SHORT PAPER

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A convenient synthesis of *threo*-4-amino-3, 4-diphenylbutanoic acid and its derivatives[1†]

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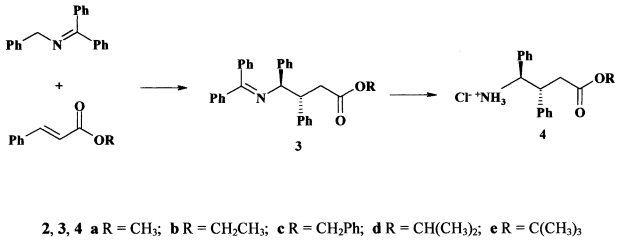
Several alkyl *threo*-4-[(diphenylmethylene)amino]-3,4-diphenylbutanoates **(3)** were prepared by phase-transfer catalysed reaction of *N*-(diphenylmethylene)benzylamine and esters of cinnamic acid; acid hydrolysis of **3** affords *threo*-4-amino-3,4-diphenylbutanoic acid.

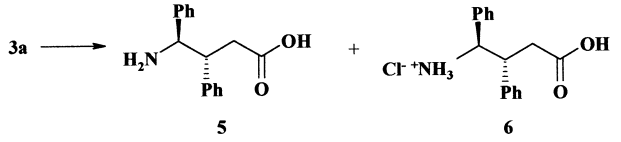
Keywords: γ-aminoacids, imines, cinnamate esters, phase-transfer catalysis

Recently we reported a simple and efficient synthesis of *erythro*-4-amino-3,4-diphenylbutanoic acid by acidic hydrolysis of *tert*-butyl *erythro*-4-[(phenylmethylene) amino]-3,4-diphenylbutanoate which, in turn, was prepared by a highly diastereoselective phase-transfer catalysed reaction of *N*-(benzylidene)benzylamine and *tert*-butyl cinnamate.[2] We now describe the reaction of *N*-(diphenylmethylene)-benzylamine (**1**) with esters of cinnamic acid (**2**) (Scheme 1), followed by acid hydrolysis of the obtained adducts **3**, resulting in the formation of *threo*-4-amino-3,4-diphenyl-butanoic acid (Scheme 2).



2, 3, 4 **a** R = CH_3; **b** R = CH_2CH_3; **c** R = CH_2Ph; **d** R = $CH(CH_3)_2$; **e** R = $C(CH_3)_3$

Scheme 1



Scheme 2

The Schiff base **1** is known to be useful synthon in organic synthesis under both anhydrous[3-6] and aqueous[7-9] conditions. An optimisation study of the reaction of **1** with methyl cinnamate (**2a**) revealed that better yields and stereoselectivity for the adduct **3a** was obtained when the reaction was performed at room temperature for one hour using acetonitrile as a solvent, with 50% NaOH and TEBA (67% yield of **3a**). Under these conditions the Schiff base **1** reacted with the cinnamates **2** to give the protected esters **3**, obtained after recrystallization in good yields as single diastereoisomers (Table 1). Treatment of the esters **3** with dilute hydrochloric acid at room temperature resulted in the hydrochlorides of the corresponding *threo*-4-amino-3,4-diphenylbutanoates **4** in good to high yields **(**Table 1). On the other hand, when the methyl ester **3a** was refluxed for 6 h with 6N hydrochloric acid, only 22% of the expected acid hydrochloride *threo*-**6** was obtained. In addition, the free *threo*-4-amino-3,4-diphenylbutanoic acid (**5**) was isolated in a yield of 56%. The acid *threo*-**5** and its hydrochloride (*threo*-**6**) were also obtained in yields of 55% and 16%, respectively, when the time of refluxing was shortened to 2 h. Moreover, attempts to convert the acid **5** into its hydrochloride (**6**) by refluxing with hydrochloric acid resulted in only a partial transformation into the hydrochloride **6**. Thus, 71% of *threo*-**5** were recovered, and only 14% of *threo*-**6** were obtained when **5** was refluxed with 6N HCl for 2 h.

Table 1 Yields of esters **3** and **4**

Entry	R	Yield[a]/%
3a	CH_3	67
3b	CH_2CH_3	62
3c	CH_2Ph	76
3d	$CH(CH_3)_2$	62
3e	$C(CH_3)_3$	48
4a	CH_3	82
4b	CH_2CH_3	69
4c	CH_2Ph	64
4d	$CH(CH_3)_2$	79
4e	$C(CH_3)_3$	60

[a]Yields of pure diastereoisomer obtained.

The esters **3** and **4**, the acid **5** and its hydrochloride **6,** obtained as single diastereoisomers, were fully characterised by elemental analyses, TLC, IR and ^{1}H NMR spectra. *Threo* configuration for the compounds **3** – **6** was assigned by comparison of their ^{1}H NMR spectra with those of *tert*-butyl *erythro*-4-[(phenylmethylene)amino]-3,4-diphenylbutanoate[10] and substituted *tert*-butyl *erythro*-4-[(phenylmethylene) amino]-3,4-diphenylbutanoates[10] prepared earlier by using *N*-(benzylidene)benzylamine as CH-acid, *erythro* configuration being determined on the grounds of different Overhouser enhancements to the signal of the methylene group.[10]

In summary, the phase-transfer catalyzed reaction of *N*-(diphenylmethylene)benzylamine with esters of cinnamic acid provides a particularly attractive method for the preparation of *threo*-4-amino-3,4-diphenylbutanoic acid and its esters, new analogues of γ-aminobutyric acid (GABA).

Experimental

Melting points were determined on a Boetius micro melting point apparatus and were uncorrected. The IR spectra were recorded on a Zeiss-Jena Specord 71. The ^{1}H NMR spectra were obtained on an Avance DRX-250 (250 MHz) spectrometer using TMS as an internal standard. TLC analysis was performed on Silufol UV 254 silica gel precoated plates using as eluents hexane/acetone (4:1) for compounds **3** and ethanol/water/acetic acid (7:3 : 0.05) for compounds **4**, **5** and **6**. The *N*-(diphenylmethylene)benzylamine,[11] isopropyl cinnamate and *tert*-butyl cinnamate[12] were prepared according to literature procedures.

Alkyl 4-[(diphenylmethylene)amino]-3,4-diphenylbutanoates **(3):** General procedure: To a stirred solution of **1** (1.36 g, 5 mmol), **2** (5

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mmol) and TEBA (0.06 g, 0.25 mmol) in acetonitrile (2.5 ml), aqueous sodium hydroxide (50%, 1.5 ml) was added. The reaction mixture was stirred magnetically until crystallisation began, and then it was left to stay at room temperature up to 1h. Water (100 ml) was added and the solid was collected, washed with water until neutral and recrystallised from ethanol. In the case of compound **3b**, the mixture was extracted with methylene chloride (3 × 25 ml), and the residue obtained after removing of the solvent was treated with ethanol to give **3b**.

Methyl ester (**3a**): m.p. 111-113 °C. IR ($CHCl_3$): 1730, 1625 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.92, 2.93 (2d, 2H, *J* = 6.6 and 8.8), 3.41 (s, 3H), 3.75 (m, 1H), 4.47 (d, 1H, *J* = 6.1), 6.57-7.72 (m, 20H). Anal. calcd. for $C_{30}H_{27}NO_2$: C, 83.11; H, 6.28; N, 3.23. Found: C, 82.90; H, 6.04; N, 4.24.

Ethyl ester (**3b**): m.p. 85-87 °C. IR ($CHCl_3$): 1725, 1625 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.98 (t, 3H, *J* = 7.1), 2.91 (2d, 2H, *J* = 6.7 and 8.8), 3.74 (m, 1H), 3.88 (q, 2H, *J* = 7.1), 4.47 (d, 1H, *J* = 6.2), 6.57-7.72 (m, 20H). Anal. calcd. for $C_{31}H_{29}NO_2$: C, 83.19; H, 6.53; N, 3.13. Found: C, 82.88; H, 6.70; N, 3.34.

Benzyl ester (**3c**): m.p. 130-131 °C. IR ($CHCl_3$): 1725, 1625 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.94 (dd, 1H, *J* = 6.0 and 15.7), 3.02 (dd, 1H, *J* = 9.5 and 15.7), 3.77 (m, 1H), 4.47 (d, 1H, *J* = 6.1), 4.85 (s, 2H), 6.55-7.72 (m, 25H). Anal. calcd. for $C_{36}H_{31}NO_2$: C, 84.85; H, 6.13; N, 2.75. Found: C, 84.89; H, 6.26; N, 2.79.

Isopropyl ester (**3d**): m.p. 102-104 °C. IR ($CHCl_3$): 1715, 1625 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.95 (d, 6H, *J* = 6.3), 2.88 (2d, 2H, *J* = 6.4 and 9.5), 3.73 (m, 1H), 4.46 (d, 1H, *J* = 6.2), 4.74 (sept, 1H, *J* = 6.3), 6.57-7.72 (m, 20H). Anal. calcd. for $C_{32}H_{31}NO_2$: C, 83.27; H, 6.77; N, 3.10. Found: C, 83.38; H, 6.77; N, 3.03.

t-Butyl ester (**3e**): m.p. 140-142 °C. IR ($CHCl_3$): 1715, 1625 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.14 (s, 9H), 2.84 (2d, 2H, *J* = 6.7 and 9.5), 3.65 (m, 1H), 4.45 (d, 1H, *J* = 6.1), 6.55-7.72 (m, 20H). Anal. calcd. for $C_{33}H_{33}NO_2$: C, 83.33; H, 7.00; N, 2.94. Found: C, 83.58; H, 7.08; N, 3.05.

Alkyl threo-4-amino-3,4-diphenylbutanoate hydrochlorides (**4**)**:** General procedure: Hydrochloric acid (8 ml, 10%) was added while stirring to the cooled to 0 °C solution of **3** (2 mmol) in 15 ml ether. The reaction mixture was stirred at room temperature for 15 hours. The precipitate was collected, washed with cool ether and recrystallised from ethanol/ether (1:1) to give compounds **4**.

Methyl ester hydrochloride **(4a):** m.p. 212-213 °C. IR (nujol): 3400-2400, 1725 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.81 (dd, 1H, *J* = 11.4 and 15.8), 3.28 (dd, 1H, *J* = 3.8 and 15.8), 3.36 (s, 3H), 3.70 (m, 1H), 4.57 (d, 1H, *J* = 9.8), 6.96-7.24 (m, 10H), 8.94 (s, 3H). Anal. calcd. for $C_{17}H_{20}ClNO_2$: C, 66.80; H, 6.59; N, 4.58. Found: C, 66.55; H, 6.39; N, 4.52.

Ethyl ester hydrochloride **(4b):** m.p. 212-214 °C. IR (nujol): 3500-2500, 1720 cm^{-1}. ^1H NMR (DMSO-d_6): δ 0.92 (t, 3H, *J* = 7.1), 2.77 (dd, 1H, *J* = 11.4 and 15.6), 3.24 (dd, 1H, *J* = 4.0 and 15.6), 3.68 (m, 1H), 3.83 (m, 2H), 4.58 (d, 1H, *J* = 9.9), 6.98-7.24 (m, 10H), 8.88 (s, 3H). Anal. calcd. for $C_{18}H_{22}ClNO_2$: C, 67.60; H, 6.93; N, 4.38. Found: C, 67.80; H, 6.75; N, 4.26.

Benzyl ester hydrochloride **(4c):** m.p. 164-166 °C. IR (nujol): 3500-2300, 1715 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.83 (dd, 1H, *J* = 11.4 and 15.7), 3.34 (dd, 1H, *J* = 4.1 and 15.7), 3.69 (m, 1H), 4.59 (d, 1H, *J* = 9.9), 4.80 (s, 2H), 6.90-7.25 (m, 15H), 8.83 (s, 3H). Anal. calcd. for $C_{23}H_{24}ClNO_2$: C, 72.33; H, 6.33; N, 3.67. Found: C, 71.98; H, 6.43; N, 3.40

Isopropyl ester hydrochloride **(4d):** m.p. 210-212 °C. IR (nujol): 3500-2400, 1720 cm^{-1}. ^1H NMR (DMSO-d_6): δ 0.86, 0.96 (2d, 6H, *J* = 6.2 and 6.3), 2.72 (dd, 1H, *J* = 11.7 and 15.1), 3.18 (dd, 1H, *J* = 4.1 and 15.1), 3.65 (m, 1H), 4.58 (d, 1H, *J* = 9.9), 4.64 (q, 1H, *J* = 6.3), 6.97-7.21 (m, 10H), 8.83 (s, 3H). Anal. calcd. for $C_{19}H_{24}ClNO_2$: C, 68.35; H, 7.24; N, 4.19. Found: C, 68.52; H, 7.51; N, 4.48.

t-Butyl ester hydrochloride **(4e):** m.p. 208-210 °C. IR (nujol): 3500-2250, 1710 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.10 (s, 9H), 2.65 (dd, 1H, *J* = 11.9 and 14.9), 3.12 (dd, 1H, *J* = 4.3 and 14.9), 3.61 (m, 1H), 4.54(d, 1H, *J* = 9.9), 6.96-7.21 (m, 10H), 8.37 (s, 3H). Anal. calcd. for $C_{20}H_{26}ClNO_2$: C, 69.05; H, 7.53; N, 4.03. Found: C, 69.28; H, 7.52; N, 4.25.

Threo-4-amino-3,4-diphenylbutanoic acid (**5**) and *threo-4-amino-3,4-diphenylbutanoic acid hydrochloride* (**6**): A mixture of 20 ml hydrochloric acid (1:1) and the methyl ester **3a** (1.08 g, 2.5 mmol) was refluxed for 6 hours. The solid obtained after cooling to room temperature was collected and washed with ether and water to give the acid *threo*-**5** (0.36 g, 56%), while evaporation to dryness of the aqueous filtrate resulted in the hydrochloride (*threo*-**6,** 0.16 g, 22%). The yields of **5** and **6** after 2 hours of reflux were 55% and 16%, respectively.

Threo-acid (**5**): m.p. 213-214 °C. IR (nujol): 3070, 3190, 1690 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.49 (dd, 1H, *J* = 10.2 and 16.5), 2.63 (dd, 1H, *J* = 8.6 and 16.5), 3.34 (m, 1H), 4.64(d, 1H, *J* = 7.9), 7.14-7.31 (m, 10H), 8.20 (s, 1H). Anal. calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.48. Found: C, 75.58; H, 6.87; N, 5.59.

Threo-acid hydrochloride (**6**): m.p. 210-212 °C. IR (nujol): 3500-2200, 1700 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.68 (dd, 1H, *J* = 11.5 and 15.9), 3.12 (dd, 1H, *J* = 3.6 and 15.9), 3.65 (m, 1H), 4.56 (d, 1H, J = 9.7), 6.97-7.27 (m, 10H), 8.95 (s, 1H). Anal. calcd. for $C_{16}H_{18}ClNO_2$: C, 65.86; H, 6.22; N, 4.80. Found: C, 65.61; H, 6.21; N, 4.60.

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