SYNTHESIS OF SOME HETEROCYCLIC COMPOUNDS VIA THE TERNARY CONDENSATION WITH 3-ACETYLPYRIDINE

Fathy F. Abdel-Latif, Rafat M. Shaker* and Naglaa S. Abdel-Aziz
Chemistry Department, Faculty of Science, El-Minia University, El-Minia 61519, A.R. Egypt

Abstract: Ternary Condensation of aromatic aldehydes with malononitrile and 3-acetyl-pyridine in the presence of ammonium acetate produced 2,3`-bipyridinyl derivatives, while ternary condensation of 3-acetylpyridine, malononitrile and some nucleophilic reagents afforded the corresponding fused pyran, thiopyran and pyrimidine derivatives.

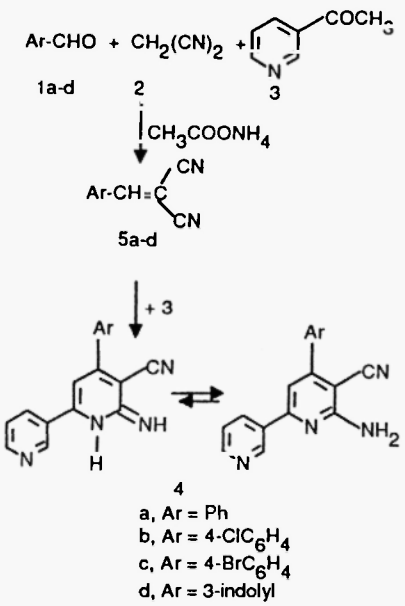
Introduction

The considrable biological activities of pyridine derivatives have stimulated enormous interest in the synthesis and chemistry of this class of compounds (1-4) . In continuation of our work on the synthesis of biologically interesting molecules via multicomponent one-flask condensation (5-8), we report herein our results for the synthesis of heterocycles containing pyridine moiety through ternary condensation reactions with 3-acetylpyridine.

Results and Discussion

It has been found that stirring an ethanolic solution of benzaldehyde **1a,** malononitrile **2** and 3-acetylpyridine **3** in a molar ratio 1:1:1 in the presence of ammonium acetate produced the bipyridinyl derivative **4a** (Scheme 1). The bipyridinyl structure **4a** was established on the basis of elemental and spectral data (Experimental). Structural proof was obtained through another route of synthesis by stirring an ethanolic solution of the benzylidene **5a** with 3-acetylpyridine **3** in the presence of ammonium acetate at room temperature (Scheme 1). In the same manner, 4-chlorobenzaldehyde **1b,** 4-bromobenzaldehyde **1c** and 3-indolecarboxaldehyde **1d** were submitted to the same reaction condition to afford the corresponding bipyridinyl derivatives **4b-d** (Scheme 1). The structures of **4b-d** were established on the basis of elemental and spectral data

(Experimental). In a similar case, it has been reported that the condensation of 2-formyl-5-nitro-benzo[b]thiophene with nitrile reagent and 4-acetylpyridine afforded the corresponding bipyridinyl derivatives (9) .

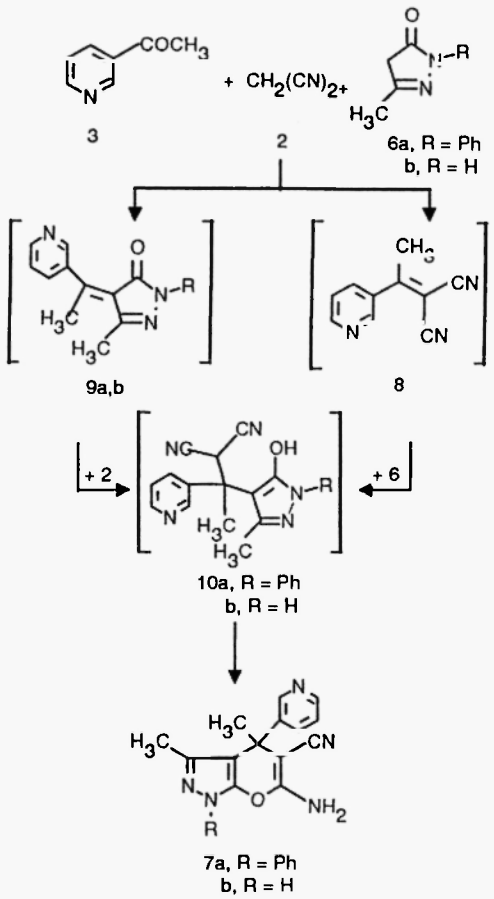


Scheme 1

In another part of this study, we report on using 3-acetylpyridine **3** as the carbonyl reagent to be condensed with an active methylene reagent in the ternary condensation reaction. As an application, stirring an ethanolic solution of equimolar amounts of **3, 2** and 3-methyl-1-phenyl-2-pyrazolin-5-one **6a** in the presence of a catalytic amount of piperidine for 3 hours at room temperature gave a solid product **7a** (Scheme 2).

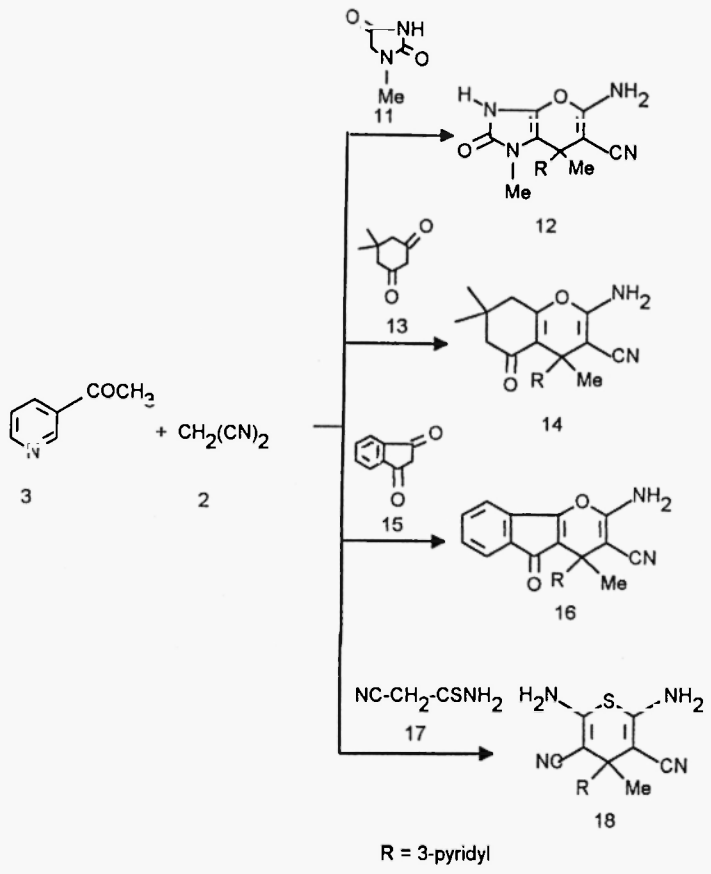
The structure of **7a** was established on the basis of elemental and spectral data (Experimental). The IR spectrum of **7a** showed absorption bands for CN and NH_2 at 2200 and 3400-3200 cm^{-1} , respectively. The ^1H NMR spectrum of **7a** showed the following signals, two singlets at 1.8 and 1.9 ppm for the pyran and pyrazole CH_3 , respectively; singlet at 7.2 ppm for NH_2 ; multiplet at 7.4-7.6 ppm for phenyl protons and at 7.7-7.9, 8.5 and 8.6 ppm for the pyridinyl protons. Formation of **7a** was rationalized in terms of the initial condensation of **3** with **2** or **6a** to afford the ylidenes **8** or **9a** , respectively ; this was followed by Michael addition of **6** to **8** or of **2** to **9a** to form the

acyclic intermediate **10a** which cyclized spontaneously to give the final product **7a** (Scheme 2). Similarly, using 3-methyl-2-pyrazolin-5-one **6b** in the previous reaction affording the corresponding pyrano[2,3-c]pyrazole derivative **7b** (Scheme 2).



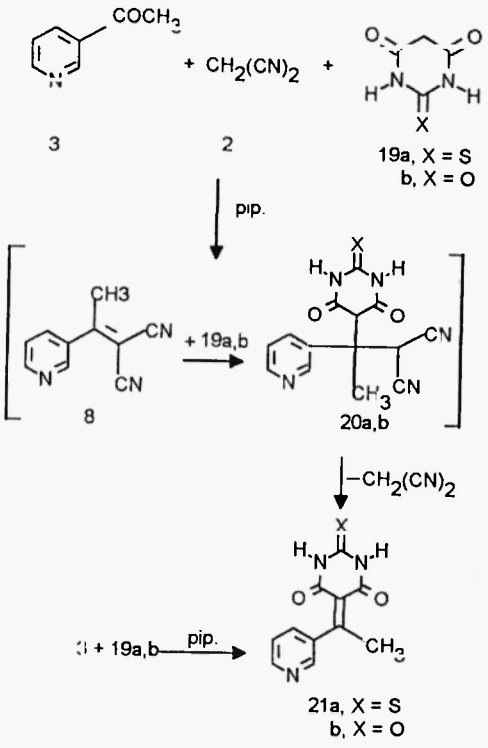
Scheme 2

In the same manner, when 1-methylhydantoin **11** was submitted to the same reaction condition to afford corresponding pyranoimidazoline derivative **12** (Scheme 3 and Experimental). Dimedone **13,** 1,3-indandione **15** and cyanothioacetamide **17** were, also submitted to the same reaction condition to afford the corresponding benzopyran **14,** indeno[1,2-b]pyran **16** and thiopyran **18** derivatives respectively. The structures of the products **14, 16** and **18** were established on grounds similar to those of **7a** (Experimental).



Scheme 3

In contrast to the previous behavior, we found that using thiobarbituric **19a** and barbituric acids **19b** in the previous reaction afforded only the corresponding ylidene derivatives **21a** and **21b** respectively (Scheme 4). The structural proof was supported by an ambiguous synthesis of **21a,b** by reacting **3** with **19a,b** respectively (Experimental). The ylidene derivatives **21a,b** were assumed to be formed via nucleophilic addition of **19a,b** to the activated double bond of the initially formed ylidene **8** followed by elimination of a malononitrile molecule from the intermediate adduct **20a,b** (Scheme 4).



Scheme 4

Experimental

All melting points were uncorrected. IR. (KBr) spectra were recorded on Shimadzu 408 Spectrophotometer. ^{1}H NMR Spectra were recorded in DMSO-d_6 on a 90 Mhz varian EM-390 Spectrometer with Me_4Si as an internal standard and chemical shifts, δ , were expressed in ppm. Analytical data were obtained from the Micro-analytical Data Unit at Cairo University.

(A): Condensation of aldehydes with malononitrile and 3-acetylpyridine: A solution of equimolar amounts (0.01 mol) of aldehydes **1a-d**, malononitrile **2** and 3-acetylpyridine **3** in ethanol (50 ml) were heated in the presence of ammonium acetate

(0.08 mol) for 10 minutes, then stirred for 3 hours at room temperature. The produced solid was collected by filtration and recrystallized from an appropriate solvent.

An alternative synthesis of 4a-d: An ethanolic solution (50 ml) containing equimolar amounts (0.01 mol) of the ylidene **5a-d** and **3** together with ammonium acetate (0.08 mol) was treated as above to afford **4a-d**.

6-Amino-5-cyano-4-phenyl-2,3`-bipyridinyl 4a: Colourless crystals (from EtOH), m.p. 255-257 °C. Yield 75 %, υ_{max} / cm^{-1} (KBr) 3490,3390 (NH_2), 2200 (CN), 1590,1640 (C=C, C=N, δ NH_2) (Found: C,74.9; H,4.6; N,20.4. $C_{17}H_{12}N_4$ (272.32) requires C,74.98; H,4.44; N,20.58 %).

6-Amino-5-cyano-4-(p-chlorophenyl)-2,3`-bipyridinyl 4b: Colourless crystals (from EtOH), m.p. > 300 °C. Yield 70 %, υ_{max} / cm^{-1} (KBr) 3480,3390 (NH_2), 2200 (CN), 1590,1640 (C=C, C=N, δ NH_2) (Found: C,66.7; H,3.5; Cl,11.4 ; N,18.4. $C_{17}H_{11}ClN_4$ (306.74) requires C,66.56; H,3.61; Cl,11.56 ;N,18.27 %).

6-Amino-5-cyano-4-(p-bromophenyl)-2,3`-bipyridinyl 4c: Pale yellow crystals (from Dioxan), m.p. > 300 °C. Yield 73 %, υ_{max} / cm^{-1} (KBr) 3480,3380 (NH_2), 2200 (CN), 1590,1640 (C=C, C=N, δ NH_2) (Found: C,58.3; H,3.2; N,15.7. $C_{17}H_{11}BrN_4$ (351.2) requires C,58.14; H,3.16; N,15.95 %).

6-Amino-5-cyano-4-(3-indolyl)-2,3`-bipyridinyl 4d: Yellowish brown crystals (from EtOH), m.p. 236-238 °C. Yield 79 %, υ_{max} / cm^{-1} (KBr) 3300,3100 (NH_2 , NH), 2200 (CN), 1590,1620 (C=C, C=N, δ NH_2) (Found: C,73.2; H,4.3; N,22.3. $C_{19}H_{13}N_5$ (311.33) requires C,73.29; H,4.21; N,22.50 %).

(B): Condensation of 3-acetylpyridine with malononitrile and active methylene reagents: A mixture of 3-acetylpyridine **3** (0.01 mol), malononitrile **2** (0.01 mol) and the appropriate active methylene reagents (0.01 mol) of either **6a,b**; **11**; **13**; **15**; 17 and **19a,b** respectively in absolute ethanol (50 ml) and catalytic amounts of piperidine was stirred at room temperature (30-35 °C). In order to complete the reaction, stirring was continued for 3 hours even if a solid precipitate was formed after a short time of stirring. The deposited solid, or that obtained after concentration of the reaction mixture, was

filtered and crystallized from the appropriate solvent to afford **7a,b**; **12**; **14**; **16**; **18** and **21a,b** respectively.

An alternative synthesis of 21a,b: An equimolar (0.01 mol) mixture of 3-acetylpyridine **3** and thiobarbituric acid **19a** or barbituric acid **19b**, respectively, in ethanol (50 ml) was treated with piperidine (0.1 ml). The reaction mixture was stirred till the ylidenes **21a,b** were precipitated, respectively.

2-Amino-4,5-dimethyl-3-cyano-7-phenyl-4-(3-pyridinyl)pyrano[2,3-c]pyrazole 7a : Colourless crystals (from EtOH), m.p. 196-198 °C. Yield 88 %, υ_{max} / cm^{-1} (KBr) 3400,3200 (NH_2), 2200 (CN), 1600,1650 (C=C, C=N, δ NH_2). δ_H ([$^2H_6$]DMSO) 1.8 (s,3H,CH_3), 1.9(s,3H,CH_3), 7.2(s,2H,NH_2), 7.4-7.6 (m,5H, phenyl protons), 7.7-7.9 (br,t,2H,pyridine H-4,H-5),8.5(d,1H,pyridine H-6),8.6(s,1H, pyridine H-2). (Found: C,70.0; H,4.8; N,20.5. $C_{20}H_{17}N_5O$ (343.38) requires C,69.95; H,4.99; N,20.40 %).

2-Amino-4,5-dimethyl-3-cyano-7H,4-(3-pyridinyl)pyrano[2,3-c]pyrazole 7b : Colourless crystals (from EtOH), m.p. 218-220 °C. Yield 83 %, υ_{max} / cm^{-1} (KBr) 3400,3100 (NH_2 , NH), 2200 (CN), 1600,1650 (C=C, C=N, δ NH_2) (Found: C,62.8; H,5.0; N,26.1. $C_{14}H_{13}N_5O$ (267.28) requires C,62.91; H,4.90; N,26.20 %).

2-Amino-3-cyano-6,7-dihydro-4,5-dimethyl-6-oxo-4-(3-pyridinyl)pyrano[3,2-d]imidazole 12: Colourless crystals (from EtOH), m.p. 217-219 °C. Yield 70 %, υ_{max} / cm^{-1} (KBr) 3330,3100 (NH_2 , NH), 2200 (CN), 1600,1660 (C=C, C=N, δ NH_2) (Found: C,59.4; H,4.7; N,24.6. $C_{14}H_{13}N_5O_2$ (283.28) requires C,59.36; H,4.62; N,24.72 %).

2-Amino-3-cyano-5-oxo-4-(3-pyridinyl)-4,7,7-trimethyl-5,6,7,8-tetrahydro-benzo[b]-pyran 14: Colourless crystals (from Dioxan), m.p. 190-192 °C. Yield 78 %, υ_{max} / cm^{-1} (KBr) 3400,3100 (NH_2), 2200 (CN), 1690 (CO), 1600,1640 (C=C, C=N, δ NH_2). δ_H ([$^2H_6$]DMSO) 0.9(s,3H,CH_3), 1.0(s,3H,CH_3), 1.8(s,3H,CH_3), 2.2 (s,2H,CH_2), 2.4 (s,2H,CH_2),7.1(s,2H,NH_2),7.4(m,1H,pyridine H-5),7.7 (d, 1H,pyridine H-4),8.4 (d,1H,pyridine H-6), 8.5 (s,1H,pyridine H-2). (Found: C,70.0; H,6.1; N,13.5. $C_{18}H_{19}N_3O_2$ (309.4) requires C,69.88; H,6.19; N,13.58 %).

2-Amino-3-cyano-4-methyl-5-oxo-4-(3-pyridinyl)indeno[3,2-b]pyran 16 : Brown crystals (from EtOH), m.p. > 300 °C. Yield 65 %, υ_{max} / cm^{-1} (KBr) 3400,3200 (NH_2),

2200 (CN), 1700 (CO), 1600,1650 (C=C, C=N, δ NH_2). (Found: C,72.4; H,4.3; N,13.1. $C_{19}H_{13}N_3O_2$ (315.31) requires C,72.37; H,4.15; N,13.33 %).

2,6-Diamino-3,5-dicyano-4-methyl-4-(3-pyridinyl)thiopyran 18 : Colourless crystals (from EtOH), m.p. 160-162 °C. Yield 70 %, υ_{max} / cm^{-1} (KBr) 3400,3200 (NH_2), 2200 (CN), 1600,1640 (C=C, C=N, δ NH_2). δ_H ([$^2H_6$]DMSO) 1.8(s,3H,CH_3), 7.0 (s,4H, $2NH_2$),7.4(m,1H,pyridine H-5),7.7 (d,1H,pyridine H-4),8.2(d,1H,pyridine H-6),8.5 (s,1H,pyridine H-2). (Found: C,57.8; H,4.2; N,26.2; S,11.8. $C_{13}H_{11}N_5S$ (269.32) requires C,57.97; H,4.12; N,26.00; S,11.91 %).

5-(Methyl(3-pyridinyl))methylene-2-thioxo-4,6-dioxo-pyrimidine 21a**:** Brown crystals (from EtOH), m.p. 250-252 °C. Yield 92 %, υ_{max} / cm^{-1} (KBr) 3100 (br, NH), 1680,1700 (CO); δ_H ([$^2H_6$]DMSO) insoluble in DMSO. (Found: C,53.5; H,3.4; N,16.8; S,13.1. $C_{11}H_9N_3O_2S$ (247.27) requires C,53.43; H,3.67; N,16.99; S,12.97 %).

5-(Methyl(3-pyridinyl))methylene-2,4,6-trioxo-pyrimidine 21b **:** Colourless powder (from EtOH), m.p. 340-342 °C. Yield 90 %, υ_{max} / cm^{-1} (KBr) 3100 (br, NH), 1680,1700 (CO). (Found: C,57.2; H,4.0; N,18.0. $C_{11}H_9N_3O_3$ (231.2) requires C,57.14; H,3.92; N,18.18 %).

References

(1) J.L. Soto, C. Seoane, P. Zamorano, F.J. Cuedrdo, Synthesis 529 (1981).
(2) M. Sammour, Egypt. J. Chem. 14, 213 (1991).
(3) F.F. Abdel-Latif, Arch. Pharm. Res.. 12(4), 254 (1989).
(4) F. Al-Omran, N. Al-Awadi, J. Chem. Res. (S) 392 (1995); (M) 2201 (1995).
(5) F.F. Abdel-Latif, Phosphorus, Sulfur and Silicon 53 , 145 (1990).
(6) F.F. Abdel-Latif, R.M. Shaker, Bull. Soc. Chim. Fr. 127, 87 (1991).
(7) F.F. Abdel-Latif, R.A. Mekheimer, M.M. Mashaly, E.Kh. Ahmed, Collect. Czech. Chem. Commun. 59, 1235 (1994).
(8) R.M. Shaker, Pharmazie 148 (1996).
(9) S.M.A.D. Zayed, A. Attia, J. Heterocycl. Chem. 20 (1), 129 (1983).

Received on March 27, 1997