CYCLOCONDENSATION REACTIONS OF NITRILIMINES: SYNTHESIS OF 1,2,4-TRIAZIN-6-ONES AND 1,2,4,5-TETRAZINES

Adel M. Awadallah*[a], Abdel-Rahman S. Ferwanah[b], Emtithal A. El-Sawi[c], Hany M. Dalloul[c]
a) Chemistry Department, Faculty of Science, Islamic University of Gaza, Gaza, Palestine. E-mail: awada@mail.iugaza.edu
b). Chemistry Department, Faculty of Science, Al-Azhar University of Gaza, P. O. Box-1277, Gaza, Palestine. E-mail: ferwanah@hotmail.com
c) Chemistry Department, University College for Women, Ain Shams University, Heliopolis, Cairo, Egypt

Abstract

Nitrilimines 2a-c react with α-amino esters 3-7 to afford 1,2,4-triazin-6-ones 9-13. The reaction of nitrilimines with the aza analogues of amnio esters 1-ethoxycarbonyl-1-methylhydrazine 8 gives the acyclic adducts 14a-c which undergo thermal oxidative cyclization at CH_3 to give the unexpected 1,2,4,5-tetrazines 15a-c rather than the expected tetrazinones 16a-c.

Introduction

Nitrilimines are known to undergo cyclocondensation reactions with nucleophiles incorporating suitably located electrophilic centers to give various heterocyclic systems (1,2). The reaction of C-acetyl-N-aryl-nitrilimines 2a with α-amino esters was recently reported to give 4,5-dihydro-1,2,4-triazin-6-ones (3,4). Their reaction with 1-ethoxycarbonyl-1-methylhydrazine (aza analogues of amino esters) was recently reported by our group to yield, however, the acyclic adducts 14a. Thermal oxidative cyclization of these compounds gave the unexpected tetrahydro-1,2,4,5-tetrazines rather than the expected tetrazinones 16a (5).

Many triazines and triazinones are biologically active (6). A number of synthetic 1,2,4-triazin-3-ones (7) and -5-ones (8) were reported to possess pronounced herbicidal and platelet aggregation activity, respectively.

The antitumor activity of 6-acetyl-4-aryl-2-ethoxycarbonyl-1,2,3,4-tetrahydro-s-tetrazines which we have recently synthesized is now under investigation by the national cancer institute (USA) (9).

In continuation of this work, we investigated the reaction of C-benzoyl and C-2-naphthoyl-N-aryl nitrilimines 2b-c with some α-amino esters 3-7 and with 1-ethoxycarbonyl-1-methylhydrazine 8 in an attempt to synthesize new substituted 1,2,4-triazin-6-ones and 1,2,4,5-tetrazines.

Experimental

Melting points were determined on Electrothermal Mel. Temp. apparatus and are uncorrected. IR spectra were obtained by using Perkin-Elmer 237 infrared specrometer (KBr discs). The vibrational frequencies are expressed in cm^{-1}. ^1H- and ^{13}C-NMR spectra were recorded on a Brucker 300 MHz instrument for solutions in $CDCl_3$ at 21 °C. Chemical shifts are expressed in parts per million (δ) downfield from internal TMS. Electron impact mass spectra were run on Finnigan Mat 8200 and 8400 spectrometers at 70 eV. Elemental analysis was done at Cairo university-Egypt. Glycine, DL-alanine, DL-

phenylglycine, L-benzylcyctine, L-histidine were purchased from Aldrich (biochemical grade). Hydrazonoyl halides 1b (10), 1c (11); amino esters 3-7 (12), 1-ethoxycarbonyl-1-methylhydrazine 8 (13) were prepared according to known literature procedures.

Reaction of Hydrazonoyl Halides (1) with α-Amino Esters 3-7

To a stirred solution of the appropriate hydrazonoyl halides 1b,c (0.01 mol) in tetrahydrofuran (100 ml) was added a solution of the particular amino acid ester hydrochloride 3-7 (0.015 mol) in methanol (40 ml). The reaction mixture was cooled (-5 – 0 °C) and triethylamine (0.05 mol) was dropwise added. Stirring was continued for 2 h (0 °C) and then for a further 12 h (20 °C). The solvent was removed under reduced pressure, and the residue was washed with water. The residual solid product was collected and recrystallized from aqueous ethanol to give the desired compounds.

The following compounds were obtained by this method:

3-Benzoyl-1-(4-chlorophenyl)-4,5-dihydro-1,2,4-triazin-6-one 9b

^{1}H NMR: 8.2-7.2 (m, 9H, aromatic protons), 6.2 (s, 1H, NH), 4.2 (s, 2H, CH_2); ^{13}C NMR: 185.49 (Ph-C=O), 158.97 (C=O), 139.07 (C=N), 142.56, 134.52, 133.67, 132.19, 131.14, 128.73, 128.24, 125.55 (8 aromatic carbons), 43.95 (CH_2); IR: 3360 (NH), 1692 (C=O), 1655 (Ph-C=O).

3-Benzoyl-1-(4-chlorophenyl)-5-methyl-4,5-dihydro-1,2,4-triazin-6-one 10b

^{1}H NMR: 8.2-7.2 (m, 9H, aromatic), 6.2 (s, 1H, NH), 4.3 (q, 1H, CH), 1.5 (d, 2H, CH_3); ^{13}C NMR: 185.69 (Ph C=O), 162.58 (C=O), 139.31 (C=N), 142.64, 134.57, 133.64, 132.09, 131.15, 128.68, 128.23, 125.62 (8 aromatic carbons), 49.65 (CH), 19.48 (CH_3); IR: 3361 (NH), 1690 (C=O), 1653 (Ph-C=O).

3-Benzoyl-1-(4-chlorophenyl)-5-phenyl-4,5-dihydro-1,2,4-triazin-6-one 11b

^{1}H NMR: 8.3-7.2 (m, 14H, aromatic protons), 6.6 (s, 1H, NH), 5.3 (s, 1H, CH); ^{13}C NMR: 185.51(Ph-C=O), 160.22 (C=O), 139.32 (C=N), 142.01, 138.14, 134.56, 133.78, 132.22, 131.25, 129.22, 129.07, 128.68, 128.30, 126.68, 125.64 (12 aromatic carbons), 57.95 (CH). IR: 3355 (NH), 1698 (C=O), 1648 (Ph-C=O).

3-Benzoyl-5-(S-benzylmethyl)-1-(4-chlorophenyl)-4,5-dihydro-1,2,4-triazin-6-one 12b

^{1}H NMR: 8.3-7.2 (m, 16H, aromatic protons), 6.6 (s, 1H, NH), 4.2 (t, 1H, CH), 3.8 (s, 2H, SCH_2Ph), 3.0 (d, 2H, CH_2S); ^{13}C NMR: δ/ppm 184.90 (Ph-C=O), 160.67 (C=O), 139.18 (C=N), 142.03, 138.17, 134.75, 133.75, 132.24, 131.25, 129.24, 129.05, 128.71, 128.35, 126.65, 125.68 (12 aromatic carbons), 53.24 (CH), 36.67 (CH_2), 35.51 (CH_2); IR: 3273 (NH), 1678 (C=O), 1652 (Ph-C=O).

3-Benzoyl-1-(4-chlorophenyl)-5-histidyl-4,5-dihydro-1,2,4-triazin-6-one 13b

^{1}H NMR: 8.2-7.3 (m, 11H, aromatic protons), 7.1 (s, 1H, NH), 6.9 (s, 1H, NH), 4.5 (t, 1H, CH), 3.1 (d, 2H, CH_2); ^{13}C NMR: 185.71 (Ph-C=O), 161.78 (C=O), 139.23 (C=N), 142.83, 135.40, 134.62, 134.40, 133.49, 132.14, 131.03, 128.64, 128.13, 125.71, 116.17 (11 aromatic carbons), 53.98 (CH), 30.96 (CH_2); IR: 3376, 3273 (NH), 1679 (C=O), 1662 (Ph-C=O).

1-(4-Chlorophenyl)-3-(2-naphthoyl)-4,5-dihydro-1,2,4-triazin-6-one 9c

^{1}H NMR: 8.9-7.2 (m, 11H, aromatic protons), 6.2 (s, 1H, NH), 4.3 (s, 2H, CH_2); ^{13}C NMR: 185.07 (2-Naph-C=O), 158.98 (C=O), 139.14 (C=N), 142.82, 135.75, 134.05, 132.23, 132.13, 131.73, 129.97, 129.06, 128.72, 127.99, 127.77, 126.91, 125.99, 125.39 (14 aromatic carbons), 43.97 (CH_2); IR: 3385 (NH), 1670 (C=O), 1638 (2-Naph-C=O).

1-(4-Chlorophenyl)-5-methyl-3-(2-naphthoyl)-4,5-dihydro-1,2,4-triazin-6-one 10c

^{1}H NMR: 8.9-7.2 (m, 11H, aromatic protons), 6.2 (s, 1H, NH), 4.3 (q, 1H, CH), 1.6 (d, 2H, CH_3); ^{13}C NMR: 185.25 (2-Naph-C=O), 162.58 (C=O), 139.40 (C=N), 142.89, 135.74, 134.04, 132.24, 132.03, 131.77, 129.98, 129.04, 128.67, 127.99, 127.78, 126.91, 126.03, 125.46 (14 aromatic carbons), 49.68 (CH), 19.46 (CH_3); IR: 3349 (NH), 1687 (C=O), 1643 (2-Naph-C=O).

1-(4-Chlorophenyl)-3-(2-naphthoyl)-5-phenyl-4,5-dihydro-1,2,4-triazin-6-one 11c

^{1}H NMR: 9.0-7.3 (m, 16H, aromatic protons), 6.7 (s, 1H, NH), 5.4 (s, 1H, CH); ^{13}C NMR: 184.99 (2-Naph-C=O), 160.13 (C=O), 139.30 (C=N), 142.17, 138.05, 135.71, 134.09, 132.17, 132.06, 131.67, 129.93, 129.15, 129.04, 128.99, 128.58, 127.97, 127.72, 126.87, 126.62, 125.97, 125.40 (18 aromatic carbons), 57.93 (CH); IR: 3367 (NH), 1682 (C=O), 1638 (2-Naph-C=O).

5-(S-Benzylmethyl)-1-(4-chlorophenyl)-3-(2-naphthoyl)-4,5-dihydro-1,2,4-triazin-6-one 12c

^{1}H NMR: 8.9-7.2 (m, 16H, aromatic protons), 6.6 (s, 1H, NH), 4.2 (t, 1H, CH), 3.79 (s, 2H, SCH_2Ph), 3.13-2.83 (d, 2H,CH_2S); ^{13}C NMR 184.99 (2-Naph-C=O), 160.67 (C=O), 139.18 (C=N), 142.32, 137.57, 135.75, 134.05, 132.24, 131.75, 129.99, 129.05, 128.99, 128.86, 128.72, 128.00, 127.80, 127.53, 126.91, 126.05, 125.48 (18 aromatic carbons), 53.04 (CH), 36.77 (CH_2), 35.60 (CH_2); IR: 3372 (NH), 1681 (C=O), 1639 (2-Naph-C=O).

1-(4-Chlorophenyl)-5-histidyl-3-(2-naphthoyl)-4,5-dihydro-1,2,4-triazin-6-one 13c

^{1}H NMR: 8.9-7.3 (m, 13H, aromatic protons), 7.1 (s, 1H, NH), 7.0 (s, 1H, NH), 4.5 (t, 3H, CH), 3.1 (d, 2H, CH_2); ^{13}C NMR: 184.10 (2-Naph-C=O), 161.13 (C=O), 139.32 (C=N), 142.71, 135.25, 134.99, 134.29, 133.87, 132.24, 132.16, 131.57, 129.91, 128.87, 128.63, 127.86, 127.72, 127.51, 126.78, 126.00, 125.54 (17 aromatic carbons), 54.02 (CH), 30.84 (CH_2). IR: 3336, 3310 (NH), 1681 (C=O), 1659 (2-Naph-C=O).

Reaction of Nitrilimines 1 with 1-Ethoxyxarbonyl-1-methylhydrazine 8

Triethylamine (5.0 g, 0.05 mol) in THF (20 mL) was dropwise added to a stirred cold solution (0 °C) of hydrazonoyl halides 1b-c (0.01 mol) and 1-ethoxycarbonyl-1-methylhydrazine 8 (0.02 mol) in THF (100 ml) Stirring was continued overnight (20 °C). The solvent was removed in vacuo, and the residue was washed with water. The resulting crude solid product was collected and recrystallized from a suitable solvent.

4-Benzoyl-6-(4-chlorophenyl)-2-methyl-2,3,5,6-tetraazahex-4-enoic acid ethyl ester 14b

^{1}H NMR: 10.35 (s, 1H, NH-Ar), 8.09-7.07 (m, 9H, aromatic), 6.54 (s, 1H, NH), 4.31-4.24 (q, 2H, CH_2, *J*=7Hz), 3.14 (s, 3H, N-CH_3), 1.34-1.29 (t, 3H, CH_3, *J*=7Hz); ^{13}C NMR: 187.52 (ph-C=O), 158.19 (O-C=O), 136.51 (C=N), 141.87, 136.40, 132.23, 130.69, 129.38, 127.90, 127.07, 115.47 (8 aromatic carbons), 63.09 (CH_2), 37.14 (N-CH_3), 14.65 (CH_3); IR: 3294, 3204 (NH), 1700 (O-C=O), 1626 (Ph-C=O), 1599 (C=N).

6-(4-Chlorophenyl)-2-methyl-4-(2-naphthoyl)-2,3,5,6-tetraazahex-4-enoic acid ethyl ester 14c

^{1}H NMR: 10.41 (s, 1H, NH-Ar), 8.72-7.1 (m, 11H, aromatic), 6.62 (s, 1H, NH), 4.32-4.25 (q, 2H, CH_2, *J*=7Hz); ^{13}C NMR: 187.22 (2-Naph-C=O), 158.2 (O-C=O), 136.63 (C=N), 141.89, 135.11, 133.55, 132.61, 132.33, 129.51, 129.39, 128.22, 127.71, 127.50, 127.00, 126.63, 126.47, 115.40 (14 aromatic carbons), 63.09 (O-CH_2), 37.20 (N-CH_3), 14.66 (CH_3); IR: 3314 (NH), 1705 (O-C=O), 1624 (C=O), 1597 (C=N).

Thermal Cyclization of Compounds 14b,c

Compounds 14b,c (0.005 mol) and charcoal (0.5 –1.0 g) in toluene (50 mL) were heated to reflux 2-4 h. The reaction mixture was filtered and the solvent was minimized. Petroleum ether (bp. 40-60 °C) was then added to effect complete crystallization of the desired cyclic compounds 15b,c.

6-Benzoyl-4-(4-chlorophenyl)-2-ethoxycarbonyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine 15b

^{1}H NMR: 9.59/9.20 (s, 1H, NH), 8.11-7.13 (m, 9 H, aromatic), 5.10/4.98 (s, 2H, NCH_2N), 4.17/4.00 (q, 2H, O-CH_2), 1.20/1.08 (t, 3H, CH_3); ^{13}C NMR: ($CDCl_3$): δ/ppm 186.49/186.00, (Ph-C=O), 156.87/152.20 (O-C=O), 143.53/141.40 (C=N), 148.83/144.26, 140.17/136.26, 135.40/133.92, 133.16/131.28, 130.76/129.49, 128.60/128.55, 126.91/125.53, 119.66/116.54 (8 aromatic carbons), 60.54/56.28 (NCH_2N), 63.22/62.24 (OCH_2), 14.82 (CH_3); IR: 3299 (NH), 1700 (O-C=O), 1632 (Ph-C=O) and 1594 (C=N).

4-(4-Chlorophenyl)-2-ethoxycarbonyl-6-(2-naphthoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazine 15c

^{1}H NMR: 9.72/9.32 (s, 1H, NH), 8.75-7.19 (m, 11 H, aromatic protons), 5.17/5.04 (s, 2H, NCH_2N), 4.21/4.04 (q, 2H, OCH_2), 1.24/1.13 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ/ppm 185.61/185.26 (2-Naph-C=O), 156.45/ 152.73 (O-C=O), 143.12/139.87 (C=N), 148.41/143.82, 135.10/ 134.73, 133.96/133.81, 133.49/132.99, 132.22/132.10, 131.82/ 131.71, 129.69/129.50, 129.06/129.01, 128.64/127.73, 127.65/ 127.55, 127.04/126.98, 126.41/125.94, 125.74/125.02, 119.20/ 116.05 (14 aromatic carbons), 60.54/56.28 (NCH_2N), 63.22/62.24 (OCH_2), 14.82 (CH_3); IR: 3314 (NH), 1702 (O-C=O), 1624 (2-Naph-C=O), 1593 (C=N).

Results and Discussion

We found that the reaction of nitrilimines 2b,c –generated in situ from the respective hydrazonoyl halides 1b,c upon treatment with triethylamine- react with α-amino esters 3-7 to afford the cyclocondensation triazinones products 9-13b,c (Scheme 1).

On the other hand, the reaction of the same nitrilimimines 2b,c with 1-ethoxycarbonyl-1-methylhydrazine gave the acyclic electrophilic addition products 14b,c and not cyclic ones 16b,c owing to the low electrophilicity of the C=O exerted by the lone pair of electrons on the neighboring nitrogen atom.

Thermal cyclization of these adducts gave the unexpected tetrazines 15b,c *via* elimination of a hydrogen molecule rather than the tetrazinones cyclocondensation products 16b,c.

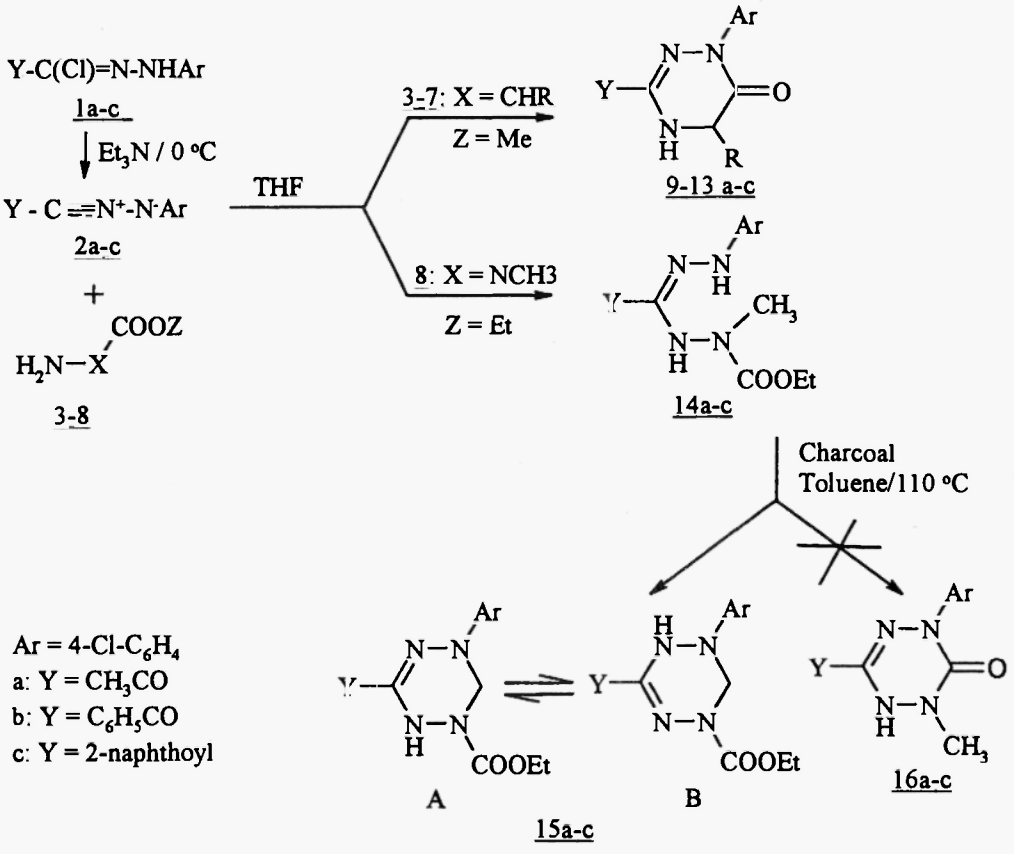
It seems to be that this cyclization starts by the oxidation of the acyclic adducts 14b,c to the respective alkyl formazanes, which cyclize as reported by Neugebauer et al. to the corresponding tetrahydro-1,2,4,5-tetrazines 15b,c (14). It is worth noting that the most frequently used method for the preparation of tetrahydro-1,2,4,5-tetrazines is the cyclization of alkylformazanes by heating or by a base treatment (15).

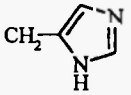
The assignment of structures 9-13b,c is based on spectral data. These compounds give satisfactory elemental analysis and correct molecular ion peaks in their mass spectra. The infrared spectra of compounds 9-13b,c reveal the presence of one N-H absorption band at 3300-3400 cm^{-1}, and two C=O absorption bands at about 1690 cm^{-1} (ring C=O) and 1650

(ArC=O). No further investigations have been performed for compounds 12b,c and 13b,c concerning their optical purity and activity.

Compounds 14b,c show two N-H bands at about 3300 and 3200 cm^{-1}, and two C=O absorption bands at about 1700 and

Scheme 1: Synthesis of 1,2,4-triazin-6-ones 9-13 and 1,2,4,5-tetrazines 15



No	3/9	4/10	5/11	6/12	7/13
R	H	CH_3	Ph	CH_2SCH_2Ph	

1600 cm^{-1} that are assigned to the lactam C=O and ArC=O, respectively. One of the N-H bands disappear in compounds 15b,c.

^1H- and ^{13}C-NMR of compounds 9-15 show all the signals of the proposed structures (experimental part). The N-CH_3 (δ = 3.0) of compounds 14b,c is replaced by a highly deshielded CH_2 (δ= 5.1, 4.9) in compounds 15b,c. All the NMR signals of compounds 15b,c are doubled, apparently, because of their presence in two tautomeric forms A & B in solution. Similar tautomerism in solution was reported by Ryabokon et al. for s-tetrazines (16).

Table 1 Physical Data and Molecular Ion Peaks for Compounds 9 – 15

Compd.	m.p (°C)	Yield (%)	Mol. Formula	$M^{+\cdot}$
9b	152-154	78	$C_{16}H_{12}ClN_3O_2$	313/315
9c	194-196	80	$C_{20}H_{14}ClN_3O_2$	363/365
10b	144-146	75	$C_{17}H_{14}ClN_3O_2$	327/329
10c	186-188	76	$C_{21}H_{16}ClN_3O_2$	377/379
11b	118-120	73	$C_{22}H_{16}ClN_3O_2$	389/391
11c	150-152	78	$C_{26}H_{18}ClN_3O_2$	439/441
12b	180-182	50	$C_{24}H_{20}ClN_3O_2S$	449/451
12c	198-200	72	$C_{28}H_{20}ClN_3O_2S$	499/501
13b	158-160	65	$C_{20}H_{16}ClN_5O_2$	393/395
13c	205-208	65	$C_{24}H_{18}ClN_5O_2$	443/445
14b	94-96	76	$C_{18}H_{19}ClN_4O_3$	374/376
14c	100-102	78	$C_{22}H_{21}ClN_4O_3$	424/426
15b	133-135	80	$C_{18}H_{17}ClN_4O_3$	372/374
15c	130-132	85	$C_{22}H_{19}ClN_4O_3$	422/424

Acknowledgement

The authors wish to thank Dr. W. Schrader, Max-Planck Institut fuer Kohlenforschung, Muelheim, Germany, for obtaining the mass spectra.

References

(1) M. M. El-Abadelah, A. Q. Hussein, M. R. Kamal, K. H. Al-Adhami, Heterocycles **27**, 917 (1988).
(2) M. M. El-Abadelah, M. Z. Nazer, N. S. El-Abadlah, H. Meier, J. Prakt. Chem. **339**, 90 (1997).
(3) M. M. El-Abadelah, A. Q. Hussein, B. A. Thaher, Heterocycles **10**, 1879. (1991).
(4) M. M. El-Abadelah, S. Saleh, A. M. Awadallah, Asian J. Chem. 9, 474. (1997).
(5) M. R. El-Haddad, A. R. S. Ferwanah, A. M. Awadallah, J. Prakt. Chem. **340**, 623. (1998).
(6) A. F. Pozharskii, A. Soldatenkov, A. R. Katritzky, Heterocycles in life and society, John Wiley, New York, 1997.
(7) R. H. Wiley, us patent 4,358,590, 1982 (Chem. Abstr. 1983, 98, 72143v).
(8) G. Pitet and F. Couret, French Patent 2,500,830, 1982 (Chem. Abstr. 1983, 98, 72140s).
(9) A. R. S. Ferwanah and A. M. Awadallah, Private communication.
(10) K. C. Joshi, V. N. Pathak, S. Sharma, Indian J. Chem. **24B**, 124 (1985).
(11) H. M. Hassaneen, A. S. Shawali, M. M. Elwan, N. M. Abonada, Sulfur Lett. **13**, 273 (1992).
(12) M. Brenner, W. Huber, Helv. Chim. Acta. **36**, 1109 (1953).
(13) W. S. Wadworth, J. Org. Chem. **34**, 2994 (1969).
(14) G. McConnachie, F. A. Neugebauer, Tetrahedron **31**, 555 (1975).
(15) H. Neunhoeffer, Tetrazines and Pentazines in Comprehensive Heterocyclic Chemistry, Vol. 3, A. R. Katritzky, C. W. Rees (eds.) Pergamon Press p 531 (1984).
(16) L. G. Ryabokon, V. N. Kalinin, O. M. Polumbrik, L. N. Markovski, Khim Geterotsikl. Soedin. **10**, 1425 (1985): Chem. Abst., *104*, 108922g (1986).

Received on February 2, 2002