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Synthesis and X-Ray Analysis of 2-Aryl-4-chloropyrrolidine-2-carbonitrile Derivatives

S. P. Gasparyan[a], M. V. Alexanyan[a], G. K. Harutyunyan[a], A. H. Martirosyan[a], R. A. Tamazyan[b], A. G. Ayvazyan[b], and H. A. Panosyan[b]

Scientific Technological Center of Organic and Pharmaceutical Chemistry, National Academy of Sciences of Armenia, pr. Azatutyan 26, Yerevan, 0014 Armenia:

[a] *Mndzhoyan Institute of Fine Organic Chemistry*

[b] *Molecular Structure Research Center*

e-mail: g_sahak@yahoo.com

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Abstract—A procedure has been developed for the synthesis of ethyl 1-benzoyl-4-chloro-2-phenylpyrrolidine-2-carboxylate and 4-chloro-5-oxo-1,2-diphenyl-, 1-benzoyl-2-(2-benzyloxy-5-chlorophenyl)-4-chloro-, and 1-benzoyl-2-(4-benzyloxyphenyl)-4-chloropyrrolidine-2-carbonitriles in high yields via intramolecular cyclization of the corresponding 2,3-dichloropropionamides under conditions of phase-transfer catalysis.

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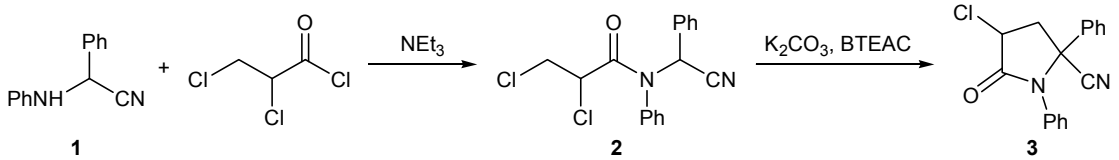
Proline and other cyclic α-amino acids are important components of many biologically active natural substances [1, 2]. In recent years functionally substituted proline derivatives have been used as starting compounds in the synthesis of new medications [3–5]. Chiral 2-substituted prolines are used not only in syntheses of new compounds but also as ligands in coordination chemistry [6–8]. Studies of chemical and biological properties of substituted prolines are limited due to the lack of accessible methods for their preparation. The known procedures are laborious and rather sensitive to reaction conditions, and the yields are generally low [9–13].

We previously proposed a procedure for the synthesis of ethyl 4-chloro-5-oxo-1,2-diphenylpyrrolidine-2-carboxylate under phase-transfer catalysis [14, 15]. In the present work we used this procedure for the preparation of 4-chloro-5-oxo-1,2-diphenylpyrrolidine-2-carbonitrile **3** (Scheme 1). For this purpose, 2-anilino-2-phenylacetonitrile (**1**) [16] was acylated with 2,3-dichloropropanoyl chloride, and the subsequent intramolecular cyclization of amide **2** under conditions of phase-transfer catalysis afforded compound **3**. The phase-transfer catalyst was benzyl(triethyl)ammonium chloride (BTEAC).

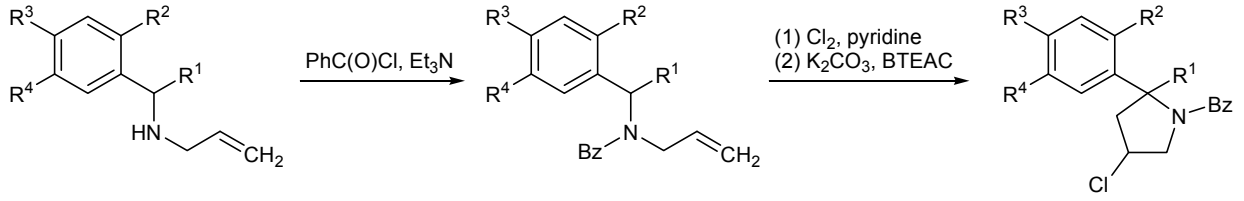
The other three chloro-substituted pyrrolidine analogs were synthesized in a different way. The alkylation of ethyl 2-bromo-2-phenylacetate with allylamine gave ethyl 2-(allylamino)-2-phenylacetate (**4**) which was acylated with benzoyl chloride in the presence of triethylamine and subjected to chlorination and intramolecular cyclization under phase-transfer conditions. We thus synthesized amide **6** (Scheme 2). The reactions of 2- and 4-benzyloxybenzaldehydes with sodium cyanide and allylamine in acid medium afforded the corresponding 2-(allylamino)-2-phenylacetonitriles **7** and **10**; their acylation with benzoyl chloride, followed by chlorination and cyclization led to the formation of 4-chloro-substituted 1-benzoylpyrrolidine-2-carbonitriles **9** and **12** (Scheme 2).

Scheme 1.



1 **2** **3**

Scheme 2.



4, **7**, **10** **5**, **8**, **11** **6**, **9**, **12**

4–**6**, R^1 = COOEt, R^2 = R^3 = R^4 = H; **7**, **8**, R^1 = CN, R^2 = $PhCH_2O$, R^3 = R^4 = H; **9**, R^1 = CN, R^2 = $PhCH_2O$, R^3 = H, R^4 = Cl; **10**–**12**, R^1 = CN, R^2 = R^3 = H, R^4 = $PhCH_2O$.

Unlike compounds **5** and **11**, the chlorination of **8** was accompanied by introduction of a chlorine atom into the 5-position of the benzene ring. The benzene ring in **8** and **11** is activated to electrophilic substitution due to the presence of an electron-donor *ortho*/*para* orienting benzyloxy group; however, the chlorination in the *ortho* position with respect to the benzyloxy group is hindered for steric reasons; therefore, the chlorine atom enters only the benzene ring in **8**, where the *para* position with respect to the benzyloxy group is free.

The proposed procedure for the synthesis of compounds **3**, **6**, **9**, and **12** is less laborious than known methods for the preparation of substituted prolines, it affords high yields, and can be used to obtain other proline derivatives.

The molecular and crystal structures of compounds **3** (Fig. 1), **6** (Fig. 2) [17], **9** (Fig. 3) [18], and **12** (Fig. 4) were determined by X-ray analysis. The principal crystallographic parameters of **3** and **12** are given in table. Their molecules each possess two asymmetric carbon atoms (C^1 and C^4 in the pyrrolidine ring); therefore, the formation of four diastereoisomers, (2*R*,4*R*), (2*R*,4*S*), (2*S*,4*R*), and (2*S*,4*S*), is possible. According to the X-ray diffraction data, all four possible stereoisomers were detected only for ethyl 1-benzoyl-4-chloro-2-phenylpyrrolidine-2-carboxylate (**6**) [17]. It crystallized in the $P2_1$ non-centrosymmetric space group, and its unit cell contained two symmetry-independent molecules. Nevertheless, all four isomers of **6** were present in crystal, and the (2*R*,4*R*)/(2*R*,4*S*)/(2*S*,4*R*)/(2*S*,4*S*) ratio was ~7:3:5:5. As a result, the structure is not ordered, and the two symmetry-independent molecules are represented by the pairs of diastereoisomers (2*R*,4*R*)/(2*R*,4*S*) and (2*S*,4*R*)/(2*S*,4*S*) (Fig. 5).

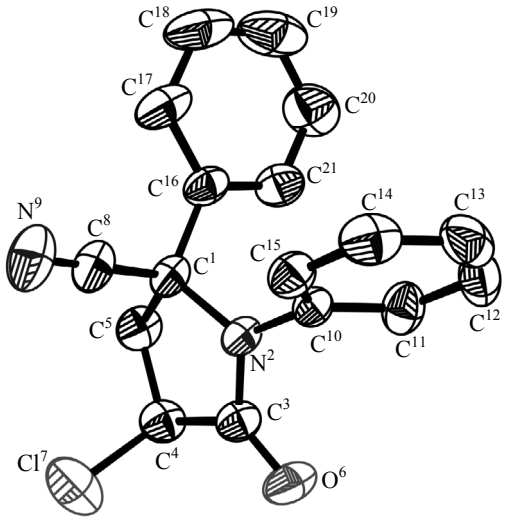


Fig. 1. Structure of the molecule of 4-chloro-5-oxo-1,2-diphenylpyrrolidine-2-carbonitrile (**3**) according to the X-ray diffraction data (arbitrary atom numbering); non-hydrogen atoms are shown as thermal vibration ellipsoids with a probability of 50%. Hereinafter, hydrogen atoms are not shown for clarity.

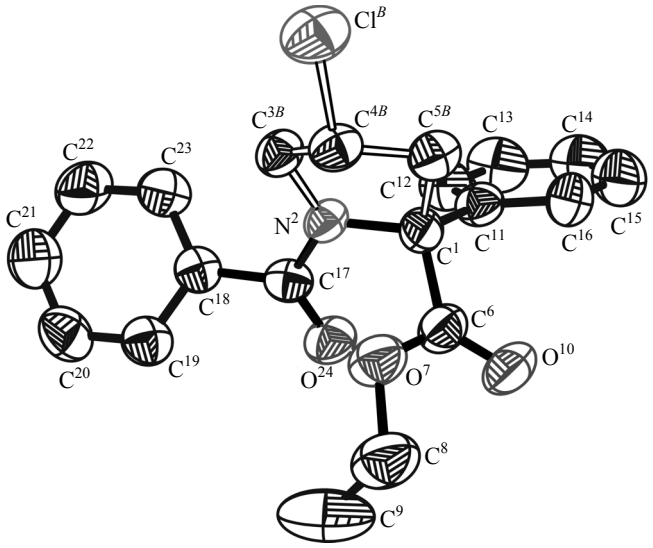


Fig. 2. Structure of the molecule of ethyl 1-benzoyl-4-chloro-2-phenylpyrrolidine-2-carboxylate (**6**) according to the X-ray diffraction data (arbitrary atom numbering); non-hydrogen atoms are shown as thermal vibration ellipsoids with a probability of 50%. Only one stereoisomer is shown.

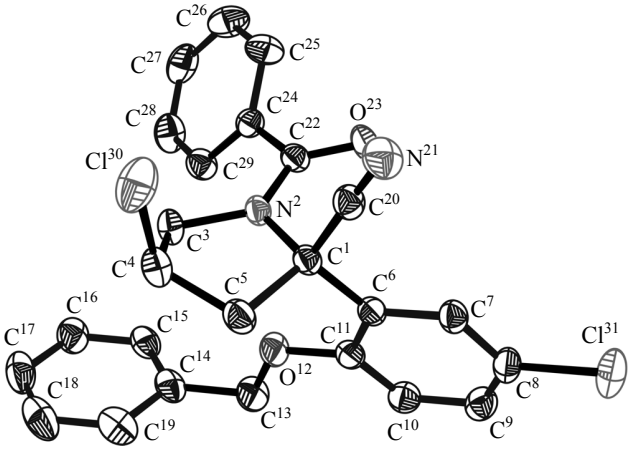


Fig. 3. Structure of the molecule of 1-benzoyl-2-(2-benzyloxy-5-chlorophenyl)-4-chloropyrrolidine-2-carbonitrile (**9**) according to the X-ray diffraction data (arbitrary atom numbering); non-hydrogen atoms are shown as thermal vibration ellipsoids with a probability of 50%.

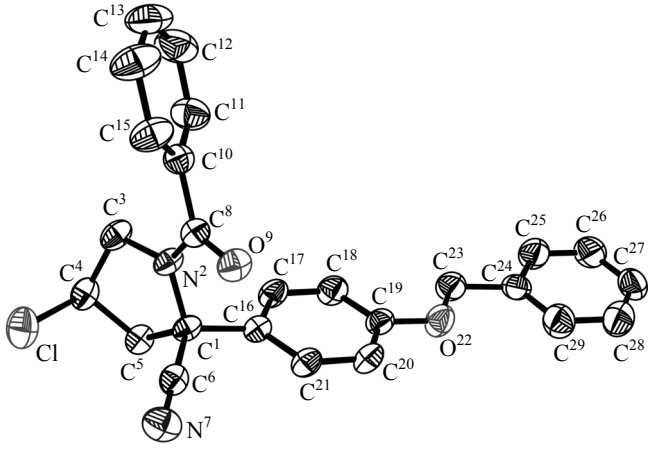


Fig. 4. Structure of the molecule of 1-benzoyl-2-(4-benzyloxyphenyl)-4-chloropyrrolidine-2-carbonitrile (**12**) according to the X-ray diffraction data (arbitrary atom numbering); non-hydrogen atoms are shown as thermal vibration ellipsoids with a probability of 50%.

Unlike ester **6**, nitriles **3**, **9**, and **12** were equimolar mixtures of only two stereoisomers, (2*R*,4*S*) and (2*S*,4*R*) (Figs. 6–8). They crystallized in centrosymmetric space groups *P*-1, $P2_1/n$, and *C*2/*c*, respectively. Presumably, the presence of a cyano group in molecules **3**, **9**, and **12** is responsible for the lack of the corresponding (2*R*,4*R*) and (2*S*,4*S*) stereoisomers.

The pyrrolidine ring in molecules **6**, **3**, **9**, and **12** adopts an *envelope* conformation, i.e., four atoms in the ring lie in one plane. This plane in **6**, **9**, and **12** includes the C^1, N^2, C^3, and C^5 atoms; the maximum deviation from the mean-square plane does not exceed 0.0120(4) Å, while the C^4 atom deviates from that plane by 0.3738(3)–0.5374(4) Å. The corresponding plane in molecule **3** is formed by the C^1, N^2, C^3, and C^4 atoms [the maximum deviation is 0.0083(2) Å], and the C^5 atom deviates from the plane by 0.374(3) Å. The observed difference in the conformations of the pyrrolidine ring in molecules **6**, **9**, and **12**, on the one hand, and **3**, on the other, is likely to be determined by different hybridizations of the C^3 atom (sp^3 in **6**, **9**, and **12** and sp^2 in **3**).

EXPERIMENTAL

The IR spectra were recorded from thin films on a Nicolet Avatar 330 FT-IR spectrometer. The ^1H and ^{13}C NMR spectra were measured from solutions in DMSO-d_6–CCl_4 (1:3) at 303 K on a Varian Mercury-300VX instrument operating at 300.078 and 75.46 MHz, respectively. Signals were assigned using DEPT and HMQC double-resonance techniques. The chemical shifts were determined relative to the residual DMSO proton signal (δ 2.50 ppm). The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using the following solvent systems: acetone–nonane, 1:1 (A), 1:2 (C), 2:1 (F), 3:2 (G); acetone–hexane, 2:1 (B), 1:1 (D), 1:2 (E); development with iodine vapor.

The X-ray diffraction data for compounds **3** and **12** were obtained at room temperature on an Enraf–

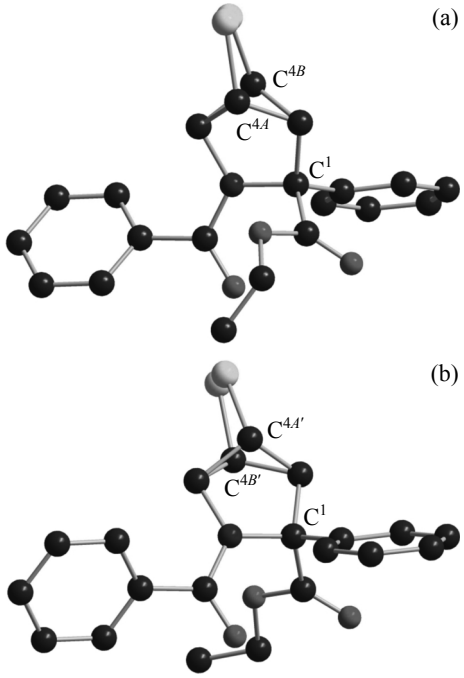


Fig. 5. (a) (2*R*,4*R*)/(2*R*,4*S*) and (b) (2*S*,4*R*)/(2*S*,4*S*) Diastereoisomer pairs of ethyl 1-benzoyl-4-chloro-2-phenylpyrrolidine-2-carboxylate (**6**). The $C^{1'}$ and $C^{4'}$ atoms correspond to C^{26} and C^{29} in [17].

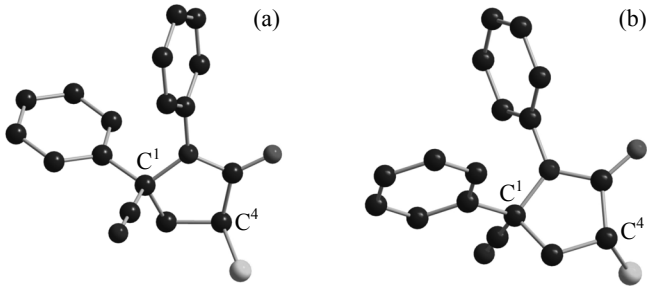


Fig. 6. (a) (2*R*,4*S*) and (b) (2*S*,4*R*) Diastereoisomers of 4-chloro-5-oxo-1,2-diphenylpyrrolidine-2-carbonitrile (**3**) symmetry-related (in crystal) through an inversion center.

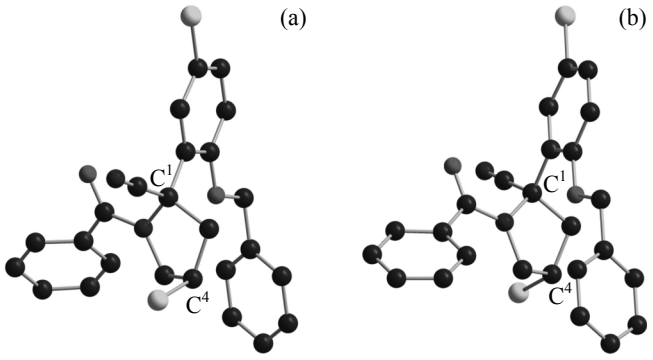


Fig. 7. (a) (2*R*,4*S*) and (b) (2*S*,4*R*) Diastereoisomers of 1-benzoyl-2-(2-benzyloxy-5-chlorophenyl)-4-chloropyrrolidine-2-carbonitrile (**9**) symmetry-related (in crystal) through an inversion center.

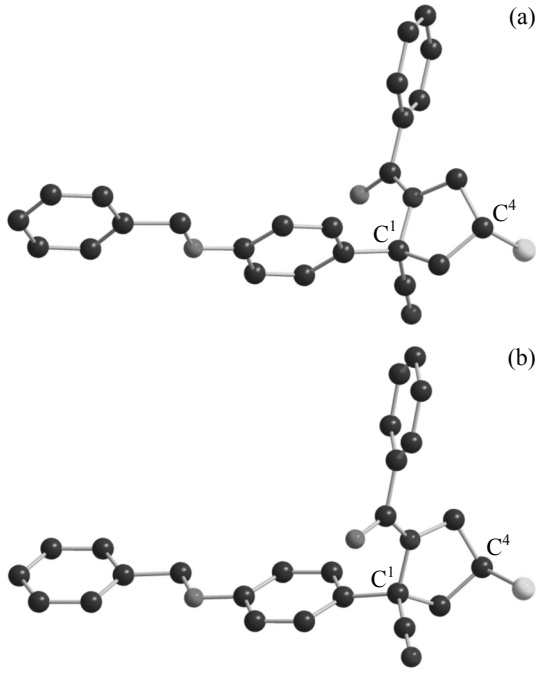


Fig. 8. (a) (2*R*,4*S*) and (b) (2*S*,4*R*) Diastereoisomers of 1-benzoyl-2-(4-benzyloxyphenyl)-4-chloropyrrolidine-2-carbonitrile (**12**) symmetry-related (in crystal) through an inversion center.

Nonius CAD-4 automated diffractometer (MoK_α radiation, graphite monochromator, θ/2θ scanning). A correction for absorption was applied by the psi scan technique [19]. The structures were solved by the direct method. The coordinates of atoms were determined from the Fourier difference syntheses. The structures were refined by the full-matrix least-squares procedure in anisotropic approximation for non-hydrogen atoms and isotropic approximation for hydrogen atoms. All calculations were performed using SHELXTL software [20]. The crystallographic data were deposited to the Cambridge Crystallographic Data Centre. The data for compounds **6** and **9** were reported in [17, 18], and the data for **3** and **12** are given in table.

2,3-Dichloro-*N*-[cyano(phenyl)methyl]-*N*-phenylpropanamide (2). A mixture of 2 g (10 mmol) of 2-anilino-2-phenylacetonitrile (**1**) [16] and 1.05 g (10 mmol) of triethylamine in 30 mL of acetone was cooled to 0–5°C, 1.6 g (10 mmol) of 2,3-dichloropropanoyl chloride was added, and the mixture was stirred for 30 min at room temperature. The solvent was distilled off, the residue was treated with 50 mL of diethyl ether, and the extract was washed with dilute aqueous HCl and water, dried over Na_2SO_4, and evaporated. Yield 2.5 g (77%), mp 94–95°C (from EtOH), R_f 0.61 (A). ^{1}H NMR spectrum, δ, ppm: 3.67 d.d (1H, CHCl, J = 8.3, 3.2 Hz), 4.09 d.d (1H, J = 9.1, 3.2 Hz) and 4.14 d.d (1H, J = 9.1, 8.3 Hz) (CH_2Cl), 6.54 br.s (1H, NCH), 7.25–7.47 m (10H, H_{arom}). Found, %: C 61.40; H 4.51; Cl 21.50; N 8.70. $C_{17}H_{14}Cl_2N_2O$. Calculated, %: C 61.28; H 4.23; Cl 21.28; N 8.4.

4-Chloro-5-oxo-1,2-diphenylpyrrolidine-2-carbonitrile (3). A mixture of 3.33 g (10 mmol) of compound **2**, 2.76 g (20 mmol) of anhydrous potassium carbonate, and 0.12 g (5 mmol) of benzyl(triethyl)ammonium chloride (BTEAC) in 20 mL of acetonitrile was stirred for 4 h at 45–50°C. The mixture was filtered, the filtrate was evaporated, the residue was dissolved in chloroform, and the solution was washed with water, dried over $CaCl_2$, and evaporated. Yield 1.9 g (58%), mp 169–171°C (from *i*-PrOH), R_f 0.47 (B). IR spectrum, ν, cm^{-1}: 2228 (C≡N), 1719 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.10 d.d (1H, J = 14.9, 2.5 Hz) and 3.28 d.d (1H, J = 14.9, 7.4 Hz) (CH_2), 4.90 d.d (1H, CHCl, J = 7.4, 2.5 Hz), 7.17–7.41 m (8H, H_{arom}), 7.58–7.63 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 45.4 (Ph**C**H_2), 51.9 (C^4), 63.8 (C^2), 118.0 (CN), 125.6 (2C, CH), 126.0 (2C, CH), 127.0 (CH), 128.3 (2C, CH), 128.5 (2C, CH), 128.9 (CH), 134.9, 135.0, 168.6 (C^5). Found, %: C 68.55; H 4.49;

Principal crystallographic parameters of 2-aryl-4-chloropyrrolidine-2-carbonitriles **3** and **12**[a]

Parameter	**3**	**12**
CCDC entry no.	1019216	1019218
Formula	$C_{17}H_{13}ClN_2O$	$C_{25}H_{21}ClN_2O_2$
Molecular weight	296.74	416.89
Space group	$P2_1/n$	$C2/c$
a, b, c, Å	8.774(2), 17.491(4), 9.350(2)	34.487(7), 6.166(1), 23.843(5)
β, deg	90.34(3)	123.14(3)
V, Å^3	1434.9(5)	4245(2)
Z	4	8
d_{calc}, g/cm^3	1.374	1.305
T_{min}/T_{max}, μ(MoK_α), mm^{-1}	0.889/0.913, 0.266	0.637/0.857, 0.204
F(000)	616	1744
Crystal dimensions, mm	0.30×0.35×0.40	0.32×0.35×0.40
$\theta_{min}/\theta_{max}$, deg	2.3, 30.0	1.4, 30.0
Scan range	–12 = h = 12, 0 = k = 24, –13 = l = 13	–48 = h = 40, 0 = k = 8, 0 = l = 33
Total reflection number	8309	8258
Number of reflections with $I > 2\sigma(I)$]	3026	3218
Number of independent reflections	4161	6186
Number of variables	202	355
R, wR_2, S	0.0629, 0.2120, 1.05	0.0602, 0.1471, 1.00
Weight scheme	$W = 1/[\sigma^2(Fo^2) + (0.1214P)^2 + 0.4422P]$[b]	$W = 1/[\sigma^2(Fo^2) + (0.0546P)^2 + 1.4026P]$[b]

[a] Monoclinic crystals, λ 0.71073 Å, 293 K.
[b] $P = (Fo^2+2Fc^2)/3$.

Cl 12.10; N 9.20. $C_{17}H_{13}ClN_2O$. Calculated, %: C 68.81; H 4.42; Cl 11.95; N 9.44.

Ethyl 2-allylamino-2-phenylacetate (4). Allylamine, 0.6 g (10 mmol), was added dropwise at 10–15°C to a mixture of 2.43 g (10 mmol) of ethyl 2-bromo-2-phenylacetate and 1.38 g (10 mmol) of potassium carbonate in 10 mL of chloroform. The mixture was stirred for 30 min at room temperature and for 2 h at 35–40°C, cooled, and filtered, and the filtrate was washed with water, dried over $CaCl_2$, and evaporated. Yield 2.1 g (98%), viscous liquid; oxalate: mp 124–128°C (decomp.), R_f 0.65 (A). ^{1}H NMR spectrum, δ, ppm: 1.21 t (3H, CH_3, J = 7.1 Hz), 3.16 d.t (2H, NCH_2, J = 6.0, 1.5 Hz), 4.08 d.q and 4.16 d.q (1H each, OCH_2, J = 10.7, 7.1 Hz), 4.39 s (1H, NCH), 5.10 d.q (1H, J = 10.4, 1.5 Hz) and 5.15 d.q (1H, J = 16.9, 1.5 Hz) (=CH_2), 5.84 d.d.t (1H, =CH, J = 16.9, 10.4, 6.0 Hz), 7.00 br.s (3H, NH, COOH), 7.23–7.38 m (5H, H_{arom}). Found, %: C 58.55; H 6.27; N 4.34. $C_{13}H_{17}NO_2 \cdot (COOH)_2$. Calculated, %: C 58.25; H 6.19; N 4.53.

Ethyl 2-(*N*-allylbenzamido)-2-phenylacetate (5). Benzoyl chloride, 1.3 g (10 mmol), was added dropwise to a mixture of 2.19 g (10 mmol) of ester **4** and 1.05 g (10 mmol) of triethylamine in 10 mL of diethyl ether, cooled to 0–5°C. The mixture was stirred for 30 min at room temperature and for 2 h at 25–30°C, cooled, and treated with 50 mL of diethyl ether. The extract was washed with water, dried over Na_2SO_4, and evaporated. Yield 2.8 g (93%), viscous liquid, R_f 0.54 (C). IR spectrum, ν, cm^{-1}: 1712 (C=O), 1680 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.28 t (3H, CH_3, J = 7.1 Hz), 3.75 d.d and 3.89 d.d (1H each, NCH_2, J = 16.9, 5.5 Hz), 4.20 d.q and 4.23 d.q (1H each, OCH_2, J = 10.7, 7.1 Hz), 4.86 d.q (1H, J = 16.9, 1.5 Hz) and 4.89 d.q (1H, J = 10.3, 1.5 Hz) (=CH_2), 5.47 d.d.t (1H, =CH, J = 16.9, 10.3, 5.5 Hz), 5.54 s (1H, NCH), 7.39–7.53 m (8H, H_{arom}), 7.94–7.98 m (2H, H_{arom}). Found, %: C 74.43; H 6.68; N 4.19. $C_{20}H_{21}NO_3$. Calculated, %: C 74.28; H 6.55; N 4.33.

Ethyl 1-benzoyl-4-chloro-2-phenylpyrrolidine-2-carboxylate (6). A mixture of 3.23 g (10 mmol) of ester **5**, 0.9 g (10 mmol) of pyridine, and 10 mL of 1,2-dichloroethane was cooled to 0–5°C and saturated with gaseous chlorine until a gain in weight of 0.71 g (10 mmol Cl_2) was attained, and the mixture was left

overnight at room temperature. The mixture was diluted with 30 mL of 1,2-dichloroethane, washed with water, dried over $CaCl_2$, and evaporated. Dry potassium carbonate, 2.76 g (20 mmol), BTEAC, 0.12 g (5 mmol), and acetonitrile, 20 mL, were added to the residue, and the mixture was stirred for 4 h at 45–50°C. The mixture was cooled and filtered, the filtrate was evaporated, the residue was dissolved in chloroform, and the solution was washed with water, dried over $CaCl_2$, and evaporated. Yield 2.35 g (66%), mp 157–159°C (from EtOH), R_f 0.45 (D). IR spectrum, ν, cm^{-1}: 1735 (C=O), 1628 (C=O). ^1H NMR spectrum (mixture of two stereoisomers at a ratio of 3:2), δ, ppm: 1.29 t (1.8H) and 1.32 t (1.2H) (CH_3, J = 7.1 Hz), 2.41 d.d (0.6H, J = 13.4, 9.2 Hz), 2.76–2.88 m (0.8H) and 3.21 d.d (0.6H, CH_2, J = 13.4, 6.5 Hz), 3.70–3.79 m (0.8H) and 3.88 d.d (0.6H) (NCH_2, J = 10.9, 8.2 Hz), 4.09–4.32 m (3.4H, OCH_2, NCH_2, CHCl), 4.62 m (0.6H, CHCl), 7.23–7.65 m (10H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 13.6 and 13.7 (CH_3), 49.3 and 49.5 (NCH_2), 51.2 and 51.6 (CH), 56.8 and 57.7 (CH_2), 60.7 and 60.8 (OCH_2), 70.5 and 70.7 (C^2), 126.0, 126.3, 126.5, 126.7, 126.8, 127.0, 127.1, 127.9, 129.4 and 130.1 (CH, Ph), 135.1 and 135.8 (C^i), 137.7 and 138.9 (C^i), 168.4 and 169.1 (CO), 169.9 (CO). Found, %: C 67.40; H 5.15; Cl 10.2; N 4.0. $C_{20}H_{20}ClNO_3$. Calculated, %: C 67.13; H 5.63; Cl 9.91; N 3.91.

2-(Allylamino)-2-(2-benzyloxyphenyl)acetonitrile (7). A solution of 0.49 g (10 mmol) of sodium cyanide in 5 mL of water was added under stirring at room temperature to a solution of 2.12 g (10 mmol) of 2-(benzyloxy)benzaldehyde in 10 mL of ethanol. The mixture was stirred for 10 min, 0.6 g (10 mmol) of acetic acid was added, the mixture was stirred for 10 min, and a solution of 1.4 g (10 mmol) of allylamine in 10 mL of ethanol was added at 25–30°C. The mixture was stirred for 2 h at that temperature, treated with 10 mL of water and extracted with 1,2-dichloroethane. The extract was washed with water, dried over $CaCl_2$, and evaporated. Nitrile **7** was isolated as a viscous liquid, 2.4 g (88%), which was characterized as oxalate, mp 112–118°C (decomp.), R_f 0.42 (E). ^1H NMR spectrum, δ, ppm: 3.28 d.d.t (1H, J = 14.0, 6.3, 1.5 Hz) and 3.39 d.d.t (1H, J = 14.0, 5.5, 1.5 Hz) (NCH_2), 4.93 s (1H, NCH), 5.07 d.d.t (1H, $=CH_2$, J = 10.2, 1.7, 1.5 Hz), 5.18 s (2H, OCH_2), 5.22 d.d.t (1H, $=CH_2$, J = 17.1, 1.7, 1.5 Hz), 5.81 d.d.d.d (1H, =CH, J = 17.1, 10.2, 6.3, 5.5 Hz), 6.98 t.d (1H, 5-H, J = 7.5, 1.0 Hz), 7.03 d.d (1H, 3-H, J = 8.2, 1.0 Hz) and 7.27–7.33 m (2H, 4-H, 6-H, C_6H_4), 7.34–7.38 m (2H) and 7.44–7.48 m (3H, C_6H_5). Found, %: C 65.04; H 5.23; N 7.88. $C_{18}H_{18}N_2O\cdot(COOH)_2$. Calculated, %: C 65.21; H 5.47; N 7.60.

***N*-Allyl-*N*-[(2-benzyloxyphenyl)(cyano)methyl]-benzamide (8)** was synthesized as described above for compound **5** from 2.78 g (10 mmol) of nitrile **7**. Yield 2.4 g (63%), mp 109–110°C (from EtOH), R_f 0.45 (D). IR spectrum, ν, cm^{-1}: 2242 (C≡N), 1656 (C=O). ^1H NMR spectrum, δ, ppm: 3.64 d.d.t (1H, J = 16.4, 6.1, 1.3 Hz) and 3.92 d.d.t (1H, J = 16.4, 5.7, 1.3 Hz) (NCH_2), 4.87 d.q (1H, J = 17.0, 1.3 Hz) and 5.01 d.q (1H, J = 10.4, 1.3 Hz) ($=CH_2$), 5.15 s (2H, OCH_2), 5.60 d.d.t (1H, =CH, J = 17.0, 10.4, 5.7 Hz), 6.64 br.s (1H, NCH), 7.03 t.d (1H, J = 7.5, 0.8 Hz), 7.09 d (1H, J = 8.3 Hz), 7.22 m (2H), 7.31–7.44 m (9H, H_{arom}) and 7.64 d.d (1H, H_{arom}, J = 7.6, 1.6 Hz). Found, %: C 78.23; H 5.95; N 7.67. $C_{25}H_{22}N_2O_2$. Calculated, %: C 78.51; H 5.80; N 7.32.

1-Benzoyl-2-(2-benzyloxy-5-chlorophenyl)-4-chloropyrrolidine-2-carbonitrile (9) was synthesized as described above for compound **6** from 3.82 g (10 mmol) of nitrile **8**. Yield 0.9 g (20%), mp 197–198°C (from EtOH), R_f 0.48 (E). IR spectrum, ν, cm^{-1}: 2242 (C≡N), 1637 (C=O). ^1H NMR spectrum, δ, ppm: 2.99 br.d (1H, J = 15.0 Hz) and 3.12 br.d.d (1H, J = 15.0, 4.6 Hz) (CH_2), 3.52 br.d (1H, J = 12.0 Hz) and 3.80 br.d.d (1H, J = 12.0, 4.0 Hz) (NCH_2), 4.60 br.d.d (1H, CHCl, J = 4.6, 4.0 Hz), 5.19 d and 5.24 d (1H each, OCH_2, J = 10.8 Hz), 7.20–7.60 m (13H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 47.4 (CH_2), 55.7 (CH), 58.9 (CH_2), 60.1 (C^2), 70.6 (OCH_2), 114.3 (CH), 117.1 (CN), 124.6, 125.9, 126.8 (CH), 127.6 (CH), 127.7 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), 129.1 (CH), 130.0 (CH), 134.6, 135.4, 153.2, 166.7 (CO). Found, %: C 66.39; H 4.81; Cl 15.44; N 6.03. $C_{25}H_{20}Cl_2N_2O_2$. Calculated, %: C 66.53; H 4.47; Cl 15.71; N 6.21.

2-(Allylamino)-2-(4-benzyloxyphenyl)acetonitrile (10) was synthesized as described above for compound **7** from 2.12 g (10 mmol) of 4-(benzyloxyphenyl)benzaldehyde and was used in the next step without isolation and purification.

***N*-Allyl-*N*-[(4-benzyloxyphenyl)(cyano)methyl]-benzamide (11).** A solution of 1.05 g (10 mmol) of triethylamine in 10 mL of diethyl ether was added to nitrile **10**, the mixture was cooled to 0–5°C, 1.3 g (10 mmol) of benzoyl chloride was added dropwise, and the mixture was stirred for 30 min at room temperature and for 2 h at 25–30°C. The mixture was cooled and treated with 50 mL of diethyl ether, and the extract was washed with water, dried over Na_2SO_4, and

evaporated. Yield 2.7 g (70%), mp 95–97°C (from EtOH), R_f 0.66 (F). IR spectrum, ν, cm^{-1}: 2238 (C≡N), 1653 (C=O), 1633 (C=O). ^1H NMR spectrum, δ, ppm: 3.73 d.d.t (1H, J = 16.5, 6.2, 1.4 Hz) and 3.99 d.d.t (1H, J = 16.5, 5.6, 1.4 Hz) (NCH_2), 4.95 d.q (1H, J = 17.0, 1.4 Hz) and 5.05 d.q (1H, J = 10.3, 1.4 Hz) (=CH_2), 5.11 s (2H, OCH_2), 5.65 d.d.d.d (1H, =CH, J = 17.0, 10.3, 6.2, 5.6 Hz), 6.51 br.s (1H, NCH), 6.97–7.08 m (2H, H_{arom}), 7.25–7.50 m (12H, H_{arom}). Found, %: C 78.34; H 5.63; N 7.09. $C_{25}H_{22}N_2O_2$. Calculated, %: C 78.51; H 5.80; N 7.32.

1-Benzoyl-2-(4-benzyloxyphenyl)-4-chloropyrrolidine-2-carbonitrile (12). A mixture of 3.82 g (10 mmol) of nitrile **11**, 0.9 g (10 mmol) of pyridine, and 10 mL of 1,2-dichloroethane was cooled to 0–5°C and saturated with gaseous chlorine until a gain in weight of 0.71 g (10 mmol of Cl_2) was attained. The mixture was left overnight at room temperature, 30 mL of 1,2-dichloroethane was added, and the mixture was washed with water, dried over $CaCl_2$, and evaporated. The residue was mixed with 2.76 g (20 mmol) of anhydrous potassium carbonate, 0.12 g (5 mmol) of BTEAC, and 20 mL of acetonitrile, and the mixture was stirred for 4 h at 45–50°C. The mixture was cooled and filtered, the filtrate was evaporated, the residue was dissolved in chloroform, and the solution was washed with water, dried over $CaCl_2$, and evaporated. Yield 1.7 g (41%), mp 110–112°C (from EtOH), R_f 0.51 (G). IR spectrum, ν, cm^{-1}: 2238 (C≡N), 1640 (C=O). ^1H NMR spectrum, δ, ppm: 2.83 br.d.d (1H, J = 14.7, 4.7 Hz) and 3.03 d.t (1H, J = 14.7, 1.9 Hz) (CH_2), 3.82 br.d (1H, J = 12.0 Hz) and 4.56 d.d (1H, J = 12.0, 4.3 Hz) (NCH_2), 4.73–4.78 m (1H, CHCl), 5.10 s (2H, OCH_2), 6.96–7.03 m (2H, H_{arom}), 7.25–7.51 m (10H, H_{arom}), 7.56–7.68 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 51.4 (CH_2), 55.4 (CH), 59.4 (NCH_2), 60.8 (C^2), 69.2 (OCH_2), 114.6 (2C, CH), 118.0 (CN), 125.6 (2C, CH), 126.9 (2C, CH), 127.0 (2C, CH), 127.2 (CH), 127.8 (2C, CH), 127.9 (2C, CH), 130.1 (CH), 130.7, 134.8, 136.4, 158.0 (CO). Found, %: C 72.34; H 5.27; Cl 8.69; N 6.44. $C_{25}H_{21}ClN_2O_2$. Calculated, %: C 72.02; H 5.08; Cl 8.50; N 6.72.

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