SYNTHESIS OF SOME NEW ENAMINOKETONES, ANALOGOUS OF MILRINONE, 4-PYRONES AND RELATED 4-PYRIDONES

*Shahrisa, Aziz**
Hemmati, Salar
Department of Organic Chemistry, Faculty of Chemistry, Tabriz University, Postcode 51664, Tabriz, Iran.

(Received: Jan. 16th, 1996 , Accepted: Mar. 11th, 1996)

ABSTRACT: *Synthesis of 4-(N,N- dimethylamino)-3-aryl-3-butene-2- one, ethyl-5-aryl-4-oxo-4H-pyran-2-carboxylate, ethyl-5-aryl-4-pyridones-2- carboxylate and 5-aryl-3-cyano-5-methyl-2-pyridones (aryl=3-thienyl, 2-furyl) are described.*

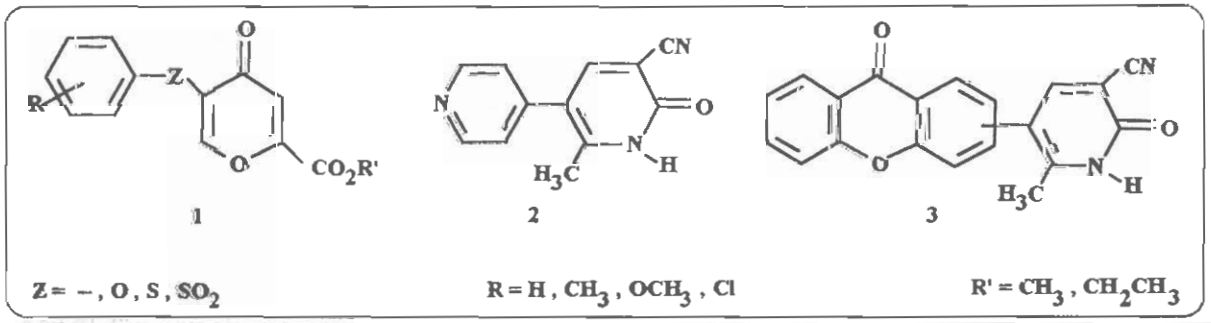
KEY WORDS: *4-(N,N-Dimethylamino)-3-butene-2-one, 4-Oxo-4H- pyran, 4-Pyridone, 2-pyridone, Milrinone.*

INTRODUCTION

Because of biological activities of some 4-pyrones derivatives, the chemistry of this class of compounds has widely been investigated [1].

It has been previously reported that some 4-pyrones possesing substituent at C-2 and C-5 positions similar to **1** show antiallergic activity in treatment of immediate hypersensitivity reactions and asthma [2].

Also digital glycosides have been the principal agents used in treating congestive heart failure for more than a century in spite of their low therapeutic index [3a,b]. Noncathecolamine and nonglycoside agents such as milrinone **2** has been developed for replacing symphathomimetic agents such as dopamine and dobutamine which are orally inactive. Research on the synthesis of milrinone [4a-c] and other analogues **3** has expanded in the recent years [5].



* *To whom correspondence should be addressed*
1021-9986/96/2/76 5 / $ / 2.50

In the previous reports the synthesis of some new derivatives of 4-pyrone possessing various substituents such as heterocycles, carboxylate, amide, nitrile and tetrazolyl at C-2 and C-6 positions, have been described [6]. In continuation of our investigations we report herein the synthesis of 2,5-disubstituted-4- pyrones **7a,b** analogous to **1**, related 4-pyridones **9a,b** and two novel 2-pyridones **8a,b** analogues of biologically active milrinone **2**.

EXPERIMENTAL

Starting materials were prepared according to the procedures described in literature: 1-(3-thienyl)-2-propanone [7], 1-(2-furyl)-2-propanone [8], nitroethane [9], N,N-dimethylformamide diethylacetal [10]. Other chemical materials were purchased from *Merck* (Darmstadt, Germany) and *Fluka* (Switzerland).

Melting points were determind in open capillary tubes in a *Electrothermal-910* instrument and are uncorrected. The IR spectra were recorded on a *Shimadzu* IR-408 spectrometer. The FTIR spectra were recorded on a FTIR *Shimadzu* DR-8001. NMR spectra were recorded on *Varian* EM-390 90 MHz using tetramethylsilane (TMS) as an internal standard. Mass spectra were determined with *Finigan-mat* 8430 GC mass spectrometer. Microanalysis were performed by Research Institute of Petroleum Industry, Ray, Iran.

General procedure for the synthesis of 6a,b.

4-(N,N- Dimethylamino)-3-(3-thienyl)-3- butene-2-one (6a)

A solution of 1-(3-thienyl)-2-propanone (**4a**) (5.6 g, 0.04 mol) and N,N-dimethylformamide diethylacetal (**5**) (6.47 g, 0.044 mol) was heated under dry nitrogen in an oil bath at 90-100°C for 2 hours. The reaction mixture was distilled under vaccuo in a semimicroscale distillation apparatus. A yellow fraction with BP_{5-8} 188-190°C was collected which on standing was crystallized to give 5.8 g (70%) of the title compound. The crude product was recrystallized from ether-petroleum ether (BP 60-80°C) which afforded white needles, MP: 80.5-81.5°C.

FTIR(KBr): 3063(s), 3042(s), 2926(s), 2814(m), 1634(s, CO ketone), 1540(s, C=C), 1527(s), 1487(s), 1444(s), 1417(s), 1400(s), 1346(s), 1307(s), 1223(s), 1213(s), 1161(s), 1147(s), 1105(s), 1086(m), 1062(m), 1022(m), 949(s), 895(m), 848(s), 812(m), 777(s), 698(s), 684(s) cm^{-1}.

^1H NMR($CDCl_3$): δ2.0(s, 3H), 2.75(s, 6H), 6.9-7.7(m, 4H) ppm.

MS: *m/z*(%),195(M^+, 86),196(M+1,14), 180(M-CH_3, 54), 162[M-(H_2O , CH_3), 100], 152(56), 137(46), 122 (46), 119(26), 109(20), 97(16), 69(18), 45(12), 42(32).

Anal. Calcd. for $C_{10}H_{13}NOS$: C, 67.02; H, 7.31.
Found: C, 66.8; H, 7.25.

4-(N,N-Dimethylamino)-3-(2-furyl)-3-butene-2-one (6b)

This compound was obtained as a yellow oil in a yield of 75%, BP_5 153-154°C. The product was unstable and on standing it decomposed.

IR(KBr): 3150(m), 3100(w), 2900-3000(s), 1650(s, CO, Ketone), 1550(s, C=C), 1535(m), 1500(m), 1420 (s), 1400(m), 1350(s), 1285(s), 1215(s), 1140(s), 1090(s), 1070(m), 1010(m), 950(s), 800(m), 735(s) cm^{-1}.

^1H NMR($CDCl_3$): δ1.9(s, 3H), 2.7(s, 6H), 6.1-6.45(m, 2H), 7.45-7.7(m, 2H) ppm.

MS: *m/z*(%), 179(M^+, 100), 180(M+1, 20), 164 (M-CH_3, 29), 136[M-(CH_3, CO), 100], 121(20), 108 (70), 93(40), 65(40), 55(100).

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 61.51; H, 6.71.
Found: C, 61.3; H, 6.55.

General procedure for synthesis of 7a,b.

Ethyl-5-(3-thienyl)-4-oxo-4H-pyran-2-carboxylate (7a)

To a stirred solution of sodium ethoxide [from sodium (0.414 g, 0.018 mol)] in absolute ethanol (12 mL) under reflux was added dropwise a mixture of **6a** (2.34 g, 0.012 mol) and diethyloxalate (3.5 g, 0.024 mol) in 6 mL absolute ethanol (in 20 minutes). The reaction mixture was heated under reflux for one hour, then cooled to room temperature. A solution of hydrochloric acid 5N (12 mL) was added to the mixture and stirred for one hour. Then cooled to 5°C and diluted with 30 mL of distilled water. The precipitate was filtered off, washed with water (2×20 mL) and air dried. The crude product was recrystallized from ethanol to give title compound as white

needles in a yield of 85%, MP: 125-126°C.
IR(KBr): 3100-2850(m), 1745(s, CO ester), 1640(s, CO pyrone),1615(s),1520(w),1480((w), 1440(m), 1425 (m),1370(m),1315(m),1250(s),1180(m),1100(m), 1030 (w), 1000(w), 940(m), 850(m), 800(m), 750 (w) cm^{-1}.
^1H NMR($CDCl_3$): δ1.4(t, 3H, J=7.3 Hz, CH_3 ester), 4.45(q, 2H, J=7.3 Hz, CH_2 ester), 7.25-7.5(m, 3H), 8.1-8.25(m, 2H) ppm.
MS: *m/z*(%), 250(M^+,66), 251(M+1,10), 205(M-OEt, 8), 177(M-CO_2Et, 100), 149(28), 108(60), 69(30), 57(18), 45(8).
Anal. Calcd. for $C_{12}H_{10}O_4S$: C, 57.59; H, 4.03.
Found: C, 57.75; H, 3.86.

Ethyl- 5- (2-furyl)- 4- oxo- 4H-pyran- 2-carboxylate (7b)

This compound was obtained as white needles in a yield of 90%, MP: 113-114°C [ethanol-water (60:40)].
IR(KBr): 3120(m), 3050(m), 2980(m), 1740(s, CO ester), 1650(s, CO pyrone), 1620(s), 1530(m), 1470 (w), 1435(m), 1415(m), 1380(m), 1320(m), 1255(s), 1170 (m), 1105(m), 1040(w), 1005(m), 950(m), 805 (m), 740(s) cm^{-1}.
^1H NMR($CDCl_3$): δ1.4(t, 3H, J=7.3 Hz, CH_3 ester), 4.45(q, 2H, J=7.3 Hz, CH_2 ester), 6.55(m, 1H, H_4-furan), 7.15(s, 1H, H_3-pyrone), 7.4-7.6(m, 2H, H_3- , H_5-furane), 8.5(s, 1H, H_6- pyrone) ppm.
MS: *m/z*(%), 234(M^+, 46), 235(M+1, 8), 189(M-OEt, 10), 161(M-CO_2Et, 4), 105(6), 93(10), 92(100), 71(8), 68(14), 64(18), 63(12), 51(10), 44(10).
Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30.
Found: C, 61.32; H, 4.12.

General procedure for synthesis of 8a,b.
1,2- Dihydro-6- methyl-2-oxo-5-(3- thienyl)-3- pyridinecarbonitrile (8a)

A mixture of sodium methoxide [from sodium (0.04 g, 0.0017 mol)], 4-(N,N-dimethylamino)-3- (3-thienyl)-3-butene-2-one (**6a**) (0.33 g, 0.0017 mol), cyanoacetamide (0.143 g, 0.0017 mol) in dry N,N-dimethylformamide (20 mL) was heated under reflux for one hour. The reaction mixture was evaporated to dryness under vaccuo and then the residue was crystallized from acetic acid [with addition of charcoal (0.5 g) for removing of dye impurities] to give title compound in a yield of 79% (0.25 g) as small yellow needles, MP: 293-294°C (dec.).
IR(KBr): 3420(s, free NH), 3200-2500(br, s, hydrogen bonding NH), 2200(s, CN), 1660(s, CO pyridone), 1605(s), 1570(s), 1525(w), 1490(s), 1430(w), 1380(m), 1330(s), 1250(m), 1230(w), 1205(w), 1165(s), 1125 (m), 1035(m), 960(m), 930(w), 860(m), 815(w), 780 (s) cm^{-1}.
^1H NMR(DMSO-d_6): δ2.35(s, 3H, -CH_3), 7.2-7.8(m, 3H, H_2-, H_4-, H_5- thiophene), 8.15(s, 1H, H_4-pyridone) ppm.
MS: *m/z*(%), 216 (M^+, 100), 217 (M+1, 18),187 (M-HCO, 18), 183(44), 171(36), 146(18), 111(14), 99(20), 83(18), 7(22), 69(16), 57(32), 43(20).
Anal. Calcd. for $C_{11}H_8N_2OS$: C, 61.09; H, 3.73.
Found: C, 60.64; H, 3.61.

1,2-Dihydro-6-methyl-2-oxo-5-(2-furyl)-3- pyridinecarbonitrile (8b)

This compound was obtained in a yield of 80%. The crude product once crystallized from acetic acid and then from methanol which afforded the title compound as small yellow needles, MP: 305-306°C (dec.).
IR(KBr): 3400(s, free NH), 3200-2500(br, s, hydrogen bonding NH), 2200(s, CN), 1655(s, CO pyridone), 1620 (s), 1570(s), 1490(m), 1475(m), 1375(s), 1325(s), 1270 (m), 1230(m), 1180(m), 1150(w), 1130(w), 1035 (w), 1010(m), 950(m), 810(w), 750(s) cm^{-1}.
^1H NMR(DMSO-d_6): δ2.5(s, 3H, -CH_3), 6.5-6.7(m, 2H, H_3-, H_4-furan), 7.7-7.8(m, 1H, H_5-furan), 8.3(s, 1H, H_4-pyridone) ppm.
MS: *m/z*(%), 200(M^+, 100), 201(M+1, 16), 171 (M-HCO, 64), 129(20), 116(14), 71(12), 57(14), 40(14).

General procedure for synthesis of 9a,b.
Ethyl-5-(3-thienyl)-4-pyridone-2-carboxylate (9a)

A sample of Ethyl-5-(3-thienyl)-4-oxo-4H-pyran-2-carboxylate (**7a**) (1.0 g, 0.004 mol) was dissolved in absolute ethanol (25 mL) then 1 mL of concentrated ammonia solution was added and the reaction mixture heated under reflux for 45 minutes. The mixture was concentrated to the volume of 25 mL and then cooled. The white needles was filtered off and washed with cooled ethanol (10 mL) and recrystallized from

ethanol to give title compound in 70% yield (0.7 g) as white needles, MP: 223-224°C.

FTIR(KBr): 3385(s, free NH), 3200-2500(s, hydrogen bonding NH), 1715(s, CO ester), 1645(s, CO pyridone), 1605(s), 1470(m), 1375(s), 1365(s), 1346 (m), 1282(s), 1138(m), 1000(s), 960(s), 912(s), 873 (m), 727(s), 600(s), 550(s) cm^{-1}.

^1H NMR(DMSO-d_6): δ1.4(t, 3H, J=7.4 Hz, CH_3 ester), 3.4(br, 1H), 4.35(q, 2H, J=7.4 Hz, CH_2 ester), 7.1-9.0(m, 5H) ppm.

MS: *m/z*(%), 249(M^+, 22), 250(M+1, 20), 204(4), 203(8), 177(M-72, 100), 149(18), 121(22), 108(26), 96(8), 83(4), 77(6), 69(16), 63(10), 45(22).

Anal. Calcd. for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45.

Found: C, 57.70; H, 4.36.

Ethyl-5-(2-furyl)-4-pyridone-2-carboxylate (9b)

This compound was obtained as white needles in a yield of 75%, MP: 227-228°C (ethanol).

FTIR(KBr): 3380(m, free NH), 3200-2500(br, s, hydrogen bonding NH), 1728(s, CO ester), 1641(s, CO pyridone), 1614(s), 1504(s), 1473(m), 1439(m), 1379(s), 1253(s), 1213(s), 1134(w), 1101(s), 1020(s), 997(m), 970(w), 939(m), 885(m), 856(m), 833(s), 800(s), 790(s), 750(m) cm^{-1}.

^1H NMR(DMSO-d_6): δ1.4(t, 3H, J=7.4 Hz, CH_3 ester), 3.35(br, 1H), 4.4(q, 2H, J=7.4 Hz, CH_2 ester), 6.5-8.2(m, 5H) ppm.

MS: *m/z*(%), 233(M^+, 78), 234(M+1, 10), 188(6), 187(16), 161(M-72, 100), 133(6), 132(18), 105(12), 92 (14), 77(12), 57(10), 40(20).

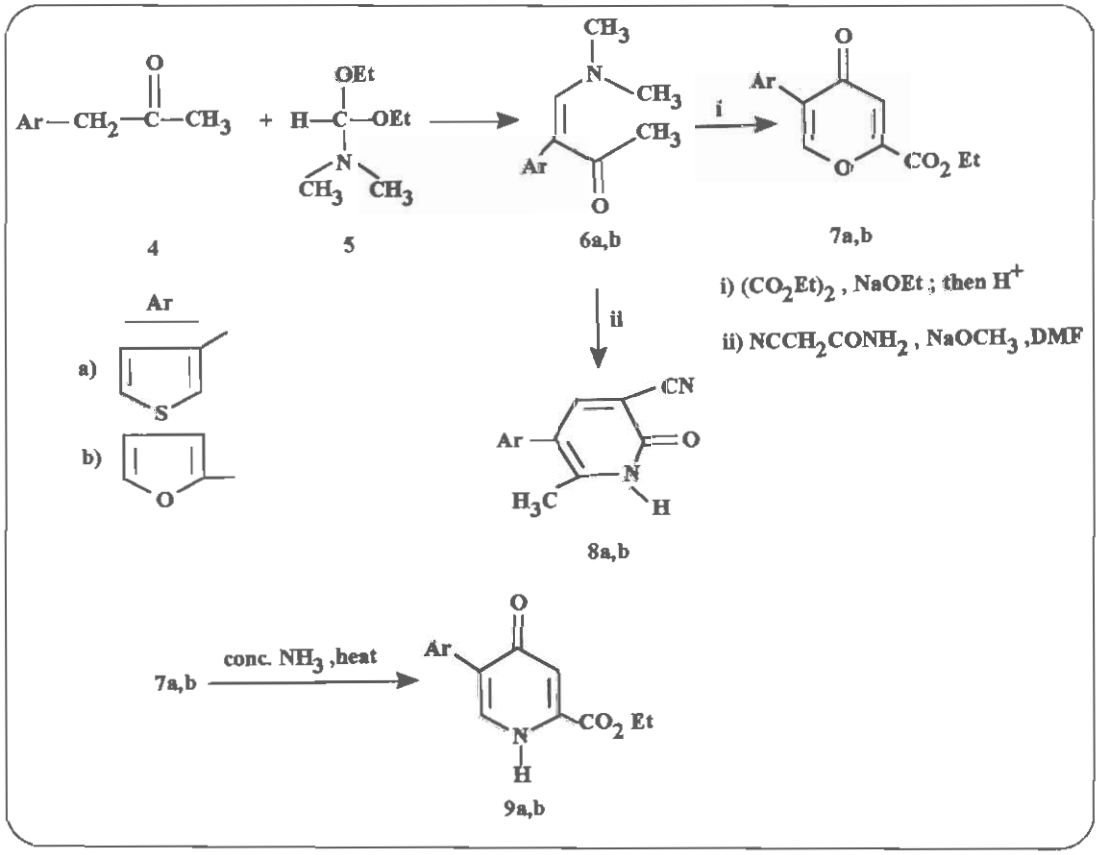
Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75.

Found: C, 61.70; H, 4.83.

RESULTS AND DISCUSSION

As scheme 1 shows, treatment of ketones **4a,b** with acetal **5** under reflux condition produced enaminoketones **6a** and **6b** in 70% and 75% yields respectively.

Treatment of enaminoketones **6a** and **6b** with



Scheme 1

sodium ethoxide in absolute ethanol and diethyloxalate followed by hydrolysis and cyclization by concentrated hydrochloric acid afforded the corresponding 4-pyrones **7a** and **7b** in 85% and 90% yields respectively.

Structures of compounds **6a,b** and **7a,b** were fully characterized as described earlier by MP, IR, ^{1}H NMR, MS data and elemental analysis.

When compounds **7a** and **7b** were dissolved in ethanol and teated with concentrated ammonia solution in reflux, the corresponding 2,5-disubstituted-4-pyridones **9a** and **9b** were produced in 70% and 75% yields respectively. Thier IR, ^{1}H NMR, MS data and elemental analysis are fully consistent with the proposed structures **9a** and **9b**.

Reaction of the enaminoketones with cyanoacetamide was the second aim of this work. Thus enaminoketones **6a,b** were treated with sodium methoxide and cyanoacetamide. The corresponding 2-pyridones **8a** (79%) and **8b** (80%) were synthesised and characterized.

ACKNOWLEDGMENT

Financial support of this work by the Research Council of Tabriz University is gratefully acknowledged. We are grateful to Dr. Mehran Ghiaci of Isfahan University of Technology for ^{1}H NMR Spectra.

REFERENCES

[1] Ellis, G. P., In "*Comprehensive Heterocyclic Chemistry*", Boulton, A. J., McKillop, A., Pergamon press, oxford UK, pp. 647-883 (1984).

[2] Clark, B. P. and Ross, J. W., *German Offen.* 3,012,597. *Chem. Abstracts,* **94,** 83945b (1981).

[3] (a) Muller, J. E., Turi, Z. G., Stone, P. H. Rude, R. E. and Braunwold, D. S., *New Engl. J. Med.,* **314,** 265(1986).
(b) Yusuf, S., Writtes, J., Bailey, K. and Furbeg, C., *Circulation,* **73,** 14 (1986).

[4] (a) Lasher, G. Y., Evert, R., Donald, F. and Chester, O. J., *Fr. Demande FR* 2,470,124. *Chem. Abstracts,* **96,** 6594a (1982).
(b) Baldev, S., *U.S. Patent* 4,347,363. *Chem. Abstracts,* **97,** 216018n (1982).
(c) Lasher, G. Y. and Philion, R. E., *U.S. Patent* 4,313,951. *Chem. Abstracts,* **97,** 216005f (1982).

[5] Montanari, P., Chiarini, A., Budriesi, R. and Valenti, P., *J. Heterocycl. Chem.,* **29,** 259 (1992).

[6] Shahrisa, A. and hemmati, S., *4th Iranian Seminar of Organic Chemistry,* Mashhad, October 17-19 (1995).

[7] Campaigne, E. E. and McCarthy, W. C., *J. Am. Chem. Soc.,* **76,** 4466 (1954).

[8] Sund, H. and Hunter, D. S., *J. Hetrocycl. Chem.,* **17,** 1123(1974).

[9] McCombie, H., Sunders, B. C. and Wild, F., *J. Chem. Soc.,* **24** (1944).

[10] Meerwein, H., Florian, W., Schon, N. and Stopp, G., *Ann.,* **641,** 1(1961).