An Efficient Synthesis of Functionalized 2-Pyridones by Direct Route or via Amide/Enolate Ammonium Salt Intermediates

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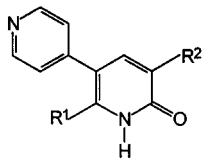
This paper is dedicated to the memory of Prof. Pietro Schenone

Abstract: A number of compounds with a 2-pyridone structure **3**, which have different substituents and are analogous to cardiotonic drugs like milrinone, have been synthesized in high yields from the appropriate enamino ketones **2** using different cyanomethylene active compounds (methyl cyanoacetate, benzoylacetonitrile and phenylsulfonylacetonitrile). In this synthetic route, the active role of the dimethylamine released in situ on the cyclization process has been underlined. In particular, its direct intervention, as a nucleophile or a base, was proven and intermediate amides **5** or enolate ammonium salts **6** were isolated and recognized by the analytical and spectral data.

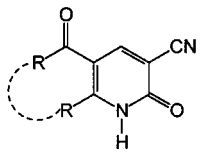
Key words: mono and polycyclic 2-pyridones, dimethylaminomethyleneketones, amide and enolate intermediates, cardiotonic agents

Congestive heart failure (CHF) is a major cause of death in patients with heart disease. For many years digitalis glycosides have been used for the treatment of CHF. This use, however, is limited by their narrow therapeutic index and their propensity to cause life-threatening arrhythmias (arrhythmogenic lability). The search for orally active nonglycosidic cardiotonic drugs displaying a greater safety profile and improved efficacy comparable to digitalis principles resulted in the discovery of a new class of agents, the cyclic adenosine 3',5'-monophosphate (cAMP) specific phosphodiesterase (PDEIII) inhibitors. These agents belong to a chemically composite group of compounds, however almost all characterized by the presence of a 2-pyridone nucleus, the prototypes being amrinone[1] and particularly milrinone.[2]



$R^1 = H$ $R^2 = NH_2$ **amrinone**

$R^1 = CH_3$ $R^2 = CN$ **milrinone**



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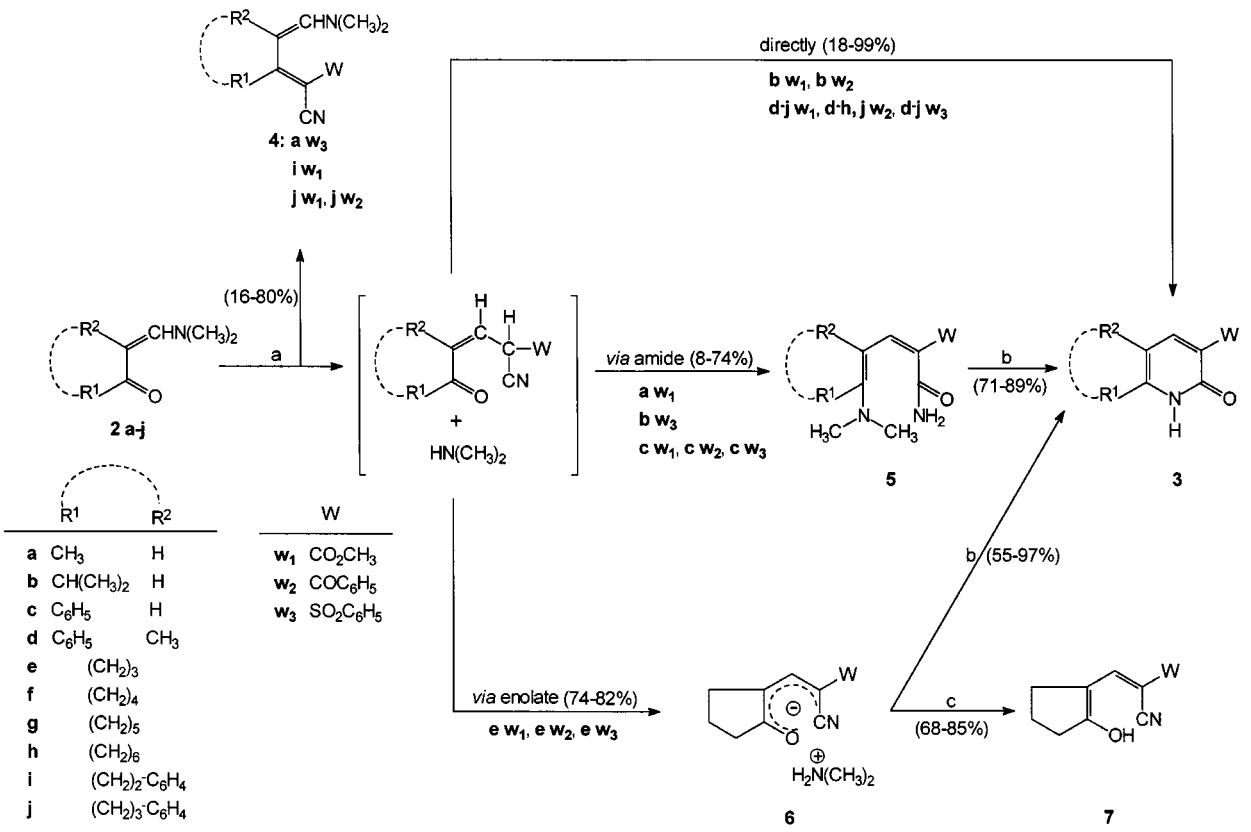
In preceding papers we reported the facile reaction of open-chain and cyclic *sym*-2-dimethylaminomethylene-1,3-diones (enamine diones) with cyanoacetamide, a 1-3 dinucleophile with *C*–C–*N* structure, as a useful method to obtain a variety of 5-acyl-1,2-dihydro-2-oxo-3-pyridinecarbonitriles **1**,[3] some of which showed a significant inotropic activity.[4] During some investigation on the reactivity of (2-dimethylaminomethylene)cyclohexanone with methyl cyanoacetate we ascertained that the closure of a 2-pyridone ring could easily be achieved in good yield. This interesting chemical behaviour prompted us to investigate more closely the reactivity of some cyanomethylene active compounds (methyl cyanoacetate, benzoylacetonitrile and phenylsulfonylacetonitrile) with a variety of open-chain and cyclic enamino ketones **2** to verify the possibility of generalizing such results and to find out a possible reaction pathway. In fact some malonic derivatives were formerly reacted with bicyclic enamino ketones in a basic medium[5] followed by acid hydrolysis to lead to α-pyrone derivatives. A unique example of reaction of aliphatic enamino ketones with cyanoacetic esters giving a pyridone derivative was reported by Krasnaya[6] but this unexpected result was not generalized. In our case, without adding a base, a number of compounds with a 2-pyridone structure **3** with different substituents, namely the simple substituted derivatives **3a–d**, the 5,6-polimethylene-1*H*-pyridin-2-ones **3e–h**, the benzoquinolin-2-ones **3i** and finally the 1,5,6,7-tetrahydro-2*H*-benzo[6,7]cyclohepta-[1,2-b]pyridin-2-ones **3j** were obtained by reaction of a variety of enaminones with activated acetonitriles (Scheme, Table). These products may represent a new class of milrinone analogous lacking their characteristic hydrogen bonding acceptor group opposite to the lactamic function and therefore could be of interest for a thorough investigation on the structure-activity relationship in the 2-pyridone family.[7,8]

Compounds **3 a–j** were synthesized from the versatile precursors **2 a–j** obtained in the past in very high yield from the corresponding α-hydroxymethylene derivatives with dimethylamine at room temperature (**2a**,[9] **2b**,[10] **2c**,[11] **2d**,[12] **2e**,[13] **2f**,[14] **2g**,[15] **2h**,[15] **2i**,[16] **2j**[17]) or, more recently, directly by refluxing a solution of the suitable ketone in amide acetals (mainly *N*,*N*-dimethylformamide dimethylacetal) (**2a**,[18] **2c**,[18] **2d**,[19] **2e**,[20] **2f**,[20] **2g**,[20] **2i**[21] and by us in the case of **2b**, **2h** and **2j**). The reaction of enamino ketones **2a–j** with the above mentioned cyano compounds, having a methylene active group, usually occurs first between the nucleophilic methylenic group and the α-enamino carbon atom, which is the most electrophilic site of the enaminone. In few cases does the nucleophilic attack also occur on the enaminone carbonyl function so as to give the meth-



Reagents and conditions: a) appropriate WCH_2CN/anhyd MeOH or EtOH, r.t., or reflux (Table); b)AcOH, anhyd toluene, reflux (Table); c) AcOH, 0 °C

Scheme

ylidene derivatives **4** as a by product or as the sole isolated product, even if in low yield (Scheme, Table). Subsequently the dimethylamine, when released in situ, mostly causes the reaction to proceed towards the direct closure of the 2-pyridone ring without isolation of intermediates.

In a few cases, we have been able to isolate intermediates that confirm this direct intervention of the dimethylamine, which may act as a nucleophile on the carbonyl group to give amides **5**,[6] or, in particular cases, as a base to form water-soluble salts **6**, well enough soluble in diethyl ether/ethyl acetate (3:1) (Scheme). These two types of intermediates, in turn, always gave the desired 2-pyridones **3** by refluxing in anhydrous toluene with a small quantity of acetic acid. The formation of enolates **6** instead of amides **5** is probably due to a stronger acidity of the enol form involved, which protonates the released dimethylamine thus forming a stable salt that hinders the normal addition on the keto group to give an amide. In the case of amides **5** the last step of the 2-pyridone ring closure might reasonably result from the amide group attack to the masked electrophilic carbonyl group, with loss of dimethylamine. For the enolates **6**, the cyclization process could not be ascertained through the identification of other intermediates and probably results via amide formation or by a sort of Dimroth[22] rearrangement of a preliminary α-iminopyran ring.[23] The amide and salt nature of compounds **5** and **6** respectively has been clarified by IR, ^{1}H NMR and ^{13}C NMR spectral data. The formation of the isolated amides **5** was in agreement with the example reported by Krasnaya.[6] In particular, ^{1}H NMR data of some amides **5** evidenced the presence of two isomeric forms due to an *s-cis/trans* isomerism (the *trans* form being the prevalent).

After careful acidification, salts **6**, which are very soluble in water, gave the corresponding unstable enols **7**, which could not be cyclized to 2-pyridones, further proving the active role of the dimethylamine in the cyclization process. Similar enolates, having an alkaline rather than a dimethylammonium counter ion, have been mentioned by Maitte et al[5] but their analytical and spectral data have not been recorded. The most interesting fact, however, is that those enolates, after acidification, always gave only α-pyrone and not 2-pyridone derivatives, exactly the opposite of our present results.

Some of these 2-pyridones, prepared by other routes with lower or unreported yields, are already known (**3a w$_1$**,[6] **3c–f w$_1$**[24]) and consequently the identity of their mps, IR and ^{1}H NMR spectral data compared to those of our com-

pounds unequivocally confirmed the pyridone structure of compounds **3**.

Finally, in view of the known biological activity of this class of compounds, a selected set was also subjected to a preliminary evaluation as cardiotonic agents. It is remarkable that none of them showed significant activity,[25] thus confirming the essential role, in the biological interaction, of the hydrogen bonding acceptor group located on the opposite site to the lactamic moiety.

Organic solvents and reagents were purified by the appropriate standard procedures. Drying of the organic extracts during the workup of reactions was performed over anhyd $MgSO_4$. Evaporation of solvents was carried out under reduced pressure with a rotatory evaporator. Purification of high boiling oils was realized by bulb-to-bulb distillation in vacuo. Mps were determined on a Fisher–Johns apparatus and are uncorrected. Microanalyses were performed on a Carlo Erba elemental analyzer (model 1106) for C, H, N. IR spectra were taken on a Perkin Elmer 398 instrument and are expressed in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 (200 and 50.30 MHz respectively) spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale downfield from TMS. Coupling constants (*J*) are expressed in Hertz (Hz). The assignments of ^{13}C signals were assisted by DEPT spectral data. Physical and chemical data of new pyridones derivatives are given in Table.

(*N*, *N*-Dimethylaminomethylene)ketones 2b, h, j; General Procedure

The method of preparation was the same as the one previously described for the other compounds 2 and realized directly by refluxing a solution of the suitable ketone (20 mmol) in *N*,*N*-dimethylformamide dimethylacetal (30 mmol) for 24 h. In the case of 3-methylbutan-2-one the reaction was carried out in sealed tube and the mixture was heated at 100°C for 72 h.

2b: bp 105–110°C/0.2 mbar; yield: 60% (Lit.[10] yield: 55%).

2h: bp 135–140 °C/0.2 mbar, yield 80% (Lit.[15] yield: 91%).

2j: bp 185–190°C/0.3 mbar, mp 90–91°C (Et_2O); yield: 91% (Lit.[17] yield: 95%).

Table Physical and Chemical Data for Compounds **3a–j w$_1$**, **3b–h, j w$_2$**, **3b–j w$_3$**, **4a w$_3$**, **4i, j w$_1$** and **4j w$_2$** (**w$_1$**=CO_2Me, **w$_2$**=COPh, **w$_3$**=SO_2Ph)

Product	R^1	R^2	mp (°C) or bp (°C)/mbar	Reaction Conditions (anhyd solvent)	Synthetic Route	Yield[a] (%)
3a w$_1$	Me	H	168–169[b]	reflux, 48h (toluene)	via amide	84
3b w$_1$	*i*-Pr	H	144–145	reflux, 6h (MeOH)	direct	20
3c w$_1$	Ph	H	176–177[c]	reflux, 48h (toluene)	via amide	87
3d w$_1$	Ph	Me	178–180[c]	reflux, 6h (MeOH)	direct	67
3e w$_1$	-$(CH_2)_3$-		175–177[c] (dec)	reflux, 6h (MeOH)	direct	23
				reflux, 12h (toluene)	via enolate	97
3f w$_1$	-$(CH_2)_4$-		197–199[c]	r.t., 4h (MeOH)	direct	70
3g w$_1$	-$(CH_2)_5$-		209–211	r.t., 4h (MeOH)	direct	85
3h w$_1$	-$(CH_2)_6$-		228–230	r.t., 4h (MeOH)	direct	79
3i w$_1$	$C_6H_4(CH_2)_2$		195–197	reflux, 12h (MeOH)	direct	29
3j w$_1$	$C_6H_4(CH_2)_3$		230–232	reflux, 6h (MeOH)	direct	25
3b w$_2$	*i*-Pr	H	174–175	reflux, 24h (EtOH)	direct	18
3c w$_2$	Ph	H	227–228	reflux ,48h (toluene)	via amide	76
3d w$_2$	Ph	Me	223–225	reflux, 24h (EtOH)	direct	61
3e w$_2$	-$(CH_2)_3$-		268–270 (dec)	reflux, 6h (EtOH)	direct	21
				reflux, 12h (toluene)	via enolate	55
3f w$_2$	-$(CH_2)_4$-		251–252	r.t., 24h (EtOH)	direct	52
3g w$_2$	-$(CH_2)_5$-		230–232	r.t., 24h (EtOH)	direct	53
3h w$_2$	-$(CH_2)_6$-		242–244	r.t., 24h (EtOH)	direct	50
3j w$_2$	$C_6H_4(CH_2)_3$		245–247	reflux, 24h (EtOH)	direct	22
3b w$_3$	*i*-Pr	H	212–213	reflux, 48h (toluene)	via amide	89
3c w$_3$	Ph	H	318–320	reflux, 48h (toluene)	via amide	71
3d w$_3$	Ph	Me	268–270	reflux, 6h (EtOH)	direct	71
3e w$_3$	-$(CH_2)_3$-		273–275 (dec)	reflux, 6h (EtOH)	direct	20
				reflux, 12h (toluene)	via enolate	58
3f w$_3$	-$(CH_2)_4$-		278–279	reflux, 4h (EtOH)	direct	93
3g w$_3$	-$(CH_2)_5$-		308–310	reflux, 4h (EtOH)	direct	95
3h w$_3$	-$(CH_2)_6$-		365–367	reflux, 4h (EtOH)	direct	99
3i w$_3$	$C_6H_4(CH_2)_2$		>350	reflux, 4h (EtOH)	direct	83
3j w$_3$	$C_6H_4(CH_2)_3$		>350	reflux, 24h (EtOH)	direct	68
4a w$_3$	Me	H	194–196	reflux, 24h (EtOH)	direct	16
4i w$_1$	$C_6H_4(CH_2)_2$		185–190/0.3	see **3i w$_1$**	direct	40
4j w$_1$	$C_6H_4(CH_2)_3$		180–185/0.1	see **3j w$_1$**	direct	54
4j w$_2$	$C_6H_4(CH_2)_3$		117–119	see **3j w$_2$**	direct	80

[a] Yield of isolated, purified products after recrystallization or distillation in vacuo.
[b] Lit.[6] mp 165–166 °C.
[c] Lit.[24] **3c w$_1$**: mp 172–173 °C; **3d w$_1$**: mp 176–177 °C; **3e w$_1$**: mp 174–175 °C; **3f w$_1$**: mp 193–194 °C.

2(*1H*)-Pyridinones 3b,d–j w_1, 3b,d–h,j w_2 , 3d–j w_3 and 4i,j w_1, 4j w_2, 4a w_3; General Direct Procedure

The suitable cyanomethylene compound (22 mmol) was added to a solution of enaminones **2a–j** (20 mmol) in anhyd MeOH or EtOH (10 mL). The mixture was stirred at r.t. or at reflux at different times (Table), then the formed crude solid was filtered, washed thoroughly with anhyd Et_2O and recrystallized (**3b, d, i w_1** from EtOAc; **3f–h, j w_1** from MeOH; **3b, d, f–h, j w_2** from EtOH; **3d, f w_3** from EtOH and **3g–j w_3** from EtOH/DMSO, (2:1). In the case of **2e**, the final reaction solution was evaporated under reduced pressure to give a thick oily mixture of the desired compounds **3e** and dimethyl ammonium salts **6e**. The pyridones **3e** were isolated with difficulty and in poor yield as solid residues after repeated washing and handling with anhyd Et_2O/EtOAc (3:1) at r.t. and recrystallized (**3e w_1** from EtOAc; **3e w_2** and **3e w_3** from EtOH). In the case of **2a**, the direct procedure did not afford the desired 2-pyridones **3**. Particularly, when phenylsulfonylacetonitrile was used as the cyanomethylene active compound **4a w_3** was obtained which was filtered and purified by recrystallization from EtOAc. On the contrary, starting from **2i** or **2j** by reaction with methyl cyanoacetate or benzoylacetonitrile, respectively, an oily mixture of desired compounds **3** together with opened derivatives **4** was obtained. This mixture was added to Et_2O (20 mL) and the derivatives **3i, j w_1** and **3j w_2** were isolated as solids in poor yield, filtered and recrystallized as previously described. The organic layer was dried and evaporated under reduced pressure. The crude oily residues were purified by bulb-to-bulb distillation in vacuo (**4i, j w_1**) or by final recrystallization from Et_2O (**4j w_2**). Finally, the reaction between **2i** and benzoylacetonitrile was disappointing, since only an intractable tar was obtained.

IR and ^{1}H NMR spectral data were fully consistent with the proposed structures; only spectral and analytical data of **3i w_1**, **3d**, **e w_2**, **3d**, **e**, **i w_3**, **4a w_3**, **4i, j w_1** and **4j w_2** are described.

Methyl 1,2,5,6-tetrahydro-2-oxo-3-benzo[*h*]quinoline carboxylate (3i w_1)

IR (KBr): ν = 3200–3000, 1728, 1628, 1550 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.82 (near s, 4 H, 5,6-CH_2), 3.85 (s, 3 H, OCH_3), 7.30–7.60 (m, 3 H, ArH), 8.12 (m, 2 H, ArH + 4-CH), 11.80 (br s, 1 H, NH, disappears with D_2O).

Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.51; H, 5.00; N, 5.60.

3-Benzoyl-5-methyl-6-phenyl-2(1*H*)-pyridinone (3d w_2)

IR ($CHCl_3$): ν = 3370, 1642, 1562 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.13 (s, 3 H, CH_3), 7.10–7.70 (m, 8 H, ArH), 7.75–8.10 (m, 3 H, ArH + 4-CH), 12.30 (br s, 1 H, NH, disappears with D_2O).

Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.85; H, 5.23; N, 4.95.

3-Benzoyl-1,5,6,7-tetrahydro-2*H*-cyclopenta[1,2-*b*]pyridin-2-one (3e w_2)

IR (KBr): ν = 3400, 3100–2500, 1638, 1562 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.05 (qui, 2 H, *J* = 7.5 Hz, 6-CH_2), 2.71 (t, 2 H, *J* = 7.5 Hz, 5-CH_2), 2.83 (t, 2 H, *J* = 7.5 Hz, 7-CH_2), 7.43–7.78 (m, 6 H, ArH + 4-CH), 12.15 (br s, 1 H, NH, disappears with D_2O).

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.37; H, 5.65; N, 5.94.

5-Methyl-6-phenyl-3-phenylsulfonyl-2(1*H*)-pyridinone (3d w_3)

IR ($CHCl_3$): ν = 3200–3000, 1650, 1552 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.17 (s, 3 H, CH_3), 7.00–7.90 (m, 10 H, ArH), 8.37 (s, 1 H, 4-CH), 13.15 (br s, 1 H, NH, disappears with D_2O).

Anal. Calcd for $C_{18}H_{15}NO_3S$: C, 66.44; H, 4.65; N, 4.30. Found: C, 66.54; H, 4.61; N, 4.28.

1,5,6,7-Tetrahydro-3-phenylsulfonylcyclopenta[1,2-*b*]pyridin-2-one (3e w_3)

IR (KBr): ν = 3200–2400, 1640, 1560 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.80–2.30 (m, 2 H, 6-CH_2), 2.50–3.00 (m, 4 H, 5,7-CH_2), 7.50–7.80 (m, 3 H, 2 ArH*m* + ArH*p*), 7.90–8.20 (m, 2 H, ArH*o*), 8.29 (s, 1 H, 4-CH), 12.50 (br s, 1 H, NH, disappears with D_2O).

Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.07; H, 4.76; N, 5.09. Found: C, 61.00; H, 4.80; N, 5.21.

5,6-Dihydro-3-phenylsulfonylbenzo[*h*]quinolin-2(1*H*)-one (3i w_3)

IR (KBr): ν = 3200–2700, 1648, 1558 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.82 (near s, 4 H, 5,6-CH_2), 7.30–8.20 (m, 9 H, Ar H), 8.34 (s, 1 H, 4-CH), 12.38 (br s, 1 H, NH, disappears with D_2O).

Anal. Calcd for $C_{19}H_{15}NO_3S$: C, 67.64; H, 4.48; N, 4.15. Found: C, 67.37; H, 4.41; N, 4.10.

5-Dimethylamino-3-methyl-2-phenylsulfonyl-2,4-pentadienenitrile (4a w_3)

IR ($CHCl_3$): ν = 2200, 1550 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.29 (s, 3 H, CH_3), 3.14, 3.26 [2 s, 6 H, $N(CH_3)_2$], 5.41 (d, 1 H, *J* = 14 Hz, 4-CH), 7.65 (m, 3 H, 2 ArH*m* + ArH*p*), 7.85 (d, 1 H, *J* = 14 Hz, 5-CH), 7.60–7.86 (m, 2 H, 2 ArH*o*).

Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14. Found: C, 60.50; H, 6.16; N, 9.93.

Methyl 1,2,3,4-tetrahydro-[2-(dimethylaminomethylene)-1-naphthylidene]cyanoacetate (4i w_1)

IR ($CHCl_3$): ν = 2218, 1708, 1546 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.80–3.00 (m, 4 H, 5,6-CH_2), 3.09 [s, 6 H, $N(CH_3)_2$], 3.91 (s, 3 H, OCH_3), 7.25–7.50 (m, 3 H, ArH), 7.82 (s, 1 H, =CHN), 8.25–8.35 (m, 1 H, ArH).

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 73.32; H, 6.42; N, 9.92. Found: C, 73.11; H, 6.20; N, 9.96.

Methyl [6,7,8,9-tetrahydro-8-(dimethylaminomethylene)-5*H*-benzocyclohepten-9-ylidene]cyanoacetate (4j w_1)

IR ($CHCl_3$): ν = 1705, 1592, 1545 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.18 (near qui 2 H, *J* = 6.6 Hz, 6-CH_2), 2.40 (t, 2 H, *J* = 6.6 Hz, 7-CH_2), 2.57 (t, 2 H, *J* = 6.6 Hz, 5-CH_2), 3.07 [s, 6 H, $N(CH_3)_2$], 3.92 (s, 3 H, OCH_3), 7.20–7.45 (m, 3 H, ArH), 7.75–7.80 (m, 1 H, ArH), 7.82 (s, 1 H, =CHN).

^{13}C NMR ($CDCl_3$): δ = 29.34, 31.86, 33.46 (3 CH_2), 41.62 (2 CH_3), 52.48 (CH_3), 110.05 (CN), 124.05 (C), 127.03 (CH), 129.12 (CH), 129.36 (CH), 140.45 (C), 140.64 (C), 141.37 (CH), 158.51 (C), 159.36 (C), 168.67 (CO).

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.03; H, 6.87; N, 9.36.

2-[6,7,8,9-Tetrahydro-8-(dimethylaminomethylene)-5*H*-benzocyclohepten-9-ylidene]-2-benzoylacetonitrile (4j w_2)

IR ($CHCl_3$): ν = 2225, 1640, 1590 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.17 (near qui, 2 H, *J* = 6.8 Hz, 6-CH_2), 2.39 (near t, 2 H, *J* = 6.8 Hz, 7-CH_2), 2.60 (near t, 2 H, *J* = 6.8 Hz, 5-CH_2), 2.98 [s, 6 H, $N(CH_3)_2$], 7.20–7.65 (m, 3 H, ArH), 7.80–8.00 (m, 7 H, 6 ArH + =CHN).

Anal. Calcd for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.47; N, 8.18. Found: C, 80.43; H, 6.67; N, 8.13.

Dimethyl Ammonium Salts of Enolate Anions 6e w_1, 6e w_2, 6e w_3; General Procedure

As mentioned above, during the synthesis of pyridones **3e**, the corresponding dimethylammonium salts **6e** were obtained as main products together with a small amount of the desired compounds. Their isolation from thick crude oily residues of the reaction was realized with a thorough washing and handling with anhyd Et_2O/EtOAc (3:1) at r.t. The organic layer was dried, filtered and evaporated under reduced pressure: the solid residue was finally recrystallized from EtOAc.

Dimethylammonium salt of the enolate anion of methyl 2-cyano-3-(2-oxocyclopentyl)propenoate (6e w_1)

Yield: 3.53 g (74%); mp 109–111°C (dec).

IR (KBr): ν = 3200–2300, 2185, 1675, 1585, 1500–1400 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.71 (qui, 2 H, J = 7.4 Hz, 4-CH_2), 1.99 (t, 2 H, J = 7.4 Hz, 5-CH_2), 2.57 [s, 6 H, $N(CH_3)_2$], 2.72 (dt, 2 H, J = 7.4, 1.7 Hz, 3-CH_2), 3.51 (s, 3 H, OCH_3), 7.36 (t, 1 H, J = 1.7 Hz, =CH), 7.50–9.00 (very br s, 2 H, OH + NH, disappears with D_2O).

^{13}C NMR (DMSO-d_6): δ = 20.09 (CH_2), 27.08 (CH_2), 34.65 (2 CH_3), 37.80 (CH_2), 50.20 (CH_3), 63.99 (C), 112.04 (CN), 124.22 (C), 136.51 (CH), 169.29 (C), 201.29 (CO).

Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.48; H, 7.61; N, 11.76. Found: C, 60.47; H, 7.61; N, 11.71.

Dimethylammonium salt of the enolate anion of 2-benzoyl-3-(2-oxocyclopentyl)propenenitrile (6e w_2)

Yield: 4.29 g (80%); mp 140–143°C (dec).

IR (KBr): ν = 3200–2300, 2175, 1640, 1560, 1500–1400 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.76 (qui, 2 H, J = 7.5 Hz, 4-CH_2), 2.05 (t, 2 H, J = 7.5 Hz, 5-CH_2), 2.55 [s, 6 H, $N(CH_3)_2$], 2.82 (dt, 2 H, J = 7.5, 1.0 Hz, 3-CH_2), 7.30–7.70 (m, 7 H, 5 ArH, and OH + NH, which disappear with D_2O).

^{13}C NMR (DMSO-d_6): δ = 20.16 (CH_2), 27.22 (CH_2), 34.66 (2 CH_3), 37.92 (CH_2), 77.80 (C), 116.38 (CN), 127.80 (2 CH + C), 128.53 (C), 129.04 (2 CH), 129.29 (CH), 134.80 (CH), 142.58 (C), 203.39 (CO).

Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.67; H, 6.94; N, 9.53.

Dimethylammonium salt of the enolate anion of 3-(2-oxocyclopentyl)-2-phenylsulfonylpropenenitrile (6e w_3)

Yield: 5.25 g (82%); mp 116–118°C (dec).

IR (KBr): ν = 3200–2300, 2175, 1642, 1588, 1500–1400 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.70 (qui, 2 H, J = 7.5 Hz, 4-CH_2), 1.99 (t, 2 H, J = 7.5 Hz, 5-CH_2), 2.56 [s, 6 H, $N(CH_3)_2$], 2.62 (dt, 2 H, J = 7.4, 1.0 Hz, 3-CH_2), 7.10 (near t, 1 H, J = 1.0 Hz, =CH), 7.50–7.60 (m, 3 H, 2 ArH*m* + ArH*p*), 7.65–7.75 (m, 2 H, 2 ArH*o*), 7.80–8.60 (very br s, 2 H, OH + NH, disappears with D_2O).

^{13}C NMR (DMSO-d_6): δ = 19.96 (CH_2, 26.86 (CH_2), 34.68 (2 CH_3), 37.77 (CH_2), 73.18 (C), 111.89 (CN), 121.70 (C), 125.34 (2CH), 129.26 (2CH), 131.33 (CH), 133.14 (CH), 146.33 (C), 201.45 (CO).

Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 59.97; H, 6.29; N, 8.74. Found: C, 59.89; H, 6.29; N, 8.71.

Enol Forms 7e w_1, 7e w_2, 7e w_3; General Procedure

A aq (20 mL) solution of the salts **6e** (10 mmol) was carefully acidified with AcOH at 0°C. The amorphous precipitate was filtered, washed thoroughly with H_2O, dried and purified with repeated washings with anhyd Et_2O.

Methyl 2-cyano-3-(2-oxocyclopentyl)propenoate (7e w_1)

Yield: 1.31 g (68%); mp 125–127 °C (dec).

IR (KBr): ν = 3300–3000, 2218, 1722, 1610, 1544, 1215 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.90 (qui, 2 H, J = 8 Hz, 4-CH_2), 2.55 (t, 2 H, J = 8 Hz, 3-CH_2), 2.76 (t, 2 H, J = 8 Hz, 5-CH_2), 3.74 (s, 3 H, OCH_3), 4.0–6.0 (very br s, 1 H, OH, disappears with D_2O), 8.11 (s, 1 H, =CH).

Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 61.94; H, 5.77; N, 7.25.

2-Benzoyl-3-(2-oxocyclopentyl)propenenitrile (7e w_2)

Yield: 1.94 g (81%); mp 128–130°C (dec).

IR (KBr): ν = 3200–2300, 2215, 1665, 1560, 1175 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.90 (qui, 2 H, J = 8 Hz, 4-CH_2), 2.32 (t, 2 H, J = 8 Hz, 3-CH_2), 2.92 (t, 2 H, J = 8 Hz, 5-CH_2), 3.50–4.50 (very br s, 1 H, OH, disappears with D_2O), 7.13 (near s, 1 H, =CH), 7.40–7.70 (m, 5 H, ArH).

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.29; H, 5.47; N, 5.85. Found: C, 74.63; H, 5.53; N, 5.96.

3-(2-Oxocyclopentyl)-2-phenylsulfonylpropenenitrile (7e w_3)

Yield: 2.34 g (85%); mp 147–150°C (dec).

IR (KBr): ν = 3300–2700, 2218, 1655, 1608, 1550 cm^{-1}.

^1H NMR not obtained owing its high instability in organic solvents.

Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.07; H, 4.76; N, 5.09. Found: C, 60.70; H, 4.77; N, 5.31.

Amides 5a w_1, 5b w_3, 5c w_1, 5c w_2, 5c w_3; General Procedure

The proper cyanomethylene compound (11 mmol) was added to a solution of enaminones **2a**, **2b** or **2c** (10 mmol) in anhyd MeOH or EtOH (20 mL). The mixture was refluxed for 24 h, then evaporated under reduced pressure. The solid residue was added with Et_2O/EtOAc (1:1), filtered and recrystallized from a suitable solvent.

Methyl 2-carbamoyl-5-dimethylamino-2,4-hexadienoate (5a w_1)

Yield: 0.47 g (22%); mp 174–176°C (E+OAc).

IR (KBr): ν = 3385, 3250–3100, 1655, 1635, 1520 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.17, 2.21 (2 s, 3 H, CH_3C), 3.11, 3.14 [2 s, 6 H, $N(CH_3)_2$], 3.64, 3.71 (2 s, 3 H, O CH_3), 6.29, 6.93 (2 d, 1 H, J = 14, 12 Hz, 4-H *trans, cis* -form), 6.60, 6.76 (2 br s, 1 H, NH, disappear with D_2O), 7.90–8.00 (br s, 1 H, NH, disappears with D_2O), 7.99, 8.35 (2 d, 1 H, J = 12, 14 Hz, 3-H *cis, trans* -form).

Anal. Calcd for C_{10} $H_{16}N_2O_3$: C, 56.60; H, 7.60; N, 13.20. Found: C, 56.70; H, 7.73; N, 13.17.

Methyl 2-carbamoyl-5-dimethylamino-5-phenyl-2,4-pentadienoate (5c w_1)

Yield: 1.73 g (63%); mp 195–197 °C (EtOAc).

IR ($CHCl_3$): ν = 3490, 3340, 1663, 1635, 1515 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.70–3.30 [br s, 6 H, $N(CH_3)_2$], 3.48 (s, 3 H, OCH_3), 5.27 (br s, 1 H, NH, disappears with D_2O), 7.15–7.27 (m, 2 H, 3,4 CH=), 7.38–7.50 (m, 5 H, ArH), 8.40 (br s, 1 H, NH, disappears with D_2O).

^{13}C NMR ($CDCl_3$): δ = 42.00 (2 CH_3), 51.49 (CH_3), 101.79 (CH), 104.17 (C), 128.99 (CH), 129.20 (CH), 129.61 (CH), 129.67 (CH), 129.97 (CH), 134.75 (C), 155.52 (CH), 167.72 (enamine C), 168.96 (amide C=O), 169.83 (ester C=O). Only in ^{13}C NMR spectrum a smaller signal was present beside each signal, probably belonging to a minor isomer.

Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.88; H, 6.81; N, 10.42.

2-Benzoyl-5-dimethylamino-5-phenyl-2,4-pentadienamide (5c w_2)

Yield: 1.83 g (57%); mp 224–226 °C (95% EtOH).

IR ($CHCl_3$): ν = 3480, 3280, 1638, 1545, 1500 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.82, 3.25 [2 br s, 6 H, $N(CH_3)_2$], 5.38 (br s, 1 H, NH, disappears with D_2O), 6.92 (d, 1 H, *J* = 13 Hz, 4-CH *trans* form), 6.95–7.30 (m, 10 H, ArH), 7.39 (d, 1 H, *J* = 13 Hz, 3-CH *trans* form), 9.08 (br s, 1 H, NH, disappears with D_2O).

Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.71; H, 6.26; N, 8.97.

6-Methyl-5-dimethylamino-2-phenylsulfonyl-2,4-heptadienamide (5b w_3)
Yield: 0.26 g (8%); mp 176–178°C (EtOAc).

IR ($CHCl_3$): ν = 3500, 3370, 1640, 1530, 1380, 1140 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.40 [d, 6 H, *J* = 7 Hz, $(CH_3)_2CH$], 2.97, 3.20 [2 s, 6 H, $N(CH_3)_2$], 2.80–3.80 [m, 1 H, $(CH_3)_2CH$], 6.63 (d, 1 H, *J* = 13 Hz, 3-CH= *trans* form), 7.60 (m, 3 H, 2 ArH*m* + ArH*p*), 7.85 (m, 2 H, ArH*o*), 5.50 (br s, 1 H, NH, disappears with D_2O), 8.30 (d, 1 H, *J* = 13 Hz, 4-CH = *trans* form), 8.50 (br s, 1 H, NH, disappears with D_2O).

Anal. Calcd for $C_{16}H_{22}N_2O_3S$: C, 59.60; H, 6.88; N, 8.69. Found: C, 59.66; H, 6.89; N, 8.67.

5-Dimethylamino-5-phenyl-2-phenylsulfonyl-2,4-pentadienamide (5c w_3)
Yield: 2.64 g (74%); mp 232–234°C (95% EtOH).

IR ($CHCl_3$): ν = 3500, 3370, 1642, 1580, 1525 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.85, 3.20 [2 br s, 6 H, $N(CH_3)_2$], 5.25 (br s, 1 H, NH, disappears with D_2O), 6.93 (d, 1 H, *J* = 13 Hz, 4-CH= *trans* form), 7.20–7.80 (m, 12 H, 10 ArH +3-CH=, and NH which disappears with D_2O).

Anal. Calcd for $C_{19}H_{20}N_2O_3S$: C, 64.02; H, 5.65; N, 7.86. Found: C, 64.30; H, 5.60; N, 7.92.

2(*1H*)-Pyridinones 3a, c, e w_1, 3c, e w_2 and 3b, c, e w_3; Procedure via Amide or Enolate Intermediates
A solution of **5** or **6** (10 mmol) and glacial AcOH (10 mmol, 0.6 g) in anhyd toluene (250 mL) was refluxed in a Dean–Stark appparatus for 12 h in the case of ammonium salts and 48 h in the case of amides. The mixture was washed with 1 M aq NaOH solution and H_2O, dried and evaporated under reduced pressure. The residue was recrystallized (**3a, c w_1** from EtOAc; **3c w_2**, **3b w_3** from EtOH; **3c w_3** from EtOH/DMSO, 2:1; for **3e** derivatives the crystallization solvents have already been described).

3-Benzoyl-6-phenyl-2(1*H*)-pyridinone (3c w_2)
IR (KBr): ν = 3410, 1645 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 6.82 (d, 1 H, *J* = 6 Hz, 5-H), 7.45–7.95 (m, 11 H, 10 ArH + 4-CH), 12.28 (br s, 1 H, NH, disappears with D_2O).

Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.57; H, 4.55; N, 5.04.

6-Isopropyl-3-phenylsulfonyl-2(1*H*)-pyridinone (3b w_3)
IR (KBr): ν = 3200–2500, 1628, 1547 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.16 [d, 6 H, *J*=7 Hz, $(CH_3)_2CH$], 2.80 [sept, 1 H, *J* = 7 Hz, $(CH_3)_2CH$], 6.35 (d, 1 H, *J* = 7.7 Hz, 5-H), 7.53–7.74 (m, 3 H, 2 ArH*m* + ArH*p*), 7.92–7.99 (m, 2 H, 2 ArHo), 8.27 (d, 1 H, *J* = 7.7 Hz, 4-CH), 12.27 (near s, 1 H, NH, disappears with D_2O).

Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.42; H, 5.42; N, 5.05.

6-Phenyl-3-phenylsulfonyl-2(1*H*)-pyridinone (3c w_3)
IR (KBr): ν = 3420, 1650, 1312, 1155 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 6.80 (d, 1 H, *J* = 7 Hz, 5-H), 7.50–7.85 (m, 8 H, ArH), 7.90–8.15 (m, 2 H, ArH), 8.40 (d, 1 H, *J* = 7 Hz, 4-CH), 12.60 (br s, 1 H, NH, disappears with D_2O).

Anal. Calcd for $C_{17}H_{13}NO_3S$: C, 65.58; H, 4.21; N, 4.50. Found: C, 65.71; H, 3.99; N, 4.44.

Physical and spectral data of compound **3e** are reported in the Table and in the General Direct Procedure.

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