3-Formylchromones in Guareschi Synthesis of 5-(2-Hydroxybenzoyl)-2-pyridones

Sergey V. Ryabukhin,[a,b] Andrey S. Plaskon,[b] Dmitriy M. Volochnyuk,*[a] Andrey A. Tolmachev[b]

[a] 'Enamine Ltd.', 23 A. Matrosova st., 01103 Kiev, Ukraine

[b] National Taras Shevchenko University, 62 Volodymyrska st., Kyiv-33, 01033, Ukraine
Fax +380(44)5373253; E-mail: dov@fosfor.kiev.ua

Received 6 May 2004

Abstract: A set of 5-(2-hydroxybenzoyl)-pyrid-2-ones, which are analogous to cardiotonic drugs such as milrinone, has been prepared in high yield by recyclization of 3-formylchromones with acetic acid amides having at the α-position an electron-withdrawing group. The best reaction conditions were found to be heating in DMF in the presence of Me_3SiCl as a promoter and water scavenger.

Key words: 3-formylchromones, cyanoacetamides, 2-pyridones, recyclization, chlorotrimethylsilane, parallel synthesis

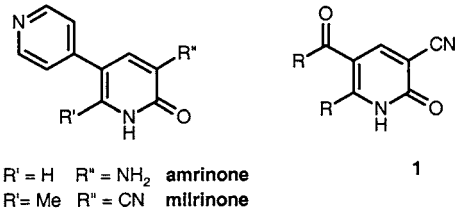
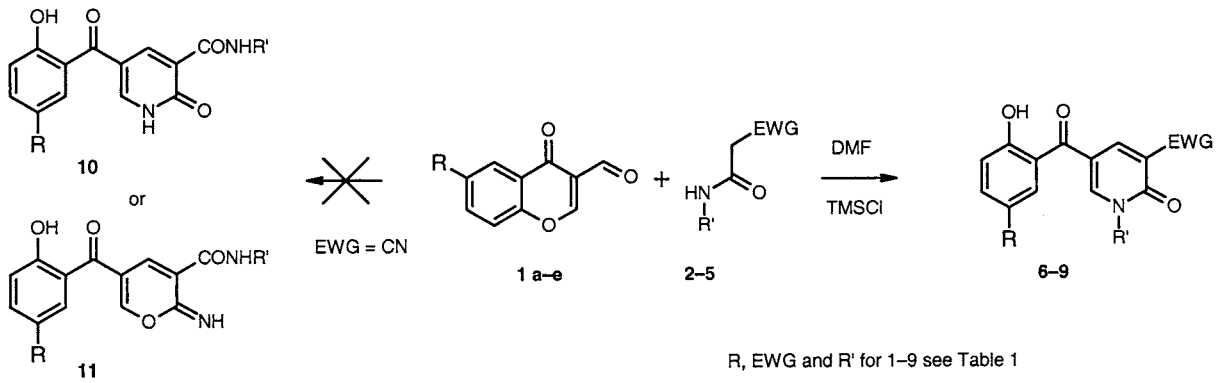


Figure 1 The structures of the cAMP PDE III inhibitors.

2-Pyridones play an important theoretical and practical role in heterocyclic chemistry.[1] Recently, interest in these compounds was reignited by the discovery of a new class of non-glycosidic cardiotonic agents, the cyclic adenosine 3′,5′-monophosphate (cAMP) specific phosphodiesterase (PDEIII) inhibitors, which have been used for the treatment of congestive heart failure. All these agents are characterized by the presence of the 2-pyridone nucleus, prototypes being amrinone[2] and particularly milrinone.[3] Searches for analogues of milrinone have revealed that 2-oxo-3-pyridinecarbonitriles (**1**) having a carbonyl moiety at the 5-position also exhibited a significant ionotropic activity (Figure 1)[4]

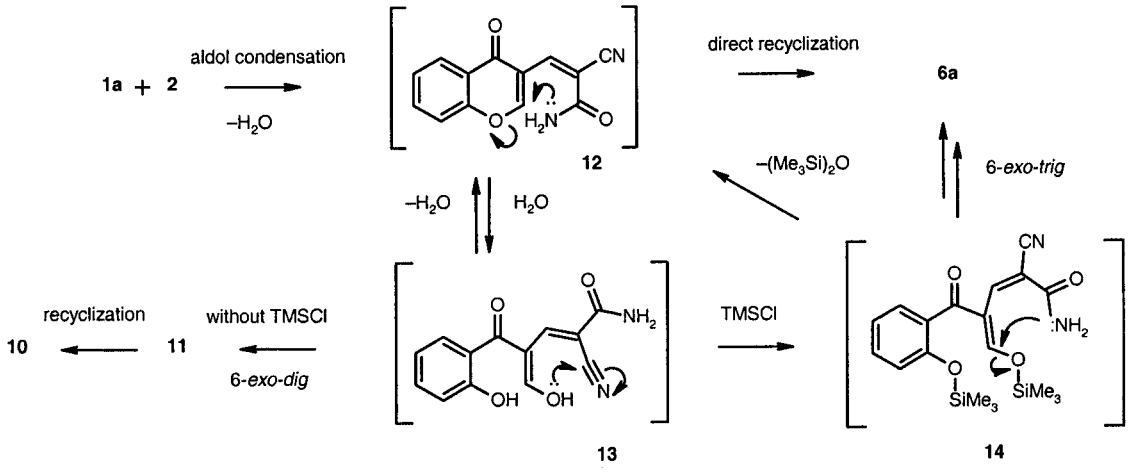
The convenient method for synthesis of 2-oxo-3-pyridinecarbonitriles having a carbonyl moiety at the 5-position is the Guareschi reaction of cyanoacetamide as 1,3-CCN-binucleophile with different 1,3-CCC-bielectrophiles having a carbonyl function at the *meso*-position, such as 2-dimethylaminomethylene-1,3-diones (enamine diones).[5] The widely used latent 1,3-dialdehydes, having at the *meso*-position a masked 2-hydroxybenzoyl fragment, are 3-formylchromones.[6] There are literature data on the reaction of 3-formylchromones with cyanoacetamide affording 5-(2-hydroxybenzoyl)-2-oxo-1,2-dihydro-pyridine-3-carbonitriles; however the reaction is accompanied with side reactions.[7] Herein, we wish to report new reaction conditions, under which only the targeted products form in nearly quantitative yield. This makes the reaction a very attractive tool for designing libraries of compounds via semi-automated parallel synthesis.

3-Formylchromones (**1**) react with cyanoacetamide (**2**) in DMF solution at 100 ° in the presence of Me_3SiCl[8] yielding 5-(2-hydroxybenzoyl)-2-oxo-1,2-dihydropyridine-3-carbonitriles (**6**) as a single product of recyclization (Scheme 1).[9] This reaction is a general one; not only does



Scheme 1

SYNLETT 2004, No. 13, pp 2287–2290
Advanced online publication: 24.09.2004
DOI: 10.1055/s-2004-832852; Art ID: D11604ST



Scheme 2

cyanoacetamide produce favorable results, but primary and secondary amides of acetic acid having an π-electron-withdrawing group at the α-position **3**–**5** do as well, affording the corresponding pyridones **6**–**9** (Scheme 1, Table 1). However, it should be noted that the use of substrates bearing an active acetyl group, such as 3-oxobutanamide (**5**), complicates the reaction and lowers the yield of targeted product **9**.

The structure of novel products was confirmed by ^{1}H NMR,[10] ^{13}C NMR,[11] IR spectroscopy,[12] mass spectrometry,[13] and elemental analysis.

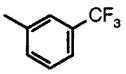
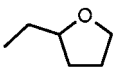
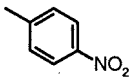
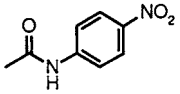
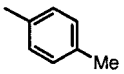
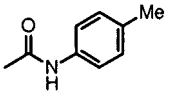
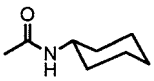
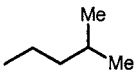
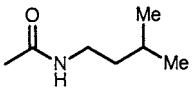
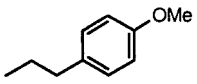
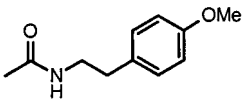
We suggest that Me_3SiCl plays several roles in the reaction. One can imagine that the reaction occurs by the following mechanism. The first stage is the aldol condensation of the amide methylene group with the aldehyde function of the the chromone leading to open-chain products **12**.[6f,7] Subsequently, **12** could undergo either recyclization to provide targeted pyridone **6** or cleavage of the chromone ring by water, formed in the first stage, to afford ketoaldehyde **13** that then leads to side reactions. The latter can undergo 6-*exo-dig* cyclization of the enol with the nitrile function, finally leading to formation of by-product iminopyrone **11** and its recyclization product, pyridone **10**.[7,14] On the other hand, under our condition, Me_3SiCl acts as a water scavenger, thus preventing the formation of ketoaldehyde **13**. Even if ketoaldehyde **13** forms in the reaction mixture, it is silylated by excess of Me_3SiCl to form the O-silylated intermediate **14**. This intermediate is unreactive with respect to the nitrile group, but is able to form either chromone **12** or the targeted pyridone **6** (Scheme 2). Finally, any water present in the reaction mixture would react with Me_3SiCl to release HCl, which catalyzes the reaction.

Our attempts to extend the procedure to primary enamines such as β-aminocrotonitrile and alkyl β-crotonates failed. In this case, due to harsh reaction conditions, destruction of starting enamines occurs and the targeted pyridines were detected only in trace amounts. For the same reason we have not been able to developed the preparative procedure for interaction of 3-formylchromones with cyanoacetic acid thioamide and its derivatives.

Table 1 Yields and Melting Points of 2-Pyridones Obtained[a]

Chromone	Amide	Product	R	R′	EWG	Yield (%)[b]	Mp (°C, solvent)[c]	[M + 1][d]
1a	**2**	**6a**	H	H	CN	75	263–265[e] (MeCN)	241
1c	**2**	**6c**	F	H	CN	73	265–266 (MeCN)	259
1d	**2**	**6d**	Cl	H	CN	84	269–270 (MeCN)	275
1e	**2**	**6e**	OMe	H	CN	70	262–263 (MeCN)	271
1d	**3a**	**7da**	Cl	CH_2Ph	CN	85	235–236 (MeCN)	365
1b	**3b**	**7bb**	Me	$CH(CH_3)_2$	CN	72	181–182 (MeOH)	297
1d	**3c**	**7dc**	Cl	CH_2CH_2OMe	CN	70	182–183 (MeOH)	333
1e	**3d**	**7ed**	OMe		CN	84	205–206 (MeOH)	353
1d	**3e**	**7de**	Cl		CN	75	227–228 (MeCN)	315

Table 1 Yields and Melting Points of 2-Pyridones Obtained[a] (continued)

Chromone	Amide	Product	R	R′	EWG	Yield (%)[b]	Mp (°C, solvent)[c]	[M + 1][d]
1d	**3f**	**7df**	Cl	Ph	CN	90	183–184 (MeCN)	351
1e	**3f**	**7ef**	OMe	Ph	CN	84	178–179 (MeOH)	347
1b	**3g**	**7bg**	Me		CN	80	178–179 (MeOH)	399
1d	**3h**	**7dh**	Cl		CN	78	206–207 (MeCN)	352
1a	**3i**	**7ai**	H		CN	87	202–203 (MeCN)	324
1d	**3j**	**7dj**	Cl		CN	72	220–221 (MeOH)	359
1b	**4a**	**8ba**	Me	CH_2Ph	$CONHCH_2Ph$	81	159–160 (MeOH)	453
1d	**4b**	**8db**	Cl	Ph	CONHPh	88	232–233 (MeCN)	445
1b	**4c**	**8bc**	Me			86	259–260 (MeCN)	515
1d	**4d**	**8dd**	Cl			90	228–229 (MeCN)	473
1c	**4e**	**8ce**	F			78	155–156 (MeOH)	441
1c	**4f**	**8cf**	F			73	166–167 (MeOH)	417
1b	**4g**	**8bg**	Me			79	140–141 (MeOH)	541
1e	**5a**	**9ea**	OMe	H	COMe	62	189–190 (MeOH)	288
1e	**5b**	**9eb**	OMe	Me	COMe	68	201–202 (MeOH)	302

[a] Satisfactory microanalysis obtained C ± 0.33; H ± 0.45; N ± 0.25.
[b] Yields refer to pure isolated product.
[c] Melting points are uncorrected.
[d] APSI MS, Agilent 1100\DAD\MSD VL G1965a instrument.
[e] Lit. 266–268 °C (dec.).[7a]

Acknowledgment

The authors acknowledge Turov A. V., Alekseev S. A. (Department of Chemistry of Kyiv National Taras Shevchenko University) and Mazepa A. V. (Bogatsky Physico-Chemical Institute, National Academy of Sciences of Ukraine, Department Molecular Structure) for spectral measurement.

References

(1) (a) Scriven, E. F. V. *Pyridines and their Benzo Derivatives: (ii) Reactivity at Ring Atoms,* In *Comprehensive Heterocyclic Chemistry*, Vol. 2; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press Ltd.: Oxford, **1984**, 165. (b) Uff, B. C. *Pyridines and their Benzo Derivatives: (iii) Reactivity of Substituents,* In *Comprehensive Heterocyclic Chemistry*, Vol. 2; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press Ltd.: Oxford, **1984**, 315.
(2) Farah, A. E.; Alousi, A. A. *Life Sci.* **1978**, *22*, 1139.
(3) Alousi, A. A.; Canter, J. M.; Monterano, M. J.; Fort, D. J.; Ferrari, R. A. *J. Cardiovasc. Pharmacol.* **1983**, *5*, 792.
(4) (a) Fossa, P.; Boggia, R.; Presti, E. L.; Dorigo, P.; Floreani, M. *Farmaco* **1997**, *52*, 523. (b) Mosti, L.; Schenone, P.; Del Mar Mahiques, M.; Dorigo, P.; Fracarollo, D.; Santostasi, G.; D'Amico, M.; Falciani, M.; Lampa, E. *Farmaco* **1994**, *49*, 559. (c) Dorigo, P.; Gaion, R. M.; Belluco, P.; Fraccarollo, D.; Maragno, I.; Bombieri, G.; Benetollo, F.; Mosti, L.; Orsisns, F. *J. Med. Chem.* **1993**, *36*, 2475.
(5) (a) Abu Shanab, F. A.; Redhouse, A. D.; Thompson, J. B.; Wacefield, B. J. *Synthesis* **1995**, 557. (b) Mosti, L.; Schenone, P.; Menozzi, G. *J. Heterocycl. Chem.* **1985**, *22*, 1503.

(6) For related cyclization reaction of 3-formylchromones, see: (a) Jones, W. D.; Albrecht, W. L. *J. Org. Chem.* **1976**, *41*, 706. (b) The cyclization of 3-formylchromones with amidines and 5-aminopyrazole afforded 5-(2-hydroxybenzoyl)-pyrimidines. See: Löwe, W. *Synthesis* **1976**, 274. (c) See also: Petersen, U.; Heitzer, H. *Liebigs Ann. Chem.* **1976**, 1663. (d) See further: Quiroga, J.; Mejia, D.; Insuasty, B.; Abonita, R.; Nogueras, M.; Sanches, A.; Cobo, J.; Low, J. N. *J. Heterocycl. Chem.* **2002**, *35*, 51. (e) The cyclization of 3-formylchromones with aminoheterocycles afforded fused β-(2-hydroxybenzoyl)pyridines. See: Haas, G.; Stanton, J. L.; von Srerecher, A.; Wenk, P. *J. Heterocycl. Chem.* **1981**, *18*, 607. (f) With hydrazines: Eiden, F.; Haverland, H. *Arch. Pharm. (Weinheim, Ger.)* **1968**, *301*, 819. (g) See also: Ghosh, C. K.; Mukhopadhyay, K. K. *J. Indian Chem. Soc.* **1978**, *55*, 386. (h) With $NH_2OH·HCl$: Hsung, R. P.; Zificsak, C. A.; Wei, L.-L.; Zehnder, L. P.; Park, F.; Kim, M.; Tran, T. T. *J. Org. Chem.* **1999**, *64*, 8736. (i) With *o*-phenylenediamine: Ghosh, C. K.; Khan, S. *Synthesis* **1980**, 701. (j) For conversion into pyrroles and thiofenes: Fitton, A. O.; Frost, J. R.; Suschitzky, H.; Houghton, P. G. *Synthesis* **1977**, 133. (k) For conversation into 4-(2′-hydroxybenzoyl)salicylic esters see: Langer, P.; Holtz, E. *Synlett* **2003**, 402.

(7) (a) Nohara, A.; Ishiguro, T.; Sanno, Y. *Tetrahedron Lett.* **1974**, 1183. (b) Hishmat, O. H.; El-Naem, Sh. I.; Magd-El-Din, A. A.; Fawzy, N. M.; Abd, E. l.-AalAS. *Egypt. J. Chem.* **2000**, *43*, 87.

(8) For using Me_3SiCl as condensation agent see: (a) Ryabykhin, S. V.; Plaskon, A. S.; Tverdokhlebov, A. V.; Tolmachev, A. A. *Synth. Commun.* **2004**, *34*, 1483. (b) Heaney, H.; Papageorgeogu, G.; Wilkins, R. F. *Tetrahedron* **1997**, *53*, 2941. (c) For using Me_3SiI as condensation agent see: Sabitha, G.; Reddy, G. S. K. K.; Reddy, K. B.; Yadav, J. S. *Synthesis* **2004**, 263. (d) Sabitha, G.; Reddy, G. S. K. K.; Reddy, C. S.; Yadav, J. S. *Synlett* **2003**, 858. (e) Sabitha, G.; Reddy, G. S. K. K.; Reddy, C. S.; Yadav, J. S. *Tetrahedron Lett.* **2003**, *44*, 4129.

(9) **General Procedure**: Amide **2**–**5** or **12** (2 mmol) and appropriate chromone **1** (2 mmol) were placed in a 10 mL flask and dissolved in DMF (5 mL). Chlorotrimethylsilane (10 mmol) was added dropwise to the solution. The flask was thoroughly sealed with a rubber stopper and heated on a water-bath for 10 h. After cooling the flask was opened (Caution! Excessive pressure inside!) and the reaction mixture was poured into H_2O (25 mL). The precipitate formed was filtered and washed with small amount of *i*-PrOH and than with MeOH. Recrystallization from an appropriate solvent yielded targeted compounds.

(10) Typical ^{1}H MNR data (Varian Mercury-400 spectrometer) of pyridones obtained: Compound **6a**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.91–6.99 (2 H, m, CH), 7.34–7.41 (2 H, m, CH), 8.05 (1 H, d, $^4J_{HH}$ = 2.8 Hz, 4-H_{Py}), 8.31 (1 H, d, $^4J_{HH}$ = 2.8 Hz, 6-H_{Py}), 10.28 (1 H, s, NH), 13.11 (1 H, br s, OH). Compound **7bb**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.42 [6 H, d, $^3J_{HH}$ = 7.6 Hz, $(CH_3)_2CH$], 2.30 (3 H, s, CH_3), 5.09 [1 H, hep, $^3J_{HH}$ = 7.6 Hz, $(CH_3)_2CH$], 6.86 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 7.16–7.20 (2 H, m, CH), 8.19 (1 H, d, $^4J_{HH}$ = 2.4 Hz, 4-H_{Py}), 8.35 (1 H, d, $^4J_{HH}$ = 2.4 Hz, 6-H_{Py}), 10.08 (1 H, s, OH). Compound **7ef**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.77 (3 H, s, CH_3), 6.90–6.99 (3 H, m, CH), 7.50–7.60 (5 H, m, CH), 8.27 (1 H, d, $^4J_{HH}$ = 2.4 Hz, 4-H_{Py}), 8.42 (1 H, d, $^4J_{HH}$ = 2.4 Hz, 6-H_{Py}), 9.89 (1 H, s, OH). Compound **8ba**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.28 (3 H, s, CH_3), 4.52 (2 H, d, $^3J_{HH}$ = 5.6 Hz, CH_2), 5.32 (2 H, s, CH_2), 6.87 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 7.15 (1 H, s, CH), 7.19–7.21 (2 H, m, CH), 7.25–7.38 (7 H, m, CH), 7.39 (2 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 8.66 (1 H, $^4J_{HH}$ = 2.0 Hz, 4-H_{Py}), 8.72 (1 H, d, $^4J_{HH}$ = 2.0 Hz, 6-H_{Py}), 9.80 (1 H, t, $^4J_{HH}$ = 5.6 Hz, 6-H_{Py}), 10.18 (1 H, s, OH). Compound **9ea**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.59 (3 H, s, $COCH_3$), 3.74 (3 H, s, OCH_3), 6.84 (1 H, d, $^4J_{HH}$ = 2.7 Hz, CH), 6.89 (1 H, d, $^3J_{HH}$ = 9.0 Hz, CH), 6.96 (1 H, dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HH}$ = 2.7 Hz, CH), 8.00 (1 H, d, $^4J_{HH}$ = 3.0 Hz, 4-H_{Py}), 8.39 (1 H, d, $^4J_{HH}$ = 3.0 Hz, 6-H_{Py}), 9.76 (1 H, s, OH), 12.55 (1 H, br s, NH). Compound **9eb**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.57 (3 H, s, $COCH_3$), 3.63 (3 H, s, NCH_3), 3.74 (3 H, s, OCH_3), 6.84 (1 H, d, $^4J_{HH}$ = 2.7 Hz, CH), 6.89 (1 H, d, $^3J_{HH}$ = 9.0 Hz, CH), 6.96 (1 H, dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HH}$ = 2.7 Hz, CH), 8.29 (1 H, d, $^4J_{HH}$ = 3.0 Hz, 4-H_{Py}), 8.56 (1 H, d, $^4J_{HH}$ = 3.0 Hz, 6-H_{Py}), 9.75 (1 H, s, OH).

(11) Typical ^{13}C MNR data (Varian Mercury-400 spectrometer) of pyridones obtained: Compound **7bb**: ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.4 [$(CH_3)_2CH$], 21.3 (CH_3), 50.3 [$(CH_3)_2CH$], 102.7 (3-C_{Py}), 116.4 (CN), 117.3 (5-C_{Py}), 117.4 (CH), 124.2 (C_q), 128.8 (CH), 131.1 (CH), 134.9 (C_q), 146.2 (4-CH_{Py}), 147.2 (6-CH_{Py}), 154.3 (2-C_{Py}), 159.5 (C_q), 190.7 (C=O). Compound **7ef**: ^{13}C NMR (100 MHz, DMSO-d_6): δ = 56.1 (CH_3O), 104.3 (3-C_{Py}), 114.1 (5-C_{Py}), 116.1 (CN), 117.3 (CH), 118.5 (CH), 120.8 (CH), 124.6 (C_q), 127.2 (CH), 129.9 (CH), 130.0 (CH), 139.8 (C_q), 148.3 (4-CH_{Py}), 150.1 (6-CH_{Py}), 150.2 (2-C_{Py}), 152.8 (C_q), 159.5 (C_q), 190.1 (C=O). Compound **8ba**: ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.4 (CH_3), 43.1 (CH_2), 53.5 (CH_2), 117.1 (3-C_{Py}), 118.2 (5-C_{Py}), 119.5 (CH), 124.9 (CH), 127.5 (CH), 128.0 (CH), 128.4 (CH), 128.5 (C_q), 128.6 (CH), 129.0 (CH), 129.3 (CH), 130.6 (CH), 134.3 (C_q), 136.5 (C_q), 139.5 (C_q), 143.9 (4-CH_{Py}), 148.9 (6-CH_{Py}), 154.1 (2-C_{Py}), 161.9 (C_q), 162.9 (CONH), 192.1 (C=O). Compound **9ea**: ^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.1 ($COCH_3$), 56.1 (CH_3O), 114.1 (CH), 116.8 (5-C_{Py}), 118.1 (CH), 119.6 (C_q), 125.7 (CH), 126.3 (3-C_{Py}), 142.9 (4-CH_{Py}), 146.9 (6-CH_{Py}), 149.9 (C_q), 152.6 (2-C_{Py}), 161.5 (C_q), 191.2 (COAr), 196.7 ($COCH_3$). Compound **9eb**: ^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.2 ($COCH_3$), 38.7 (NCH_3), 56.1 (CH_3O), 114.1 (CH), 116.5 (5-C_{Py}), 118.2 (CH), 119.8 (C_q), 124.8 (CH), 125.5 (3-C_{Py}), 142.6 (4-CH_{Py}), 149.8 (C_q), 150.2 (6-CH_{Py}), 152.6 (2-C_{Py}), 161.5 (C_q), 191.5 (COAr), 196.9 ($COCH_3$).

(12) Typical IR data (Nexus-470 spectrometer) of pyridones obtained: Compound **7bb**: IR (KBr): ν = 3400–2700 (br, OH), 3068, 2985, 2932, 2226 (C≡N), 1671 (C=O), 1654 (C=O_{Py}), 1630, 1577, 1532, 1482 cm^{-1}. Compound **7ef**: IR (KBr): ν = 3470–3150 (br, OH), 2231 (C≡N), 1677 (C=O), 1660 (C=O_{Py}), 1539, 1508, 1417 cm^{-1}. Compound **8ba**: IR (KBr): ν = 3600–3100 (br, OH), 3288 (NH), 3056, 3023, 2952, 1675 (C=O), 1664 (sh, C=O_{Py}), 1632 ($CONHCH_2Ph$), 1603, 1528 cm^{-1}. Compound **9ea**: IR (KBr): ν = 3600–3200 (br, OH, NH), 3056, 2917, 2835, 1685 (COMe), 1665 (C=O_{Ph}), 1637, 1593, 1485, 1218 cm^{-1}. Compound **9eb**: 3500–3100 (br, OH), 3078, 2960, 1677 (COMe), 1646 (C=O_{Py}), 1538, 1508, 1413 cm^{-1}.

(13) Typical MS data (MX-1321 instrument) of pyridones obtained: Compound **6a**: MS (EI, 70 eV): *m/z* (%) = 240 (39) [M$^+$], 147 (19), 121 (86), 120 (100), 92 (45), 65 (54), 39 (43). Compound **7ef**: MS (EI, 70 eV): *m/z* (%) = 346 (30) [M$^+$], 254 (11), 150 (100). Compound **8ba**: MS (EI, 70 eV): *m/z* (%) = 452 (19) [M$^+$], 106 (100), 91 (54). Compound **9ea**: MS (EI, 70 eV): *m/z* (%) = 287 (76) [M$^+$], 272 (10), 150 (100), 135 (21), 43 (24).Compound **9eb**: MS (EI, 70 eV): *m/z* (%) = 301 (64) [M$^+$], 286 (17), 150 (100), 135 (12).

(14) For related interactions of enolates with nitrile groups affording 2-pyridone ring see: Bondavalli, F.; Bruno, O.; Lo Presty, E.; Menozzy, G.; Mosti, L. *Synthesis* **1999**, 1169.