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NEW METHOD FOR THE SYNTHESIS OF 2-PHENYLPROLINE AND ITS DERIVATIVES

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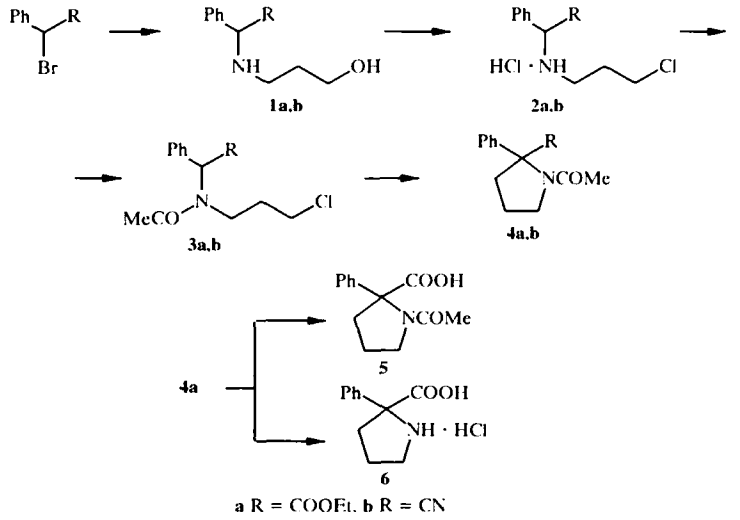
A new method has been developed for the synthesis of 2-phenylproline and its derivatives by intramolecular cyclization of the corresponding derivatives of N-(3-chloro- or 1-oxo-3-chloropropyl)-α-phenylglycine under phase transfer catalysis conditions.

Keywords: amino acids, phenylproline, intramolecular cyclization, phase-transfer catalysis.

Derivatives of proline which are a very important component of proteins hold interest as starting materials for the synthesis of new drugs. However, their use has been limited by the restricted number of available pathways for the synthesis of cyclic α-amino acids. Such methods include the intramolecular cyclization of 5-methyl- and 5-phenyl-5-(3-hydroxypropyl)hydantoins [1] and the reaction of suitable isonitriles with dibromoethane in the presence of sodium hydride [2]. These methods are laborious, rather sensitive to the reaction conditions, and do not give the desired products in high yield.

We propose a method for the synthesis of 2-phenylproline derivatives by intramolecular cyclization of the corresponding N-(3-chloro- or 1-oxo-3-chloropropyl)-α-phenylglycine under phase transfer catalysis conditions in acetonitrile in the presence of potassium carbonate and triethylbenzylammonium chloride as catalyst. Thus, treatment of the nitrile or ethyl ester of α-bromophenylacetic acid with 1-amino-3-hydroxypropane according to



a R = COOEt, b R = CN

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TABLE 1. Physical Characteristics of Synthesized Compounds*

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	R_f (solvent system)	^{1}H NMR spectrum, δ, ppm*^{2} (J, Hz)	Yield %
		C	H	N	Cl				
1	2	3	4	5	6	7	8	9	10
1a	$C_{13}H_{19}NO_3$	65.93 / 65.80	7.90 / 8.07	6.04 / 5.90	—	129-130 (oxalate)	0.60 (a)	7.42 (5H, s, C_6H_5); 5.02 (1H, s, CH); 4.18 (2H, q, J = 7.0, CH_2); 3.65 (2H, t, J = 6.5, CH_2O); 3.02-2.76 (2H, m, CH_2N); 1.90-1.70 (2H, m, CH_2); 1.15 (3H, t, J = 7.0, CH_3)	90
1b	$C_{11}H_{14}N_2O$	63.91 / 64.07	6.60 / 6.79	13.71 / 13.59	—	125-126 (oxalate)	0.60 (a)	7.80(5H, s, C_6H_5); 5.80 (1H, s, CH); 3.60 (2H, t, J = 6.5, CH_2O); 3.20 (2H, t, J = 6.5, CH_2N); 2.40-1.80 (2H, m, CH_2)	89
2a	$C_{13}H_{18}ClNO_2 \cdot HCl$	53.13 / 53.42	6.32 / 6.55	4.89 / 4.79	24.52 / 24.29	213 (dec.)	0.50 (d)	7.45 (5H, s, C_6H_5); 5.18 (1H, s, CH); 4.22 (2H, q, J = 7.0, CH_2); 3.60 (2H, t, J = 6.5, CH_2Cl); 3.20-2.90 (2H, m, CH_2N); 2.24-2.00 (2H, m, CH_2); 1.18 (3H, t, 7-7.0, CH_3)	89
2b	$C_{11}H_{13}ClN_2 \cdot HCl$	54.00 / 53.87	5.70 / 5.75	11.65 / 11.42	29.01 / 28.95	140-141	0.54 (d)	7.80 (5H, s, C_6H_5); 6.00 (1H, s, CH); 3.70 (2H, t, J = 6.5, CH_2Cl); 3.40 (2H, t, J = 6.5, m, CH_2N); 2.60-2.00 (2H, m, CH_2)	90
3a	$C_{15}H_{20}ClNO_3$	60.32 / 60.49	6.58 / 6.77	4.81 / 4.70	12.07 / 11.91	-	0.32 (a)	7.20 (5H, s, C_6H_5); 6.80 (1H, s, CH); 4.00 (2H, q, J = 7.0, CH_2); 3.40-3.00 (4H, m, CH_2N and CH_2Cl); 2.00 (3H, s, CH_3CO); 1.80-1.40 (2H, m, CH_2); 1.15 (3H, t, J = 7.0, CH_3)	94
3b	$C_{13}H_{15}ClN_2O$	62.50 / 62.27	5.84 / 6.03	11.06 / 11.16	13.90 / 14.16	62-63	0.55 (a)	7.40 (5H, s, C_6H_5); 6.90 (1H, s, CH); 3.60-3.10 (4H, m, CH_2N and CH_2Cl); 2.15 (3H, s, CH_3CO); 2.10-1.40 (2H, m, CH_2)	80
4a	$C_{15}H_{19}NO_3$	69.12 / 68.94	7.58 / 7.33	5.50 / 5.36	—	-	0.40 (a)	7.18 (5H, s, C_6H_5); 4.05 (2H, q, J = 7.0, CH_2); 3.80-3.40 (2H, m, CH_2N); 2.00 (3H, s, CH_3CO); 2.60-1.60 (4H, m, $2CH_2$); 1.15 (3H, t, J = 7.0, CH_3)	96

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10
4b	$C_{13}H_{14}N_2O$	73.10 72.88	6.54 6.59	13.18 13.07	—	120-121	0.50 (a)	7.30 (5H, s, C_6H_5); 3.65 (2H, t, J = 6.5, CH_2N); 2.00 (3H, s, CH_3CO); 2.80-1.70 (4H, m, $2CH_2$)	90
5	$C_{13}H_{15}NO_3$*[3]	67.13 66.94	6.64 6.48	6.17 6.00	—	156-157	0.60 (c)	10.50 (1H, s, COOH); 7.20 (5H, s, C_6H_5); 4.05 (2H, t, J = 6.5, CH_2N); 3.20-1.80 (4H, m, $2CH_2$); 2.20 (3H, s, CH_3CO)	80
6	$C_{11}H_{13}NO_2 \cdot HCl$*[3]	58.72 58.53	6.05 5.76	6.35 6.21	16.00 15.74	265-267 (dec.)	0.45 (d)	7.40 (5H, s, C_6H_5); 3.45 (2H, t, J = 6.5, CH_2N); 3.20-1.80 (4H, m, $2CH_2$)	90
7	$C_{17}H_{19}NO_2$	76.05 75.84	7.21 7.06	5.32 5.20	—	89-90	0.48 (c)	7.80-7.30 (10H, s, $2C_6H_5$); 4.60 and 3.40 (2H, dd, J = 14.0, CH_2N); 4.55 (1H, s, CH); 4.15 (2H, q, J = 7.0, CH_2O); 1.15 (3H, t, J = 7.0, CH_3)	86
8	$C_{20}H_{22}ClNO_3$	66.92 66.75	6.23 6.16	4.01 3.89	10.02 9.86	82-83	0.70 (a)	7.40-7.00 (10H, m, $2C_6H_5$); 6.00 (1H, s, CH); 4.70 and 4.40 (2H, dd, J = 18.0, CH_2N); 4.15 (2H, q, J = 7.0, CH_2O); 3.80 (2H, t, J = 6.0, CH_2Cl); 2.80 (2H, t, J = 6.0, CH_2CO); 1.15 (3H, t, J = 7.0)	75
9	$C_{20}H_{21}NO_3$	74.19 74.28	6.67 6.55	4.50 4.33	--	64-65	0.65 (a)	7.50-7.00 (10H, m, $2C_6H_5$); 4.70 and 4.40 (2H, dd, J = 17.0, CH_2N); 4.05-3.75 (2H, m, CH_2O); 3.10-2.20 (4H, m, $2CH_2$); 1.15 (3H, t, J = 7.0, CH_3)	97
10	$C_{18}H_{17}NO_3$*[3]	73.28 73.20	5.64 5.80	4.96 4.74	—	189-190	0.47 (a)	7.40-7.00 (10H, m, $2C_6H_5$); 4.80 and 4.50 (2H, dd, J = 17.0, CH_2N); 3.20-2.20 (4H, m, $2CH_2$)	70

* The mp and R_f data for **1b**, **6**, and **7** are in accord with literature data [4, 1, 3].

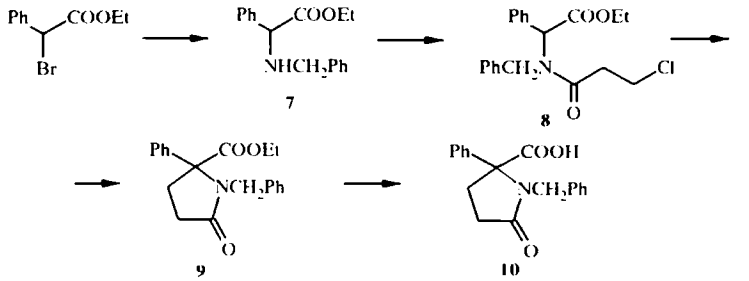
*[2] The spectra for **1a**, **1b**, **2a**, and **2b** were taken for solutions in CD_3OD. The spectra for **3a** and **3b** were taken for solutions in CCl_4. The spectra for **4a**, **4b**, **5**, and **7-10** were taken for solutions in $CDCl_3$. The spectrum for **6** was taken for a solution in D_2O.

*[3] The M^+ values were determined mass spectrometrically for **5** (233), **6** (191), and **10** (295).

the scheme below yielded the corresponding aminopropanol derivatives **1a,b**, which were converted by the action of thionyl chloride into chloro derivatives **2a,b**. The direct cyclization of these intermediates gave a mixture of the products of dehydrocyanation and N- and C-alkylation.

We were able to avoid the formation of side-products by prior acylation of **2a,b** to the corresponding acetamido derivatives **3a,b**, which were cyclized to give the desired proline derivatives **4a,b** in high yields. The partial or complete hydrolysis of **4a** led to acids **5** and **6**, respectively.

The action of benzylamine on the ester of α-bromophenylacetic acid give the corresponding N-benzyl ester **7**, which upon treatment with β-chloropropionyl chloride led to oxochloride **8**.



Cyclization of **8** under phase transfer catalysis conditions gave ester **9** in high yield. Hydrolysis of **9** gave acid **10**.

Proline derivatives **5**, **6**, and **10** synthesized by this method lacked optical activity (racemic mixtures were obtained). In this regard, further studies using chiral quaternary ammonium salts hold considerable interest. The purity of synthesized products was demonstrated by ^{1}H NMR spectroscopy, mass spectrometry, and thin-layer chromatography.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Varian Mercury 300 spectrometer with HMDS as the internal standard. The mass spectra were taken on an MX-1321A mass spectrometer. Thin-layer chromatography was carried out on Silufol UV-254 plates. The R_f values were determined for elution with a) 1:1 acetone–hexane, b) 2:1 acetone–hexane, c) 1:2 acetone–hexane, and d) 4:1 propanol–water. The physical characteristics of the products synthesized are given in Table 1.

Ethyl Ester of N-(3-Hydroxypropyl)-α-phenylglycine (1a). A sample 1-amino-3-hydroxypropane (0.75 g, 0.01 mol) was added with stirring to a mixture of ethyl α-bromophenylacetate (2.43 g, 0.01 mol) and K_2CO_3 (2.8 g, 0.02 mol) in chloroform (20 ml) at 40-45°C and stirred at this temperature for 2 h. The reaction mixture was filtered. The filtrate was washed with water and dried over Na_2SO_4. Chloroform was distilled off to give ester **1a** (2.1 g) as a viscous liquid.

Hydrochloride of the Ethyl Ester of N-(3-Chloropropyl)-α-phenylglycine (2a). A sample of ester **1a** (2.37 g, 0.01 mol) in chloroform (20 ml) was added to a mixture of $SOCl_2$ (1.33 g, 0.012 mol) and chloroform (10 ml) maintained at 50°C. The reaction mixture was stirred at 50°C for 3 h. Chloroform was distilled off. The crystalline residue was washed with ether and recrystallized from ethanol to give compound **2a** (2.5 g).

Ethyl Ester of N-Acetyl-N-(3-chloropropyl)-α-phenylglycine (3a). A mixture of hydrochloride **2a** (2.92 g, 0.01 mol), sodium acetate (2.44 g, 0.03 mol), and acetic anhydride (3.06 g, 0.03 mol) was maintained on a steam bath for 4 h. After cooling, the reaction mixture was dissolved in 50 ml chloroform. The solution was washed with 5% aq. Na_2CO_3 and water and dried over Na_2SO_4. Chloroform was distilled off to give ester **3a** (2.8 g) as a viscous mass.

Ethyl Ester of 1-Acetyl-2-phenylproline (4a). A mixture of ester **3a** (2.97 g, 0.01 mol), dry K_2CO_3 (4.0 g, 0.03 mol), triethylbenzylammonium chloride (0.12 g, 5 mmol) in acetonitrile (20 ml) was stirred at 45-50°C for 4 h. The reaction mixture was filtered and the filtrate was evaporated. The residue was dissolved in chloroform,

washed with water, and dried over Na_2SO_4. Chloroform was distilled off to give 2.5 g ester **4a** as a noncrystallizing viscous mass, which decomposes upon attempted distillation.

Products **1b-4b** were synthesized analogously from α-bromophenylacetonitrile.

1-Acetyl-2-phenylproline (5). A mixture of ester **4a** (2.61 g, 0.01 mol) and NaOH (0.4 g, 0.01 mol) in methanol (20 ml) was heated at reflux for 4 h. Then, methanol was distilled off and the residue was dissolved in water (20 ml). The solution was washed with ether and acidified by adding 0.1N hydrochloric acid. The precipitate formed was filtered off and recrystallized from toluene to give **5** (1.8 g).

Hydrochloride of 2-Phenylproline (6). A mixture of **4a** (2.61 g, 0.01 mol) and 5% hydrochloric acid (50 ml) was heated at reflux until a clear solution was obtained. Then, activated charcoal (0.5 g) was added to the hot solution. The reaction mixture was filtered and the filtrate was evaporated in vacuum. The dry residue was washed with ether, recrystallized from ethanol, and dried in a desiccator over P_2O_5 to give hydrochloride **6** (2.0 g).

Ethyl Ester of N-Benzyl-α-phenylglycine (7). A sample of benzylamine (1.07 g, 0.01 mol) was added to a mixture of ethyl α-bromophenylacetate (2.43 g, 0.01 mol), K_2CO_3 (2.8 g, 0.02 mol), and chloroform (20 ml) at 40-45°C. Stirring was continued for 2 h. The reaction mixture was filtered. The filtrate was washed with water and dried over Na_2SO_4. Chloroform was distilled off to give ester **7** (2.3 g).

Ethyl Ester of N-Benzyl-N-(β-chloropropionyl)-α-phenylglycine (8). A sample of β-chloropropionyl chloride (1.3 g, 0.01 mol) was added to a mixture of ester **7** (2.7 g, 0.01 mol) and triethylamine (1.05 g, 0.01 mol) in acetone (30 ml) at 0-5°C. Acetone was distilled off. The residue was dissolved in 100 ml ether. The solution was washed with dilute hydrochloric acid and water and dried over Na_2SO_4. Ether was distilled off to give amide **8** (2.7 g).

Ethyl Ester of 1-Benzyl-5-oxo-2-phenylproline (9). A mixture of amide **8** (3.6 g, 0.01 mol), dry K_2CO_3 (4.0 g, 0.03 mol), and triethylbenzylammonium chloride (0.12 g, 5 mmol) in acetonitrile (20 ml) was stirred at 45-50°C for 4 h. The reaction mixture was filtered off and the filtrate was evaporated. The residue was dissolved in chloroform. The solution was washed with water and dried over Na_2SO_4. Chloroform was distilled off to give ester **9** (3.1 g).

1-Benzyl-5-oxo-2-phenylproline (10). A mixture of ester **9** (3.2 g, 0.01 mol) and NaOH (0.4 g, 0.01 mol) in methanol (20 ml) was heated at reflux for 4 h. Methanol was then distilled off and the residue was dissolved in water (20 ml). The solution was washed with ether and acidified by adding 0.1N hydrochloric acid. The precipitate formed was filtered off and recrystallized from benzene to give **10** (2.1 g).

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