Synthesis of 1-Alkyl-5-phenyl-4(1*H*)pyrimidinones

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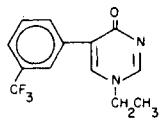
Received December 8, 1975

1-Alkyl-5-phenyl-4(1*H*)pyrimidinones are readily synthesized by condensing β-(dimethylamino)-*N*-[(dimethylamino)methylene]atropamides with methyl or ethyl amine. The latter compounds are prepared from phenylacetamides and dimethylformamide dimethyl acetal.

J. Heterocyclic Chem., 13, 605 (1976).

Davies and Piggott (1) reported the synthesis of 1-methyl-5-phenyl-4(1*H*)pyrimidinone (**2a**) by hydrolyzing the methiodide derivative of 4-amino-5-phenylpyrimidine. The yield was not given and the structural assignment was ambiguous, since the product could have been 3-methyl-5-phenyl-4(1*H*)pyrimidinone. Brown and Lee (2) reported supporting evidence for the structural assignment by examination of the ultraviolet spectra of the two possible isomers.

We required an unambiguous synthesis for the preparation of a variety of 1-alkyl-5-aryl-4(1*H*)pyrimidinones. Bredereck and co-workers (3) had described the synthesis of β-dimethylamino-*N*[(dimethylamino)methylene]atropamide (**1**, X = H) by the reaction of phenylacetamide and dimethylformamide di-(*t*-butyl)acetal. This type of intermediate appeared to be an excellent precursor for our desired pyrimidinones. Indeed, condensation of this compound with methylamine in methanol gave 1-methyl-5-phenyl-4(1*H*)pyrimidinone (**2a**), but the yield was only 20%. The reaction was, however, used for the synthesis of substituted phenyl derivatives, and the yields were in the range of 60-70% (Table II). Similarly, condensation of **1a** with ethylamine gave the 1-ethyl derivative **3** (76%). The atropamide derivatives (Table I) were prepared by heating the appropriate arylacetamide with dimethylformamide dimethyl acetal. The above synthesis represents the first unambiguous preparation of 1-alkyl-5-aryl-4(1*H*)pyrimidinones.



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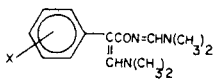
EXPERIMENTAL (4)

General Procedure for β-(Dimethylamino)-*N*-[(dimethylamino)-methylene]atropamides.

A solution containing 0.05 mole of the substituted phenylacetamide and 0.125 mole of dimethylformamide dimethyl acetal in 125 ml. of DMF was stirred and heated at 110-120° for several

Table I

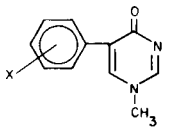
β-(Dimethylamino)-*N*-[(dimethylamino)methylene]atropamides



Compound	X	M.p. °C	Yield, %	Elemental Analysis Calcd. C	H	N	Found C	H	N
1a	3-CF_3	120-125	89	57.50	5.79	13.41	57.71	5.64	13.67
1b	3-Br	120-121	80	51.86	5.60	12.96	51.64	5.34	12.84
1c	3-Cl	116-117	72	60.10	6.49	15.02	60.29	6.20	15.21
1d	4-Cl	155-156	29	60.10	6.49	15.02	60.06	6.72	14.82

Table II

1-Methyl-5-phenyl-4(1*H*)pyrimidinones



Compound	X	M.p. °C	Yield, %	Elemental Analysis					
				Calcd.			Found		
				C	H	N	C	H	N
2a	H	175-176 (a)	20	70.95	5.41	15.04	70.69	5.17	14.89
2b	3-CF_3	155-156	71	56.70	3.57	11.02	56.44	3.66	11.02
2c	3-Br	218-219	65	49.84	3.42	10.57	49.56	3.62	10.53
2d	3-Cl	213-214	58	59.88	4.11	12.70	60.07	4.05	12.71
2e	4-Cl	220-221	62	59.88	4.11	12.70	59.60	3.96	12.73

(a) Lit. m.p. 171-172° (1)

hours, until tlc (silica gel, ethyl acetate:hexane, 1:1) showed no starting material present. The mixture was poured into ice water. The crude solid was collected and crystallized from benzene-hexane to yield the desired product (Table I).

General Procedure for 1-Methyl-5-phenyl-4(1*H*)pyrimidinones.

Methylamine was bubbled into 100 ml. of methanol for several minutes. The atropamide derivative above (20 mmoles) was added and the mixture was heated to reflux for 6 hours. The solvent was removed and the crude material was crystallized from benzene to yield the desired product (Table II).

1-Ethyl-5-phenyl-4(1*H*)pyrimidinone (**3**).

A solution of 2.0 g. of **1a** (6.4 mmoles) and 1 ml. of 20% aqueous ethylamine solution in 20 ml. of methanol was heated to reflux for 6 hours. The solvent was removed and the crude material was crystallized from ethyl acetate-hexane to yield 1.3 g. (76%) of product, m.p. 172-173°.

Anal. Calcd. for $C_{13}H_{11}F_3N_2O$: C, 58.21; H, 4.13; N, 10.44. Found: C, 58.29; H, 3.96; N, 10.48.

REFERENCES AND NOTES

(1) W. H. Davies and H. A. Piggott, *J. Chem. Soc.*, 347 (1945).

(2) D. J. Brown and T. C. Lee, *J. Chem. Soc.* (C), 214 (1970).

(3) H. Bredereck, G. Simchen, and B. Funke, *Chem. Ber.*, 2709 (1971).

(4) Melting points were determined on a Mel-Temp apparatus and are uncorrected.