Reformatsky Reaction on Aroylketene *S,N*-Acetals: A Facile Route to 4-Amino-6-aryl-2*H*-pyran-2-ones[1]

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The aroylketene *S,N*-acetals **1a–j** are shown to undergo regioselective conjugate 1,4-addition with Reformatsky reagent derived from ethyl bromoacetate, followed by cyclization to give novel 4-amino-6-aryl-2*H*-pyran-2-ones **3a–j** in good yields.

Although Reformatsky reaction has been extensively used in new C–C bond formation reactions on carbonyl compounds involving 1,2-additon,[2–5] the examples of 1,4-conjugate additions to α,β-unsaturated carbonyl compounds are very few. Only the reagents derived from α-bromopropionate and α-bromobutyrate/isobutyrate are known to undergo either partial or exclusive 1,4-additions,[6–7] while there is no record of conjugate addition with Reformatsky reagent from ethyl bromoacetate. We have recently reported[8] that aroylketene dithioacetals undergo Reformatsky reaction with ethyl bromoacetate to yield novel 3-substituted-1,1-bis(methylthio)-4-ethoxycarbonyl-1,3-butadienes by exclusive 1,2-addition.

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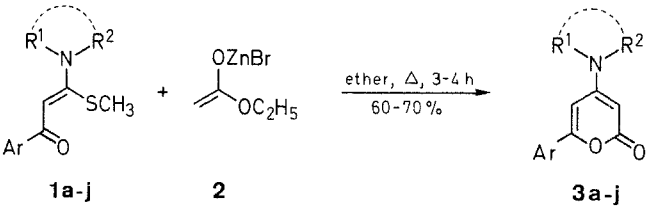
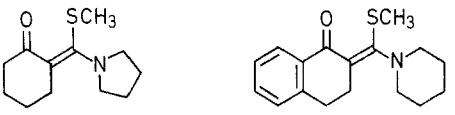
However, when the corresponding aroylketene *S,N*-acetals **1** were reacted with the same reagent **2** under identical conditions, the title pyrones **3** were obtained in good yields by initial 1,4-addition of **2** to **1**. The results of these studies are reported in this communication.

When **1a** was reacted with **2** in refluxing ether/benzene, the reaction mixture after work-up yielded a colorless solid, which was characterized as 4-morpholino-6-phenyl-2*H*-pyran-2-one **(3a)** on the basis of its spectral and analytical data (Table). The acidic hydrolysis of **3a** gave the corresponding α-benzoylacetone in 72% yield, thus ruling out the possible 6-morpholino-4-phenyl-2*H*-pyran-2-one as an alternate structural isomer, which would be formed by 1,2-addition of **2** on **1a**. The reaction was found to be general with other substituted *S,N*-acetals **1b–j**, which yielded the corresponding 4-aminopyrones **3b–j** in 60–72% overall yields. However, attempted reaction of cyclic *S,N*-acetals 1k and **1l** with **2** under identical conditions yielded only complex mixture of products (Scheme **A**). Similarly the reaction of Reformatsky reagent from ethyl α-bromopropionate with **1a** did not afford any identifiable product.

The probable mechanism for the formation of **3** from **1** and **2** is depicted in Scheme **B**. The Reformatsky reagent **2** undergoes 1,4-addition to **1** followed by elimination of methylthio group to give the intermediate adduct **6** which on subsequent cyclization assisted by lone pair of nitrogen gives the products **3**. The α-oxoketene *S,N*-acetals behave in this reaction like enaminones, which are known to undergo conjugate 1,4-ad-



1a-j **2** **3a-j**



1k **1l**

1, 3	Ar	R^1	R^2
a	C_6H_5	$-(CH_2)_2O(CH_2)_2-$	
b	4-ClC_6H_4	$-(CH_2)_2O(CH_2)_2-$	
c	4-$CH_3C_6H_4$	$-(CH_2)_2O(CH_2)_2-$	
d	4-$CH_3OC_6H_4$	$-(CH_2)_4-$	
e	4-ClC_6H_4	$-(CH_2)_4-$	
f	4-$CH_3C_6H_4$	$-(CH_2)_4-$	
g	4-ClC_6H_4	$-(CH_2)_5-$	
h	C_6H_5	CH_3	CH_3
i	4-ClC_6H_4	CH_3	CH_3
j	4-$CH_3OC_6H_4$	CH_3	CH_3

Scheme **A**

Table. 4-Amino-6-aryl-2*H*-pyran-2-ones **3a–j** Prepared

Product	Yield[a] (%)	mp (°C)	Molecular Formula[b]	IR (KBr)[c] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$)[d] δ, J(Hz)	MS (70 eV)[e] *m/z* (%)
3a	65	238	$C_{15}H_{15}NO_3$ (257.3)	1680, 1630	3.41 ((t, 4H, NCH_2); 3.83 (t, 4H, OCH_2); 5.30 (d, J = 2, 1H, H-3); 6.51 (d, J = 2, 1H, H-5); 7.45–7.90 (m, 5H_{arom})	257 (M^+, 55); 229 (44)
3b	68	249–250	$C_{15}H_{14}ClNO_3$ (291.7)	1689, 1629	3.25 (t, 4H, NCH_2); 3.70 (t, 4H, OCH_2); 5.22 (d, J = 2, 1H, H-3); 6.35 (d, J = 2, 1H, H-5); 7.22–7.55 (dd, A_2B_2, 4H_{arom})	293, 291 (M^+, 35, 100); 247 (68)
3c	60	224–225	$C_{16}H_{17}NO_3$ (271.3)	1690, 1622	2.40 (s, 3H, CH_3); 3.40 (t, 4H, NCH_2); 3.81 (t, 4H, OCH_2); 5.33 (d, J = 2, 1H, H-3); 6.45 (d, J = 2, 1H, H-5); 7.20–7.82 (dd, A_2B_2, 4H_{arom})	271 (M^+, 100); 243 (46)
3d	72	205–206	$C_{16}H_{17}NO_3$ (271.3)	1677, 1630	1.81 (m, 4H, CH_2); 3.20 (m, 4H, NCH_2); 3.74 (s, 3H, OCH_3); 4.67 (d, J = 2, 1H, H-3); 6.01 (d, J = 2, 1H, H-5); 6.72–7.70 (dd, A_2B_2, 4H_{arom})	271 (M^+, 100); 243 (76)
3e	72	227	$C_{15}H_{14}ClNO_2$ (275.8)	1678, 1632	2.11 (m, 4H, CH_2); 3.4 (m, 4H, NCH_2); 4.95 (d, J = 2, 1H, H-3); 6.35 (d, J = 2, 1H, H-5); 7.30–7.85 (dd, A_2B_2, 4H_{arom})[f]	277, 275 (M^+, 18, 53); 247 (54)
3f	66	207–208	$C_{16}H_{17}NO_2$ (255.3)	1679, 1632	1.91 (m, 4H, CH_2); 2.34 (s, 3H, CH_3); 3.30 (m, 4H, NCH_2); 4.82 (d, J = 2, 1H, H-3); 6.22 (d, J = 2, 1H, H-5); 7.0–7.70 (dd, A_2B_2, 4H_{arom})	255 (M^+, 100); 227 (81)
3g	69	202–203	$C_{16}H_{16}ClNO_2$ (289.8)	1692, 1629	1.72 (br s, 6H, CH_2); 3.41 (m, 4H, NCH_2); 5.15 (d, J = 2, 1H, H-3); 6.50 (d, J = 2, 1H, H-5); 7.32–7.82 (dd, A_2B_2, 4H_{arom})	291, 289 (M^+, 27, 85); 261 (78)
3h	62	178–179	$C_{13}H_{13}NO_2$ (215.3)	1680, 1635	3.11 (s, 6H, NCH_3); 5.13 (d, J = 2, 1H, H-3); 6.40 (d, J = 2, 1H, H-5); 7.40–7.91 (m, 5H_{arom})	215 (M^+, 100); 187 (73)
3i	65	200	$C_{13}H_{12}ClNO_2$ (249.7)	1680, 1639	3.12 (s, 6H, NCH_3); 5.24 (d, J = 2, 1H, H-3); 6.52 (d, J = 2, 1H, H-5); 7.41–7.90 (dd, A_2B_2, 4H_{arom})	251, 249 (M^+, 31, 64); 221 (84)
3j	60	188–189	$C_{14}H_{15}NO_3$ (245.3)	1675, 1623	3.10 (s, 6H, NCH_3); 5.03 (d, J = 2, 1H, H-3); 6.33 (d, J = 2, 1H, H-5); 6.85–7.81 (dd, A_2B_2, 4H_{arom})	245 (M^+, 32); 217 (23)

[a] Yield of pure isolated product.
[b] Satisfactory microanalyses obtained: C ± 0.13, H ± 0.22, N ± 0.31.
[c] Recorded on Perkin-Elmer 297 spectrophotometer.
[d] Recorded on Varian EM-390 spectrometer.
[e] Recorded on Jeol JMS D-300 spectrometer.
[f] ^{13}C-NMR ($CDCl_3$): δ = 24.86 ($\underline{C}CH_2$); 47.56 (NCH_2); 82.35 (C-3); 95.47 (C-5); 126.39, 129.10 ($\underline{C}H$, aryl); 130.58, 136.30 (C-1′, C-4′, aryl); 155.55 (C-4); 158.09 (C-6); 163.38 (C=O).

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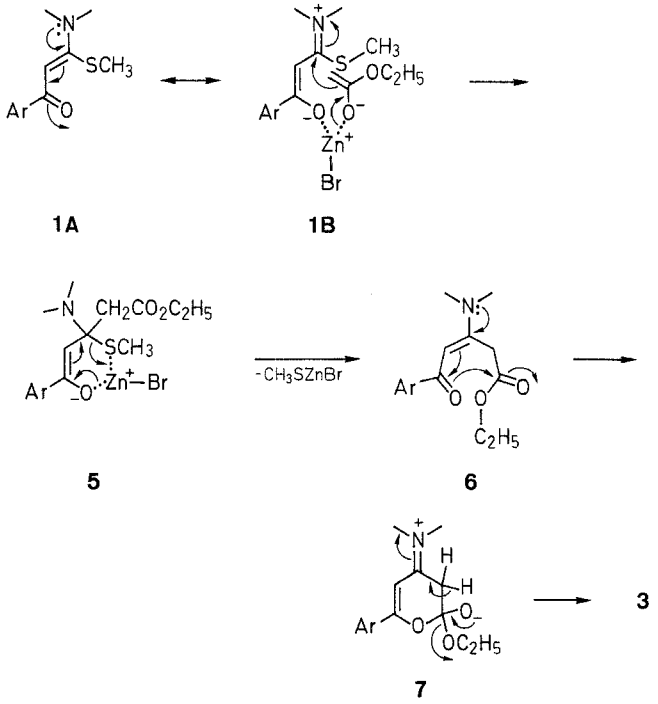
dition with organometallic reagents.[9] The difference in the behavior of aroylketene *S,S*-acetals and **1** towards **2** to give 1,2- and 1,4-addition products respectively could be attributed to the reduced electrophilic character of carbonyl group in **1** due to delocalization of lone pair of nitrogen (structure **1B**) with concomitant relative increase in electrophilic character of β-carbon. However, it has been pointed out that such a delocalization of sulphur lone pair in ketene dithioacetals is not significant, since it requires a relatively unfavorable overlap of sulphur 3p orbitals with carbon 2p orbitals.[10]



Scheme **B**

The reaction provides a facile entry to hitherto unreported 4-amino-6-aryl-2*H*-pyran-2-ones. A few of the 4-amino-6-methyl-2*H*-pyran-2-ones have been reported in the literature which are obtained either through the reaction of ketene *O,N*- or *N,N*-acetals with excess of ketene[11] or by condensation of 4-dimethylamino-3-penten-2-one with trichloroacetyl chloride followed by cyclization in presence of piperidine.[12] Also, the condensation of β-diethylaminocrotonate and benzoyl chloride is reported to yield the corresponding 3-benzoyl-4-diethylamino-6-phenyl-2*H*-pyran-2-one.[13]

The desired aroylketene *S,N*-acetals were prepared according to the earlier reported procedure.[14]

4-Dimethylamino- 4-Morpholino- 4-Piperidino- and 4-(1-Pyrrolidinyl)-6-aryl-2*H*-pyran-2-ones 3a–j: General Procedure:

A suspension of activated zinc (heated at 100–110°C for 1 h) (2.6 g, 0.04 g atom), ethyl bromoacetate (3.18 g, 0.02 mol) and a few crystals of iodine in dry ether (30 mL) is refluxed for 45 min with stirring. A solution of the respective aroylketene *S,N*-acetal **1** (0.01 mol) in dry benzene (50 mL) is added dropwise with stirring and the mixture is further refluxed for 3–4 h. The mixture is then poured over ice-cold dilute 3% H_2SO_4 (100 mL), the organic layer separated and the aqueous layer extracted with EtOAc (50 mL). The combined extract is washed with water (100 mL), dried (Na_2SO_4) and the solvent evaporated to give crude pyrones **3**, which are further purified by passing through neutral alumina column. Elution with EtOAc/hexane (1:4) yields the pure pyrones **3a–j** which are crystallized from EtOAc/hexane (Table).

Hydrolysis of 3a; Typical Procedure:

A suspension of pyrone **3a** (0.25 g, 0.001 mol) in dilute 10% HCl (10 mL) is heated with stirring at 70–80° for 1 h. The mixture is then diluted with water (25 mL) and extracted with ether (2 × 50 mL) and the combined extract is washed successively with dilute 20% $NaHCO_3$ solution (100 mL) and water (100 mL), dried (Na_2SO_4) and evaporated to give a viscous liquid, which is chromatographed on silica gel column. Elution with hexane gives *benzoylacetone*; yield: 0.1 g (72%); mp 58–59°C (Lit.[15] mp 61°C) (superimposable IR and ^{1}H-NMR spectra).

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(2) Rathke, M.W. *Org. React.* **1975**, *22*, 423.
(3) Dekker, J., Boersma, J., van der Kerk, G.J.M. *J. Chem. Soc. Chem. Commun.* **1983**, 553, and references cited therein.
(4) Harada, T., Mukaiyama, T. *Chem. Lett.* **1982**, *161*.
(5) Orsini, F., Pelizzoni, F., Ricca, G. *Tetrahedron Lett.* **1982**, *23*, 3945.
(6) Nützel, K., in: *Houben-Weyl*, Vol XIII/2a, Georg Thieme Verlag, Stuttgart, 1973, pp. 826–827.
(7) Gandolfi, C., Doria, G., Amendola, M., Dradi, E. *Tetrahedron Lett.* **1970**, 3923.
(8) Apparao, S., Datta, A., Ila, H., Junjappa, H. *Synthesis* **1985**, 169.
(9) Greenhill, J.V. *Chem. Soc. Rev.* **1977**, *6*, 277.
(10) Carey, F.A., Neergaard, J.R. *J. Org. Chem.* **1971**, *36*, 2731; and references cited therein.
(11) Hasek, R.H., Gott, P.G., Martin, J.C. *J. Org. Chem.* **1964**, *29*, 2513.
Opitz, G., Zimmermann, F. *Chem. Ber.* **1964**, *97*, 1266.
(12) Bohme, H., Tränka, M. *Liebigs Ann. Chem.* **1985**, 149.
(13) Lauer, W.M., Cromwell, N.H. *J. Am. Chem. Soc.* **1942**, *64*, 612.
(14) Vishwakarma, J.N., Apparao, S., Ila, H., Junjappa, H. *Indian J. Chem. Sect. B* **1985**, *24*, 466.
(15) *Dictionary of Organic Compounds*, 5th ed. Buckingham, J. (ed.), Chapman and Hall, New York, 1982. p. 4605.

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