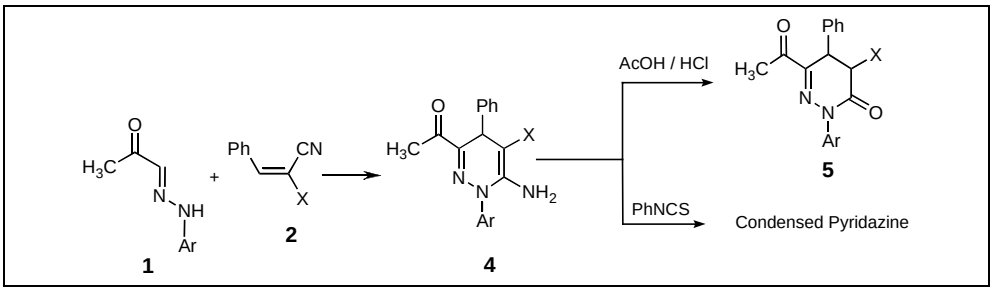
Studies with Enamines and Azaenamines: A Novel Efficient Route to 6-Amino-1,4-dihydropyridazines and their Condensed Derivatives.

Said A. S. Ghozlan*, Ismail A. Abdelhamid, Hamdi M. Hassaneen, and Mohamed H. Elnagdi*

Department of Chemistry, Faculty of Science, Cairo University, Giza, A. R. Egypt
E-mail: **shelmy@access.com.eg, S_ghozlan@yahoo.com,**

Received March 20, 2006

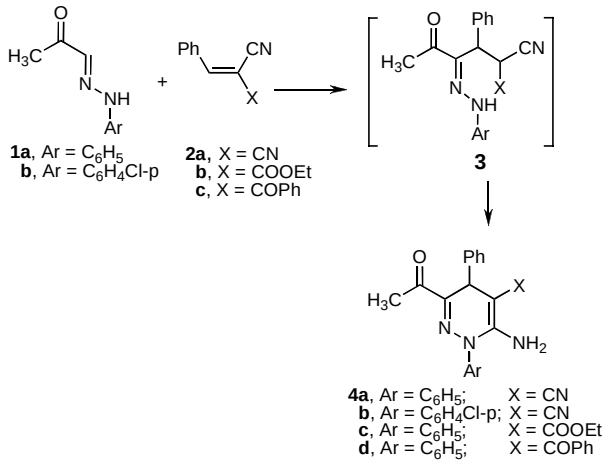


1-Arylhydrazonopyruvaldehydes **1** react with α,β-unsaturated nitriles **2** to yield 6-amino-1,4-dihydropyridazines **4** that are converted into pyridazinones **5** *via* refluxing in an acetic acid/hydrochloric acid mixture and into the ethylidenemalononitrile derivatives **6** on reflux with malononitrile in ethanolic/piperidine solution.

J. Heterocyclic Chem., **44**, 105 (2007).

Enamines are versatile reagents and the nucleophilic character of C-2 has found extensive applications in synthetic organic chemistry [1,2]. Aldehyde hydrazones can also be considered as azaenamines and aldehydic carbon is also nucleophilic. Although this may be considered as a way of umpoulung (dipole inversion of aldehydic carbon) only few synthetic applications of this phenomenon has so far been reported and are basically limited to few Mannich alkylations [3-6], Vilsmayer formylation [7], reactions with aldehydes [4] and quinones [8]. The recently reported reactivity of pyruvaldehyde-1-arylhydrazones with quinones [8] prompted us to investigate the possibility that these pyruvaldehyde-1-arylhydrazones can also undergo Michael addition to α-substituted cinnamonitriles thus affording a novel simple and efficient approach to 1,4- dihydropyridazines. In conjunction with our interest in developing synthesis for biologically interesting pyridazines [9-16] we investigated this type of Michael addition. Thus it has been found that refluxing pyruvaldehyde-1-arylhydrazones **1a-c** with benzylidene-malononitrile **2a** afford 1:1 adducts. Several isomeric structures seemed possible. Structures involving addition of acyl methyl were readily eliminated as ^{1}H NMR revealed methyl signal at δ 2.33 ppm. Acyclic structure **3** was readily also excluded based on ^{1}H NMR and IR spectra which revealed amino signals and bands. Thus structures **4a, b** were established. We have extended our investigation on this type of addition and have found that ethyl benzylidenecyanoacetate **2b** also adds to **1a** to yield ethyl 6-aminopyridazine-5-carboxylate **4c**. Also 2-benzoyl-3-phenyl-acrylonitrile **2c** adds to **1a** to yield 6-amino-5-benzoyl-pyridazine **4d**.

Scheme 1



Formation of **4** is assumed to proceed *via* initial addition of hydrazone CH to the activated double bond in **2** to yield **3** that readily cyclizes into **4**. NMR can not however exclude the possible initial addition of hydrazone NH to activated double bond in **2** yielding 6-H-pyridazine derivatives, however, X-ray analysis of **4d** confirmed that 4-H-pyridazine **4** are the actual products (*cf* figure 1) [17]. X-ray clearly indicates existence of intramolecular hydrogen bonding between NH_2 and benzoyl carbonyl moiety.

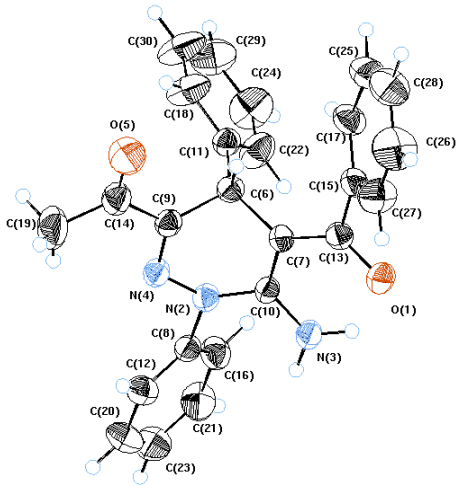
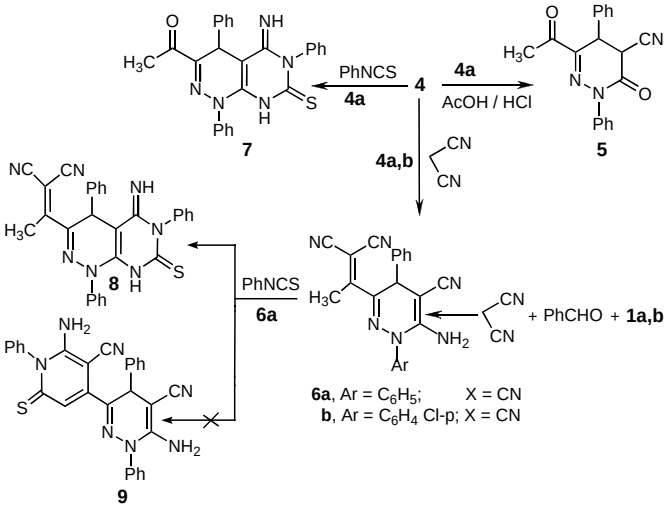


Figure 1. X-ray crystal structure of compound **4d**.

Compound **4a** was readily converted into **5** *via* refluxing **4a** in an acetic acid/hydrochloric acid mixture. Structure **5** was established based on IR which revealed absence of NH_2 band and also ^1H NMR revealed the appearance of two doublets at δ 4.96 (J = 7.2 Hz), and 5.34 ppm (J = 7.2 Hz). In an attempt to synthesis **4a** from reaction of a mixture of benzaldehyde, malononitrile, and **1a** in ethanolic/piperidine solution only **6** was formed. This could be also obtained on reacting **4a** with malononitrile. Typical of the established behaviour of enaminonitriles [18] compound **4a** reacted with phenylisothiocyanate to yield **7**. Also **6** affords **8**. Possible isomeric **9** was excluded based on ^1H NMR that revealed presence of methyl signal at δ 3.58 ppm and absence of amino signal as required for structure **8**. Finally, the formation of pyrimidines from the reaction of enamines with isothiocyanates is a well established behaviour of enaminonitriles [19].

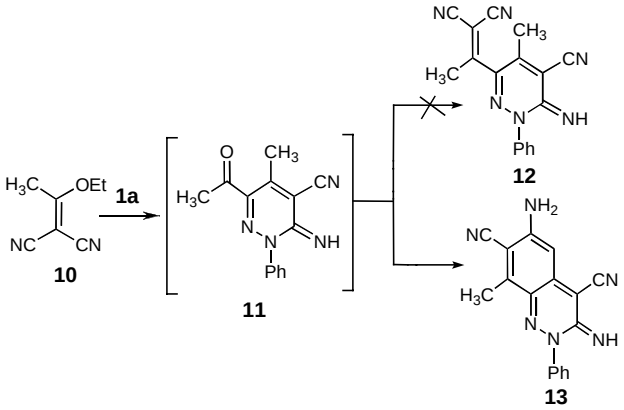
Scheme 2



Reacting **1a** with ethoxyethylidenemalononitrile **10** resulted in the formation of a product that may be formulated as **12** or **13**. ^1H NMR clearly revealed that the reaction product is corresponds to **13** as only one methyl signal is observed. It is possible that **11** is an intermediate. Formation of **13** is assumed to take place *via* condensing **10** with **1a** to yield intermediate **11**, which condenses with malononitrile that results most likely from hydrolysis of unreacted **10** under these reaction conditions.

In conclusion the addition of hydrozone CH to activated double bonds is seemingly general reaction that can be adopted at least for synthesis of functionally substituted pyridazines.

Scheme 3



EXPERIMENTAL

Melting points were determined on a Stuart melting point apparatus and are uncorrected. The ir spectra were recorded as KBr pellets using a Bruker-vector 22 spectrophotometer FTIR. The ^1H and ^{13}C nmr spectra were recorded in DMSO-d_6 as solvent at 300 MHz on Varian Gemini NMR spectrometer using TMS as internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were measured on a Shimadzu GMSS -QP-1000 EX mass spectrometer at 70 eV. The crystal structure was determined by the X-ray unit at the National Research Center, Dokki, Cairo. Microwave experiments were conducted in a DAEWOO, editionII (KOR-8667) at full power. The reactants were placed in a glass conical container and the oven was placed in an efficient hood. No special precautions were used as we did not experience any bumping during our experiments. The experiments were repeated in CEM Explorer focused microwave oven. Yields in both cases were almost the same.

General Procedures for Compounds 4a-d. Method A: A mixture of azaenamine 1 (10 mmol), and benzylidene derivatives **2a-c** was refluxed in ethanol (20 ml) in presence of piperidine (0.5 ml) for 1 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from ethanol.

Methode B: A solution of each of **1a-d** (10 mmol) was treated with the benzylidene **2a-c** (10 mmol) in pyridine (2 ml) was irradiated in a microwave oven for two minutes, then

poured onto water and acidified with dilute hydrochloric acid. The solid product obtained was crystallized from ethanol.

6-Acetyl-3-amino-2,5-diphenyl-2,5-dihydro-pyridazine-4-carbonitrile (4a). Yield: (78% thermal, 86% microwave), mp: 228-230 °C; ir (KBr): ν 3409 and 3313 (NH_2), 2191 (CN), 1678 (CO) cm^{-1}; ^1H nmr (DMSO-d6): δ = 2.33 (s, 3H, C*H*$_3$-CO), 4.79 (s, 1H, C*H* pyridazine), 6.01 (s, 2H, N*H*$_2$), 7.21 - 7.52 (m, 10H, Ph *H*); ^{13}C nmr (DMSO-d6): δ = 24.68 (CH_3), 36.11 (CH pyridazine), 57.05 (C-CN), 120.52 (CN), 125.73, 126.83, 127.29, 127.91, 128.99, 129.54, 140.16, 142.11 (CH aromatic), 143.99 (C-$COCH_3$), 150.30 (C- NH_2), 195.79 (CO); MS (EI): m/z (%) = 316 (M^+). *Anal.* Calcd. for $C_{19}H_{16}N_4O$ (316.37): C, 72.14; H, 5.10; N, 17.71. Found: C, 72.20; H, 5.31; N, 17.65.

6-Acetyl-3-amino-2-(4-chlorophenyl)-5-diphenyl-2,5-dihydro-pyridazine-4-carbonitrile (4b). Yield: (82% thermal, 87% microwave), mp: 198-200 °C; ir (KBr): ν 3405 and 3303 (NH_2), 2191 (CN), 1680 (CO) cm^{-1}; ^1H nmr (DMSO-d6): δ = 2.33 (s, 3H, C*H*$_3$-CO), 4.77 (s, 1H, C*H* pyridazine), 6.15 (s, 2H, N*H*$_2$), 7.18-7.59 (m, 9H, Ar *H*); ^{13}C nmr (DMSO-d6): δ = 18.62 (CH_3), 24.69 (CH pyridazine), 57.17 (C-CN), 120.43 (CN), 126.83, 127.30, 127.45, 128.99, 129.74, 132.20, 139.10, 141.90 (CH aromatic), 144.32 (C-$COCH_3$), 150.29 (C-NH_2), 195.71(CO); MS (EI): m/z (%) = 350 (M^+). *Anal.* Calcd. for $C_{19}H_{15}C1N_4O$ (350.81): C, 65.05; H, 4.31; N, 15.97. Found: C, 65.16; H, 4.45; N, 16.1.

Ethyl 6-Acetyl-3-amino-2,5-diphenyl-2,5-dihydropyridazine-4-Carboxylate (4c). Yield: (80% thermal, 87% microwave), m.p = 126-128 °C; ir (KBr): ν 3417.6 and 3301.9 (NH_2), 1658.7 (CH_3CO), 1616.2 (COOEt) cm^{-1}; ^1H nmr (DMSO-d6): δ = 1.17 (t, 3H, C*H*$_3$-CH_2, J = 7.2 Hz), 2.33 (s, 3H, C*H*$_3$-CO), 4.08 (q, 2H, C*H*$_2$, J = 7.2 Hz), 5.2 (s, 1H, C*H* pyridazine), 6.88 (s, 2H, N*H*$_2$), 7.17-7.56 (m, 10H, Ph H); ^{13}C nmr (DMSO-d6): δ = 14.47, 24.66 (CH_3), 33.91 (CH pyridazine), 58.89 (CH_2), 75.92 (C -COOEt), 125.69, 126.67, 127.09, 127.87, 128.59, 129.64, 140.06, 143.22 (CH aromatic), 147 (C-$COCH_3$), 151.04 (C-NH_2), 168.11(COOEt), 196.03 (CO); MS (EI): m/z (%) = 363 (M^+). *Anal.* Calcd. for $C_{21}H_{21}N_3O_3$ (363.42): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.22; H, 5.91; N, 11.35.

1-(6-Amino-5-benzoyl-1,4-diphenyl-1,4-dihydropyridazine-3-yl)ethanone (4d). Yield: (82% thermal, 89% microwave), mp: 185-187°C; ir (KBr): ν 3448.5 and 3302 (NH_2), 1681.8 ($COCH_3$), 1612 (COPh) cm^{-1}; ^1H nmr (DMSO-d6): δ = 2.39 (s, 3H, C*H*$_3$-CO), 5.28 (s, 1H, C*H* pyridazine), 7.01-7.62 (m, 15H, Ph *H*), 8.50 (br, 2H, N*H*$_2$); ^{13}C nmr (DMSO-d6): δ = 24.74 (CH_3), 35.41 (CH pyridazine), 85.50 (CH-COPh), 125.61, 126.51, 126.76, 126.92, 128.14, 128.81, 129.22, 129.46, 129.85, 139.59, 141.24, 142.18 (CH aromatic), 148.45 (C-$COCH_3$), 153.47 (C-NH_2), 192.55 (COPh), 195.92 ($COCH_3$); MS (EI): m/z (%) = 395 (M^+). *Anal.* Calcd. for $C_{25}H_{21}N_3O_2$ (395.47): C, 75.93; H, 5.35; N, 10.63. Found: C, 76.11; H, 5.25; N, 10.72.

6-Acetyl-3-oxo-2,5-diphenyl-2,3,4,5-tetrahydropyridazine-4-carbonitrile (5). A solution of **4a** (0.01 mol) in acetic acid (15 ml)/hydrochloric acid (2 ml) was refluxed for 2 hrs, and then the reaction mixture is poured into water. The solid product so formed was collected by filtration and crystallized from ethanol. Yield: (72%), mp: 150-152 °C; ir (KBr): ν 2260 (CN), 1650 (CO), 1693 ($COCH_3$) cm^{-1}; ^1H nmr (DMSO-d6): δ = 2.40 (s, 3H, C*H*$_3$-CO), 4.96 (d, 1H, C*H* pyridazine, J = 7.2 Hz), 5.34 (d, 1H, C*H* pyridazine, J = 7.2 Hz), 7.24-7.65 (m, 10H, Ph *H*); ^{13}C nmr (DMSO-d6): δ = 24.65 (CH_3), 39.07 (CH-CN), 39.12 (CH-Ph) 114.50 (CN), 125.04, 127.80, 127.93, 128.80, 129.04, 129.46, 133.47, 139.94 (CH aromatic), 149.38 (C-$COCH_3$), 159.1 (CO), 194.55 ($COCH_3$): MS (EI): m/z (%) = 317 (M^+). *Anal.* Calcd. for $C_{19}H_{15}N_3O_2$ (317.35): C, 71.91; H, 4.76; N, 13.24. Found: C, 72.11; H, 4.85; N, 13.46.

General procedures for Preparation of compounds 6a,b. ***Method A:*** A mixture of azaenamines **1a, b** (10 mmol), benzaldehyde (10 mmol), and malononitrile (10 mmol) was refluxed in ethanol (20 ml) in presence of piperidine for 1 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from ethanol/Dioxan.

Method B: A mixture of pyridazines **1a, b**, and malononitrile (10 mmol) was refluxed in ethanol (20 ml) in presence of piperidine (0.5 ml) for 1 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from ethanol/Dioxan.

[1-(6-Amino-5-cyano-1,4-diphenyl-1,4-dihydropyridazine-3-yl)ethylidene]malononitrile (6a). Yield: (88%), mp: 310°C; ir (KBr): ν 3433 and 3328 (NH_2), 2198.7 (CN) cm^{-1}; ^1H nmr (DMSO-d6): δ = 2.32 (s, 3H, C*H*$_3$), 4.77 (s, 1H, C*H* pyridazine), 5.99 (s, 2H, N*H*$_2$), 7.0-8.33 (m, 10H, Ph *H*); MS (EI): m/z (%) = 364 (M^+). *Anal.* Calcd. for $C_{22}H_{16}N_6$ (364.41): C, 72.51; H, 4.43; N, 23.06. Found: C, 72.33; H, 4.65; N, 23.41.

{1-[6-Amino-1-(4-chlorophenyl)-5-cyano-4-phenyl-1,4-dihydropyridazine-3-yl]ethylidene}malononitrile (6b). Yield: (86%), mp: 320 °C; ir (KBr): ν 3325 and 3324.8 (NH_2), 2194.8 (CN) cm^{-1}; MS (EI): m/z (%) = 398 (M^+). *Anal.* Calcd. for $C_{22}H_{15}C1N_6$ (398.86): C, 66.25; H, 3.79; N, 21.07. Found: C, 66.39; H, 3.86; N, 21.19.

1-(5-Imino-1,4,6-triphenyl-7-thioxo-1,4,5,6,7,8-hexahydro-pyrimido-[4,5-*c*]pyridazin-3-yl)-ethanone (7). A mixture of pyridazine **4a** (10 mmol), and phenyl isothiocyanate (10 mmol) was stirred in DMF in the presence of KOH for 5 hrs and then left over night. The reaction mixture was then poured onto water and acidified with dilute hydrochloric acid. The solid product obtained was crystallized from ethanol; Yield: (69%), mp: 248-250°C; ir (KBr): ν 3440.8 and 3282.2 (2 NH), 1685.7 (CO), 1639.4 (C=NH) cm^{-1}; ^1H nmr (DMSO-d6): δ = 2.39 (s, 3H, C*H*$_3$-CO), 5.70 (s, 1H, C*H* pyridazine), 7.08 (br, 1H, N*H*), 7.11 (br, 1H, N*H*) 7.14-7.64 (m, 15 H, Ph *H*); ^{13}C nmr (DMSO-d6): δ = 24.89 (CH_3), 32.38 (CH pyridazine), 85.22 (C4-pyridazine), 125.96, 126.89, 127.44, 127.63, 128.45, 128.61, 128.89, 129.11, 130.17, 130.38, 138.77, 140.36 (CH aromatic), 145 (C=NH), 150.74(C-$COCH_3$), 155.24 (C3-pyridazine), 178.4 (C=S), 195.55 (CO); MS (EI): m/z (%) = 451 (M^+). *Anal.* Calcd. for $C_{26}H_{21}N_5OS$ (451.55): C, 69.16; H, 4.69; N, 15.51. Found: C, 68.96; H, 4.83; N, 15.87.

[1-(5-Imino-1,4,6-triphenyl-7-thioxo-1,4,5,6,7,8-hexahydro-pyrimido[4,5-*c*]pyridazin-3-yl)ethylidene]malononitrile (8). A mixture of pyridazine **6a** (10 mmol), and phenyl isothiocyanate (10 mmol) was stirred in DMF in presence of KOH for 5 hrs and then left over night at which time the reaction mixture was poured onto water and acidified with dilute hydrochloric acid. The solid product obtained was crystallized from ethanol/ Dioxan. Yield: (61 %), mp: 245-247 °C; ir (KBr): ν 3406 (NH), 2198.7 (CN), 1701 (C=NH) cm^{-1}; ^1H nmr (DMSO-d6): δ = 2.38 (s, 3H, C*H*$_3$), 3.56 (s, 1H, C*H* pyridazine),7.28-7.69 (m, 15H, Ph *H*), 8.46 (s, 1H, N*H*), 11.11 (s, 1H, N*H*). MS (EI): m/z (%) = 499 (M^+). *Anal.* Calcd. for $C_{29}H_{21}N_7S$ (499.60): C, 69.72; H, 4.24; N, 19.63. Found: C, 69.92; H, 4.12; N, 19.73.

6-Amino-3-imino-8-methyl-2-phenyl-2,3-dihydrocinnoline-4, 7-dicarbonitrle (13). A mixture of azaenamine **1** (10 mmol), and ethylidene malononitrile derivatives **10** was refluxed in Dioxan (20 ml) in the presence of piperidine for 1 h. The solvent was evaporated under vacuum and the crude product was

collected and crystallized from Dioxan. Yield: (80%), mp: 245-247 °C; ir (KBr): ν 3440.8 (NH) 3294.2 and 3201.6 (NH_2), 2194.8 (CN), 1639.4 (C=NH) cm^{-1}; ^1H nmr (DMSO-d6): δ = 2.45 (s, 3H, CH_3), 6.15 (s, 1H, C*H* phenyl), 7.51 (br, 2H, NH_2), 7.51-7.60 (m, 5 H, Ph *H*), 8.46 (s, 1H, N*H*); ^{13}C nmr (DMSO-d6): δ = 21.03 (CH_3), 78.60 (C-CN), 102.17 (C-CN), 114.86 (CH phenyl), 116.47 (CN), 117.39, 120.67, 120.72 (CH aromatic), 126.88 (C-CH_3), 130.2 (CH aromatic), 139.24 (C-NH_2), 139.34 (C=N), 152.4 (C aromatic), 165 (C=NH); MS (EI): m/z (%) = 300 (M^+). *Anal*. Calcd. for $C_{17}H_{12}N_6$ (300.33): C, 67.99; H, 4.03; N, 27.98. Found: C, 67.73; H, 3.85; N, 27.61.

REFERENCES

[1] M. B. Smith, Mc Graw Hill, London, Organic Synthesis, 2nd edition, (2002).

[2] S. Patai, Ed, The Chemistry of Enamines, J. Wiley and Sons, New York New York, (1994).

[3] R. Breme, G. Reck, B. Schulz, R Radeglia, *Synthesis*, 1620 (2003).

[4] L. El-Kaim, L. Gautier, L. Grimaud, V. Michaut, *Synlett*, 1844 (2003).

[5] J. E. Ancel, L. El Kaiim, A. Gadras, L. Grimaud, N. K. Jana, *Tetrahedron Letters*, **43**, 8319 (2002).

[6] V. Atlan, H. Bienayme, L. El-Kaim, A. Majee, *Chem. Commmun*., 1585 (2000).

[7] R. Brehme, H. Nikolajewski, *Z. Chem*., **8**, 226 (1968).

[8] H. Buff, U. Kucklander, *Tetrahedron*, **56,** 5137 (2000).

[9] H. M. Fahmy, N. M. Abed, R. M. Mohareb, M. H. Elnagdi, *Synthesis*, 490 (1982).

[10] K. U. Sadek, M. H. Elnagdi, *Synthesis*, 483 (1988).

[11] M. H. Elnagdi, N. S. Ibrahim, K. U. Sadek, M. H. Mohamed, *Liebgs Ann. Chem*., 1009 (1988).

[12] M. H. Elnagdi, A. M. Negm, A. W. Erian, *Liebgs Ann. Chem*., 1255 (1989).

[13] M. H. Elnagdi, A. W. Erian, *Liebgs Ann. Chem*., 1215 (1990).

[14] H. Al-Awadi, F. Al-Omran, M. H. Elnagdi, L. Infants, C. Foces-foces, N. Jagerovic, J. Elguero, *Tetrahedron*, **51**, 12745 (1995).

[15] F. Al-Omran, M. M. Abdelkhalik, A. A. Elkhair, M. H. Elnagdi, *Synthesis*, 91 (1997).

[16] H. M. Hassaneen, T. M. Abdelkhalik, H. Hassaneen, *J. Chem. Res*., in press (2006).

[17] Further details of the crystal structure of **4d** will be available in the Cambridge Crystallographic Data center under deposit numbers CCDC 616675.

[18] H. Wamhoff, J. Dzenis, K. Hirota, *Adv. Hetrocycl. Chem*., **55**, 129 (1992).

[19] U. Michal, I. Dusan, F. Josef, S. Katarina, *Collect. Czech. Chem. Commun*., **46**, 3128 (1981).