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A NEW AND GENERAL PYRIDAZINE SYNTHESIS

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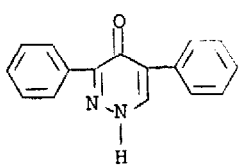
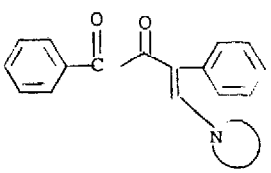
The synthesis of pyridazines may be approached from three general directions: (1) ring closure of acyclic components; (2) reactions on pyridazines themselves; and (3) the conversion of other heterocycles to the pyridazine unit[1]. We were interested in the preparation of 3,5-diaryl-4(1H)-pyridazones (I) and the corresponding thiones (I). Breslow[2], and Izzo and Kende[3], had independently prepared 3,5-diphenyl-4(1H)-pyridazone by the cycloaddition and ring-enlargement reaction between diarylcyclopropenones and diazomethane, a procedure which was self-limiting in utility owing to the hazardous nature of the reactants and their sensitivity as wel as by the difficulty of access to the starting materials. An alternate, efficient route to 4-pyridazones was therefore required and approach (1) was chosen. The mai problem of such an approach was that the candidate substrates of choice, namely hydrazine and a 1,4-dicarbonyl system, afford mixtures of required pyridazine contaminated with 1-aminopyrroles[4]. This obstacle was overcome by choosing a 1,4-dicarbonyl compound in which one "keto" group was disguised as an enamine and the on reactive center for hydrazine, or a substituted hydrazine was the unmasked carbony group. The synthesis thus centered upon the ability to prepare the intermediate (II).



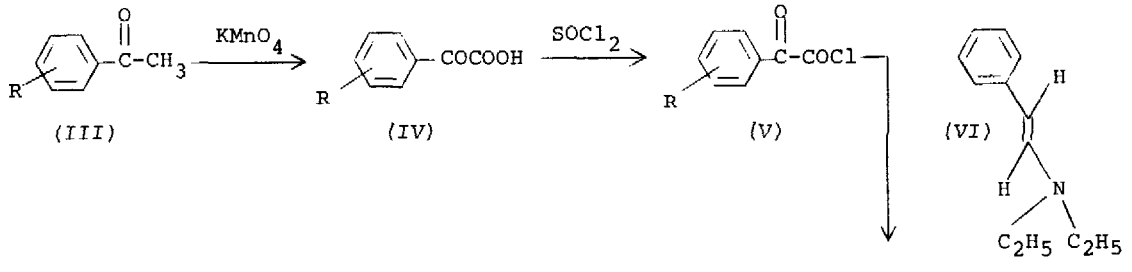
(I)



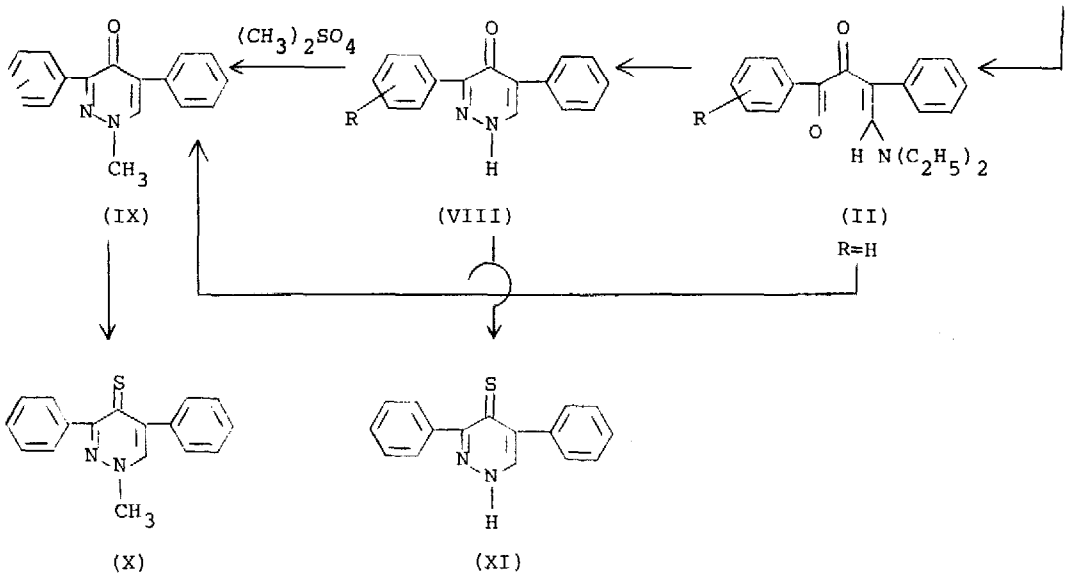
(II)

The formation of (II) was achieved in essentially quantitative yield by treating an anhydrous ether solution of diethylstyrylamine[5] with benzoylformyl chloride at 0°C, in the presence of a slight excess of triethylamine in the strict absence of moisture. The reaction was completed in 1 hr. The ether solution was filtered to remove the triethylamine hydrochloride, and the addition of anhydrous hydrazine and some 2-propanol (needed to dissolve an oily substance that separated on addition of hydrazine) gave a yellow solution which deposited a fine microcrystalline ppt of compound (I) in 60% overall yield. Ir (Nujol): $\bar{\nu}$ cm^{-1} 3185 (N-H), 1580 (C=O); NMR (CF_3COOH): δ ppm 7.58-8.08 (m, 10H) aryl groups, 9.08 (s, 1H) H_6 proton; UV: λ_{max}^{Glyme} 329 (14,766); Mass Spect: M^+ m/e 248; mp 328-332°C (Lit.[2] 326-328°C); Anal. Calcd. for $C_{16}H_{12}N_2O$, % C = 77.40, H = 4.87, N = 11.28; Found % C = 77.21, H = 5.12, N = 11.28. Table 1 lists some representative 4(1H)-pyridazones that have been made by the procedure outlined in Scheme 1. Alkylation of (I) at pH 12 using dimethylsulfate or in DMF solution using NaH/alkyl iodide was a quantitative process and afforded only the N-alkylated materials. This was proved by the unequivocal synthesis of the N-methylated derivative by reaction of the intermediate (II) with methylhydrazine which gave a product identical in all respects to the product formed by the alkylation of (I) with dimethylsulfate in aqueous alkali at 0°C. The 1-alkyl-3,5-diaryl-4(1H)-pyridazones or their corresponding unalkylated precursors were readily converted to the 4-thiones by refluxing a pyridine solution of the pyridazones with P_2S_5 for 2-4 hrs. The synthesis of the indoloid derivative (Im) was done using commercially available indole-3-glyoxylylchloride, but some of the substituted benzoylformic acids needed for the synthesis were prepared by the $KMnO_4$ oxidation of the corresponding substituted acetophenones in pyridine solution at 10°C[6].

Scheme 1



(III) (IV) (V) (VI)



The sequence described above is completely general and is the only synthesis of 4(1H)-pyridazones in which there are, in principle, no limitations on the nature of the ring substituents (the 3 or 5 substituents may be aromatic, aliphatic, or heterocyclic, as well as H). The full potential of this method is currently being explored and will be described elsewhere.

References

1. J. W. Mason and D. L. Aldous, Heterocyclic Compounds, Ed. R. N. Castle, 23 (1973), John Wiley & Sons, Inc., New York.

2. R. Breslow, T. Eicher, A. Krebs, R. A. Peterson, and J. Posner, J. Amer. Chem. Soc., 87, 1320 (1965).

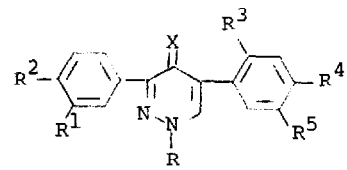
3. P. T. Izzo and A. S. Kende, Chem. Ind., 839 (1964).

4. Ref. 1, pp 28.

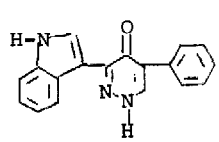
5. C. Mannich and H. Davidsen, Chem. Ber., 69, 2106 (1936).

6. J. C. Craig, J. W. Loder, and B. Moore, Australian J. of Chem., 9, 222 (1956). The procedure is essentially a variation of the method of A. Peter, Chem. Ber., 18, 537 (1885) and is attended by the concomitant formation of substantial amounts of the benzoic acid.

TABLE 1



(I)

No.	R	R^1	R^2	R^3	R^4	R^5	X	mp °C	Recryst. Solv.	NMR ppm H_6
Ia	H	H	H	H	H	H	O	328-332	DMF/Methanol	9.08 (a)
Ib	CH_3	H	H	H	H	H	O	165-167	Hexane/2-Propanol	8.53 (b)
Ic	C_2H_5	H	H	H	H	H	O	124-125	Cyclohexane	8.00 (c)
Id	n-C_3H_7	H	H	H	H	H	O	90-93	H_2O/2-Propanol	7.96 (c)
Ie	H	H	H	H	H	H	S	222-224	2-Propanol/DMF/H_2O	8.27 (b)
If	CH_3	H	H	H	H	H	S	122-123	2-Propanol/Hexane	7.50 (c)
Ig	H	H	Br	H	H	H	O	300	DMF/Methanol	8.47 (b)
Ih	CH_3	H	Br	H	H	H	O	159-160	Hexane/2-Propanol	8.60 (b)
Ii	H	H	H	NO_2	Cl	OCH_3	O	270-272	DMF/Methanol	8.63 (b)
Ij	CH_3	H	H	NO_2	Cl	OCH_3	O	224-225	Hexane/2-Propanol	8.67 (b)
Ik	H	CF_3	H	H	H	H	O	300	DMF/Methanol	8.47 (b)
Il	CH_3	CF_3	H	H	H	H	O	110-112	2-Propanol/H_2O	7.83 (c)
Im								360	DMF/2-Propanol	6.80 (b)

NMR spectra were run on a Varian T-60 spectrometer with tetramethylsilane as internal reference: (a) CF_3COOH, (b) d_6-DMSO, (c) $CDCl_3$. All of the compounds listed above had satisfactory mass spectral fragmentation data and microanalyses. Mass spectra were determined on a Consolidated Electrodynamics Corporation 110 Spectrometer at 70 ev.