A New Method for the Synthesis of 2,6-Disubstituted 4(3*H*)-Pyrimidinones from Benzamidine

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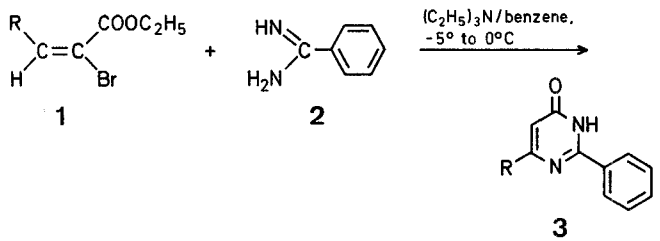
Pyrimidinones are well known as therapeutic agents. The current literature contains a considerable number of methods leading to these heterocyclic compounds[1-4] only a few of them being convenient. We report here a new easy method for the synthesis of 2,6-disubstituted 4(3*H*)-pyrimidinones under mild conditions. This cyclocondensation between 2-halo-2-alkenoic esters and amidines or isourea derivatives has not yet been described in literature. Ethyl α-bromocinnamates **(1)**, easily available in high yields, were allowed to react with benzamidine **(2)** in the presence of excess triethylamine in dry benzene at low temperature to give, within a few hours, 2,6-disubstituted 4(3*H*)-pyrimidinones **(3)** in pure form and in good yields. Our method fails with acetamidine, guanidine, and *o*-methylisourea, even in presence of potassium hydroxide as catalyst and ethanol as solvent, the starting 2-halo-2-alkenoic esters being recovered.



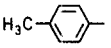
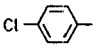
6-Substituted 4-Oxo-2-phenyl-3,4-dihydropyrimidines (3); General Procedure:

A solution of the ethyl 2-bromo-2-alkenoate **1** (25 mmol) in dry benzene (20 ml) is added dropwise to a stirred mixture of benzamidine (**2**; 4.51 g, 37.5 mmol), triethylamine (2.834 g, 28 mmol), and dry benzene (20 ml) at −5 to 0 °C. After the addition is complete the ice bath is removed and stirring is continued for 6 h at room temperature. The mixture is filtered under vacuum and the filtrate is evaporated. The residue is stirred with 25% hydrochloric acid (100 ml). The resultant aqueous solution is discarded and ether (20 ml) is added to the residue. The suspension thus obtained is filtered under vacuum, and the crude product recrystallized from dimethyl sulfoxide.

Ethyl 2-Bromo-2-alkenoates (1); General Procedure[5]**:**

To a stirred solution of the appropriate ethyl 2,3-dibromoalkanoate (0.2 mol) in chloroform (200 ml), a solution of triethylamine (22.262 g, 0.22 mol) is added dropwise at room temperature. Triethylamine hydrobromide is then filtered off, the filtrate evaporated, and the residual product distilled under reduced pressure.

Table 1. 6-Substituted 4-Oxo-2-phenyl-3,4-dihydropyrimidines [**3**, 2,6-Disubstituted 4(3*H*)-Pyrimidinones]

3	R	Yield [%]	m.p. [°C]	Molecular formula[a] or Lit. m.p. [°C]	
a	CH_3	23	219–220°	223–225°[6]	
b	C_2H_5	26	221–222°	$C_{12}H_{12}N_2O$	(200.2)
c		60	282–283°	284°[7]	
d		57	270–271°	$C_{17}H_{14}N_2O$	(262.3)
e		56	285–286°	$C_{16}H_{11}ClN_2O$	(282.8)
f		76	239–240°	$C_{16}H_{11}ClN_2O$	(282.8)

[a] The microanalysis were in satisfactory agreement with the calculated values: C, ±0.35; H, ±0.25; N, ±0.31. Exception: **3b**; (C, −0.37).

Table 2. Spectrometric Data of Compounds **3**

3	M.S. *m/e* ($M^{+\cdot}$)	I.R. (KBr) ν_{CO} [cm^{-1}]	^{1}H-N.M.R. (100 MHz, DMSO-d_6/TMS_{int}) δ [ppm]
a	186.2	1660	2.3 (d, 3H, J=0.8 Hz, CH_3); 6.2 (d, 1H, 5-H, J=0.8 Hz); 7.5–8.2 (5 H_{arom})
b	200.2	1660	1.3 (t, 3H, CH_2—CH_3); 4.2 (q, 2H, CH_2—CH_3); 6.2 (d, 1H, 5-H); 7.5–8.2 (5 H_{arom})
c	248.1	1660	6.9 (s, 1H, 5-H); 7.5–8.5 (10 H_{arom})
d	262.5	1660	6.9 (s, 1H, 5-H); 7.3–8.3 (9 H_{arom})
e	282.5	1660	6.6 (s, 1H, 5-H); 7.4–8.3 (9 H_{arom})
f	282.5	1675	6.2 (s, 1H, 5-H); 7.3–8.4 (9 H_{arom})

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[1] For reviews, see:
D. J. Brown, *The Pyrimidines*, in: *The Chemistry of Heterocyclic Compounds*, A. Weissberger, ed., Vol. 16, Interscience Publishers, New York, 1962, chapters II and III.
D. J. Brown, *The Pyrimidines*, Supplement I, Wiley-Interscience, New York, 1970, chapters II and III.
[2] W. Ziegler, E. Argyrides, A. Steiger, *Monatsh. Chem.* **102**, 301 (1971).
[3] A. V. Dean, R. C. Anderson, *Synthesis* **1974**, 286.
[4] K. A. Gupta, A. Saxena, P. C. Jain, *Synthesis* **1981**, 905.
[5] L. Wartski, C. Wakselman, *Bull. Soc. Chim. Fr.* **1972**, 1978.
[6] A. Pinner, *Ber. Dtsch. Chem. Ges.* **23**, 3820 (1890).
[7] A. Pinner, *Ber. Dtsch. Chem. Ges.* **22**, 1626 (1889).

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