AM 300 spectrometer in $CDCl_3$ solutions with $SiMe_4$ as an internal standard (*J* values in Hz). IR spectra were recorded on a Perkin-Elmer 298 spectrometer in $CHCl_3$ solutions. Thin layer chromatography was done on pre-coated silica gel plates. Titanium(IV) isopropoxide and 1-adamantyl

Table 1 Representative reductive aminations of 1-adamantyl methyl ketone using titanium(IV) isopropoxide and sodium borohydride

Entry	Substrate[a]	Time (t/h)	Product amine[c] (Ad = 1-Adamantyl)	Yield (%)[d]
1	NH_4Cl[b]	24	$AdCH(Me)NH_2$	80
2	$MeNH_2 \cdot HCl$[b]	24	AdCH(Me)NHMe	93
3	$BuNH_2$	17	AdCH(Me)NHBu	90
4	Bu^sNH_2	17	$AdCH(Me)NHBu^s$	80
5	Cyclohexylamine	17	AdCH(Me)NH(cyclohexyl)	80
6	$HOCH_2CH_2NH_2$	18	$AdCH(Me)NHCH_2CH_2OH$	80
7	$HOCH_2CH_2CH_2NH_2$	18	$AdCH(Me)NHCH_2CH_2CH_2OH$	85

[a] The starting amines (entries 3–7) were distilled over KOH prior to use, ratio of adamantyl methyl ketone : amine : titanium(IV) isopropoxide : sodium borohydride: 1 : 2 : 2 : 2. [b] Excess of triethylamine was added in the reaction mixture to liberate ammonia/methylamine. [c] Spectroscopic and physical constant data for known compounds were in complete agreement with the literature data or authentic samples, all new products exhibited satisfactory analytical and spectral data. [d] Yields are of isolated and purified products.

methyl ketone were purchased from Aldrich Chemical Co. All commercial amines were distilled over KOH prior to use.

General procedure for the reductive amination of 1-acetyladamantane

A mixture of 1-acetyladamantane (1.78 g, 10 mmol), titanium(IV) isopropoxide (5.7 g, 20 mmol) and the starting amine (20 mmol) was stirred at 25 °C for 5–6 h. Sodium borohydride (0.76 g, 20 mmol) and absolute ethanol (15 cm^3) were added to the mixture which was then stirred for a further 12–13 h at 25 °C. The reaction was quenched with aqueous ammonia (2 mol dm^{-3}; 30 cm^3) and the resulting inorganic precipitate was filtered off and washed with Et_2O (50 cm^3); the aqueous solution was extracted with Et_2O (50 cm^3 × 2). The combined Et_2O washings and extracts were next extracted with hydrochloric acid (1 mol dm^{-3}; 10 cm^3 × 2) to separate the neutral materials. The acidic aqueous solution was made alkaline (pH 10) by slow addition of aqueous NaOH (10%, w/v) and extracted with dichloromethane (50 cm^3 × 2). The combined extracts were dried (K_2CO_3) and concentrated under reduced pressure to give pure 1-adamantylethylamines.

For the preparations involving amine salts (entries 1 and 2), the same general procedure was used except that a mixture of 1-acetyladamantane (1.78 g, 10 mmol), ammonium chloride or methylamine hydrochloride (20 mmol), triethylamine (25 mmol) and titanium(IV) isopropoxide (5.7 g, 20 mmol) in absolute ethanol (15 cm^3) was stirred at room temperature for 12 h to form the intermediate adduct. Sodium borohydride (0.76 g, 20 mmol) was added to the mixture which was then further stirred for 12 h with isolation of the products as described above.

Data below corresponds to the entries in Table 1.

1. ν_{max}/cm^{-1} 3675br, 2906, 2849, 1450, 1362, 1345, 1026, 938, 912, 908, 900, 895, 867 and 846; δ 0.98 (3 H, d, J 6.6), 1.35 (2 H, br s), 1.45–1.78 (12 H, m), 1.95–2.04 (3 H, m) and 2.4 (1 H, q, J 6.6) (Found: C, 80.1; H, 11.9; N, 7.75. $C_{12}H_{21}N$ requires C, 80.38; H, 11.8; N, 7.81).

2. ν_{max}/cm^{-1} 3587br, 2907, 2850, 1449, 1362, 1153, 1094, 939, 925, 920, 912 and 905; δ 0.96 (3 H, d, J 6.5), 1.46–1.75 (12 H, m), 1.9–2.04 (5 H, m) and 2.41 (3 H, s) (Found: C, 80.5; H, 12.1; N, 7.1. $C_{13}H_{23}N$ requires C, 80.76; H, 11.99; N, 7.24).

3. ν_{max}/cm^{-1} 3688br, 2961, 2907, 2849, 1455, 1362, 1114 and 924; δ 0.92 (3 H, t, J 8.5), 0.95 (3 H, d, J 6.6), 1.28–1.74 (17 H, m), 1.92–2.01 (3 H, m), 2.05 (1 H, q, J 6.6), 2.41 (1 H, dt, J 15 and 8.5) and 2.73 (1 H, dt, J 15 and 8.5) (Found: C, 81.9; H, 12.7; N, 5.8. $C_{16}H_{29}N$ requires C, 81.63; H, 12.42; N, 5.95).

4. ν_{max}/cm^{-1} 3626br, 2963, 2906, 2849, 1450, 1145, 1086, 920, 912, 907, 898 and 889; δ 0.83–1.02 (9 H, m), 1.2–1.75 (15 H, m), 1.92–2.02 (3 H, m), 2.07 (1 H, q, J 6.5) and 2.43–2.58 (1 H, m) (Found: C, 81.8; H, 12.2; N, 5.7. $C_{16}H_{29}N$ requires C, 81.63; H, 12.42; N, 5.95).

5. ν_{max}/cm^{-1} 3647br, 2926, 2849, 1450, 1344, 923, 917, 913 and 908; δ 0.94 (3 H, d, J 6.5), 0.96–1.32 (6 H, m), 1.42–1.51 (3 H, m), 1.56–1.93 (14 H, m), 1.95–2.03 (3 H, m), 2.13 (1 H, q, J 6.5) and 2.31–2.42 (1 H, m) (Found: C, 83.0, H, 11.7; N, 5.6. $C_{18}H_{31}N$ requires C, 82.69, H, 11.95; N, 5.36).

6. ν_{max}/cm^{-1} 3628br, 2906, 2849, 1447, 1045, 930, 920, 912, 906, 893 and 885; δ 0.98 (3 H, d, J 6.5), 1.44–1.78 (12 H, m), 1.94–2.0 (3 H, m), 2.06 (1 H, q, J 6.5), 2.18 (2 H, br s), 2.57–2.68 (1 H, m), 2.89–2.99 (1 H, m) and 3.5–3.65 (2 H, m) (Found: C, 75.0, H, 11.5; N, 6.5. $C_{14}H_{25}NO$ requires C, 75.28; H, 11.28; N, 6.27).

7. ν_{max}/cm^{-1} 3620br, 3238br, 2908, 2849, 1450, 1380, 1345, 1097, 1075, 962, 931, 927, 922, 908, 900 and 878; δ 0.98 (3 H, J 6.5), 1.44–1.78 (16 H, m), 1.95–2.02 (3 H, m), 2.08 (1 H, q, J 6.5), 2.6–2.7 (1 H, m), 3.03–3.13 (1 H, m) and 3.82 (2 H, t, J 6.2) (Found: C, 75.65; H, 11.7; N, 6.1. $C_{15}H_{27}NO$ requires C, 75.9; H, 11.46; N, 5.9).

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