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A Method of Synthesizing Pyrimidine Derivatives

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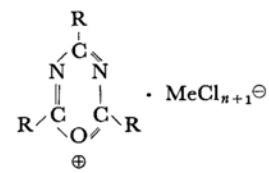
The reaction of nitriles (2 mol), 1 mol of acid chlorides, and 1 mol of metal chlorides (Lewis acids) gives 1,3,5-oxadiazin-1-ium salts (I), while I gives various heterocyclic compounds, such as *s*-triazine, triazole, and oxadiazole derivatives, when treated with ammonia, hydrazine, hydroxylamine, and urea.[1)]

The present report is concerned with the reaction of Ia with substituted acetonitriles (XCH_2CN), *i. e.*, malonitrile (X: CN), methyl cyanoacetate (X: $COOCH_3$), and benzoylacetonitrile (X: COC_6H_5).

When Ia was refluxed with each of the above-mentioned reagents under basic conditions, II, III, and IV respectively were obtained in good yields. The molecular weights of II, III and IV were

$$2RCN + RCOCl + MeCl_n \rightarrow$$



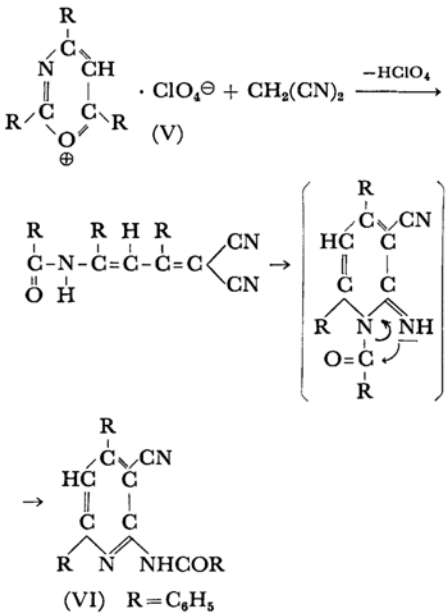
(I)

Ia: $R = C_6H_5$
$MeCl_n = SnCl_4$

1) R. R. Schmidt, *Chem. Ber.*, **98**, 334 (1965).

determined to be 376, 409, and 455 respectively by the mass spectrometric method. These results and the elementary analysis showed that these compounds are the adducts of the cation from Ia and of the anions from substituted acetonitriles. The fact that the IR spectra of these compounds were very similar to one another except for the characteristic absorptions of substituted groups of acetonitriles strongly suggests that these compounds all have a structure containing the same heterocyclic ring.

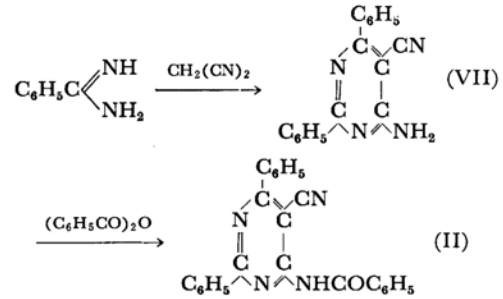
On the other hand, 1,3-oxazin-1-ium salt (V), which is regarded as a compound analogous to I, gives the acylaminopyridine derivative (VI) when treated with malononitrile;[2] the mechanism of this reaction has been proposed to be as follows;



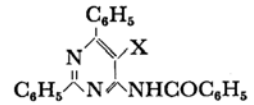
(V) (VI) $R = C_6H_5$

Therefore, it was supposed that the reaction of Ia with substituted acetonitriles would proceed in a manner similar to that of the above reaction, and that II, III, and IV would be the corresponding pyrimidine derivatives.

II was identified as follows:



4-amino-5-cyano-2,6-diphenylpyrimidine (VII) was derived from benzamidine and malononitrile,[3] and its benzoyl derivative was prepared by heating VII with benzoic anhydride. The IR and mass spectra of II were in good agreement with those of this benzoyl derivative. A mixed-melting-point determination with both samples showed no depression. It was, consequently, concluded that II was 4-benzoylamino-5-cyano-2,6-diphenylpyrimidine, and that III and IV were the corresponding pyrimidine derivatives. It was thus proved that pyrimidine derivatives are synthesized from 1,3,5-oxadiazin-1-ium salt in good yields by the treatment with substituted acetonitriles, and it was inferred that the mechanism of these reactions is similar to that of the reaction of 1,3-oxazin-1-ium salt with malononitrile.



(II), (III), (IV)

II: X = -CN
III: = -COOCH$_3$
IV: = -C$_6$H$_5$

Experimental

4-Benzoylamino-5-substituted-2,6-diphenylpyrimidine (II), (III), and (IV). To a solution of 0.002 mol of each of the substituted acetonitriles and 0.30 g of triethylamine in 10 m*l* of dioxane, 1.30 g of Ia were added, and then the mixture was refluxed for 1 hr. The solvent was distilled off under reduced pressure, and the residue was washed with dilute hydrochloric acid, aqueous sodium hydroxide, and water, and recrystallized from acetic acid (II), ethanol (III), and acetone

TABLE 1. 4-BENZOYLAMINO-5-SUBSTITUTED-2,6-DIPHENYLPYRIMIDINES

Substituent (X)		Yield (%)	Mp (°C)	Mol wt*	Elementary analysis						
					Found			Calcd for			
					C(%)	H(%)	N(%)	Fomula	C(%)	H(%)	N(%)
II	CN	95	240.5	376	76.64	4.35	14.65	$C_{24}H_{16}N_4O$	76.58	4.29	14.88
III	$COOCH_3$	86	186	409	73.18	4.84	10.21	$C_{25}H_{19}N_3O_3$	73.34	4.68	10.26
IV	COC_6H_5	66	200	455	79.11	4.50	9.35	$C_{30}H_{21}N_3O_2$	79.10	4.65	9.22

* Parent peaks of the mass spectra.

2) R. R. Schmidt, *ibid.*, **98**, 3892 (1965).
3) G. W. Kenner, B. Lythgoe, A. R. Todd and A. Topham, *J. Chem. Soc.*, **1943**, 388.

(IV) respectively. IR (II): 3240, 2210 (CN), 1671, 1559, 1475, 1380, 1269 cm^{-1}, (III): 3320, 1721 (ester), 1686, 1588, 1468, 1372, 1268, 1243 (ester) cm^{-1}, (IV): 3270, 1680, 1662 (C=O), 1559, 1478, 1382, 1277 cm^{-1}. The yield, mp, mol wt, and results of elementary analysis of these compounds are listed in Table 1.

4-Benzoylamino-5-cyano-2,6-diphenylpyrimidine (II) from VII. A mixture of 100 mg of VII and 0.5 g of benzoic anhydride was heated at 170—175°C for 30 min; the mixture was then washed with ethanol and recrystallized from acetic acid to give 105 mg of II; yield 78%; mp 240.5°C. Found: C, 76.80; H, 4.12; N, 14.82%. Calcd for $C_{24}H_{16}N_4O$: C, 76.58; H, 4.29; N, 14.88%.