Chemistry of Heterocyclic Compounds, Vol. 44, No. 8, 2008

SYNTHESIS OF NOVEL FUNCTIONALLY SUBSTITUTED PYRIDAZINES AND OXAZINES

M. Hammouda, Z. M. Abou Zeid, M. A. Metwally

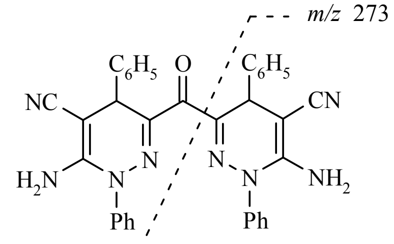
Acetone 1,3-di(phenylhydrazone) reacts with arylidenemalononitriles in the presence of piperidine to give the coressponding 3,3'-carbonylbispyridazine derivatives. Under the same reaction conditions dioxime reacts with arylidenemalononitriles to give the corresponding 3,3'-carbonylbis-1,2-oxazines. Dioxime reacts with primary aromatic amines and formalin in a molar ratio of 1:1:2 to give 1-arylidene-3,5-dihydroxyimino- piperidine-4-ones.

Keywords: acetone 1,3-dioxime,acetone 1,3-diphenylhydrazone,1,2-dioximes, pyridazines.

Although β-aminoenones and β-nitroenamines are already established as synthetic intermediates, particularly, in heterocyclic chemistry [1–5], the utility of phenylhydrazones and oximes, which have closely related structures to them, is little studied [6–8]. In this paper we describe the reaction of cyanoolefins **1** with diphenylhydrazone **2** and dioxime **3** as a route to functionally substituted pyridazines and oxazines, respectively.

The reaction of electrophiles such as compound **1** with nucleophiles such as compound **2** is of interest because it may occur either at the nitrogen atom of the NH group or at the carbon atom of the cyano group. Thus, condensation of diphenylhydrazone **2** [9] with activated cyanoolefins **1a–c** in a molar ratio of 1:2 in refluxing ethanolic piperidine afforded 3,3'-carbonylbis(6-amino-4-aryl-5-cyano-1-phenylpyridazine) **4a–e** (Scheme 1).

The structure of compound **4** was established for the reaction product, and the structure **5** was excluded, based on analytical and spectral data (cf. Experimental). The ^{1}H NMR spectrum of compound **4c** exhibited a four proton singlet at δ 5.55 (s, $2NH_2$), a two-proton singlet at δ 4.42 due to H-4 of pyridazine, and eighteen proton multiplets at δ 7.27-7.62 (Ar).



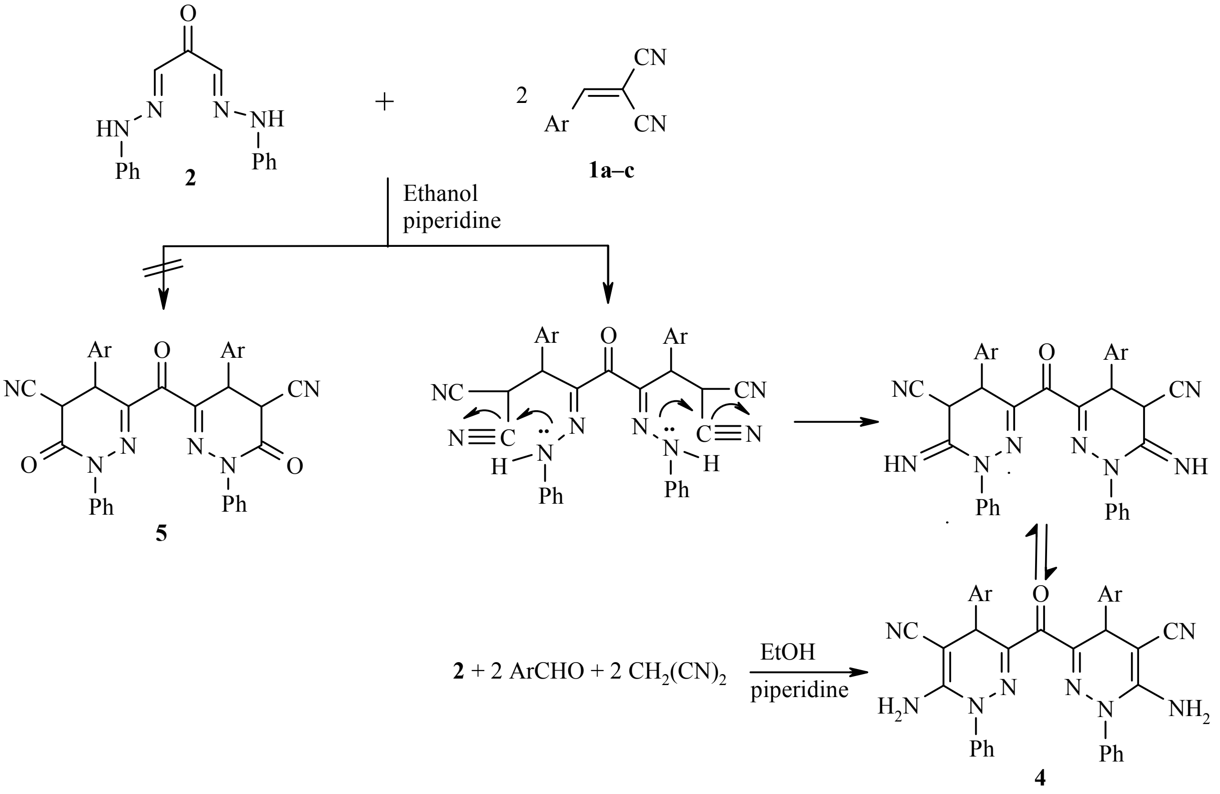
4a

The mass spectrum of compound **4a** showed a molecular ion at *m/z* 573 [M^+–H], *m/z* 273 [pyridazine], *m/z* 301 [pyridazine–CO], *m/z* 196 [pyridazine–C_6H_5], and *m/z* 77 base peak [C_6H_5].

Department of Chemistry, Faculty of Science, University ofMansoura, Mansoura, Egypt; e-mail: mamegs@mans.edu.eg Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1223-1229, August, 2008. Original article submitted May 21, 2007. In revised form March 10, 2008.

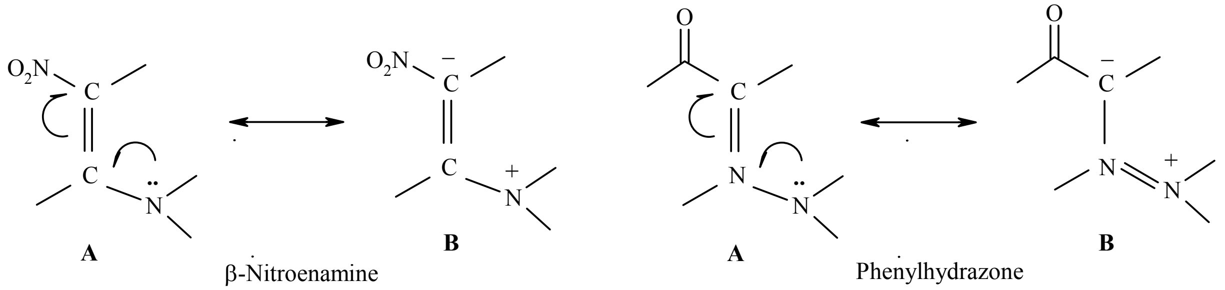
The formation of compound **4** can be explained *via* initital Michael addition of compound **2** to the ylidene bond in compound **1** forming an acyclic intermediate which is cyclized by nucleophilic attack of the NH group at the cyano carbon, followed by tautomerization to the final product **4** (Scheme 1).

Scheme 1



4 a Ar = Ph, **b** Ar = p-ClC$_6$H$_4$, **c** Ar = p-BrC$_6$H$_4$, **d** Ar = p-O$_2$NC$_6$H$_4$,
e Ar = C$_6$H$_3$OCH$_2$O-3,4

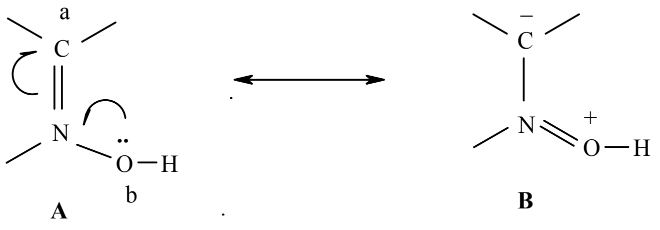
The reactivity of compound **2** towards the β-carbon in compound **1** can be accounted for by the contribution of a resonance structure **B** analogously to β-nitroenamines [10].



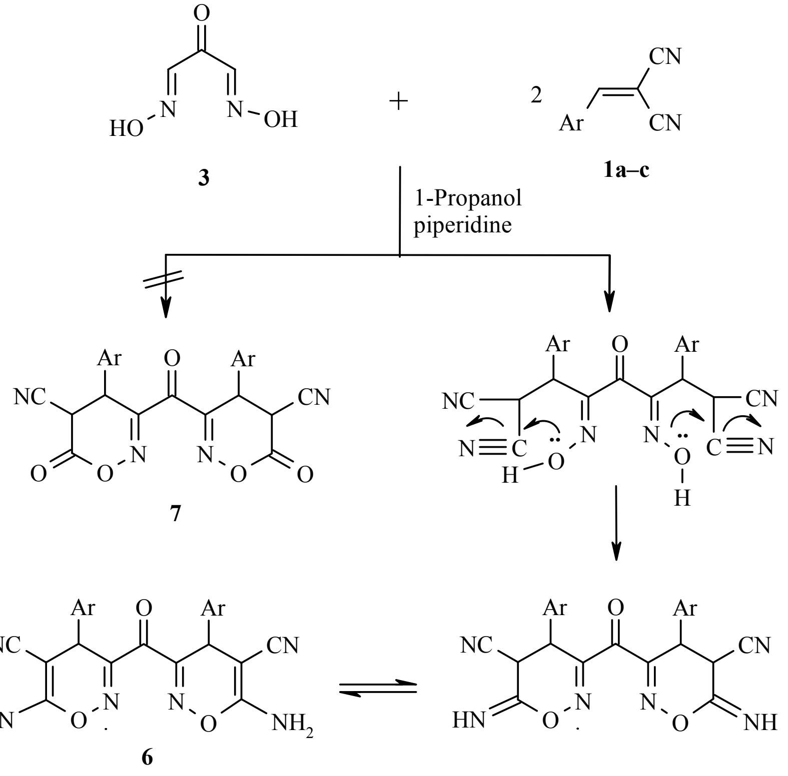
In view of the previous discussion, it might be expected that dioxime **3** [11] which has a closely related structure to phenylhydrazone **2**, will react with compound **1**. Therefore, the authors investigated the reactivity of compound **3** towards compound **1**. Indeed, the treatment of dioxime **3** with activated cyanoolefins **1a–c** in a molar ratio of 1:2 in refluxing 1-propanol in the presence of a catalytic amount of piperidine gave carbonyl bis-oxazine derivatives **6a–c** rather than **7** (Scheme 2).

The structure of compounds **6** was established for the reaction products based on analytical and spectral data (cf. Experimental). The mass spectrum of compound **6c** showed a molecular ion at *m/z* 408 (base peak), *m/z* 307 [oxazine–CO+2H], 279 [oxazine + 2H], 270 [M^+–$2C_6H_4Br$], and 121 [oxazine–C_6H_4Br].

The reactivity of compound **3** towards the β-carbon in compound **1** can be accounted for by the contribution of a resonance structure **B** in the oxime, and its behavior as a bidentate (sites a and b) towards nucleophiles.

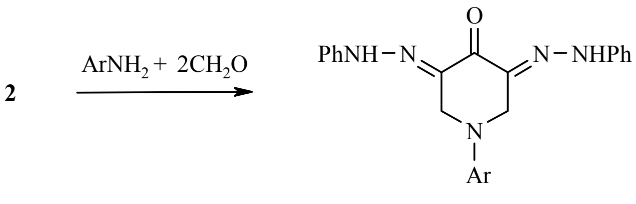


Scheme2



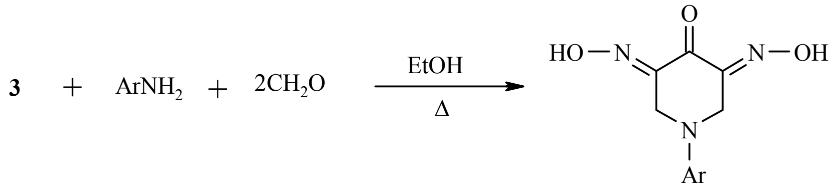
6 a Ar = Ph, **b** Ar = *p*-ClC_6H_4, **c** Ar = *p*-BrC_6H_4

It has been shown [9] that diphenylhydrazone **2** undergoes a double Mannich reaction with primary aromatic amines and formalin to give piperidone diphenylhydrazone **10**.



10

In view of this report and in view of the similarity of dioxime **3** with diphenylhydrazone **2**, it appeared of interest to study the behavior of dioxime **3** toward a double Mannich reaction. Thus, the treatment of compound **3** with primary aromatic amines and formalin in a molar ratio of 1:1:2 in refluxing ethanol afforded 1-aryl-3,5-dioximes of piperidine-3,4,5-triones **11a–c**.



11

11 a Ar = Ph,**b** Ar = *p*-MeOC_6H_4.**c** Ar = *p*-ClC_6H_4

The structure of compound **11** was established for the reaction product based on analytical and spectral data (cf. Experimental). The ^{1}H NMR of compound **11c a** exhibited a four-proton singlet at δ 2.11 due to CH_2 groups, four aromatic protons at δ 7.50-7.92, and a two-proton broad singlet at δ 10.91 due to OH of oxime groups.

The mass spectrum of compound **11c** showed an intense peak at *m/z* 156 [M^+–C_6H_4Cl] resulting from cleavage of the N–C_6H_4Cl bond . The base peak is at *m/z* 139 [156 – OH], and there is another intense peak at *m/z* 111 [base peak–CO].

EXPERIMENTAL

Melting points (uncorrected) were taken on a Fisher electric melting point apparatus. Elemental analyses were carried out in the Microanalytical Unit, Faculty of Science, Mansoura and Cairo Universities. IR spectra were recorded on a SP-2000 Pye-Unicam Spectrometer (KBr). ^{1}H NMR spectra were obtained with Varian-Gemini 200 MHz and Brucker 250 MHz, TMS (an internal standard). Mass spectra were recorded on a GCMS QP1000EX Schimadzu mass spectrometer at 70 eV. The purity of the synthesized compounds was tested by thin layer chromatography (TLC), and no by products were noticed in all cases.

3,3'-Carbonylbis(6-amino-4-aryl-5-cyano-1,4-dihydro-1-phenylpyridazines) 4a-**e**.

A. A mixture of diphenylhydrazone **2** [9] (2.5 mmol) and the appropriate arylidenemalononitriles **1a-e** (5 mmol) in absolute ethanol (40 ml) and piperidine (0.1 ml) was refluxed for 8 h. The solid products obtained were filtered off and crystallized from ethanol to give compounds **4a-e** .

B. A mixture of compound **2** [9] (2.5 mmol), the appropriate aldehyde (5 mmol), and malononitrile (5 mmol) in absolute ethanol (40 ml) and piperidine (0.1 ml) were refluxed for 8 h. The solid products separated was filtered off and crystallized from ethanol to give compounds **4a-c** (mp and mixed mp).

Compound 4a is obtained as yellow crystals. Yield 74%; mp 218-220°C. IR spectrum, ν, cm^{-1}: 3449, 3225 (NH_2), 2190 (C≡N), 1634 (CO). Mass spectrum, *m/z* (I_{rel}, %): 573 [M^+–H] (2), 273 [pyridazine] (29), 301 [pyridazine+CO] (4), 196 [pyridazine–C_6H_5] (6), 77 [C_6H_5] (a base peak) (100). Found, %: C 73.23; H 4.67; N 19.59. $C_{35}H_{26}N_8O$. Calculated, %: C 73.16; H 4.56; N 19.50.

Compound 4b is obtained as yellow crystals. Yield 75%; mp 198-201°C. IR spectrum, ν, cm^{-1}: 3433, 3240 (NH_2), 2183 (C≡N), 1640 (CO). Found, %: C 65.22; H 3.68; N 17.29. $C_{35}H_{24}Cl_2N_8O$. Calculated, %: C 65.32; H 3.76; N 17.41.

Compound 4cis obtained as red crstals. Yield 71%; mp 282-285°C. IR spectrum, ν, cm^{-1}: 3450, 3300 (NH_2), 2185 (CN), 1640 (CO). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.42 (2H, s, H-4 pyridazine); 5.55 (4H, s, 2NH$_2$); 7.27-7.62 (18H, m, Ar). Mass spectrum, *m/z* (I_{rel}, %): 730 [M$^+$–2H] (2), 352 [pyridazine] (33), 380 [pyridazine+CO] (8), 196 [pyridazine–C_6H_4Br] (4). Found, %: 57.48; H 3.39; N 15.42. $C_{35}H_{24}Br_2N_8O$. Calculated, %: C 57.39; H 3.30; N 15.30.

Compound 4d is obtained as brown crystals. Yield 64%; mp 232–235°C. IR spectrum, ν, cm^{-1}: 3420, 3320 (NH$_2$), 2180 (C≡N), 1640 (CO). Found, %: C 63.33; H 3.72; N 21.35. $C_{35}H_{24}N_{10}O_5$. Calculated, %: C 63.25; H 3.64; N 21.08.

Compound 4e is obtained as brown crystals. Yield 68%; mp 219-221°C. IR spectrum, ν, cm^{-1}: 3418, 3347 (NH$_2$), 2205 (C≡N), 1640 (CO) .^{1}H NMR spectrum (CDCl$_3$), δ, ppm: 4.38 (2H, s, H-4 pyridazine); 5.05 (4H, s, 2O–CH$_2$–O); 5.92 (4H, s, 2NH$_2$); 7.28–7.65 (16H, m, Ar). Found, %: C 66.94; H 4.12; N 16.94. $C_{37}H_{26}N_8O_5$. Calculated, %:C 67.06; H 3.66; N 16.91.

3,3′-Carbonylbis(6-amino-4-aryl-5-cyano-4H-1,2-oxazine) 6a-c (General Method). A mixture of dioxime **3** [11] (2.5 mmol) and the appropriate arylidenemalononitriles **1a-c** (5 mmol) in 1-propanol (25 ml) and piperidine (0.1 ml) was refluxed for 8 h. The reaction mixture was cooled, poured into water, and acidified with diluted HCl (1:1). The precipitated materials were filtered off and crysallized from ethanol to give brown crystals of **6a-c**.

Compound 6a. Yield 79%; mp > 300°C. IR spectrum (KBr), ν, cm^{-1}: 3469, 3315 (NH$_2$), 2185 (C≡N), 1629 (CO) . Found, %: C 65.21; H 3.92; N 19.95. $C_{23}H_{16}N_6O_3$. Calculated, %: C 65.09; H 3.80; N 19.80.

Compound 6b. Yield 80%; mp > 300°C. IR spectrum, ν, cm^{-1}: 3453, 3338 (NH$_2$), 2195 (C≡), 1630 (CO). Found, %: C 56.12; H 2.94; N 17.13. $C_{23}H_{14}Cl_2N_6O_3$. Calculated, %: C 56.01; H 2.86; N 17.04.

Compound 6c. Yield 78%; mp >300°C. IR spectrum, ν, cm^{-1}: 3420, 3332(NH$_2$), 2201 (C≡N), 1630 (CO). Mass spectrum, *m/z* (I_{rel}, %): 408 [base peak] (100), 307 [oxazine–CO+2H] (33), 279 [oxazine+2H] (21), 270 [M$^+$–C_6H_4Br] (14), 194 [oxazine–C–C_6H_4Br] (15.3) and 121 [oxazine–C_6H_4Br] (18). Found, %: C 47.34; H 2.35; N 14.31. $C_{23}H_{14}Br_2N_6O_3$. Calculated, %: C 47.44; H 2.42; N 14.44.

1-Aryl-3,5-dioximes of piperidine-3,4,5-triones 11a-c (General Method). A mixture of compound **3** [11] (2.5 mmol), the appropriate aromatic amine (2.5 mmol), and (5 mmol) formalin in ethanol (30 ml) was refluxed for 6 h. The reaction mixture was cooled, poured into water, and acidified with diluted HCl (1:1). The precipitated materials were filtered off and crystallized from ethanol to give brown crystals of compounds **11a-c**.

Compound 11a. Yield 54%, mp 177-180°C. IR spectrum, ν, cm^{-1}: 3400 (OH), 1730 (CO), 1660 (C≡N). Found, %: C 56.52; H 4.63; N 18.12. $C_{11}H_{11}N_3O_3$. Calculated, %: C 56.65; H 4.76; N 18.02.

Compound 11b. Yield 56%; mp 167-170°C. IR spectrum, ν, cm^{-1}: 3408 (OH), 1730 (CO), 1663 (C≡N). Found, %: C 54.62; H 4.88; N 15.86. $C_{12}H_{13}N_3O_4$. Calculated, %: C 54.75; H 4.98; N 15.97.

Compound 11c. Yield 57%; mp 258-261°C. IR spectrum, ν, cm^{-1}: 3440 (OH), 1735 (CO).^{1}H NMR (DMSO), δ, ppm: 2.11 (4H, s, 2CH$_2$); 7.50-7.92 (4H, m, Ar); 10.91 (2H, br. s, 2OH oxime). Mass spectrum, *m/z* (I_{rel}, %): 156 [M$^+$–C_6H_4Cl] (8), 139 [156–OH] (base peak) (100), 111 [base peak–CO]. Found, %: C 49.24; H 3.64; N 15.56. $C_{11}H_{10}ClN_3O_3$. Calculated, %: C 49.35; H 3.77; N 15.70.

REFERENCES

1. J. V. Greenhill, *Chem. Soc. Rev.*, **6**, 277 (1937).
2. M. E.Kuehne, *Synthesis*, 510 (1970) .
3. J. V. Greenhill and Lue Ping, *Adv. Heterocycl. Chem.*, **67**, 209 (1997) .
4. M. Hammouda, M. M. Mashaly, and A. A. Fadda, *Arch. Pharm. Res.*, **18**, 213 (1995).
5. M. Hammouda, M. M. Mashaly, and E. M. Afsah, *Pharmazie*, **49**, 365 (1994).
6. E. M. Afsah, M. Hammouda, H. Zoorob, M. M. Khalifa, and M. T. Zimaity, *Z. Naturforsch.*, **45b**, 80 (1990).

7. W. E. Hahn and H. Zawadzka, *Roczniki Chem*., **38**, 557 (1964). *Chim. Acta*, **61**, 10685 (1964).
8. V. Boehnisch, G. Burzev, and H. Neurhoeffer, *Liebigs Ann*. *Chem*., 1713 (1977).
9. W. E. Hahn, R. Bartnik, and J. Epsztajn, *Roczniki Chem*. **36**, 1645 (1962). C. A., **59**, 8747 (1962).
10. T. Tokumitsu and T. Hayashi, *J*. *Org*. *Chem*., **50**, 1547 (1985).
11. H. Geissman, W.Schlatter, and V. Webb, *J*. *Org*. *Chem*., **11**, 737 (1964).