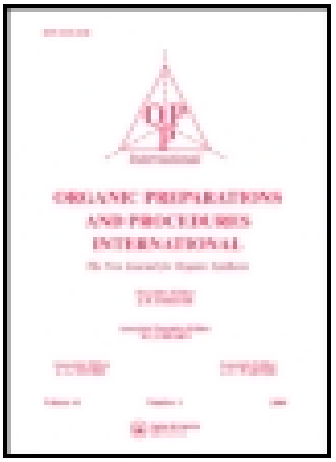

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A SIMPLE AND EFFICIENT SYNTHESIS OF γ-AMINOBUTYRIC ACID (GABA) DERIVATIVES

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A SIMPLE AND EFFICIENT SYNTHESIS OF γ-AMINOBUTYRIC ACID (GABA) DERIVATIVES†

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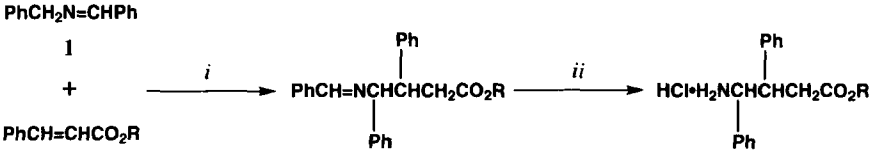
γ-Aminobutyric acid (GABA) is regarded as the main inhibitory neurotransmitter in the central nervous system[1,2] and is involved in the development of certain neurological and psychiatric diseases.[2] Thus, derivatives of GABA have attracted much attention due to their important role in life processes and biological activitiy. Structural analogs of GABA possessing a phenyl group in α-, β-, or γ-position, especially β-phenyl-γ-aminobutyric acid, have also received considerable scrutiny.[1-5] The β-phenyl-GABA (*phenibut*) is useful as a central nervous system depressant, tranquilizer, anticonvulsant.[3,4] According to literature data, increasing the number of the phenyl groups of GABA increases its ability to penetrate through the blood-brain barrier.[1,2] Therefore, it was of great interest to develop convenient procedures for the synthesis of GABA derivatives possessing two or more phenyl groups as substituents. In 1979 it was found in our laboratory that under phase-transfer catalysis conditions N-(benzylidene)benzylamine (**1**) reacted with cinnamonitrile to give the nitrile of N-(benzylidene)-β,γ-diphenyl-GABA (4-[(phenylmethylene)amino]-3,4-diphenylbutanoic acid).[6] This acid and a number of 4-amino-3-aryl-4-phenylbutanoic acids were prepared in moderate yields (37-62%) by one-pot procedure, involving phase-transfer catalyzed reaction of N-(benzylidene)benzylamine and esters of cinnamic acids, followed by acid hydrolysis of the crude reaction product.[7] Our attempts to prepare 4-amino-3,4-diphenylbutanoic acid from **1** and ethyl cinnamate after the described procedure were not successful. Low diastereoselectivity and reproducibility was observed, these facts being recognized by the Russian authors in a second paper of the study.[8] We now report an improved and highly diastereoselective synthesis of 4-amino-3,4-diphenylbutanoic acid (**4f**, R=H), as well as a convenient procedure for the preparation of its esters **3** and **4**.



2, 3, 4 a) R = CH_3 b) R = CH_2CH_3 c) R = CH_2Ph d) R = $CHMe_2$ e) R = CMe_3

i) 50% NaOH, TEBA, CH_3CN *ii*) HCl

In order to optimize the yields of **3**, various conditions including solvents, catalyst, reaction time, temperature, aqueous sodium hydroxide concentration, etc. were used for the reaction of **1** and

benzyl cinnamate (**2c**). Best yield of the addition product **3c**, isolated in all cases as diastereoisomeric mixture, was obtained when the following reagents were used: 50% NaOH, acetonitrile as a solvent and benzyltriethylammonium chloride (TEBA) as a catalyst. The reaction was performed at 0° for one hour to give the amino ester **3c** as diastereoisomeric mixture of 81% yield. Lower yield of **3c** (43%) was obtained when the reaction was carried out at room temperature. Decreasing of the reaction time to 10 min resulted in a significant decrease of the yield at room temperature (16%), while at 0° the addition product did not form. Lower yields of **3c** were also obtained with methylene chloride instead of acetonitrile as solvent, when other quaternary ammonium salts (Aliquat, Bu_4NBr) were used as catalyst, by the use of larger volume of the solvent or longer reaction times, etc. In addition, no product was isolated by using benzene as a solvent, as well as Me_3PhPBr as a catalyst. In all cases, cinnamic acid resulting from the hydrolysis of the starting benzyl cinnamate, was isolated as a side-product in yields varying from 3% to 37%.

Reaction of N-(benzylidene)benzylamine with the cinnamates **2** in acetonitrile at 0° in the presence of aqueous sodium hydroxide and TEBA gave the corresponding 4-[(phenylmethylene)-amino]-3,4-diphenylbutanoates **3** as mixtures of diastereoisomers (Table 1). Single diastereoisomers were isolated after repeated recrystallization and the best yield was achieved for the *tert*-butyl ester **3e** (63%); this may be due either to the higher stability of *tert*-butyl esters under phase-transfer catalysis conditions[9] or to the lower rate of the retro-Michael reaction of the ester **3e**, since it crystallized from the reaction mixture in less than 10 min after the addition of the base. The same reaction performed at room temperature led to the complete crystallization of the reaction mixture in about 3 min; after an additional 7 min, the ester **3e** was obtained in 75% yield as single diastereoisomer, which exists in two polymorphic forms with melting points in the ranges 129-131° and 144-146°.

Treatment of the esters **3** with hydrochloric acid at room temperature led to the hydrochlorides of the corresponding 4-amino-3,4-diphenylbutanoates **4** in high yields (Table 1) while refluxing led to both deprotection and hydrolysis of the ester function. Thus, the hydrochloride of 4-amino-3,4-diphenylbutanoic acid (**4f**), isolated as single isomer was obtained in a yield of 83% from *tert*-butyl ester **3e**, while the benzyl ester **3c** gave a mixture of the diastereoisomers of the acid. The esters **3** and **4** and the pure diastereoisomer of the acid (**4f**) are new compounds, which were fully characterized by elemental analyses, IR and ^1H NMR spectra.

In conclusion, the phase-transfer catalysed reaction of N-(benzylidene)benzylamine with esters of cinnamic acid offers a convenient and efficient route for the preparation of 4-amino-3,4-diphenylbutanoic acid and its esters.

EXPERIMENTAL SECTION

Melting points were determined on a Boetius micro melting point apparatus and are uncorrected. The IR spectra were recorded on a Zeiss-Jena Specord 71. The ^1H NMR spectra were obtained on Bruker WM-250 spectrometer (250 MHz) using TMS as an internal standard. TLC analysis was performed on silica gel precoated plates "Silufol UV 254" using as eluents hexane/acetone (4:1) for compounds **3** and ethanol/water/acetic acid (7:3:0.5) for compounds **4**. N-(benzylidene)benzylamine,[10] isopropyl

cinnamate and *tert*-butyl cinnamate[11] were prepared according to literature procedures.

TABLE 1. Yields, mps and Elemental Analyses of Compounds **3** and **4**

Cmpd	Yield[a] (%)	mp. (°C)	Elemental Analyses (Found) C	H	N
3a	85[b] (14)	109-111	80.64 (80.00)	6.49 (6.39)	3.92 (3.81)
3b	63[b] (11)	93-96	80.83 (80.57)	6.78 (7.01)	3.77 (3.63)
3c	81[b]	82-84	83.11 (83.02)	6.28 (6.39)	3.23 (3.47)
3d	64[b] (50)	113-115	81.01 (81.27)	7.06 (7.05)	3.63 (3.80)
3e	81[b] (63, 75[c])	144-146 (129-131)[d]	81.17 (81.38)	7.32 (7.16)	3.51 (3.61)
4a	86	196-198	66.76 (66.96)	6.59 (6.54)	4.56 (4.54)
4b	91	199-201	67.70 (68.23)	6.93 (7.22)	4.38 (4.67)
4c	83[b]	190-192	72.34 (72.49)	6.33 (6.18)	3.67 (3.64)
4d	91	212-214	68.35 (68.44)	7.24 (7.34)	4.19 (4.45)
4e	88	226-228	69.05 (69.21)	7.53 (7.53)	4.03 (4.15)
4f	83	205-207 (198-200)	65.86 (65.86)	6.22 (6.21)	4.80 (5.06)

a) Yield of pure diastereoisomer. b) Yields refer to mixture of diastereoisomers (undetermined ratio) obtained after recrystallization. c) Yield of **2e** obtained at room temperature, reaction time 10 min. d) Mp of another polymorphic form.

Alkyl 4-[(Phenylmethylene)amino]-3,4-diphenylbutanoates (3). General Procedure.- To a cooled to 0° stirred solution of N-(benzylidene)benzylamine (**1**, 0.98 g, 5 mmol), **2** (5 mmol) and TEBA (0.06 g, 0.25 mmol) in 2.5 mL acetonitrile, was added aqueous sodium hydroxide (50%, 1.5 mL). The reaction mixture was stirred magnetically until crystallization began (7-40 min) and than it was left to stand at 0° up to one hour. Water (100 mL) was added and the solid was collected, washed with water until neutral and recrystallized from ethanol to give **3** as white crystals (Tables 1 and 2).

Alkyl 4-Amino-3,4-diphenylbutanoates Hydrochloride (4). General Procedure.- Hydrochloric acid (8 mL, 10%) was added to the solution of **3** (2 mmol) in 15 mL ether (20 mL in the case of **3e**) and the reaction mixture was stirred at room temperature for 10 hrs. The precipitate was collected, washed with cooled ether and recrystallized from ethanol to yield **4** as white crystals (Tables 1 and 2).

TABLE 2. Spectral Data of Compounds **3** and **4**

Cmpd	IR (cm^{-1})[a]	^1H NMR (d, Hz)[b]
3a	1645, 1730	2.64, 2.73 (2dd, 2H, J_1 = 9.0 and 15.7, J_2 = 6.4 and 15.6), 3.47 (s, 3H), 3.73 (ddd, 1H, J_1 = 8.9, J_2 = 6.8, J_3 = 6.7), 4.46 (d, 1H, J = 7.0), 7.05-7.66 (m, 15H), 8.01 (s, 1H)
3b	1645, 1720	1.04 (t, 3H, J = 7.1), 2.62, 2.70 (2dd, 2H, J_1 = 9.1 and 15.6, J_2 = 6.7 and 15.6), 3.72 (ddd, 1H, J_1 = 8.8, J_2 = 6.9, J_3 = 6.9), 3.92 (dq, 2H, J = 1.2 and 7.2), 4.46 (d, 1H, J = 7.0), 7.10-7.65 (m, 15H), 8.01 (s, 1H)
3c	1645, 1730	2.70, 2.77 (2dd, 2H, J_1 = 9.0 and 15.5, J_2 = 6.6 and 15.3), 3.73 (ddd, 1H, J_1 = 8.8, J_2 = 6.9, J_3 = 6.9), 4.45 (d, 1H, J = 6.9), 4.84, 4.87 (2s, 2H), 7.03-7.64 (m, 20H), 7.97 (s, 1H)
3d	1645, 1720	1.00 (dd, 6H, J = 6.3 and 10.1), 2.62 (2d, 2H, J_1 = 7.3, J_2 = 8.6), 3.69 (ddd, 1H, J_1 = 8.5, J_2 = 7.2, J_3 = 7.3), 4.45 (d, 1H, J = 6.9), 4.77 (sept, 1H, J = 6.3), 7.05-7.67 (m, 15H), 8.01 (s, 1H)
3e	1645, 1715	1.19 (s, 9H), 2.55 (2d, 2H, J_1 = 7.9, J_2 = 8.3), 3.63 (dt, 1H, J_1 = 8.2, J_2 = 7.5), 4.43 (d, 1H, J = 7.0), 7.10-7.67 (m, 15H), 7.99 (s, 1H)
4a	1725, 2400-2700	2.36, 2.58 (2dd, 2H, J_1 = 4.5 and 15.8, J_2 = 10.7 and 15.8), 3.28 (s, 3H), 3.68 (ddd, 1H, J_1 = 4.5, J_2 = 8.2, J_3 = 15.7), 4.51 (d, 1H, J = 9.5), 7.29-7.63 (m, 10H), 8.48 (s, 2H)
4b	1720, 2400-2700	0.88 (t, 3H, J = 7.1), 2.30, 2.65 (2dd, 2H, J_1 = 4.5 and 15.6, J_2 = 10.9[c]), 3.73 (m, 3H), 4.50 (d, 1H, J = 9.6), 7.15-7.63 (m, 12H), 8.49 (s, 2H)
4c	1725, 2400-2700	2.38, 2.66 (2dd, 2H, J_1 = 4.3 and 15.7, J_2 = 11.1 and 15.7), 3.68 (ddd, 1H, J_1 = 11.8, J_2 = 8.7. J_3 = 4.3), 4.52 (d, 1H, J = 9.6), 4.78, 4.79 (2s, 2H), 7.00-7.58 (m, 15H), 8.43 (br s, 2H)
4d	1720, 2400-2700	0.86 (dd, 6H, J_1 = 6.3, J_2 = 17.3), 2.24 (dd, 1H, J = 4.3 and 15.2), 3.64 (m, 1H), 4.50 (d, 1H, J = 9.2), 4.53 (sept, 1H, J = 6.3), 7.26-7.62 (m, 10H), 8.49 (s, 2H)
4e	1710, 2400-2700	1.06 (s, 9H), 2.11, 2.42 (2dd, 2H, J_1 = 4.2 and 15.3, J_2 = 11.4[c]), 3.50 (ddd, 1H, J_1 = 4.5, J_2 = 9.0, J_3 = 12.1), 4.49 (d, 1H, J = 9.8), 7.31-7.58 (m, 10H), 8.23 (s, 2H)
4f	1710, 2200-3300	2.32, 2.49 (2dd, 2H, J_1 = 4.0 and 15.9, J_2 = 11.1 and 16.0), 3.72 (ddd, 1H, J_1 = 4.0, J_2 = 10.7, J_3 = 10.0), 4.48 (d, 1H, J = 9.0), 7.29-7.61 (m, 10H)

a) Measured in $CHCl_3$. b) Recorded in $CDCl_3$ (**3**) and DMSO-d_6 (**4**). c) Overlapped with DMSO signal.

4-Amino-3,4-diphenylbutanoic Acid Hydrochloride (4f).- A mixture of 40 mL hydrochloric acid (1:1) and **3e** (2.0 g, 5 mmol) was refluxed for 2 hr. The solid was collected, washed with ether and recrystallized from ethanol to give **4f**.

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