Ring Size Influence on the Cyclocondensation Mode of GABA – Nitrile Imine Adducts

Bassam A. Abu Thaher[a], Jalal A. Zahra[b], Mustafa M. El-Abadelah[b], and W. Voelter[c]

[a] Chemistry Department, Faculty of Science, Islamic University of Gaza, Gaza Strip
[b] Chemistry Department, Faculty of Science, University of Jordan, Amman, Jordan
[c] Abteilung für Physikalische Biochemie, Physiologisch-chemisches Institut der Universität Tübingen, Hoppe-Seyler-Straße 4, D-72076 Tübingen, Germany

Reprint requests to Prof. Dr. W. Voelter. E-mail: wolfgang.voelter@uni-tuebingen.de

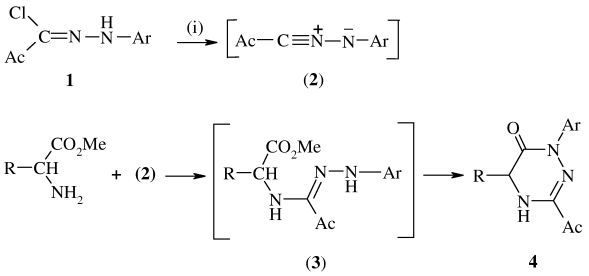
Z. Naturforsch. **59b,** 930 – 933 (2004); received April 27, 2004

γ-Aminobutyric acid (GABA) adds onto nitrile imine 1,3-dipolar species (generated *in situ* from their *N*-arylhydrazonoyl chloride precursors **1a-c**) to deliver the corresponding acyclic amidrazone adducts **10a-c**. In the presence of 1,1'-carbonyldiimidazole, the latter adducts undergo cyclocondensation involving the activated carboxyl and the amidrazone–CH_2NH groups to afford the respective *N*-[1-(arylhydrazono)-2-oxopropan-1-yl] pyrrolidin-2-ones (**11a-c**). The constitution of **10** and **11** is evidenced from analytical and spectral (IR , MS and NMR) data.

Key words: γ-Aminobutyric Acid (GABA), Nitrile Imine-GABA Adducts, Cyclocondensation, Pyrrolidin-2-ones

Introduction

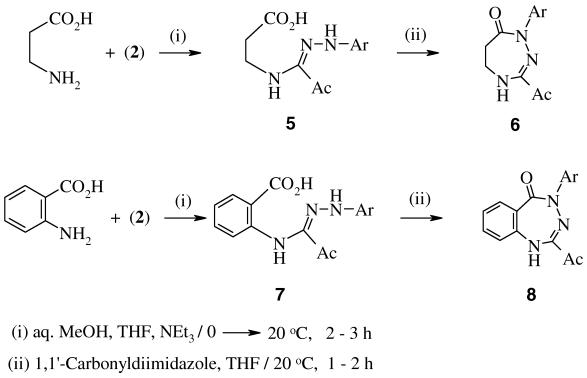
Recently we reported on the reaction of α-amino esters with nitrile imines **2** (generated from **1**), whereby the intermediate acyclic adducts **3** underwent spontaneous cyclocondensation to deliver the corresponding 4,5-dihydro-1,2,4-triazin-6-ones **4** (Scheme 1) [1]. The oxime and bis-imine derivatives of **4** were shown to act as a unique class of bidentate chelating agents, and their derived transition metal complexes, exemplified by Ni(II) [2], Cu(II) [3], and Pd(II) [4] bis-ligand complexes, display quite interesting structural features and properties.



(i) MeOH, THF, NEt_3 / 0 ⟶ 20 °C, 4 - 10 h

Scheme 1.

On the other hand, β-amino acids (exemplified by β-propionic and anthranilic acids) produce in their reaction with nitrile imines **2** the respective acyclic amidrazone adducts, **5** [5] and **7** [6, 7] as stable solid intermediates. Cyclization of the latter isolable adducts promoted by acetic anhydride or 1,1'-carbonyldiimidazole (CDI), yielded the corresponding seven-membered heterocyclic system, namely tetrahydro-1,2,4-triazepin-7-ones (**6**) [5] and 1,4-dihydro-1,3,4-benzotriazepin-5-ones (**8**) (Scheme 2) [6].



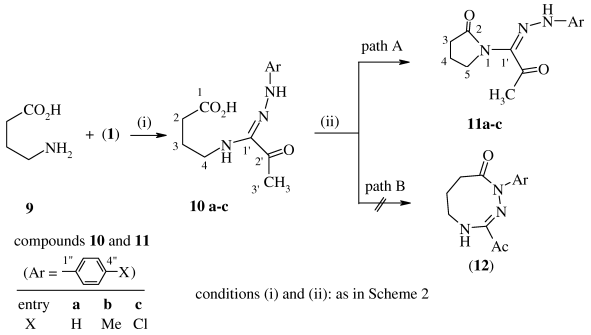
(i) aq. MeOH, THF, NEt_3 / 0 ⟶ 20 °C, 2 - 3 h

(ii) 1,1'-Carbonyldiimidazole, THF / 20 °C, 1 - 2 h

Scheme 2.

The present work aims at the investigation of the cyclocondensation of model acyclic amidrazone homologs **10a – c** which can be made accessible from interaction of γ-aminobutyric acid (GABA / **9**) with the

0932–0776 / 04 / 0800–0930 $ 06.00 © 2004 Verlag der Zeitschrift für Naturforschung, Tübingen · http://znaturforsch.com



Scheme 3.

appropriate *N*-arylhydrazonoyl chlorides **1a – c** and triethylamine (Scheme 3).

Results and Discussion

The reaction of γ-aminobutyric acid (**9**) with nitrile imines (1,3-dipoles, generated *in situ* from the corresponding hydrazonoyl chlorides **1a – c** by the action of triethylamine) is hitherto undescribed. Comparable to anthranilic acid [6, 7] and β-aminopropionic acid [5], compound **9** is expected to add selectively onto nitrile imines under basic conditons to produce the respective acyclic amidrazone adducts **10a – c**. Subsequent intramolecular cyclocondensation of adducts **10a – c** requires activation of the carboxyl group, brought about in this case by CDI as the coupling reagent. In principle, nucleophilic displacement at the activated carbonyl carbon (C-1) could involve either: (i) the amidrazone nitrogen CH_2-*N*H leading to five-membered pyrrolidin-2-ones (**11a – c**, path A / Scheme 3) or (ii) the hydrazone nitrogen Ar–*N*H that would form eight-membered 1,2,4-triazocine-5-ones **12a – c** (path B / Scheme 3). In practice, cyclocondensation of **10a – c** followed path A (a 5-*exo-trig* process) to deliver the corresponding *N*-substituted pyrrolidin-2-one derivatives **11a – c** (γ–lactams). Apparently, the course of cyclization is largely influenced by the ring size of the cyclic product and is demonstrated herein by the GABA adducts **10a – c** which result in the preferred formation of a five-membered ring over an eight-membered ring.

The constitutional formulae proposed for adducts **10a – c** and products **11a – c** are in accordance with elemental analyses, IR, MS, and NMR spectral data that are given in the Experimental Section. Thus, their IR spectra exhibit medium bands in the region 3200 – 3280 cm^{-1} (N-H stretching) and tow strong bands in the range of 1660 – 1710 cm^{-1} (C=O stretching). The MS spectra display the correct molecular ions for which the high resolution (HRMS) data are in good agreement with the calculated values. ^{1}H and ^{13}C signal assignments are based on DEPT and 2D (COSY, HMQC and HMBC) experiments. The ^{1}H NMR spectra of the acyclic adducts **10a – c** display two exchangeable singlet signals around δ 5.35 and 9.15 ppm assigned to the amidrazone N-*H* and the hydrazone ArN-*H* protons, respectively. By comparison, the former N-*H* signal is absent in the ^{1}H NMR spectra of the cyclic products **11a – c** while the hydrazone ArN-H signal is retained as a singlet around δ 10.45 ppm. Moreover, clear correlations are observed between the ArN-H proton and each of C=N / C-1" carbon resonances in HMBC experiments for the cyclic compounds **11a – c** as well as for their acyclic precursors **10a – c**. Collectively, these NMR data constitute diagnostic criteria with regard to the participation of the amidrazone nitrogen CH_2-*N*H (but not the hydrazone nitrogen Ar-*N*H) in the cyclization process (**10a – c** → **11a – c**).

In conclusion, amino acid – nitrile imine adducts show, in their cyclocondensation reactions, contrasting selectivity modes that are largely influenced by the ring size of the cyclized products. α-Amino esters produce six-membered triazinones, β-amino acids produce seven-membered triazepinones, whereas γ-amino acids (exemplified by GABA) produce five-membered pyrrolidinones.

γ-Aminobutyric acid (GABA) functions as an important inhibitory neurotransmitter [8]. The synthesized compounds **10a – c** and **11a – c** encompass GABA moiety as integral part of their constitution, and might thus exhibit interesting bioactivity.

Experimental Section

γ-Aminobutyric acid (GABA), 3-chloropentane-2,4-dione and 1,1'-carbonyldiimidazole were purchased from Acros. Melting points (uncorrected) were determined on a Gallenkamp apparatus. ^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX-300 instrument with Me_3Si as internal reference. EIMS spectra were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV at an ion source temperature of 200 °C. IR spectra were recorded as KBr discs on a Nicolet Impact-400 FT-IR spectrophotometer. Microanalyses were preformed at the Microanalytical Laboratory – Inorganic Chemistry Department, Tübingen University, Germany.

*1-(N-Arylhydrazono)-1-chloropropanones (***1a** – **c***)*

The hydrazonoyl chlorides **1a** [1, 9, 10], **1b** [1, 9] and **1c** [1, 9, 10] were previously characterized and were prepared in

this study *via* the Japp-Klingemann reaction [11, 12] involving direct coupling of the appropriate arenediazonium chloride with 3-chloropentane-2,4-dione in aqueous pyridine, following standard procedures [1, 9].

*4-{[2-Oxo-1-(phenylhydrazono)propan-1-yl]amino}-butanoic acid (***10a***)*

To a stirred and cooled (0 °C) solution of 1-(*N*-phenylhydrazono)-1-chloropropanone **1a** (2.15 g, 11 mmol) in tetrahydrofuran (40 ml) was added dropwise a solution of γ-aminobutyric acid (**9**) (1.0 g, 10 mmol) in water–methanol (30 ml, 5:1 v/v) and triethylamine (5.0 g, 50 mmol). The resultant mixture was stirred at 2 – 10 °C for 3 h. The organic solvents were then removed *in vacuo* and the remaining aqueous solution was acidified with glacial acetic acid (3 ml) whereby a gummy product was formed. This crude product was purified using silica gel column chromatography, with dichloromethane-methanol (1 – 10% v/v) as eluent, to afford the pure title compound. Yield of **10a**: 1.50 g (57%), m. p. 92 – 93 °C. – IR(KBr): $\tilde{\nu}$ = 3272 (br, N-H), 3026, 2958, 2932 (C-H), 1710 (C=O), 1672, 1602, 1494, 1362, 1292, 1233, 1167 cm^{-1}. – MS: *m/z* (%) = 263 (88) [M^+], 245 (27), 228 (16), 202 (23), 177 (17), 149 (93), 118 (20), 108 (100), 92 (52). – HRMS for $C_{13}H_{17}N_3O_3$: calcd. 263.12699, found 263.12510. – ^{1}H NMR (300 MHz, [D_6]-DMSO): δ = 1.61 (tt, J = 7.1 Hz, 6.8 Hz, 2H, 3-H_2), 2.23 (t, J = 7.1 Hz, 2H, 2-H_2), 2.34 (s, 3H, CH_3), 3.22 (br t, J = 6.8 Hz, 2H, 4-H_2), 5.29 (br s, 1H, (Ar) N-*H*), 6.75 (t, J = 7.0 Hz, 1H, 4”-H), 7.12 (d, J = 8.0 Hz, 2H, 2”-H / 6”-H), 7.18 (dd, J = 7.0 Hz, 8.0 Hz, 2H, 3”-H / 5”-H), 9.13 (s, 1H, (C4) N-*H*). – ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 25.7 (CH_3), 26.6 (C-3), 31.4 (C-2), 42.7 (C-4), 113.5 (C-2” / C-6”), 120.0 (C-4”), 129.5 (C-3” / C-5”), 141.8 (N=*C*-1’), 145.8 (C-1”), 174.8 (O=*C*-OH), 194.5 (Me-*C*=O). – $C_{13}H_{17}N_3O_3$ (263.30): calcd. C 59.30, H 6.51, N 15.96; found C 59.41, H 6.56, N 15.68.

*4-{[(1-(4-Methylphenylhydrazono)-2-oxopropan-1-yl]-amino}butanoic acid (***10b***)*

This compound was prepared from the reaction of **9** (1.0 g, 10 mmol) and 1-chloro-1-(4-methylphenylhydrazono)propanone **(1b)** (2.3 g, 11 mmol) by following the same procedure and experimental conditions as described above for obtaining **10a**. Yield of **10b**: 1.47 g (53%), m. p. 111 – 112 °C. – IR (KBr): $\tilde{\nu}$ = 3264 (N-H), 3249 (N-H), 3023, 2921, 2906 (C-H), 1706 (C=O), 1665, 1588, 1532, 1476, 1364, 1241, 1183, 1110 cm^{-1}. – MS: *m/z* (%) = 277 (91) [M^+], 259 (100), 242 (44), 216 (35), 201 (30), 164 (18), 149 (34), 132 (27), 122 (74), 106 (87), 91 (46). – HRMS for $C_{14}H_{19}N_3O_3$: calcd. 277.14264, found 277.14369. – ^{1}H NMR (300 MHz, [D_6]-DMSO): δ = 1.59 (m, 2H, 3-H_2), 2.15 (s, 3H, Ar-CH_3), 2.22 (t, J = 6.5 Hz, 2H, 2-H_2), 3.18 (br t, 2H, 4-H_2), 2.31 (s, 3H, CH_3-CO), 5.32 (br s, 1H, (C4)N-*H*), 7.03 (d, J = 8.0 Hz, 2H, 2”-H / 6”-H), 6.98 (d, J = 8.0 Hz, 2H, 3”-H / 5”-H”), 9.17 (s, 1H, Ar N-*H*). – ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 20.8 (Ar-*C*H_3), 25.7 (*C*H_3CO), 26.8 (C-3), 31.8 (C-2), 42.9 (C-4), 113.4 (C-2” / C-6”), 128.5 (C-4”), 129.9 (C-3” / C-5”), 141.5 (N=*C*-1’), 143.5 (C-1”), 175.3 (O=*C*-OH), 194.3 (Me-*C*=O). – $C_{14}H_{19}N_3O_3$ (277.33): calcd. C 60.63, H 6.91, N 15.15; found C 60.44, H 6.78, N 14.92.

*4-{[(1-(4-Chlorophenylhydrazono)-2-oxopropan-1-yl]-amino}butanoic acid (***10c***)*

This compound was prepared from the reaction of **9** (1.0 g, 10 mmol) and 1-chloro-1-(4-chlorophenylhydrazono)propanone **(1c)** (2.5 g, 11 mmol) by following the same procedure and experimental conditions as described above for obtaining **10a**. Yield of **10c**: 1.88 g (63%), m. p. 109 – 110 °C. – IR (KBr): $\tilde{\nu}$ = 3277 (N-H), 3236 (N-H), 3031, 2940, 2927 (C-H), 1710 (C=O), 1663, 1590, 1496, 1473, 1364, 1241, 1196, 1170, 1117 cm^{-1}. – MS: *m/z* (%) = 297 (65) [M^+], 279 (9), 236 (11), 219 (100), 193 (27), 164 (73), 149 (40), 142 (66), 127 (65), 99 (35). – HRMS: for $C_{13}H_{16}N_3O_3Cl$: calcd. 297.08802, found 297.08651. – ^{1}H NMR (300 MHz , [D_6]-DMSO): δ = 1.61 (tt, J = 6.0 Hz, 7.2 Hz, 2H, 3-H_2), 2.19 (t, J = 7.2 Hz, 2H, 2-H_2), 2.34 (s, 3H, CH_3), 3.22 (t, J = 6.0 Hz, 2H, 4-H_2), 5.39 (s, 1H, (C4) N-*H*), 7.11 (d, J = 8.8 Hz, 2H, 2”-H / 6”-H), 7.21 (d, 2H, J = 8.8 Hz, 2H, 3”-H / 5”-H), 9.20 (s, 1H, (Ar) N-*H*). – ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 25.8 (CH_3), 26.4 (C-3), 26.7 (C-2), 42.9 (C-4), 114.9 (C-2” / C-6”), 123.2 (C-4”), 129.2 (C-3” / C-5”), 142.2 (N=*C*-1’), 144.8 (C-1”), 174.9 (O=*C*-OH), 194.3 (Me-*C*=O). – $C_{14}H_{19}N_3O_3$ (297.74): calcd. C 52.44, H 5.42, N 14.11, Cl 11.91; found C 52.16, H 5.32, N 14.04, Cl 11.65.

*N-[2-Oxo-1-(phenylhydrazono)propan-1-yl]pyrrolidin-2-one (***11a***)*

To a stirred and cooled (0 °C) solution of **10a** (1.3 g, 5 mmol) in dry tetrahydrofuran (80 ml) 1,1’-carbonyldiimidazole (CDI / 1.0 g , 6.2 mmol) was added portionwise. The reaction mixture was further stirred at 0 – 5 °C for 2 h and then treated with cold water (100 ml). The organic solvent was evaporated under reduced pressure and the remaining aqueous solution was extracted with dichloromethane (2 × 60 ml). The residual crude product was purified by column chromatography on silica gel, eluting with dichloromethane–methanol (1 – 5% v/v) to deliver the pure title compound. Yield of **11a**: 0.59 g (48%), m. p. 139 – 140 °C. – IR (KBr): $\tilde{\nu}$ = 3202 (N-H), 2960, 2893 (C-H), 1698 (C=O), 1670 (C=O, lactam), 1601, 1557, 1493, 1398, 1356, 1268, 1242, 1163 cm^{-1}. – MS: *m/z* (%) = 245 (100) [M^+], 228 (61), 217 (2), 202 (58), 185 (50),

160 (23), 149 (18), 130 (40), 118 (15), 92 (36). – HRMS for $C_{13}H_{15}N_3O_2$: calcd. 245.11643, found 245.11587. – ^{1}H NMR (300 MHz, [D$_6$]-DMSO): $\delta = 2.15$ (tt, $J = 6.8$ Hz, 7.2 Hz, 2H, 4-H$_2$), 2.36 (t, $J = 7.2$ Hz, 2H, 3-H$_2$), 2.38 (s, 3H, CH$_3$), 3.43 (t, $J = 6.8$ Hz, 2H, 5-H$_2$), 6.99 (m, 1H, 4”-H), 7.33 (m, 4H, 2”-H/ 6”-H, 3”-H/ 5”-H), 10.50 (s, 1H, N-H). – ^{13}C NMR (75 MHz, [D$_6$]-DMSO): $\delta = 19.3$ (C-4), 25.2 (CH$_3$), 30.4 (C-3), 46.3 (C-5), 114.9 (C-2” / C-6”), 122.7 (C-4”), 129.8 (C-3” / C-5”), 132.5 (N=*C*-1’), 143.5 (C-1”), 176.1 (C-2), 191.5 (Me-*C*=O). – $C_{13}H_{15}N_3O_2$ (245.28): calcd. C 63.66, H 6.16, N 17.13; found C 63.60, H 6.02, N 16.88.

*N-[1-(4-Methylphenylhydrazono)-2-oxopropan-1-yl]-pyrrolidin-2-one (***11b***)*

This compound was prepared from **10b** (1.4 g , 5 mmol) and CDI (1.0 g, 6.2 mmol) by following the same procedure and experimental conditions as described above for the preparation of **11a**. Yield of **11b**: 0.57 g (44%), m. p. 149 – 150 °C. – IR (KBr): $\tilde{\nu} = 3230$ (N-H), 2921 (C-H), 1694 (C=O), 1668 (C=O, lactam), 1614, 1551, 1518, 1457, 1407, 1331, 1244, 1155 cm^{-1}. – MS: *m/z* (%) = 259 (100) [M$^+$], 242 (52), 231 (2), 216 (35), 199 (31), 174 (15), 149 (27), 144 (23), 132 (16), 105 (64), 91 (19). – HRMS for $C_{14}H_{17}N_3O_2$: calcd. 259.13208, found 259.13378. – ^{1}H NMR (300 MHz, [D$_6$]-DMSO): $\delta = 2.12$ (m, 2H, 4-H$_2$), 2.16 (s, 3H, Ar-C*H*$_3$), 2.33 (br t, 2H, 3-H$_2$), 2.37 (s, 3H, C*H*$_3$-CO), 3.41 (t, $J = 6.6$ Hz, 2H, 5-H$_2$), 7.14 (d, $J = 7.9$ Hz, 2H, 3”-H / 5”-H), 7.26 (d, $J = 7.9$ Hz, 2H, 2”-H / 6”-H), 10.42 (s, 1H, N-H). – ^{13}C NMR (75 MHz, [D$_6$]-DMSO): $\delta = 19.3$ (C-4), 20.8 (Ar-*C*H$_3$), 25.1 (*C*H$_3$CO), 30.4 (C-3), 46.2 (C-5), 114.9 (C-2” / C-6”), 130.2 (C-3” / C-5”), 131.7 (C-4”), 132.1 (N=*C*-1’), 141.2 (C-1”), 176.1 (C-2), 191.3 (Me-*C*=O). – $C_{14}H_{17}N_3O_2$ (259.31): calcd. C 64.85, H 6.61, N 16.20; found C 64.37, H 6.48, N 16.12.

*N-[1-(4-Chlorophenylhydrazono)-2-oxopropan-1-yl]-pyrrolidin-2-one (***11c***)*

This compound was prepared from **10c** (1.5 g, 5 mmol) and CDI (1.0 g, 6.2 mmol) by following the same procedure and experimental conditions as described above for the preparation of **11a**. Yield of **11c**: 0.77 g (55%), m. p. 171 – 172 °C. – IR (KBr): $\tilde{\nu} = 3256$ (N-H), 3076, 2938 (C-H), 1686 (C=O), 1661 (C=O, lactam), 1597, 1562, 1504, 1361, 1327, 1246, 1153, 1087cm^{-1}. – MS: *m/z* (%) = 279 (100) [M$^+$], 262 (53), 251 (2), 236 (48), 219 (22), 194 (27), 164 (18), 152 (26), 125 (46), 111 (21), 99 (35). – HRMS for $C_{13}H_{14}N_3O_2Cl$: calcd. 279.07746, found 279.07977. – ^{1}H NMR (300 MHz, [D$_6$]-DMSO): $\delta = 2.15$ (tt, $J = 6.9$ Hz, 7.4 Hz, 2H, 4-H$_2$), 2.36 (t, $J = 7.4$ Hz, 2H, 3-H$_2$), 2.38 (s, 3H, CH$_3$), 3.42 (t, $J = 6.9$ Hz, 2H, 5-H$_2$), 7.35 (d, $J = 9.2$ Hz, 2H, 2”-H / 6”-H), 7.38 (d, $J = 9.2$ Hz, 2H, 3”-H / 5”-H), 10.51 (s, 1H, N-H). – ^{13}C NMR (75 MHz, [D$_6$]-DMSO): $\delta = 19.4$ (C-4), 25.2 (CH$_3$), 30.4 (C-3), 46.3 (C-5), 116.5 (C-2” / C-6”), 126.2 (C-4”), 129.7 (C-3” / C-5”), 133.1 (N=*C*-1’), 142.5 (C-1”), 176.1 (C-2), 191.5 (Me-*C*=O). – $C_{13}H_{14}N_3O_2Cl$ (279.73): calcd. C 55.82, H 5.04, N 15.02, Cl 12.67; found C 55.68, H 5.12, N 14.74, Cl 12.35.

Acknowledgements

We thank the Deanship of Scientific Research-Jordan University (Amman) and BMBF (Bonn, Germany) for financial support.

[1] M. M. El-Abadelah, A. Q. Hussein, B. A. Abu Thaher, Heterocycles **32**, 1879 (1991).
[2] a) A. S. Abushamleh, M. M. El-Abadelah, W. Voelter, Z. Naturforsch. **55b**, 1074 (2000); b) A. S. Abushamleh, M. M. El-Abadelah, C. M. Mössmer, Heterocycles **53**, 1155 (2000).
[3] M. M. El-Abadelah, A. S. Abushamleh, C. M. Mössmer, W. Voelter, Z. Naturforsch. **57b**, 547 (2002).
[4] a) A. S. Abushamleh, M. M. El-Abadelah, C. M. Mössmer, Heterocycles **53**, 1737 (2000); b) A. S. Abushamleh, M. M. El-Abadelah, W. Voelter, J. Chem. Soc. Pak. **24**, 31 (2002).
[5] B. A. Abu Thaher, J. A. Zahra, M. M. El-Abadelah, H.-H. Otto, Monatsh. Chem. **135**, 435 (2004).
[6] a) B. A. Abu Thaher, J. A. Zahra, M. M. El-Abadelah, J. Heterocycl. Chem. **39**, 901 (2002); b) J. A. Zahra, B. A. Abu Thaher, M. M. El-Abadelah, M. Klinga, Heterocycles **57**, 2365 (2002).
[7] P. Trimarco, C. Lastrucci, J. Heterocycl. Chem. **13**, 913 (1976).
[8] E. Roberts, M. A. Sherman, Neurochem Res. **18**, 365 (1993).
[9] N. F. Eweiss, A. Osman, J. Heterocycl. Chem. **17**, 1713 (1980).
[10] R. Fusco, R. Romani, Gazz. Chem. Ital. **76**, 419 (1946).
[11] a) R. R. Phillips, Org. Reactions **10**, 143 (1959); b) H. C. Yao, P. Resnick, J. Am. Chem. Soc. **84**, 3514 (1962).
[12] G. C. Barrett, M. M. El-Abadelah, M. K. Hargreaves, J. Chem. Soc. (C) 1986 (1970).