A New Route to the Synthesis of Oxazines, Condensed Oxazines, Polyfunctionally Substituted Pyran and Pyridine

[1]A.M. RADWAN, [1]E.E. ESLAM, [1]R. KASSAB AND [2]M.H. ELNAGDI
[1]*Chemistry Department, Faculty of Science, (For Girsl) Al-Azhar, University, Egypt*
[2]*Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt*

(Received 10th June, 1994, revised 4th Feburary, 1996)

Summary: Reactions of benzilmonoxime with malononitrile-ammonium acetate, cyanothioacetamide, malononitrile-resorcinol, 1,1,3-tricyano-2-aminopropeneresorcinol have been studied. Also, reactions of benzil with ethyl cyanoacetate-β-naphthol, ethyl cyanoacetate - aminopyrazole, pyrazolone and ethyl cyanoacetate - resorcinal have also been studied.

Introduction

As a continuation of our recent work [1-4] in developing new simple and efficient approaches for the synthesis of polyfunctionalized substituted heteroaromatic utilising simple inexpensive and readily obtainable starting meterial, the present work reports the results of the investigation on the potential of benzilmonoxime as a precursors for synthesis of hetero aromatic compounds. The various synthesized compounds are presented in Scheme-1.

Thus, benzilmonoxime (**2**), prepared from benzil (**1**) and hydroxylamine hydrochloride, reacts with malononitrile in the presence of ammonium acetate to yield a condensation product as **3**. Its IR* spectrum revealed νC=N at 2200, and ν=N-OH at 3400. Cyclization of compound **3** in the presence of acetic acid led to the formation of 3,4-diphenyl-5-,1,5-cyano-6-imino-1,2-oxazine (**4**).

IR spectrum showed νNH at 3300, νC=N at 2200, νN=O at 1440 and νC-O at 1200.

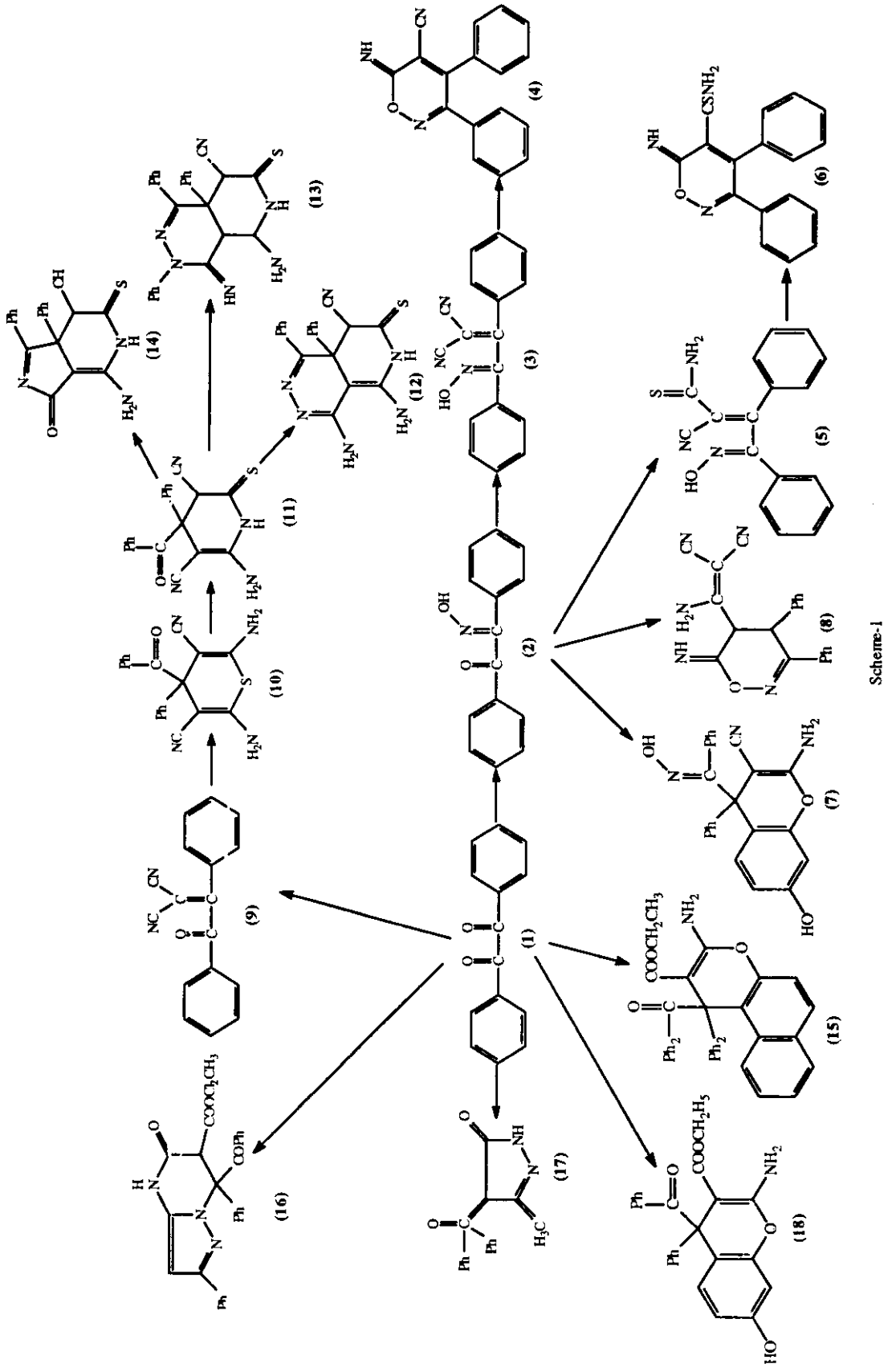
Similarly, compound **2** condensed with cyanothioacetamide to yield 3-C-phenyl oxime-2-cyano-3-thio-3-amino-benzylidene malononitrile (**5**). Its IR spectrum showed νOH, NH_2 at 3400-2900, νCN at 2250, νC=C at 1620 and ν=N-O at 1420. The reaction of compound **5** with acetic acid gave the cyclised product 6-imino-3,4-diphenyl-1,2-oxazine-5-thiocarboxamine (**6**) which further proved the structure of compound 5. Its IR spectrum showed νNH_2 at 3300, νC=C at 1580 and ν=N-O at 1420.

Study of the behaviour of compound **2** was continued. Thus, compound (**2**), reacts with malononitrile and resorcinol in presence of few drops of triethylamine to give 2-amino-3-cyano-4-phenyl-oxime-7-hydroxylbenzopyran (**7**). Its infrared spectrum showed νOH, NH_2 at 3400, 2500, νCN at 2200, νC=C at 1610, ν=N-O at 1450 and νC-O at 1220. On the other hand, reaction of **2** with 1,1,3-tricyano-2-aminopropene in the presence of resorcinol and ammonium acetate give 1-cyano-2-amino (6-imino-3,4,2-diphenyl)1,2-oxazin-5-yl acrylonitrile (**8**). Its IR spectrum showed νNH_2 at 3600, νCN at 2200, νC=C at 1640, ν=N-O at 1440 and ν=C-O at 1200.

Reaction of benzil mononitrile (**9**) and cyanothioacetamide in the presence of few drops of triethylamine give 2,6-diamino-4-benzoyl-4-phenyl -4-(H), 3,5-dicarbonitrile thiopyrane (**10**). Its IR spectrum showed νNH_2 at 3400, νCN at 2230, ν C=O at 1730 and νC=C at 1620 cm^{-1}.

Treatment of compound **10** with 10% sodium hydroxide solution yields 1,2,3,4-tetrahydro-6-amino-2-thioxy-4-benzoyl-4-phenylpyridine-3, 5-dicarbonitrile (**11**). Its IR spectrum showed νNH_2 at 3400, νCN at 2200 and νC=O at 1680.

The pyridine thione (**11**) was condensed with hydrazines namely, hydrazine hydrate and phenylhydrazine to give 1,8-diamino-4,4-a-diphenyl-6-thioxypyrido [3,4d] pyridazine-5-carbonitrile (**12**) and 1-imino [2,4,4a] triphenyl-8-amino-6-thioxy-pyrido-[3,4d]pyridazine-5-carboni-



Scheme-1

trile (13). The IR spectrum of **12** showed νNH_2 at 3400, νCN at 2200 and that of **13** showed νNH_2 at 3600, νCN at 2150 and νC=C at 1620.

When pyridine thione (**11**) was refluxed with a mixture of acetic acid and hydrochloric acid 1:1, it gives 7-amino-[3a,4,5,6] tetrahydro[3,3a] diphenyl-1-oxo-5-thioxo-l(H)-pyrazolo-[3,4-c)-pyridine (**14**). Its IR spectrum showed νNH_2 at 3600, νCN at 2150, νC=C at 1620 and ν-N-O at 1440. The ^{1}H-NMR (DMSO-d_6) spectrum of **14** showed signals at 8-7.4 (10H, m, Ar-H), 8.7 (1H, s, NH), 3.4 (1H, s, CH) and 2.5 (2H, s, NH_2).

The behaviour of benzil towards a variety of reagents has been studied. Thus, benzil racts with a mixture of ethyl cyanoacetate and β-napthol, amino -pyrazole and ethyl cyanoacetate, pyrazolone, and resorcinol and ethyl cyanoacetate to give 1-benzoyl-1-phenyl-3-amino-4H-naphtho[2,1b] pyran -2-ethyl-carboxylate(**15**), 2,7-diphenyl-7-benzoyl-4,5,6,7-tetrahydro-5-oxapyrazolo-[1,5-a]-pyrimi dine-6-ethyl carboxylate (**16**), 4-α-benzoylidine-3-methyl-2-pyrazolin-5-one (**17**) and -2-amino-7-hydroxy-4-benzoyl-4-phenyl-4(H)-benzo-pyrane-3-ethyl carboxylate (**18**).

Compound **15** showed frequency at 3200, νC=O (ester) at 1720, νC=O at 1660 and νC=C at 1620. The ^{1}H-NMR DMSO-d_6 spectrum of **15** showed signals at 8.1-7.4 (16H, m, ArH), 4.2 (2H, s, CH_2), 2.4 (2H, s, NH_2) and 1.1 (3H, s, $3CH_3$).

The IR spectrum of **16** showed νNH_2 at 3300, νC=O at 1660 and νC=C at 1580.

Spectra of compound **17** showed νNH at 3100 CH_3 at 2960 νC=O at 1650 and νC=C at 1600.

Spectra of compound **18** showed νOH at 3300, νNH_2 at 3000, νC=O (ester) at 1720 and νC=O at 1660. The ^{1}H-NMR (DMSO-d_6) spectrum of **18** showed signals at 8.0-7.5 (13H, m, Ar-H), 9.7 (1H, s, OH), 4.1 (2H, s, CH_2), 2.5 (2H, s, NH_2) and 1.0 (3H, s, CH_3).

Experimental

All melting points are uncorrected. IR spectra, were recorded in KBr Van Shimadzu 440 IR spectrometer. ^{1}H-NMR were performed in DMSO-d_6 on Varian 200 MHz using TMS as internal standard. Analytical data were performed in analytical data unit at the International Research Centre in Cairo, Dokki.

Reaction of benzil with NH_2OH HCl: Formation of 2

A mixture of benzil (0.01 mol) and $NH_2OH.HCl$ (0.1 mol) in absolute ethanol (30 ml) containing anhydrous sodium acetate (5 g) was refluxed for 4 h., then poured in ice and HCl, the resulting solid produced was collected by filtration and crystallized from petroleum ether 90-110°C to give **2**, m.p. 95°C, yield 65% (Found: C, 73.80; H, 5.10; N, 5.90 $C_{14}H_{11}NO_2$ Requires: C, 74.66; H, 4.88; N, 6.22%.

Reaction of 2 with malononitrile: Formation of 3

A mixture of benzilmonoxime (0.01 mol) and malononitrile (0.01 mol), ammonium acetate in 20 ml of acetic acid (20 ml) was refluxed for 3 h. The solid that separated after concntration and cooling was crystallized from ethanol to give **3**, m.p. 210°C, yield 65% (Found: C. 73.90; H, 4.00; $C_{17}H_{11}N_3O$ Requires: C. 74.28; H, 4.31 %).

Reaction of 2 with cyanothioacetamide: Formation of 5

A mixture of **2** (0.01 mol) (2.2 g) and cyanothioacetamide (0.01 mol) were fused at 110°C for 30 minutes then left to cool. The reaction mixture was triturated with ethanol, the resulting solid was crystallized from ethanol to give **5**, m.p. 190°C, yield 60% (Found : C, 66.90; H, 3.90 $C_{17}H_{13}N_3OS$ Requires C. 66.44; H, 4.23 %).

Refluxing 3 and 5 in acetic acid: Formation of 4 and 6

Compound **3** or **5** (0.01 mol) (2.7 g) in acetic acid (30 ml) refluxed for 30 minutes. After concentration and cooling, the solid products obtained was crystallized from ethanol to give **4** and **6**, respectively. **4**: m.p. 140°C yield 80% (Found: C, 74.60; H, 4.09 $C_{17}H_{11}N_3O$ Requires: C, 74.72; H, 4.02 %). **6**: m.p. 210°C, yield 50% (Found: C, 66.80; H, 4.10 $C_{17}H_{13}N_3OS$ Requires: C, 66.44; H, 4.23%).

Reaction of 2 with malonnitrile and resorcinol: Formation of 7

A solution of **2** (0.01 mol) (2.2 g) malononitrie (0.01 mol) and resorcinol (0.01 mol) in absoute ethanol and few drops of triethylamine was refluxed for 5 h. The solid obtained after cooling and pouring in ice-HCl acid was crystallized from ethanol to give **7** m.p. 170°C, yield 60% (Found: C, 71.90; H, 4.70 ($C_{23}H_{17}N_3O_3$ Requires: C, 72.06; H, 4.44%).

Reaction of 2 with 1,1,3-tricyano-2-aminopropene and resorcinol:Formation of 8

A mixture of **2** (0.01 mol), (2.2 g) resorcinol (0.01 mol) and 1,1,3-tricyano-2-aminopropene (0.01 mol) was fused with ammonium acetate and few drops of triethylamine at 140°C, then added ethanol which crystallized from it to give **8**, m.p. 165°C, yield 50% (Found: C, 71.00; H, 4.10 $C_{20}H_{15}N_5O$ Requires: C, 70.38; H, 4.39%).

Reaction of 9 with cyanothioacetamide: Formation of 10

A solution of **9** (0.01 mol) and cyanothioacetamide in absolute ethanol and few drops of triethylamine as catalyst was refluxed for 5 h. The solid obtained after cooling and acidification with ice-HCl was crystallized from benzene to give **10**, m.p. 135°C, yield 85% (Found: C, 67.80; H, 4.10 $C_{20}H_{14}N_4SO$ Requires: C, 67.03; H, 3.91%).

Reaction of 10 with sodium hydroxide: Formation of 11

A solution of **10** (0.01 mol) (3.5 g) in sodium hydroxide solution (30 ml, 10%) was refluxed for 5 h.The solid obtained after cooling and acidification with HCl was crystallized from benzene to give **11**, m.p. 250°C, yield 85% (Found: C, 68.90; H, 3.90 $C_{20}H_{14}N_4OS$ Requires: C, 69.60; H, 4.06%).

Reaction of 11 with hydrazines: Formation of 12 and 13

A mixture of **11** (0.01 mol), (3.5 g) hydrazine hydrate or phenyl-hydrazine (0.01 mol) was fused at 100°C for 30 minutes. The solid obtained after trituration with ethanol was crystallized from the same solvent to give **12** and **13** respectively. **12**: m.p. 230°C, yield 55% (Found: C, 64.80; H, 4.90 $C_{20}H_{16}N_6S$ Requires: C, 64.51; H, 4.30%). **13**: m.p. 235°C; yield 60% (Found: C, 69.80; H, 5.00; $C_{26}H_{22}N_6S$ Requires: C, 69.33; H, 5.47%).

Reaction of 11 with CH_3COOH/HCl: Formation of 14

A solution of 11 (0.01 mol) (3.5 g) in acetic acid - hydrochloric acid (30 ml: 1:1) was heated under reflux for about 30 minutes, then the excess of acid was neutralized with sodium carbonate. The solid produced was crystallized from ethanol to give **14**, m.p. 175°C; yield 90% (Found: C, 66.60; H, 4.30 $C_{20}H_{14}N_4OS$ Requires C. 66.29; H, 4.94%).

Reaction of 1 with ethyl cyanoacetate, β-naphthol, aminopyrazole, 3-methyl-2-pyrazolin-5-one, resorcinol: Formation of 15 - 18

A mixture of **1** (0.01 mol), β-naphthol, aminopyrazole, 3-methyl-2-pyrazolin-5-one and/or resorcinol (0.01 mol) with ethyl cyanoacetate (0.01 mol) in ethanol (30 ml) and few drops of triethylamine was refluxed for 4 hr. The solid obtained after cooling and acidification with ice - HCl was crystallised from ethanol (**15**, **16**) petroleum ether 90 - 100°C (**17**) or petroleum ether 60 - 80°C (**18**). **15**: m.p. 80°C; yield 70% (Found: C, 78.00; H, 5.00; $C_{29}H_{23}NO_4$ Requires: C, 77.50; H, 5.12%). **16**: m.p. 210°C; yield 50% (Found: C, 72.60; H, 5.20 $C_{28}H_{23}N_3O_4$ Requires: C, 72.25; H, 4.94%). **17**: m.p. 190°C yield 50% (Found: C, 74.60; H, 4.60 $C_{18}H_{14}N_2O_2$ Requires: C, 74.41; H, 4.82%). **18**: m.p. 100°C, yield 75% (Found: C, 72.00; H, 5.00 $C_{25}H_{21}NO_5$ Requires: C, 72.28; H, 5.06%)

References

1. G.E.H. Elgemeie, M.M.M. Sallam, S.M. Sherif and M.H. Elnagdi, *Heterocycles*, **23**, 3107 (1985).
2. G.E.H. Elgemeie, S.M. Sherif, F.A.E.M, Abdel Ali and M.H. Elnagdi, *Z. Naturforsch.*, **41b**, 781 (1986).
3. F.M. Abdel - Galil, S.M. Sherif and M.H. Elnagdi, *Heterocycles*, **24**, 2023 (1986).
4. M.H. Elnagdi, S.A.S. Ghozlan, F.M. Abdelrazek and M.A. Selim, *J. Chem. Res.* (S), 116 (1991).