A New Modification of the Pechmann Reaction

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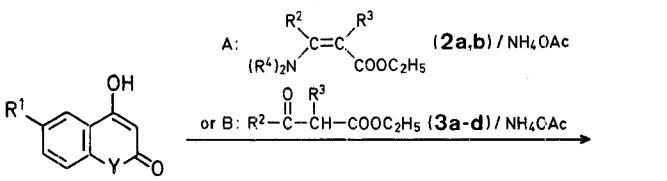
The condensation of β-keto esters with phenolic compounds in the presence of concentrated sulfuric acid yields coumarin derivatives[1]. This synthesis, known as the Pechmann reaction[2], has found extensive applications and has been used in the synthesis of many naturally occurring coumarins. So far, only acidic catalysts such as aluminium trichloride, zinc chloride, phosphoryl chloride, phosphoric acid, polyphosphoric acid, trifluoroacetic acid, and hydrochloric acid have been used.

Several years ago, we described a modification of this reaction using β-enamino esters which react with electron-rich phenols under the loss of ammonia and alcohol to yield the coumarins in excellent yields[3,4,5]. However, β-enamino esters are not always easily available from the corresponding β-keto esters.

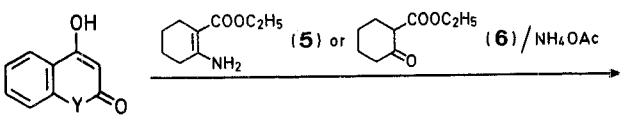
In this communication, we describe a new modification of the Pechmann reaction using β-keto esters directly and an ammonium salt as a source of ammonia. In this respect ammonium acetate proved to be most useful. As examples we report the reaction of 4-hydroxycoumarin **(1a)** and some 4-hydroxy-2-quinolones **1b-d** with β-enamino esters **2** (in such cases where these are readily available from the corresponding **3**, Method A) and with β-keto esters **3** themselves in the presence of 5 equivalents of ammonium acetate (Method B).



1a Y = O, R^1 = H
b Y = NH, R^1 = H
c Y = NH, R^1 = CH_3
d Y = NCH_3, R^1 = H

4a-i

The results are summarized and the yields compared in the Table. It should be noted that for the preparation of **4b** and **4f-h**, only the β-keto esters **3b-d** are available. In other cases the yields obtained by both methods are comparable; for the preparation of **7b**, method B gives better results. The unsubstituted compound **4e** could be obtained in 12% yield only, using ethyl β-dimethylaminoacrylate **(2b)**. All reactions with 4-hydroxycoumarin **(1a)** were carried out without a solvent at 185 °C, while reactions with 4-hydroxy-2-quinolones **1b-d** had to be performed at 200 °C in nitrobenzene as solvent.



1a,b

7a,b

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Table. Pyrones **4a–i** and **7a, b** prepared

Product No.	Y	R^1	R^2	R^3	Method[a]	Yield [%]	m.p. [°C] (solvent) crystal form	Molecular formula[b]	I.R. (KBr) ν [cm^{-1}] 2-Lactone	Lactam	C=C-Aromatic
4a	O	H	CH_3	H	A	85	242–245°[c]	$C_{13}H_8O_4$	1750 sh,	—	1620 m, 1580 w,
					B	55	(ethanol) prism	(228.2)	1730–1700 s		1610 w, 1530 m
4b	O	H	CH_3	$CH_2C_6H_5$	B	59	207–210° (AcOH) plates	$C_{20}H_{14}O_4$ (318.3)	1740–1690 s	—	1615 s, 1575 w, 1605 w, 1540 s
4c	NH	H	CH_3	H	A	75	350–355°	$C_{13}H_9NO_3$	1745 s	1660 b, s	1610 w, 1580 w,
					B	73	(DMF) needles	(227.2)			1530 m
4d	NH	CH_3	CH_3	H	A	94	319–320°	$C_{14}H_{11}NO_3$	1740 s,	1655 s	1605 w, 1535 w
					B	76	(AcOH) needles	(241.2)	1715 sh		
4e	NH	H	H	H	A	12	325–335°[d] (1-butanol) plates	$C_{12}H_7NO_3$ (213.2)	1735 s, 1710 sh	1650 s	1605 w, 1580 w, 1550 s
4f	NH	H	CH_3	$CH_2C_6H_5$	B	83	308–311°[d] (DMF) needles	$C_{20}H_{15}NO_3$ (317.3)	1715 s	1655 s	1610 w, 1540 m
4g	NH	H	C_6H_5	H	B	47	313–316°[d] (1-butanol) needles	$C_{18}H_{11}NO_3$ (289.3)	1755 s	1670 s	1615 m, 1530 m
4h	NCH_3	H	$CH_2COOC_2H_5$	H	B	29[e]	182–183° (methanol) prism	$C_{17}H_{15}NO_5$ (313.3)	1750 s, 1725 s (ester)	1670 s	1610 m, 1590 w, 1595 s
4i	NCH_3	H	CH_3	H	A	91	283–284°	$C_{14}H_{11}NO_3$	1770 sh,	1660 s	1630 w, 1590 m,
					B	79	(DMF) prism	(241.2)	1750, 1730 s		1605 m, 1550 s
7a	O	H	—$(CH_2)_3$—		A	86	212–213°	$C_{16}H_{12}O_4$	1750,	—	1620 m, 1580 w,
					B	58	(DMF) prism	(268.3)	1700 b, s		1605 w, 1545 s
7b	NH	H	—$(CH_2)_3$—		A	42	350–353°[d]	$C_{16}H_{13}NO_3$	1715 s	1645 s	1600 w, 1535 s
					B	54	(DMF) plates	(267.3)			

[a] A: Reaction with β-enaminoesters **2**; B: with β-ketoesters **3** and ammonium acetate.
[b] All new compounds gave satisfactory microanalyses (C ±0.27, H ±0.19, N ±0.24).
[c] Lit. m.p. 242 °C[8,9], 245–246 °C[10], 241–243 °C[11].
[d] With decomposition.
[e] In this reaction **4i** is also formed in 58% yield[7].

We have used the present procedure successfully with a number of electron-rich phenols and phenolic heterocycles, such as 4-hydroxy-2-pyrones and 4-hydroxypyridones, where the usual Pechmann conditions gave only poor results[6].

β-Enamino esters employed in Method A: ethyl β-aminocrotonate **(2a)**, ethyl β-dimethylaminoacrylate **(2b)**, ethyl 2-amino-cyclohexene-1-carboxylate **(5)**.

β-Keto esters employed in Method B: ethyl acetoacetate **(3a)**, ethyl 2-benzylacetoacetate **(3b)**, ethyl benzoylacetate **(3c)**, diethyl 3-oxoglutarate **(3d)**, ethyl 2-oxo-cyclohexane-1-carboxylate **(6)**.

Pechmann Reaction of 4-Hydroxycoumarin (1a) and 4-Hydroxy-2-quinolones 1b–d; General Procedures:

Method A with **1a:** A mixture of **1a** (10 mmol) and **2** (15 mmol) is heated under nitrogen in an oil bath at 185 °C under a short air condenser for 1 h. Ethanol and ammonia are liberated during the first 30 min. The reaction mixture is broken up and stirred with 4% sodium carbonate solution (150 ml) overnight to remove starting material. Recrystallization from the appropriate solvent yields the pyrones **4a, b,** and **7a** (Table).

Method A with **1b–d:** A mixture of **1b–d** (10 mmol) and **2** (15 mmol) in nitrobenzene (10–15 ml) is heated at 200 °C for 1 h. The reaction mixture is quenched with benzene (100–150 ml), the resulting material is filtered, and dried. The removal of starting material is achieved with sodium carbonate solution as described above.

Method B with **1a:** A mixture of **1a** (10 mmol), **3** (15 mmol), and ammonium acetate (50 mmol) is heated in an oil bath at 185 °C for 2 h (with **3a**) or at 200 °C for 1 h (with **3b, 6**), and worked up as described under Method A.

Method B with **1b–d:** A mixture of **1b–d** (10 mmol), **3** (15 mmol), and ammonium acetate (50 mmol) in nitrobenzene (10–15 ml) is heated at 200 °C for 1 h and then worked up as described under Method A.

Compound **4h** is prepared with **3d** using refluxing bromobenzene (15 ml) as solvent. Even under these conditions the major product (58%) is **4i**[7].

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