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Synthesis of Methyl 3-Aryl 2-Isopropyl-aminomethylpropanoates Through Reduction of Methyl 3-Aryl 2-Isopropyl Aminomethylacrylates

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SYNTHESIS OF METHYL 3-ARYL 2-ISOPROPYL-AMINOMETHYLPROPANOATES THROUGH REDUCTION OF METHYL 3-ARYL 2-ISOPROPYL AMINOMETHYLACRYLATES.

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Abstract - Hydrogenation of Boc-protected 3-aryl 2-aminomethylacrylic acid esters over 10 % palladium on carbon in ethanol gives the Boc-protected β-amino esters **4**. Deprotection of **4** with anhydrous hydrochloric acid gives the β-aminoester hydrochlorides **5**. The treatment of **5** with sodium carbonate yields saturated β-amino esters **6**.

β-Aminoacid esters are important as components of peptides and as precursors of β-lactames [1-4]. We wish to report here a simple and efficient method for the preparation of racemic β-amino esters through hydrogenation of some 3-aryl 2-aminomethylacrylic esters **1** which are readily available [5]. The direct hydrogenation of the amino ester **1b** over a 5 % Pd-C catalyst gave the ester **2**. It is necessary to prepare suitably protected amines. Starting from aminoesters **1** of E configuration, Boc-protected [6,7] aminoesters **3** (E) were prepared. The signal of the olefinic proton of **3** in the ^1H NMR spectra, deshielded by the neighbouring cis carbonyl group was at δ 7.40 - 7.77, consistent with the E geometry [8,9].

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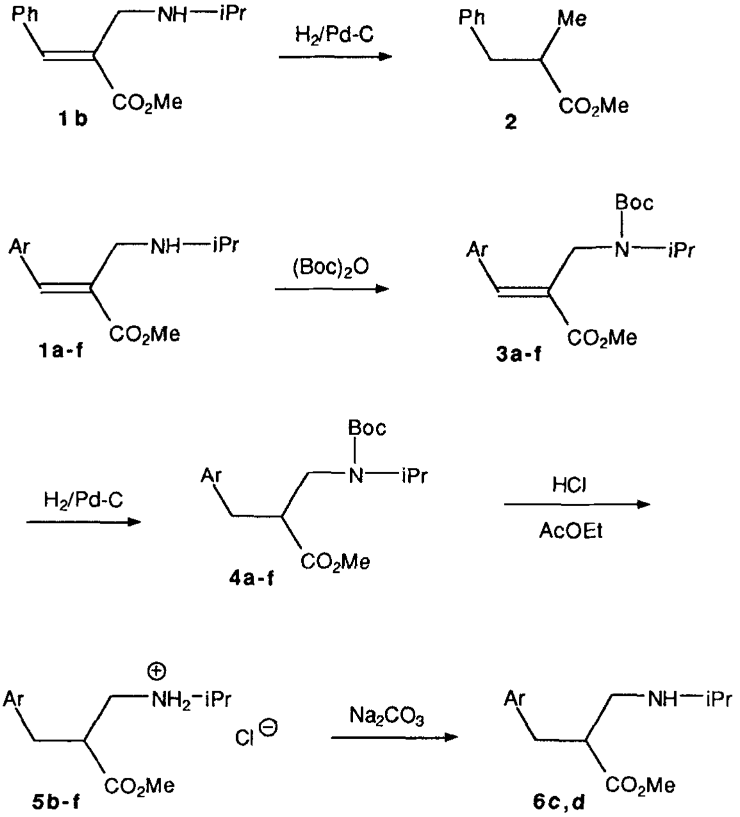
Hydrogenation of amino esters **3** (H_2/Pd-C) afforded Boc-protected amino esters **4**. Deprotection of **4** with anhydrous hydrochloric acid gave saturated β-amino ester hydrochlorides **5** with good yields.

In conclusion, this method is a useful synthetic route to substituted β-amino esters, because the starting product, esters **1**, are easily prepared with good yields in three steps from aldehyde ArCHO and methyl acrylate.

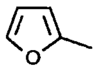


EXPERIMENTAL

Boc-protected amino esters 3a (E). Typical procedure

Amino ester **1a** (25 mmol.) is dissolved in CH_2Cl_2 (40 ml). NaOH 1M is added and di tert-butyldicarbonate (5.18 g, 37.25 mmol) in CH_2Cl_2 (15 ml) is

Table 1 - Protected amino esters **3** (E).

	Ar	Yield (%)	^{1}H NMR ($CDCl_3$/TMS). δ, J (Hz)
3a		83	1.15 (d, 6H, J = 7), 1.49 (s, 9H), 3.62 (m, 1H), 3.76 (s, 3H), 4.63 (s, 2H), 6.50 (m, 1H), 6.67 (m, 1H), 7.40 (s, 1H), 7.53 (s, 1H).
3b	Ph	75	1.02 (d, 6H, J = 7), 1.45 (s, 9H), 3.52 (m, 1H), 3.77 (s, 3H), 4.41 (s, 2H), 7.34 (s, 5H), 7.67 (s, 1H)
3c	2 $MeOC_6H_4$	86	1.00 (d, 6H, J = 6), 1.42 (s, 9H), 3.77 (s, 3H), 3.82 (s, 3H), 3.80 (m, 1H), 4.30 (s, 2H), 7.07 (m, 4H), 7.77 (s, 1H).
3d	4 $MeOC_6H_4$	83	1.05 (d, 6H, J = 7), 1.43 (s, 9H), 3.57 (m, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 4.67 (s, 2H), 7.00 (m, 4H), 7.67 (s, 1H).
3e	4 ClC_6H_4	80	1.02 (d, 6H, J = 6), 1.40 (s, 9H), 3.50 (m, 1H), 3.77 (s, 3H), 4.35 (s, 2H), 7.27 (m, 4H), 7.60 (s, 1H).
3f	4 MeC_6H_4	76	1.00 (d, 6H, J = 7), 1.42 (s, 9H), 2.32 (s, 3H), 3.50 (m, 1H), 3.76 (s, 3H), 4.41 (s, 2H), 7.22 (s, 4H), 7.68 (s, 1H).

added dropwise at 10°C, under stirring. After stirring for 12 h, the solution is washed with water (2 x 20 ml), dried ($MgSO_4$), then evaporated to give **3a** (E) as an oil which is used without further purification (table 1).

Ester 2 and β-amino esters 4. General procedure

Solution of **1b** or **3** (5 mmol) in absolute EtOH (30 ml) is hydrogenated over 10 % Pd-C catalyst (0.2 g) at a pressure of 1 atm. After one equivalent of H_2 has been consumed (20 min.), the mixture is filtered and then concentrated under reduced pressure to give the amino ester **4** or the ester **2** which is purified by bulb to bulb distillation.

Methyl 2-benzylpropanoate 2.

$bp_{0.02}$ = 90°C.

^1H NMR δ 1.12 (d, 3H, J = 7 Hz), 2.57 - 3.07 (m, 3H), 3.58 (s, 3H), 7.17 (s, 5H).

^{13}C NMR δ 16.8, 39.7, 41.4, 51.6, 126.3, 128.4, 128.9, 139.4, 176.6. IR ν = 1728 cm^{-1}.

Anal. calcd. for $C_{11}H_{14}O_2$: C 73.12, H 7.91. Found C 73.42, H 7.86.

4a, $bp_{0.01}$ = 160°C, 78 %. ^{1} H NMR δ 1.08 (dd, 6H, J = 7 Hz), 1.42 (s, 9H), 2.87 (m, 2H), 3.05 (m, 1H), 3.30 (m, 2H), 3.57 (s, 3H), 3.92 (m, 1H), 6.00 (m, 1H), 6.25 (m, 1H), 7.27 (s, 1H).

^{13}C NMR δ 20.5, 28.4, 28.8, 46.0, 51.7, 76.7, 77.1, 77.5, 79.7, 106.4, 110.2, 141.4, 152.7, 174.6.

Anal. calcd. for $C_{17}H_{27}NO_5$: C 62.75, H 8.36, N 4.30. Found : C 62.07, H 8.23, N 4.08.

^{13}C NMR δ 20.6, 21.1, 28.4, 36.8, 47.0, 48.9, 51.5, 51.7, 79.9, 128.6, 129.1, 135.7, 135.9, 155.8, 175.1.

HRMS Found m/z 349.2252. Calcd for $C_{20}H_{31}NO_4$ 349.2249.

At room temperature, the ^{13}C signals at δ = 32.0 - 48.5 ppm are broadened, indicating that the rate of rotation around the CO-N bond is not extremely rapid.

Amino ester hydrochlorides 5

A solution of **4** (10 mmol) in EtOAc (50 ml) is saturated with anhydrous HCl for 12 min. After stirring at room temperature for 12 h, the solvent is removed under reduced pressure to give the deprotected amine hydrochloride **5** recrystallized from CCl_4 or MeCN.

5b, mp 128°C (CCl_4), 69 %. ^{1} H NMR δ 1.32, 1.35 (dd, 6H, J = 6.3 Hz), 3.52 - 3.00 (m, 6H), 3.66 (s, 3H), 7.21 (s, 5H), 9.00 (br.s, 1H), 9.60 (br.s, 1H).

^{13}C NMR δ 18.8, 36.4, 43.3, 44.2, 51.1, 52.4, 126.9, 128.6, 129.0, 136.6, 172.9.

Anal. calcd. for $C_{14}H_{22}NO_2Cl$: C 61.86, H 8.16, N 5.15, Cl 13.04. Found : C 61.47, H 8.14, N 5.15, Cl 12.85.

5c, mp 140°C (MeCN), 81 %. ^{1} H NMR δ 1.31-1.36 (dd, 6H, J = 6 Hz), 3.25 (m, 6H), 3.67 (s, 3H), 3.77 (s, 3H), 6.82-7.12 (m, 4H), 8.88 (br.s, 1H), 9.37 (br.s, 1H).

^{13}C NMR δ 18.7, 31.1, 41.8, 44.1, 50.5, 52.2, 55.2, 110.3, 120.5, 124.8, 128.3, 130.7, 157.4, 173.1.

Anal. calcd. for $C_{15}H_{24}NO_3Cl$: C 59.69, H 8.01, N 4.64, Cl 11.74. Found : C 59.67, H 8.07, N 4.68, Cl 11.64.

5d, mp 119°C (CCl_4), 72 %. ^{1} H NMR δ 1.30 (d, 6H, J = 6 Hz), 2.90-3.50 (m, 6H), 3.66 (s, 3H), 3.71 (s, 3H), 6.77-7.12 (m, 4H), 8.90 (br.s, 1H), 9.48 (br.s, 1H).

^{13}C NMR δ 18.7, 35.4, 43.4, 44.1, 51.1, 52.3, 55.1, 113.8, 128.4, 129.9, 158.3, 172.8.

Anal. calcd. for $C_{15}H_{24}NO_3Cl$: C 59.69, H 8.01, N 4.64, Cl 11.74. Found : C 59.56, H 8.08, N 4.82, Cl 12.05.

5e, mp 125°C (CCl_4), 70 %. ^{1} H NMR δ 1.35 (d, 6H, J = 6 Hz), 3.00-3.50 (m, 6H), 3.66 (s, 3H), 7.20 (s, 4H), 9.13 (br.s, 1H), 9.60 (br.s, 1H).

^{13}C NMR δ 18.7, 35.6, 43.3, 44.3, 51.5, 52.4, 128.5, 128.8, 130.4, 133.1, 172.5.

Anal. calcd. for $C_{14}H_{21}NO_2Cl_2$: C 54.90, H 6.91, N 4.67. Found : C 54.98, H 8.08, N 6.82, Cl 4.67.

5e, mp 122°C (CCl_4), 84 %. ^{1} H NMR δ 1.32-1.37 (dd, 6H, J = 6 Hz), 2.25 (s, 3H), 3.22 - 3.57 (m, 6H), 3.67 (s, 3H), 7.17 (s, 4H), 8.95 (br. s, 1H), 9.57 (br. s, 1H).

^{13}C NMR δ 18.8, 21.1, 35.9, 43.2, 44.2, 51.1, 52.4, 128.8, 129.3, 133.4, 136.4, 172.9.

HRMS Found m/z = 249.1728 ; calcd for $C_{15}H_{23}NO_2$: 249.1724.

β-aminoesters 6

To a solution of **5** (5 mmol) in ether (30 ml) is added Na_2CO_3 1M (15 ml). After stirring for 15 min, the organic phase is washed with water (3 x 10 ml), dried (Na_2SO_4) and concentrated. The residue is purified by bulb to bulb distillation.

6c, $bp_{0.02}$ = 150°C, 79 %. ^{1}H NMR δ 0.95 (d, 6H, J = 8 Hz), 1.22 (s, 1H), 2.77 (m, 7H), 3.56 (s, 3H), 3.77 (s, 3H), 6.72 - 7.27 (m, 4H). ^{13} C NMR δ 23.19, 31.18, 45.38, 46.36, 48.05, 48.57, 53.33, 110.48, 119.09, 125.75, 127.02, 130.67, 161.79, 186.4.

IR ν : 1730, 3330 cm^{-1}.

Anal. calcd for $C_{15}H_{23}NO_3$, 1/2 H_2O : C 65.93, H 8.42, N 5.13. Found C 66.04, H 8.56, N 4.89.

6d, bp$_{0.02}$ = 140°C, 87 %. ^{1}H NMR δ 0.95 (d, 6H, J = 6 Hz), 1.38 (s, 1H), 2.78 (m, 6H), 3.65 (s, 3H), 3.78 (s, 3H), 6.80 - 7.08 (m, 4H). ^{13}C NMR δ 22.8, 35.6, 48.3, 48.4, 48.5, 51.5, 55.2, 133.8, 129.7, 131.1, 158.1, 175.4.

IR ν : 1730, 3340 cm^{-1}.

Anal. calcd for $C_{15}H_{23}NO_3$: C 67.83, H 8.73, N 5.27. Found C 67.64, H 8.67, N 5.20.

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