Generation and in Situ Acylation of Enaminone Anions: A Convenient Synthesis of 3-Carbethoxy-4(1*H*)-pyridinones and -4-pyrones and Related Compounds

Stuart W. McCombie,* William A. Metz, Dennis Nazareno, Bandarpalle B. Shankar, and Jayaram Tagat

Chemical Research, Schering-Plough Corporation, 60 Orange Street, Bloomfield, New Jersey 07003

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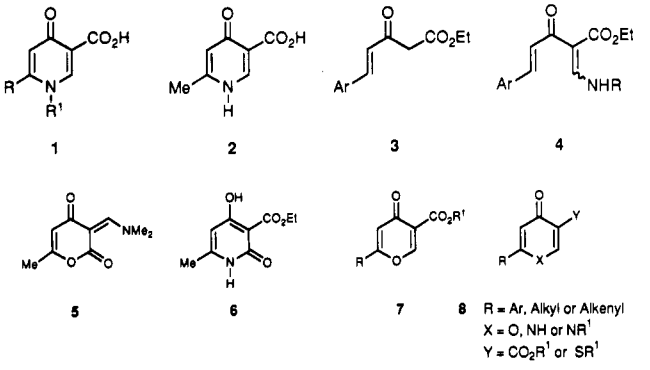
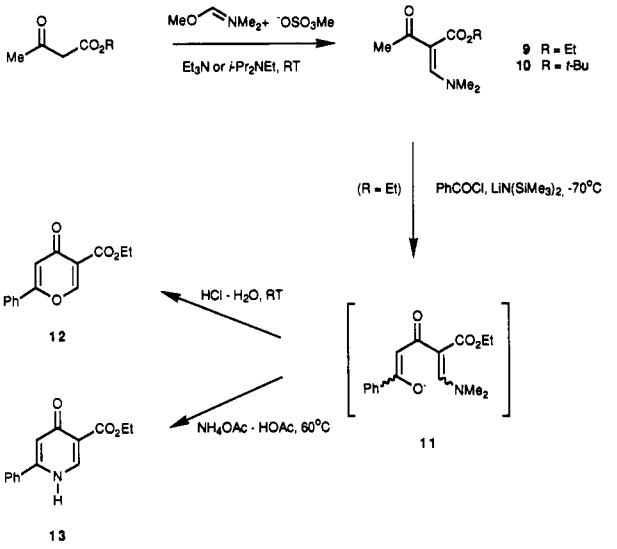
Treatment of 2-[(dimethylamino)methylene]-3-oxobutanoates **9** or **10** with $LiN(SiMe_3)_2$ in the presence of RCOCl results in C-acylation. The resulting intermediate, without isolation, may be converted to 6-R 3-Carbethoxy-4-pyrones (e.g., **12**) by H_3O^+ or to the corresponding pyridinones (e.g., **13**) by NH_4OAc. Typically, yields are 55–75% for R groups lacking acidic α or γ protons and ca. 30% for R = Me_2CH or MeCH=CH. Replacing **9** with $MeCOC(=CHNMe_2)SCH_2Ph$ (from $MeCOCH_2SCH_2Ph$ and $Me_2NCH(OMe)_2$ similarly affords 3-($PhCH_2S$)-substituted products such as **29**. Alkylation of the pyridinone anions produces mixtures of N- and O-substituted compounds, with the latter predominating; aminolysis of the isolated pyrones ($R'NH_2$-HOAc, where R' = alkyl, Ar, HO, etc.) is the preferred route to the 1-R'-substituted pyridinones.

6-Substituted 3-carboxy-4(1*H*)-pyridinones **1** are compounds of some interest with respect to biological activity. Antibacterial[1,2] and CNS stimulatory[1] activity have been claimed for N-substituted examples, while the 6-methyl derivative **2** and related, N-unsubstituted compounds are side-chain constituents in penicillins and cephalosporins posessing high-activity vs Gram-negative organisms.[3] The 6-aryl 3-esters have been obtained[1,2] from ArCHO through keto ester **3** via **4**, which was subjected to cyclization and final dehydrogenation. The 6-methyl acid **2**, which is also a precursor to 6-(2-arylethenyl) analogues,[4] has been prepared by two alternative routes: from dehydroacetic acid via **5** followed by aminolysis–rearrangement[5] or from aminocrotonic ester via **6**, with substituent manipulations.[6] The pyridinones **1** would obviously be available by aminolysis of the corresponding pyrones **7**, but these substances have not heretofore been described.[7] In this paper, we report a concise synthesis of 3,6-disubstituted 4-(1*H*)-pyridinones and 4-pyrones of general structure **8**, which we required as intermediates to polycyclic systems.



Scheme I



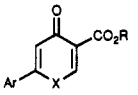
The underlying chemistry is illustrated by Scheme I, which shows the synthesis of 3-carbethoxy-6-phenyl-4-pyrone **12** and the corresponding pyridinone ester **13** in two operations from ethyl acetoacetate.

Enaminone **9** has been obtained from ethyl acetoacetate using DMF acetals,[8] the Vilsmeier reagent,[9] and Brederick's reagent.[10] As indicated, we found that the DMF–dimethyl sulfate adduct, in combination with a tertiary amine, was convenient for preparing **9** and the corresponding *tert*-butyl ester **10** under mild conditions. Although **9** has been used to synthesize a variety of heterocyclic systems through initial nucleophilic attack at the (dimethylamino)methylene carbon,[11] the derived *enolate anion* has not been used as a synthon. In fact, deprotonation of **9** with LDA or lithium hexamethyldisilazide (LHMDS) at −70 °C, followed by acidification after 15 min at that temperature, gave considerable amounts of complex

(1) *Ger. Offen.* 2,901,868, 1979; *Chem. Abstr.* 1979, *91*, 211273h.
(2) *Jpn. Kokai Tokkyo Koho.* JP 61,246,163, 1986; *Chem. Abstr.* 1987, *106*, 156278q.
(3) Yamada, H.; Tobiki, H.; Jimpo, K.; Gooda, K.; Takeuchi, Y.; Ueda, S.; Kamatsu, T.; Okuda, T.; Noguchi, H.; Irie, K.; Nakagome, T. *J. Antibiot.* 1983, *36*, 532. DeJohn, D.; Domagala, J. M.; Haskell, T. H.; Heifetz, C. L.; Huang, C-G.; Kaltenbronn, J. S.; Krolls, U. *J. Antibiot.* 1985, *38*, 372.
(4) DeJohn, D.; Domagala, J. M.; Kaltenbronn, J. S.; Krolls, U. *J. Heterocycl. Chem.* 1983, *20*, 1295.
(5) Kilbourn, E.; Seidel, M. C. *J. Org. Chem.* 1972, *37*, 1145.
(6) Mittelbach, M. *Synthesis* 1988, 479.
(7) A CAS online search for 6-substituted 3-carbethoxy-4-pyrones was negative; more highly substituted 3-carbethoxypyrone are known.
(8) Meerwein, H.; Florian, W.; Schon, N.; Stopp, G. *Ann.* 1961, *641*, 1.
(9) *Brit. Pat.* 917,436, 1963; *Chem. Abstr.* 1963, *58*, 12425g.
(10) Benett, G. B.; Mason, R. B. *Org. Prep. Proc. Int.* 1978, *10*, 67.
(11) For example, α-aminocarbonyl compounds give pyrroles: Cohnen, E.; DeWald, R. *Synthesis* 1987, 566. Hydrazines afford pyrazoles: Mennozi, G.; Mosti, L.; Schenone, P. *J. Heterocycl. Chem.* 1987, *24*, 1669. Cyanoacetamide derivatives give polysubstituted 2(1*H*)-pyridinones: *Eur. Pat. Appl.* EP 124,090, 1984; *Chem. Abstr.* 1985, *102*, 113308z.

0022-3263/91/1956-4963$02.50/0

Table I. One-Pot Synthesis of 6-Aryl-3-carbethoxy-4-pyrone and -4(1*H*)-pyridinone from 2-[(Dimethylamino)methylene]-3-oxobutanoates



compd no.	Ar	X	R	% yield[a]	mp[b] (°C)	^{1}H MR (δ, $CDCl_3$)[c]
12	C_6H_5	O	Et	63	90–92	6.87, 8.58
13	C_6H_5	NH	Et	58	115–117	7.26–8.99
14	C_6H_5	O	*t*-Bu	78	99–102	6.92, 8.58
15	C_6H_5	NH	*t*-Bu	66	159–161	7.25, 8.92
16	2-BrC_6H_4	O	Et	35	71–73	6.69, 8.58
17	4-$NO_2C_6H_4$	O	*t*-Bu	60	196–200 dec	6.95, 8.94
18	4-$NO_2C_6H_4$	NH	Et	75	191–193	7.33, 8.95
19	2-$BnOC_6H_4$	NH	Et	35	149–150	7.57, 9.01
20	3,4-$(OCH_2O)_{C_6}H_3$	O	Et	63	127–128	6.74, 8.55

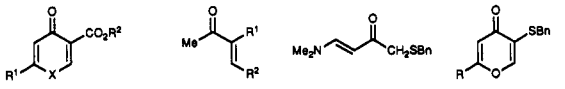
[a] Based on $AcC(=CHNMe_2)CO_2R$, 1.1–1.2 equiv of ArCOCl was used, with 2.3–2.5 equiv of $LiN(SiMe_3)_2$. [b] Uncorrected. All crystalline compounds gave satisfactory microanalyses (see Experimental Section). [c] For the pyrone of pyridinone ring protons.

side products (TLC) in addition to recovered **9**.[12] However, the enolate could be generated *in the presence* of acid chlorides as trapping agents by adding a mixture of **9** and, for example, PhCOCl (1.1–1.2 equiv) to LHMDS (2.2–2.5 equiv) in THF–hexanes at −70 °C. The (presumed) intermediate species **11** could be converted to *either* pyrone or pyridinone simply by selecting the appropriate workup. Stirring with $HCl–H_2O–Et_2O$ effected cyclization with dimethylamine elimination to give pyrone ester **12**, isolated by rapid silica gel chromatography[13] in 63% yield. Alternatively, addition of HOAc and NH_4OAc[14] followed by evaporation of THF and heating at 60 °C gave the N-unsubstituted pyridinone ester **13** in 58% yield.

These conditions were applied to a number of aromatic acid chlorides,[15] and the results are shown in Table I. Clearly, a variety of substituents on the aromatic ring are tolerated, although acidic or otherwise reactive groups (phenolic OH, aldehyde, ketone) require appropriate protection.

This methodology also proved satisfactory for preparing compounds with an alkyl or alkenyl residue at C-6. Substituting *t*-BuCOCl for PhCOCl in the standard procedure gave the liquid pyrone ester **21** in 63% yield, and cinnamoyl chloride afforded **22** and **23** uneventfully. Somewhat lower yields were encountered when the standard conditions were applied to substrates with acidic α or γ protons. By use of the NH_4OAc workup, isobutyryl chloride gave 16% of **24** and crotonoyl chloride gave 23% of **25**. The actual yields were somewhat better (ca. 30% by ^{1}H NMR), since these figures refer to first crops after silica gel filtration and crystallization; the liquors contained additional pyridinone plus an oily, yellow compound that proved to be **26**, formed by aminolysis of unreacted **9**.

The process was extended to provide 3-alkylthio-substituted products. Treatment of 1-[(phenylmethyl)thio]-2-propanone with $Me_2NCH(OR)_2$ gave **27**, free from regioisomeric **28**, and subjecting this enaminone to the standard conditions with PhCOCl and with 3,4-(methylenedioxy)benzoyl chloride produced, after acidic workup, the pyrones **29** and **30**.



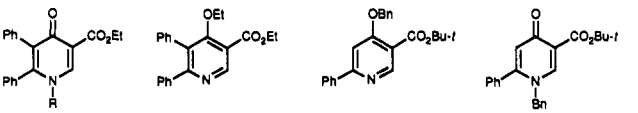
21 R^1 = *t*-Bu, R^2 = Et, X = O
22 R^1 = *E*-CH=CHPh, R^2 = *t*-Bu, X = O
23 R^1 = *E*-CH=CHPh, R^2 = *t*-Bu, X = NH
24 R^1 = Me_2CH, R^2 = Et, X = NH
25 R^1 = *E*-CH=CHMe, R^2 = Et, X = NH

26 R^1 = CO_2Et, R^2 = NH_2
27 R^1 = SBn, R^2 = NMe_2

28

29 R = Ph
30 R = 3,4-$(OCH_2O)C_6H_4$

In addition to their intrinsic novelty, a significant advantage to obtaining the 4-pyrones from these reactions lies in the preparation of a variety of N-substituted 4-(1*H*)-pyridinones, free from their O-alkylated isomers. The latter were observed to be significant side products in the alkylation of 5,6-disubstituted 3-carbethoxypyridinones[16] (ethylation of **31** gave a 2:1 mixture of **32** and **33**) and were major products from alkylations of our 6-substituted compounds; benzylation ($PhCH_2Br$, K_2CO_3, $DMF–H_2O$) converted **15** to **34**, with only 15% of N-substituted compound **35**.



31 R = H
32 R = Et

33

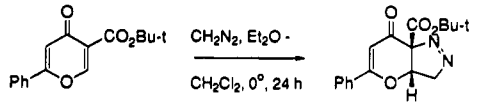
34

35

As anticipated, aminolysis of the pyrones proceeded readily to afford 4(1*H*)-pyridinones in good to excellent yields. For example, **17** reacted with $EtNH_2$ in EtOH–HOAc to give **36** in high yield; an initially rapid reaction produced (TLC) an intermediate,[17] which was converted

(12) Simple enaminones have been deprotonated and the anions subjected to γ alkylation: Yoshimoto, M.; Ishida, N.; Hiraoka, T. *Tetrahedron Lett.* **1973**, 39. Bryson, T. A.; Gammill, R. B. *Ibid.* **1973**, 3963.

(13) These 3-carbethoxypyrone were sensitive to nucleophilic attack at C-2; slight "tailing" was seen on silica, necessitating rapid chromatography, and heating in hydroxylic solvents was inadvisable. The analogous chromone-3-carboxylates are known to undergo conjugate and cycloadditions to the 2,3-double bond: Cremins, P. J.; Fitton, A. O.; Suschitzky, H.; Wallace, T. W. *Tetrahedron Lett.* **1986**, *27*, 91. Cremins, P. J.; Saengchantara, S. T.; Wallace, T. W. *Tetrahedron* **1987**, *43*, 3075. Our 3-carbethoxypyrones showed similar reactivity, as exemplified by the cycloaddition below:



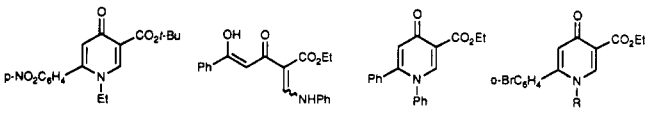
(14) Some NH_4OAc is generated from $HN(SiMe_3)_2$ and HOAc; addition of a further quantity ensures complete conversion to the pyridinone.

(15) Methyl esters have not sufficiently reactive, but comparable yields of **13** were realized when the PhCOCl was replaced with $(PhCO)_2O$ or *N*-benzoylimidazole.

(16) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Wakisawa, K.; Kusama, O.; Sugi, H.; Kawasaki, K. *J. Heterocycl. Chem.* **1977**, *14*, 477.

(17) A related cyclisation is presumably involved in the conversion of **5** to **2** by NH_3. For the reaction of a bis[(dimethylamino)methylene] compound with NH_4OAc to give a dihydropyrazine 3,5-diester, see: Chorvat, R. J.; Rorig, K. J. *J. Org. Chem.* **1988**, *53*, 5779.

to the *N*-ethylpyridinone upon refluxing. In the case of aniline, the lower reaction rates permitted isolation of the intermediates: $PhNH_2$ and **12**, upon refluxing in EtOH–HOAc, rapidly formed a yellow, solid intermediate **37**, which was clearly a mixture of tautomeric forms in solution (PMR). Conversion to the *N*-phenylpyridinone **38** required refluxing in neat HOAc. Functionalized amines could also be used, as exemplified by conversions of the 6-(2-bromophenyl)pyrone **16** to **39** and **40** by reaction with NH_2OH and $NCCH_2NH_2$, respectively.



36 **37** **38** **39** R = OH **40** R = CH_2CN

In summary, we have described a concise route from readily available starting materials to 6-substituted 4-pyrones and 4(1*H*)-pyridinones bearing an anion-stabilizing group at C-3. Aminolysis of the pyrones in a separate step with aliphatic and aromatic amines and hydroxylamines further extends the range of substituents accessible in the final product.

Experimental Section

Melting points are uncorrected. Column chromatography was performed on Baker silica gel (SG60–200 mesh). All solvents and reagents were the purest commercial grade and were used as received, except for tetrahydrofuran (THF), which was freshly distilled from sodium benzophenone ketyl. All reactions were carried out in an atmosphere of dry, oxygen-free nitrogen.

Enaminones. Ethyl 2-[(Dimethylamino)methylene]-3-oxobutanoate (9). Ethyl 3-oxobutanoate (29.5 g, 0.226 mol) and the DMF–Me_2SO_4 adduct (60 g of the mixture obtained by keeping a mixture of 1.05 mol of DMF and 1.0 mol of Me_2SO_4 at 40 °C/4 h, then rt/48 h) were stirred in CH_2Cl_2 (350 mL) at 5–10 °C, and Et_3N (45 mL) was added over 15 min. The mixture was stirred for 2 h at rt and then washed with aqueous tartaric acid (10% w/v, 250 mL) and water (250 mL), dried (MgSO4), and filtered through SG (30 g), washing with 10:1 CH_2Cl_2–Et_2O. After evaporation, the residual oil was rapidly vacuum distilled to give the *enaminone* **9** (34.0 g, 81%). The pale yellow oil became orange on standing, but this did not affect subsequent reactions.

1,1-Dimethylethyl 2-[(Dimethylamino)methylene]-3-oxobutanoate (10). This preparation was carried out as in the preceding example, using *tert*-butyl 3-oxobutanoate (6.0 g), CH_2Cl_2 (40 mL), DMF–Me_2SO_4 (10.0 g), and diisopropylethylamine (8.0 mL). The crude product was filtered through SG (20 g), eluting with 20:1 CH_2Cl_2–Et_2O to give the *enaminone* **10** as a yellow oil (7.41 g, 92%) containing a trace of CH_2Cl_2. This material was of suitable quality for subsequent reactions. This enaminone decomposed on attempted distillation and upon prolonged storage at rt: ^1H NMR δ 1.54 (s, 9 H), 2.28 (s, 3 H), 3.00 (s, 6 H), 7.52 (s, 1 H).

1-[(Phenylmethyl)thio]-1-[(dimethylamino)methylene]-2-propanone (27). A mixture of 1-[(phenylmethyl)thio]-2-propanone (1.5 g, 8.3 mmol), dimethoxy(dimethylamino)methane (1.2 mL, 9.16 mmol), and *p*-toluenesulfonic acid (0.1 g) in CH_2Cl_2 (10 mL) was refluxed for 7 h. After washing (H_2O), the solution was chromatographed on SG (10% EtOAc–CH_2Cl_2) to afford the *enaminone* as an orange gum (1.50 g, 77%) that was used immediately: ^1H NMR δ 2.30 (s, 3 H), 2.99 (s, 6 H), 3.60 (s, 2 H), 7.1–7.4 (m, 5 H), 7.86 (s, 1 H).

Pyrones and Pyridinones by Ring Construction. 3-Carbethoxy-6-phenyl-4-pyrone (12). A solution of hexamethyldisilazane (5.1 mL) in THF (30 mL) was stirred at 0 °C, and *n*-BuLi in hexanes (9.5 mL of a 2.5 M solution) was added. After the mixture was cooled to −70 °C, a solution of enaminone **9** (1.85 g, 10 mmol) and benzoyl chloride (1.40 mL, 11.9 mmol) of THF (20 mL) was added over 1–2 min. The cooling bath was removed, and after 2–3 min, Et_2O (100 mL) was added followed by 3 M aqueous HCl (40 mL). The mixture was stirred rapidly for 45 min, and the organic phase was washed with saturated aqueous $NaHCO_3$ and H_2O, dried ($MgSO_4$), and evaporated. The residue was chromatographed rapidly on SG (1:1 hexanes–CH_2Cl_2, then 0–10% Et_2O in CH_2Cl_2) to afford the *pyrone ester* **12** as a pale brown solid (1.55 g, 63%). The analytical sample was recrystallized from CH_2Cl_2–hexanes: IR (Nujol) 1695, 1650 cm^{-1}. Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.92. Found: C, 69.15; H, 4.73.

3-Carbethoxy-6-phenyl-4(1*H*)-pyridinone (13). The foregoing procedure for the preparation of **12** was followed. After the mixture was removed from the cooling bath and stirred for 2–3 min, HOAc (20 mL) and NH_4OAc (1.0 g) were added and most of the THF was removed by rotary evaporation at 60 °C (100–150 mm). The residue was heated for 1.5 h at 60–65 °C, cooled and worked up in H_2O–CH_2Cl_2. The organic phase was washed with H_2O (3×) and aqueous $NaHCO_3$, dried, and evaporated. SG chromatography (100:1 CH_2Cl_2–Et_2O), evaporation of pure fractions, and trituration with hexanes containing a little Et_2O gave the *pyridinone* as pale yellow crystals (1.41 g, 58%): IR (Nujol) 1665 cm^{-1}; Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.13; H, 5.39; N, 5.76. Found: C, 69.15; H, 5.35; N, 5.67.

The following pyrone and pyridinone esters (yields, melting points, and NMR data for compounds **12** to **20** are given in Table I) were prepared by the procedures described previously for **12** and **13**.

3-(*tert*-Butoxycarbonyl)-6-phenyl-4-pyrone (14). Chromatographed rapidly on SG with 0–5% Me_2CO–CH_2Cl_2. Crystallized from Et_2O-hexanes: IR (Nujol) 1735, 1650, 1625 cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.88. Found: C, 70.43; H, 5.93.

3-(*tert*-Butoxycarbonyl)-6-phenyl-4(1*H*)-pyridinone (15). Chromatographed on SG with 50–100% CH_2Cl_2–hexanes. Crystallized from Et_2O–hexanes. Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.85; H, 6.27; N, 5.17. Found: C, 71.12; H, 6.06; N, 5.10.

3-Carbethoxy-6-(2-bromophenyl)-4-pyrone (16). Chromatographed on SG with 25% EtOAc–hexanes. Crystallized from Et_2O–hexanes. Anal. Calcd for $C_{14}H_{11}BrO_4$: C, 52.04; H, 3.43. Found: C, 52.16; H, 3.54.

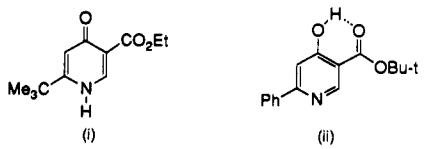
3-(*tert*-Butoxycarbonyl)-6-(4-nitrophenyl)-4-pyrone (17). This substance was quite unstable to SG; after rapid filtration of the crude material through a pad of SG and subsequent evaporation, satisfactory product was obtained by trituration with ether. A sample from CH_2Cl_2–hexanes formed slightly greenish prisms. Anal. Calcd for $C_{16}H_{15}NO_6$: C, 60.57; H, 4.71; N, 4.41. Found: C, 60.39; H, 4.64; N, 4.34.

3-Carbethoxy-6-(4-nitrophenyl)-4(1*H*)-pyridinones (18). After chromatography on SG with 2% Et_2O–CH_2Cl_2, trituration with 1:1 Et_2O–hexanes gave cream needles. Anal. Calcd for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.20; H, 4.06; N, 9.66.

3-Carbethoxy-6-[2-(phenylmethoxy)phenyl]-4(1*H*)-pyridinone (19). Chromatographed on SG with CH_2Cl_2. Crystallized from CH_2Cl_2–hexanes. Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.37; H, 5.37; N, 3.82.

3-Carbethoxy-6-[3,4-(methylenedioxy)phenyl]-4-pyrone (20). Chromatographed with EtOAc–hexanes. Crystallized from Et_2O. Anal. Calcd for $C_{15}H_{12}O_6$: C, 62.50; H, 4.19. Found: C, 62.56; H, 3.95.

(18) A comment on polarity is appropriate: whereas the simple *N*-alkylpyridinone esters were always much more polar than the starting pyrone esters, this was not necessarily the case for the *N*-unsubstituted compounds, where the polarity varied greatly, depending on the 6-substituent. For example, the 6-phenylpyridinone **15** was of very similar polarity to the corresponding pyrone **14**. In contrast, aminolysis (NH_4OAc) of the 6-(1,1-dimethylethyl)pyrone ester **21** gave the corresponding pyridinone i, a far more polar substance. Possibly, the C-6 substituent determines the dominant tautomer, the 6-phenyl compound **15** presumably being in the chelated, nonpolar 4-hydroxynicotinate form ii.



3-Carbethoxy-6-(1,1-dimethylethyl)-4-pyrone (21). A solution of enaminone **9** (1.85 g, 10 mmol) and trimethylacetyl chloride (1.25 mL, 10.2 mmol) in THF (20 mL) was added over 1–2 min to a solution of $LiN(SiMe_3)_2$ prepared in the usual manner from *n*-BuLi (2.5 M in hexanes, 9.5 mL) and HMDS (5.1 mL) in THF (30 mL) and cooled to −70 °C. After being stirred for 10 min at −70 °C, Et_2O (100 mL) and a mixture of concd HCl (10 mL) and H_2O (40 mL) were added, and the mixture was stirred rapidly without cooling for 10 min. The organic phase was washed (H_2O; aqueous $NaHCO_3$), dried ($MgSO_4$), and evaporated, and the products were chromatographed on SG, eluting initially with 1:1 CH_2Cl_2–hexanes, then 0–5% Et_2O–CH_2Cl_2. Fractions containing the product plus traces of a less polar contaminant were evaporated to give the *pyrone ester* (1.41 g, 63%) as a pale brown oil: IR (film) 3050, 2850, 1740, 1705, 1660, 1405, 1340, 1290, 1215, 1105, 1045, 920, 865 cm^{-1}; ^1H NMR δ 1.27 (s, 9 H), 1.35 (t, 3 H, J = 7 Hz), 4.37 (q, 2 H, J = 7 Hz), 6.27 (s, 1 H), 8.43 (s, 1 H).

3-(*tert*-Butoxycarbonyl)-6-((*E*)-2-phenylethenyl)-4-(1*H*)-pyridinone (23). This substance was prepared according to the general procedure described previously for the preparation of **13**, replacing the PhCOCl with an equivalent amount of cinnamoyl chloride. After SG chromatography and recrystallization from Et_2O–hexanes, the *pyridinone* **23** was obtained in 45% yield as pale yellow needles, mp 163–165 °C: ^1H NMR δ 1.62 (s, 9 H), 6.82 (s, 1 H), 7.0–7.7 (m, 7 H), 8.83 (s, 1 H), 11.9 (br s, 1 H, exch by D_2O). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.72; H, 6.39; N, 4.71. Found: C, 72.51; H, 6.44; N, 4.55.

3-Carbethoxy-6-(1-methylethyl)-4(1*H*)-pyridinone (24). The procedure described for **13** was followed, replacing the PhCOCl with $Me_2CHCOCl$ (1.20 mL). Chromatography of the crude product of SG with 0–10% Et_2O–CH_2Cl_2 gave a 3:1 mixture (0.8 g, corresponding to 30% of the desired product) of **24** with the unsubstituted enaminone **26**. Recrystallization from Et_2O–hexanes gave the *pyridinone* (0.49 g, 23%), mp 152–154 °C: ^1H NMR δ 1.28 (d, 6 H, J = 7 Hz), 1.40 (t, 3 H, J = 7 Hz), 2.98 (septet, 1 H, J = 7 Hz), 4.40 (q, 2 H, J = 7 Hz), 6.71 (s, 1 H), 8.84 (s, 1 H), 11.1 (br s, 1 H, exch D_2O). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.75; H, 7.21; N, 6.75. Early fractions from the chromatography contained mostly the *enaminone* **26**, a somewhat unstable, yellow oil: ^1H NMR showed one major isomer δ 1.30 (t, 3 H, J = 7 Hz), 2.48 (s, 3 H), 4.19 (q, 2 H, J = 7 Hz), 6.1 (br, 1 H), 8.12 (dd, 1 H, J = 9 and 16 Hz), 10.3 (br, 1 H).

3-Carbethoxy-6-((*E*)-1-propenyl)-4(1*H*)-pyridinone (25). The standard procedure as described for **13** was followed, using enaminone **9** (1.85 g, 10 mmol) and freshly distilled crotonoyl chloride (1.1 mL). After workup, the crude product was chromatographed on SG with CH_2Cl_2 to obtain a mixture (0.9 g, corresponding to approximately a 30% yield) of the desired ester with unsubstituted enaminone **26** in 3:1 ratio (NMR). Recrystallization from Et_2O–hexanes gave a first crop (0.34 g, 16%) of the *pyridinone* **25** as needles, mp 139–141 °C: ^1H NMR δ 1.43 (t, 3 H, J = 7 Hz), 1.95 (dd, 3 H, J = 9 and 2 Hz), 4.44 (q, 2 H, J = 7 Hz), 6.45 (dq, 1 H, J = 16 and 2 Hz), 6.77 (s, 1 H), 6.90 (dq, 1 H, J = 16 and 9 Hz), 8.87 (s, 1 H), 11.9 (br s, 1 H). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.36; H, 6.19; N, 6.70.

3-[(Phenylmethyl)thio]-6-phenyl-4-pyrone (29). LHMDS in THF (1M, 30 mL, 30 mmol) was cooled and stirred at −70 °C and a solution of the enaminone **27** (3.2 g, 13.6 mmol) and PhCOCl (1.9 mL, 16.3 mmol) in THF (50 mL) was added over 10 min. After a further 10 min, Et_2O (200 mL) and 2 M aqueous HCl (500 mL) were added, and stirring was continued at RT for 3 h. The organic phase was washed with H_2O, dried ($MgSO_4$), and evaporated, and the products were chromatographed on SG, eluting with 25% EtOAc–hexanes. Evaporation of pure fractions gave the *pyrone* (3.0 g, 75%) as a pale yellow solid, mp 121–123 °C: IR (KBr pellet) 1624, 1606 cm^{-1}; ^1H NMR δ 4.08 (s, 2 H), 6.87 (s, 1 H), 7.15–7.35 (m, 5 H), 7.4–7.55 (m, 3 H), 7.7 (m, 2 H), 7.77 (s, 1 H). Anal. Calcd for $C_{18}H_{14}O_2S$: C, 73.44; H, 4.79; S, 10.89. Found: C, 73.27; H, 4.74; S, 11.10.

Alkylation of Pyridinones. 3-(*tert*-Butoxycarbonyl)-4-(phenylmethoxy)-6-phenylpyridine (34) and 3-(*tert*-Butoxycarbonyl)-1-(phenylmethyl)-6-phenyl-4(1*H*)-pyridinone (35). A mixture of the N-unsubstituted pyridinone **15** (2.71 g, 10 mmol), dimethyl sulfoxide (30 mL), benzyl bromide (2.25 g), powdered anhydrous K_2CO_3 (3.0 g), and tricaprylmethylammonium chloride (Aliquat 336, 0.2 g) was stirred for 48 h at rt and then partitioned in Et_2O–H_2O. The organic phase was washed (2 × H_2O), dried, and evaporated, and the residue was chromatographed on SG. Elution with 2:1 hexanes–CH_2Cl_2 removed nonpolar, reagent-derived materials, and increasing through to pure CH_2Cl_2 gave the *O-benzyl compound* **34** as a white foam (R_f = 0.5 in CH_2Cl_2; 2.01 g, 56%): ^1H NMR δ 1.54 (s, 9 H), 5.23 (s, 2 H), 7.1–7.5 (m, 8 H), 7.34 (s, 1 H), 7.75–7.85 (m, 2 H), 8.86 (s, 1 H). Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.86. Found: C, 75.95; H, 6.66; N, 3.61.

Further elution with 2–10% Me_2CO–CH_2Cl_2 gave the *N-substituted pyridinone* **35**[18] as an oil, which eventually solidified (R_f = 0.2 in 10% Me_2CO–CH_2Cl_2; 0.51 g, 14%), mp 69–72 °C: ^1H NMR δ 1.54 (s, 9 H), 4.90 (s, 2 H), 6.38 (s, 1 H), 6.7–7.5 (m, 10 H), 8.15 (s, 1 H). Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.86. Found: C, 76.02; H, 6.45; N, 4.01.

Pyridinones from Aminolysis of Pyrones. 3-(*tert*-Butoxycarbonyl)-1-ethyl-6-(4-nitrophenyl)-4(1*H*)-pyridinone (36). A mixture of pyrone ester **18** (0.50 g, 1.58 mmol), EtOH (10 mL), HOAc (3 mL), and aqueous ethylamine (0.3 mL) was refluxed for 0.5 h. The mixture was cooled and partitioned in H_2O–CH_2Cl_2 and the organic phase dried ($MgSO_4$) and evaporated to leave essentially pure product. Recrystallization from CH_2Cl_2–hexanes gave the *pyridinone* **36** as cream needles (0.425 g, 78%), mp 181–182.5 °C: ^1H NMR δ 1.24 (t, 3 H, J = 7 Hz), 1.58 (s, 9 H), 3.77 (q, 2 H, J = 7 Hz), 6.38 (s, 1 H), 7.57 (d, 2 H, J = 11 Hz), 8.15 (s, 1 H), 8.38 (d, 2 H, J = 11 Hz). Anal. Calcd for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.14. Found: C, 62.70; H, 5.91; N, 7.83.

3-Carbethoxy-1,6-diphenyl-4(1*H*)-pyridinone (38). Step A. A mixture of the 6-phenylpyrone ester **12** (1.22 g, 5 mmol), EtOH (20 mL), HOAc (1.5 mL), and aniline (0.9 g) was refluxed for 15 min, cooled, and diluted with H_2O (50 mL). The solid was collected, washed with several small portions of 10% HOAc–H_2O, and dried at rt in high vacuum to a bright yellow powder (1.63 g), consisting of the *acyclic intermediate* **37**: IR (Nujol) 1705, 1525–1590 (several overlapping absorptions), 1370 1235, 1050 cm^{-1}; a freshly prepared $CDCl_3$ solution showed two major isomers, in approximately 4:1 ratio, with the following signals (in addition to Ar*H* multiplets at 7.2–8.0) δ (major) 1.38 (t, J = 7 Hz), 4.30 (q, J = 7 Hz), 8.62 (d, J = 13 Hz), 12.4 (br d, J = 13 Hz); δ (minor) 1.51 (t, J = 7 Hz), 4.42 (q, J = 7 Hz), 8.81 (d, J = 14 Hz), 11.1 (br d, J = 14 Hz).

Step B. A solution of the foregoing product (1.61 g) and aniline (0.3 g) in HOAc (25 mL) was refluxed (oil bath, 130 °C) for 2 h and then added to stirred H_2O (150 mL). The precipitate was collected and dried at rt and then chromatographed onSG, eluting with 0–20% Et_2O–CH_2Cl_2. After elution of less polar by products, the *pyridinone* was eluted and was recrystallized from CH_2Cl_2–hexanes as fibrous needles (0.89 g, 57% from **12**), mp 214–216 °C: IR (Nujol) 3095, 1740, 1645, 1595, 1495, 1310, 1210, 1055 cm^{-1}; ^1H NMR δ 1.39 (t, 3 H, J = 7 Hz), 4.40 (q, 2 H, J = 7 Hz), 6.65 (s, 1 H), 7.0–7.4 (m, 10 H), 8.37 (s, 1 H). Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.33; N, 4.39. Found: C, 74.69; H, 5.33; N, 4.20.

3-Carbethoxy-1-hydroxy-6-(2-bromophenyl)-4(1*H*)-pyridinone (39). A solution of the pyrone ester **16** (2.10 g, 6.5 mmol), hydroxylamine hydrochloride (0.50 g, 7.15 mmol), and NEt_3 (1.0 mL) in MeCN (10 mL) was refluxed for 4 h, cooled, added to 1 N HCl(aq), and extracted with CH_2Cl_2. The extracts were washed (H_2O), dried ($MgSO_4$), and evaporated to a red gum, which was chromatographed (SG, 25% EtOAc–CH_2Cl_2) to give the *N-hydroxypyridinone* **39** (1.40 g, 64%) as a tan solid, mp 184–186 °C: ^1H NMR δ 1.41 (t, 3 H, J = 7 Hz), 1.64 (br s, 1 H, exch by D_2O), 4.40 (q, 2 H, J = 7 Hz), 6.32 (s, 1 H), 7.37 (m, 4 H), 7.67 (d, 1 H, J = 8 Hz). Anal. Calcd for $C_{14}H_{12}BrNO_4$: C, 49.72; H, 3.57; N, 41.4. Found: C, 49.82; H, 3.49; N, 3.98.

3-Carbethoxy-1-(cyanomethyl)-6-(2-bromophenyl)-4(1*H*)-pyridinone (40). A mixture of pyrone ester **16** (0.97 g, 3.0 mmol), aminoacetonitrile hydrochloride (0.33 g, 3.6 mmol), NaOAc (0.5 g), and MeCN (10 mL) was refluxed for 1 h, resulting in conversion to a less polar, yellow substance. Standard workup in CH_2Cl_2–H_2O gave, after evaporation, an oil, which was refluxed for 4 h in HOAc (10 mL). The solution was cooled, diluted, and extracted with CH_2Cl_2, and the extracts were washed (H_2O, then

$NaHCO_3$(aq)), dried, and evaporated. SG chromatography (20% Me_2CO–CH_2Cl_2) gave the *pyridinone* **40** (0.80 g, 67%) as a yellow powder, mp 188–189 °C: ^1H NMR δ 1.39 (t, 3 H, J = 7 Hz), 4.38 (q, 2 H, J = 7 Hz), 4.60 (AB, 2 H, J = 17 Hz), 6.43 (s, 1 H), 7.50 (m, 3 H), 7.74 (d, 1 H, J = 6 Hz), 8.36 (s, 1 H). Anal. Calcd for $C_{16}H_{13}BrN_2O_3$: C, 53.20; H, 3.63; N, 7.76. Found: C, 53.44; H, 3.65; N, 7.74.

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Notes

Effect of Water on Solid–Liquid Phase-Transfer Reaction of Activated Aryl Halides with Nitrite Salts and Change in Course of Reaction

Nishi Bhati, Arvind Kabra, Chander K. Narang,* and Nawal K. Mathur

Department of Chemistry, University of Jodhpur, Jodhpur 342 001, India

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Activated aryl halides undergo a variety of nucleophilic substitution reactions in homogeneous[1] and phase-transfer catalyzed conditions.[2] Nitrite ion as a Nu has been used for substitution in alkyl and aryl halides under SLPTC conditions using crown ether as PTC.[3] Dehmlow et al.[4] and Sasson et al.[5-7] have reported that with quaternary ammonium salts as PTC a trace amount of water is essential and the rate of reaction is a function of the amount of water in SLPTC reactions. The kinetics of the overall reaction depends on the relative solubilities[5,8] of the attacking Nu (Y^-) and the displaced ion (X^-) in the solid (eqs 1 and 2).[9]

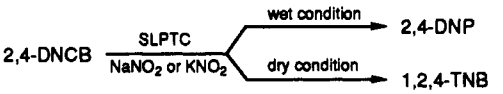
$$-d(RX)/dt = k_2(RX)(QY)_{org} \quad (1)$$

$$(QY)_{org} = (QX)_{org}K_{Y/X}^{Sel}(Y^-)_{aq}/(X^-)_{aq} \quad (2)$$

In this paper, we report the formation of 1,2,4-TNB and 2,4-DNP from 2,4-DNCB at different water contents in the system (Scheme I). Therefore, in this reaction, not only rate constants varied with the water content of system but also a change in course of reaction was observed.

Nitrite ion is a poor Nu due to its high solvation in LLPTC, in contrast to when it is used in SLPTC conditions.[3] Conventionally, the nitro group is introduced in the benzene nucleus either by electrophilic substitution[10] or by free-radical substitution of a diazonium group,[11] and not by nucleophilic substitution. Since an activated aryl

Scheme I



nitro group is also a good nucleofuge,[12] it can also be hydrolyzed after its substitution in the presence of an aqueous environment. However, use of apolar aprotic solvent in the presence of a trace amount of water minimizes the possibility of its hydrolysis. Therefore, the nitro group is likely to stay once it is introduced in the benzene nucleus. We have prepared 1,2,4-TNB and *o*-dinitrobenzene by carrying out displacement of chlorine in 2,4-DNCB and *o*-chloronitrobenzene, respectively, by NO_2^- in toluene containing BTEAC and solid KNO_2 or $NaNO_2$ under "dry" SLPTC conditions.[13]

If the water content of the system was increased in the previous reaction, i.e., in "wet" SLPTC conditions, 2,4-DNP and *o*-nitrophenol, respectively, were formed after 5 h of heating at 70 °C. In these reactions, $NaHCO_3$ was used as an acid scavenger. Conventionally, these hydrolysis reactions are carried out in 20% Na_2CO_3 solution at 130 °C for 24 h.[14] Thus, under PTC conditions, the rate was enhanced. It has been observed by TLC and UV spectra that there was no simultaneous formation of 1,2,4-TNB and 2,4-DNP at any water content. Therefore, once 2,4-DNP started forming, water generated by neutralization of HCl by $NaHCO_3$ not only leveled the concentration of water in the organic phase but also kept the reaction moving in a forward direction. The formation of nearly 86% product in the reaction mixture using nearly 0.5 mol of water per mole of 2,4-DNCB supported the earlier contention. Of course, total water is not available as a Nu due to its partitioning between the organic and solid phase.

2,4-DNP was also formed when a 20% aqueous solution of KNO_2, $NaNO_2$, $NaHCO_3$, Na_2CO_3, or KCl was used under LLPTC conditions. But when 20% $NaClO_4$ was used, 2,4-DNP was not formed. ClO_4^- ion, being a lipophilic anion, carried almost negligible water into the organic phase. Therefore, higher reaction time for such reactions without using PTC can be attributed to the poor miscibility of reactants. It has also been reported[15] that, although water is a weak Nu, it can hydrolyze benzyl and allyl halides in certain solvents, e.g., hexamethylphosphoric triamide and *N*-methyl-2-pyrrolidone. This suggested that water when finely dispersed in a nonpolar aprotic solvent

(1) Bunett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273. Weaver, W. M. *The Chemistry of nitro and nitroso groups Part II*; Wiley-Interscience: New York, 1970; pp 1–48.
(2) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*, 2nd ed.; Verlag Chemie: Weinheim, 1983; pp 199–202.
(3) Zubrick, J. W.; Dunbar, B. I.; Durst, H. D. *Tetrahedron Lett.* **1975**, *71*. Sane, P. V.; Sharma, M. M. *OPII* **1988**, *20*, 598.
(4) Dehmlow, E. V.; Raths, H. C. *J. Chem. Res., Miniprint* **1988**, 2901.
(5) Arrad, O.; Sasson, Y. *J. Am. Chem. Soc.* **1988**, *110*, 185.
(6) Sasson, Y.; Zahalka, H. A. *J. Chem. Soc., Chem. Commun.* **1984**, 1652.
(7) Sasson, Y.; Weiss, M.; Loupy, A.; Bram, G.; Pardo, C. *J. Chem. Soc., Chem. Commun.* **1986**, 1250.
(8) Sasson, Y.; Weiss, Y. M. *Isr. J. Chem.* **1985**, *26*, 243.
(9) Stark, C. M.; Liotta, C. *Phase Transfer Catalysis Principles and Technique*; Academic Press: New York, 1978; Chapter 2.
(10) Schofield, K. *Aromatic Nitration*; Cambridge University Press: Cambridge, 1980.
(11) Bagal, L. I.; Pevzner, M. S.; Frolov, A. N. *J. Org. Chem. USSR (Engl. Trans.)* **1969**, *5*, 1767.
(12) Beck, J. R. *Tetrahedron* **1978**, *34*, 2057.
(13) Mathur, N. K.; Menaria, K. L.; Narang, C. K. *Chem. Educ.* **1989**, April–June, 37.
(14) Furniss, B. S.; Hannatord, A. J.; Rogers, V.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 4th ed.; Longman: Essex, 1978; p 740.
(15) March, J. *Advanced Organic Chemistry*: Wiley: New York, 1985; p 326. Huchins, R. O.; Taffer, I. M. *J. Org. Chem.* **1985**, *26*, 263.

0022-3263/91/1956-4967$02.50/0