

The Reaction of Enamines with  $\beta$ -Ketoesters: A Route to  $\gamma$ -Pyrones

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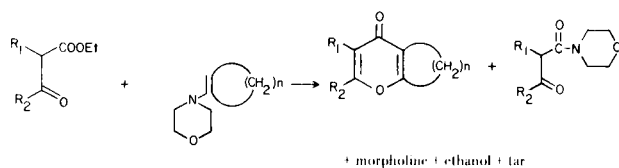
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$\beta$ -Ketoesters and enamines are found to react at elevated temperatures to give  $\gamma$ -pyrones in yields of 10 to 50%.

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The reaction enamines with ketenes (1), salicylaldehydes (2), salicylic acid derivatives (3) and  $\beta$ -ketoacid derivatives (3) has been reported to afford  $\gamma$ -pyrones. We report here on the reaction of enamines with  $\beta$ -ketoesters at elevated temperatures. The reaction appears to be quite general, although the yields of  $\gamma$ -pyrones are highly variable.



The equimolar mixture of enamine and  $\beta$ -ketoester is refluxed for the periods shown in the Table. In several instances, xylene was employed as a solvent, with the result that longer reaction times were required. In every case, it was necessary to allow ethanol and morpholine to distil slowly from the reaction vessel in order for the reaction to proceed to completion.

The resultant reaction mixture contains the pyrone, the morpholide of the starting ketoester, and varying amounts of tar. The pyrone is isolated by treating the reaction mixture with saturated aqueous sodium bisulfite. This treatment hydrolyzes the morpholide and precipitates the bisulfite addition product of the decarboxylated ketone. Filtration of the mixture and thorough washing of the residue with ether or chloroform gives the crude pyrone in solution. Alternatively, the reaction mixture may be distilled and the distillate treated with bisulfite to liberate the pyrone. The results of several such runs are given in the Table. Isolated yields of pyrones obtained by this method range from 10 to 50%. The procedure has the obvious advantage that many  $\beta$ -ketoesters are readily available.

## EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are corrected; boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer, nmr spectra on a Jeolco Model C-60 spectrometer with chemical shifts expressed in  $\delta$  (ppm) relative to TMS as internal standard. Microanalyses were performed by Chemical Analytical Services, University of California, Berkeley, California. Unless otherwise indicated, starting materials were commercially available and were used without further purification.

$\gamma$ -Pyrone. General Procedure. Method A (No Solvent).


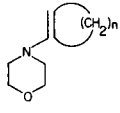
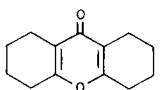
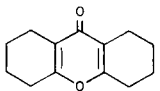
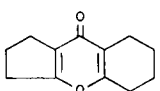
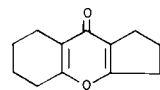
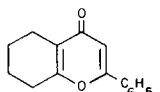
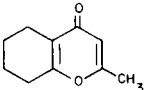
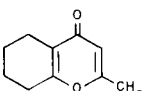
The ketoester (0.1 mole) and the enamine (0.1 mole) are combined in a suitable reaction vessel with openings protected from moisture. The mixture is heated slowly until reflux commences, and morpholine and ethanol are allowed to distil slowly from the pot. The pot temperature increases 30-40° during this heating, which requires 30-50 minutes to bring the reaction to completion. The reaction mixture is cooled and then stirred for several hours at room temperature with a mixture of 80 ml. of 40% aqueous sodium bisulfite solution and 20 ml. of 95% ethanol. (Compounds **2** and **4** prepared by this method were accompanied by substantial amounts of tar, so that vacuum distillation was performed on the reaction mixture prior to bisulfite treatment.) The resulting slurry is filtered and the residue washed thoroughly with ether giving a two phase filtrate. The filtrate is well mixed and the ethereal layer is separated, dried (anhydrous sodium sulfate), and the ether evaporated affording the crude pyrone. Recrystallization from hexane gives the pyrone in a good state of purity.

Method B (In Xylene).

The ketoester (0.1 mole) and the enamine (0.1 mole) are dissolved in 50 ml. of xylene in a set-up as described in Method A and brought to reflux. Morpholine and ethanol are allowed to distil from the reaction vessel over a period of 20-94 hours as shown in the Table. The pot temperature increases only slightly (about 5°) during this heating. After cooling, the xylene is evaporated under reduced pressure. The residue is treated with sodium bisulfite solution and further purified as described in Method A. Octahydroxanthone (**1**).

The application of Method A to 2-carbethoxycyclohexanone

Table  
Reaction of Ketoesters and Enamines

Ketoester		Enamine	Product	Reaction Temperature (°C)	Reaction Time (hours)	Yield (%)	M.p. (°C)	Lit. M.p. (°C)
								
R <sub>1</sub>	R <sub>2</sub>	n						
(CH <sub>2</sub> ) <sub>4</sub> -		4		210-250 (a)	0.8	42 (c)	130-132	132 (e)
(CH <sub>2</sub> ) <sub>4</sub> -		4		150 (b)	94	51 (c)	130-132	132 (e)
(CH <sub>2</sub> ) <sub>3</sub> -		4		220-256 (a)	.7	9.5 (d)	66-68	(f)
(CH <sub>2</sub> ) <sub>4</sub> -		3		150 (b)	20	27 (c)	68-69	(f)
H-	C <sub>6</sub> H <sub>5</sub> -	4		143 (b)	70	29 (c)	122-123	121-123 (g)
H-	CH <sub>3</sub> -	4		149 (b)	42	32 (c)	95-97	97-98 (h)
H-	CH <sub>3</sub> -	4		185-226 (a)	.6	31 (d)	95-97	97-98 (h)

(a) No solvent. (b) Xylene as solvent. (c) Bisulfite treatment of crude reaction mixture. (d) Bisulfite treatment of distilled reaction mixture. (e) Reference 4. (f) Satisfactory spectra and analysis ( $\pm 0.3\%$  C,H) have been obtained for this compound. (g) Reference 5. (h) Reference 1.

and 1-morpholinocyclohexene afforded 42% of octahydroxanthone which was recrystallized from hexane, m.p. 130-132° (lit. (4) m.p. 132°). Method B gave a 51% yield of the same material.

#### Morpholine Amide of 2-Carboxycyclohexanone.

When Method B was carried out to prepare octahydroxanthone, several recrystallizations of the crude product prior to bisulfite treatment gave a small amount of the morpholine amide of 2-carboxycyclohexanone confirming that this material was a by-product. The compound was recrystallized several times from hexane, m.p. 81-83°; ir (nujol): 5.88 and 6.08  $\mu$ ; nmr (deuteriochloroform):  $\delta$  3.7 (m, 9), 2.3 (m, 8).

*Anal.* Calcd. for  $C_{11}H_{17}NO_3$ : C, 62.53; H, 8.11; N, 6.63. Found: C, 62.41; H, 7.86; N, 6.69.

#### 2,3-Cyclohexano-5,6-cyclopentano-4-pyrone (2).

Method A was applied to 2-carbomethoxycyclopentanone and 1-morpholinocyclohexene. The cooled, dark reaction mixture was distilled prior to the bisulfite treatment, b.p. 126-148° (0.05 mm). Recrystallization from hexane gave 9.5% of the product, m.p. 66-68°; ir (nujol): 6.02 and 6.12  $\mu$ ; nmr (deuteriochloroform):  $\delta$  1.67 (m), 1.97 (m), 2.5 (m) (poor resolution and overlapping of these multiplets prevented their integration).

*Anal.* Calcd. for  $C_{12}H_{14}O_2$ : C, 75.76; H, 7.36. Found: C, 75.57; H, 7.49.

Method B was applied to 2-carbomethoxycyclohexanone and 1-morpholinocyclopentene affording 27% of the same product, m.p. 68-69°.

#### 5,6,7,8-Tetrahydroflavone (3).

Method B was applied to ethyl benzoylacetate and 1-morpholinocyclohexene affording 96% of crude 3. Recrystallization from cyclohexane gave a 29% yield, m.p. 122-123° (lit. (5) m.p. 121-123°).

#### 2-Methyl-5,6,7,8-Tetrahydrochromone (4).

Ethyl acetoacetate and 1-morpholinocyclohexene were treated according to Method B giving 32% of 4. Recrystallization from hexane gave material of m.p. 95-97° (lit. (1) m.p. 97-98°). Application of Method A gave a dark product which was distilled prior to the bisulfite treatment, b.p. 120-160° (0.1 mm). After purification and recrystallization from hexane, the product had m.p. 95-97°.

#### REFERENCES AND NOTES

- (1) S. Hünig, E. Benzing, and K. Hübner, *Chem. Ber.*, **94**, 486 (1961).
- (2) L. A. Paquette and H. Stucki, *J. Org. Chem.*, **31**, 1232 (1966).
- (3) G. V. Boyd and D. Hewson, *Chem. Commun.*, 536 (1965).
- (4) G. Gatti and C. Morandi, *J. Heterocyclic Chem.*, **5**, 145 (1968).
- (5) R. J. Light and C. R. Hauser, *J. Org. Chem.*, **25**, 538 (1960).