A New Method for the Synthesis of α-Substituted Phenethylamines via Titanium Amide Complexes

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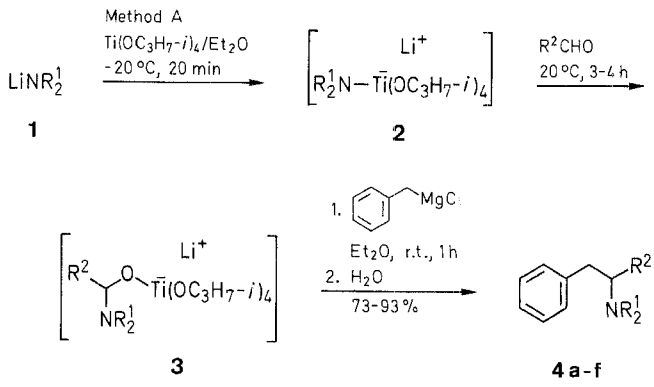
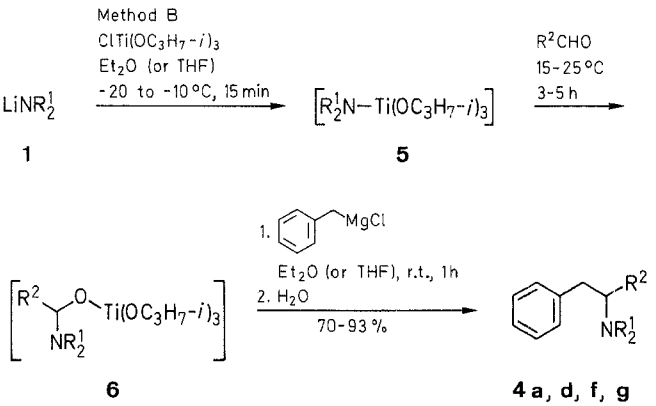
Substituted phenethylamines (1-substituted 2-phenylethylamines) **4** are obtained in high yields by a new, facile reaction of titanium amide complexes with aldehydes and benzylmagnesium chloride.

The phenethylamine moiety is an extremely important component in the structures of medicinal agents, and we have already reported the synthesis and the analgesic activity of several α-substituted phenethylamines.[1,2] Now, we wish to report a new method for the synthesis of the α-substituted phenethylamines from the aldehydes and benzylmagnesium chloride using titanium amide complexes.



4	NR^1_2	R^2
a	$N(C_2H_5)_2$	C_6H_5
b	$N(C_2H_5)_2$	$4\text{-}CH_3C_6H_4$
c	$N(C_2H_5)_2$	$4\text{-}CH_3O\text{-}C_6H_4$
d	$N(C_2H_5)_2$	$c\text{-}C_6H_{11}$
e	1-pyrrolidinyl	C_6H_5
f	1-pyrrolidinyl	$c\text{-}C_6H_{11}$

The preparation of the titanium amide complexes **2** from lithium diethylamide or lithium pyrrolidide was accomplished *in situ* by treatment with an equimolar amount of the commercially available titanium tetraisopropoxide. The dialkylamido ligands of complexes **2** were converted into dialkylaminomethanolato ligands by reaction with an equimolar amount of the aldehyde to form complexes **3**. The structures of **2** and **3** are proposed on the basis of the reported chloromagnesium tetrakis(dimethylamido)allyltitanate and (diethylaminomethanolato)tris(dimethylamido)allyltitanate.[3] In the proposed reaction mechanism, the titanium atom approaches the oxygen atom of the aldehyde, and then the dialkylamido ligand is transferred to the carbonyl carbon atom. The complexes **3** were finally converted into the desired α-substituted phenethylamines **4a–f** in 73–93% yields by addition of benzylmagnesium chloride and subsequent treatment with water.



4	NR^1_2	R^2
a	$N(C_2H_5)_2$	C_6H_5
d	$N(C_2H_5)_2$	$c\text{-}C_6H_{11}$
f	1-pyrrolidinyl	$c\text{-}C_6H_{11}$
g	$N(i\text{-}C_3H_7)_2$	C_6H_5

Table. α-Substituted Phenethylamines **4a–g** Prepared

Product	Method	Yield[a] (%)	mp (°C)[b] (solvent) or bp (°C)/Torr	Molecular Formula[c] or Lit. Data	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, J(Hz)	MS (CI/200 eV)[e] m/z (%)
4a	A B	92 93	92–94/0.1	–[6,f]	0.99 (t, 6H, J = 7.1, $NCH_2C\underline{H}_3$); 2.46 (q, 2H, J = 7.1, $NC\underline{H}_2CH_3$); 2.64 (q, 2H, J = 7.1, $NC\underline{H}_2CH_3$); 2.90 (dd, 1H, J = 9.0, 13.2, $CHC\underline{H}_2Ph$); 3.26 (dd, 1H, J = 5.4, 13.2, $CHC\underline{H}_2Ph$); 3.88 (dd, 1H, J = 5.4, 9.0, $NC\underline{H}CH_2$); 6.9–7.2 (m, $10H_{arom}$)	254 (MH^+, 65); 162 [$C_6H_5CH{=}N^+(C_2H_5)_2$, 100]
4b	A	90	192–193[g] (benzene)	$C_{19}H_{25}NHCl$ (303.9)	0.98 (t, 6H, J = 7.1, $NCH_2C\underline{H}_3$); 2.25 (s, 3H, CH_3); 2.43 (q, 2H, J = 7.1, $NC\underline{H}_2CH_3$); 2.63 (q, 2H, J = 7.1, $NC\underline{H}_2CH_3$); 2.90 (dd, 1H, J = 9.0, 13.4, $CHC\underline{H}_2Ph$); 3.23 (dd, 1H, J = 5.6, 13.4, $CHC\underline{H}_2Ph$); 3.87 (dd, 1H, J = 5.6, 9.0, $NC\underline{H}CH_2$); 6.9–7.2 (m, $9H_{arom}$)	268 (MH^+, 54); 176 [$CH_3C_6H_4CH{=}N^+(C_2H_5)_2$, 100]
4c	A	91	158–159[g] (benzene)	$C_{19}H_{25}NOHCl$ (319.9)	0.99 (t, 6H, J = 7.1, $NCH_2C\underline{H}_3$); 2.45 (q, 2H, J = 7.1, $NC\underline{H}_2CH_3$); 2.63 (q, 2H, J = 7.1, $NC\underline{H}_2CH_3$); 2.88 (dd, 1H, J = 9.3, 13.2, $CHC\underline{H}_2Ph$); 3.23 (dd, 1H, J = 5.1, 13.2, $CHC\underline{H}_2Ph$); 3.71 (s, 3H, OCH_3); 3.84 (dd, 1H, J = 5.1, 9.3, $C\underline{H}CH_2Ph$); 6.7–7.2 (m, $9H_{arom}$)	284 (MH^+, 32); 192 [$CH_3OC_6H_4CH{=}N^+(C_2H_5)_2$, 100]
4d	A B	93 73	125–126[g] (benzene)	$C_{18}H_{29}NHCl$ (295.9)	0.92 (t, 6H, J = 7.1, $NCH_2C\underline{H}_3$); 1.1–1.3 (m, 6H); 1.6–1.8 (m, 5H); 2.50 (q, 4H, J = 7.1, $NC\underline{H}_2CH_3$); 2.5–2.8 (m, 3H, $NC\underline{H}C\underline{H}_2Ph$); 7.1–7.2 (m, $5H_{arom}$)	260 (MH^+, 81); 168 [$C_6H_{11}CH{=}N^+(C_2H_5)_2$, 100]
4e	A	75	115–118/0.5	125–127/0.8[7]	1.7–1.9 (m, 4H); 2.3–2.7 (m, 4H); 2.89 (dd, 1H, J = 11.2, 13.6, $CHC\underline{H}_2Ph$); 3.2–3.5 (m, 2H, $C\underline{H}C\underline{H}_2Ph$); 6.7–7.2 (m, $10H_{arom}$)	252 (MH^+, 100); 160 ($C_6H_5CH{=}N^+C_4H_8$, 78)
4f	A B	73 70	195–196[g] (benzene)	$C_{18}H_{27}NHCl$ (293.9)	1.1–1.2 (m, 6H); 1.6–1.9 (m, 9H); 2.5–2.6 (m, 4H); 2.6–2.9 (m, 3H, $NC\underline{H}C\underline{H}_2Ph$); 7.1–7.2 (m, $5H_{arom}$)	258 (MH^+, 75); 166 ($C_6H_{11}CH{=}N^+C_4H_8$, 100)
4g	B	85	96–98/0.1	–[6,f]	0.89 (d, 6H, J = 6.8, $CH(C\underline{H}_3)_2$); 1.05 [d, 6H, J = 6.6, $CH(C\underline{H}_3)_2$]; 3.11 (dd, 1H, J = 8.8, 13.9, $CHC\underline{H}_2Ph$); 3.16 (dd, 1H, J = 5.9, 13.9, $CHC\underline{H}_2Ph$); 3.2–3.4 [m, 2H, $C\underline{H}(CH_3)_2$]; 4.19 (dd, 1H, J = 5.9, 8.8, $CH_2C\underline{H}Ph$); 7.0–7.3 (m, $10H_{arom}$)	282 (MH^+, 55); 190 [$C_6H_5CH{=}N^+(C_3H_7)_2$, 100]

[a] Yield of isolated product based on **1**.
[b] Uncorrected, measured with a Yanagimoto micromelting point apparatus.
[c] Satisfactory microanalyses obtained: C ±0.25, H ±0.16, N ±0.05.
[d] Recorded on a JEOL JNM-FX100 spectrometer.
[e] Recorded on a JEOL-D300 spectrometer by using chemical ionization (isobutane).
[f] The bp was not reported.
[g] Hydrochloride salt.

The titanium amide complexes **5** were prepared by treating lithium diethylamide, lithium pyrrolidide, or lithium diisopropylamide with an equimolar amount of chlorotitanium triisopropoxide. The reaction of **5** proceeded smoothly with an equimolar amount of the aldehyde to give **6**. The structures of **5** and **6** are proposed in analogy with the reported (dialkyl-aminomethanolato)tris(dialkylamido)titanium[4] and (dimethylaminomethanolato)bis(dialkylamido)methyltitanium.[5] The reactions of **6** with benzylmagnesium chloride afforded the α-substituted phenethylamines **4a, d, f, g** in 70–93% yields.

The free bases of the new compounds **4b–d** and **4f** were converted into the hydrochloride salts by treatment with hydrogen chloride methanol solution.

In conclusion, it was found that the synthesis of α-substituted phenethylamines by means of titanium amide complexes, e.g., titanium amide tetraisopropoxide ate-complexes and titanium amide triisopropoxides, is facile and proceeds in high yields.

α-Substituted Phenethylamines; General Procedure:

Method A (for **4a–f**): A solution of titanium tetraisopropoxide (1.42 g, 5 mmol) in dry ether (2.5 mL) is added dropwise to a stirring mixture of $LiNR_2$ [prepared by addition at –78 °C of BuLi (5 mmol) in hexane (3.2 mL) to a solution of amine (diethylamine or pyrrolidine; 5 mmol) in ether (1.75 mL), and stirred at –20 °C under a nitrogen atmosphere for 20 min to give a light colored mixture. Successively, an aldehyde (benzaldehyde, *p*-tolylcarbaldehyde, *p*-methoxyphenylcarbaldehyde, or cyclohexanecarbaldehyde; 5 mmol) is added dropwise to this mixture. After the mixture has stirred at 20 °C for 3–4 h, benzylmagnesium chloride (5 mmol) in ether (12.5 mL) is added dropwise and stirring is continued for 1 h at room temperature. Then, the reaction mixture is treated with a small amount of water (ca. 1 mL), the resulting white precipitate is filtered, and the filtrate is dried (Na_2SO_4). Removal of the solvent *in vacuo* gives colorless oil, which is subjected to column chromatography on silica gel (*n*-hexane/EtOAc, 5:1, as eluent) to give **4a–f** as a colorless oils (see Table).

Method B (for **4a, d, f, g**): A solution of chlorotitanium triisopropoxide (5 mmol) in ether (or THF; 5 mL) is added dropwise to the stirring mixture of $LiNR_2$ prepared as described above (5 mmol), and stirred at –20 to –10 °C under a nitrogen atmosphere for 15 min. An aldehyde (benzaldehyde or cyclohexanecarbaldehyde; 5 mmol) is added dropwise to the mixture, and stirring is continued at 15–20 °C for 3–5 h. After the addition of the benzylmagnesium chloride (5 mmol) in ether (or THF; 12.5 mL), the reaction mixture is worked up as described above to give **4a, d, f, g** as colorless oils (see Table).

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