1*H*-Pyrazolo[3,4-*b*]pyridines

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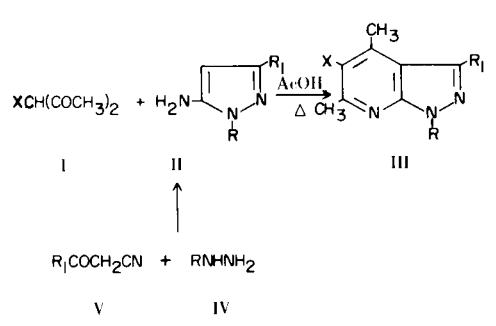
Received August 11, 1975

During the course of an investigation of purine-related compounds, it was of interest to prepare several 1*H*-pyrazolo[3,4-*b*]pyridines. The original synthesis of 1*H*-pyrazolo[3,4-*b*]pyridines as reported by Bulow (1) included the condensation of 2,4-pentanedione (I, X = H) with 5-amino-1-substituted pyrazoles (II) in glacial acetic acid (see Scheme I). This reaction was repeated with several 5-amino-3- and/or 1-substituted pyrazoles (II) to yield the desired pyrazolo[3,4-*b*]pyridines (IIIa-c).

In order to extend the versatility of this synthesis, the reaction of 3-chloro- and 3-acetoxy-2,4-pentanedione (I, X = Cl and AcO) with II was studied. These condensations took place smoothly in refluxing acetic acid to yield the compounds IIId-k. The physical constants and data for all of the pyrazolo[3,4-*b*]pyridines (III) are given in Table I.

The majority of the required 5-amino-3- and/or 1-substituted pyrazoles (II) were prepared by the procedures reported in the literature. The synthesis of 5-amino-3-phenyl-1-(2-pyridyl)pyrazole (II; R = 2-C_5H_4N, R_1 = C_6H_5) was accomplished by condensing 2-pyridylhydrazine (IV, R = 2-C_5H_4N) with benzoylacetonitrile (V, R_1 = C_6H_5) (2) (see Scheme I). In a similar manner, 5-amino-1-benzyl-3-phenylpyrazole (II, R = $CH_2C_6H_5$, R_1 = C_6H_5) (3) was prepared from V (R_1 = C_6H_5) and benzylhydrazine (IV, R = $CH_2C_6H_5$). The preparation of 5-amino-3-(2-furyl)-1-phenylpyrazole (II, R = C_6H_5, R_1 = 2-C_4H_3O) (4) was effected by condensing phenylhydrazine (IV, R = C_6H_5) with 2-furoylacetonitrile (V, R_1 = 2-C_4H_3O) (5).

Scheme I



I II III

V IV

EXPERIMENTAL

The following 5-aminopyrazoles were prepared as described in the literature: 5-amino-1-phenylpyrazole (7); 5-amino-1-benzylpyrazole (8); 5-amino-3-methyl-1-phenylpyrazole (9); 5-amino-1,3-diphenylpyrazole (9); and 5-amino-1-isopropyl-3-phenylpyrazole (10). The melting points were determined on a hot stage melting point apparatus (Fisher-Johns) and are uncorrected.

1-Isopropyl-4,6-dimethyl-3-phenylpyrazolo[3,4-*b*]pyridine (IIIb).

The general procedure for the preparation of III can be exemplified by the synthesis of IIIb. A mixture of 2,4-pentanedione (I, X = H) (20.0 g., 0.2 mole) and 5-amino-1-isopropyl-3-phenylpyrazole (II, R = $CHMe_2$, R_1 = C_6H_5) (40.2 g., 0.2 mole) was placed in a flask together with glacial acetic acid (100 ml.). The mixture was heated at reflux for four hours, cooled and filtered to yield IIIb (38.8 g.). The filtrate was diluted with water, cooled and filtered to yield a second crop of IIIb (7.8 g.). The total yield, 46.6 g., was recrystallized.

In a similar manner, compounds IIIa and IIIb were prepared from I, X = H and the appropriate II. The use of 3-chloro-2,4-pentanedione (I, X = Cl) (11) and the required II yielded IIId-h; and the use of 3-acetoxy-2,4-pentanedione (I, X = AcO) (12) afforded IIIi-k.

5-Amino-3-phenyl-1-(2-pyridyl)pyrazole (II; R = 2-C_5H_4N, R_1 = C_6H_5).

Benzoylacetonitrile (V, R_1 = C_6H_5) (2) (133.0 g., 0.92 mole) and 2-pyridylhydrazine (IV, R = 2-C_5H_4N) (100.0 g., 0.92 mole) were placed in a flask together with absolute ethanol (2000 ml.). The mixture was refluxed for four hours, cooled and filtered to yield the product, 146.0 g., m.p. 158-159°. An additional amount of material (24.0 g.) was obtained by concentrating the filtrate. The total yield was 170.0 g. (79%). An analytical sample was prepared by recrystallization from absolute ethanol, m.p. 158.5-159.5°.

Anal. Calcd. for $C_{14}H_{12}N_4$: C, 71.16; H, 5.12; N, 23.72. Found: C, 71.03; H, 5.15; N, 23.50.

In a similar manner, V (R_1 = C_6H_5) was condensed with benzylhydrazine (IV, R = $CH_2C_6H_5$) to yield II (R = $CH_2C_6H_5$, R_1 = C_6H_5) in a 98% yield, m.p. 127-128° (95% ethanol) [Lit. 129-130° (3)]. The use of phenylhydrazine (IV, R = C_6H_5) and furoylacetonitrile (V, R_1 = 2-C_4H_3O) (5) under the same conditions gave II (R = C_6H_5, R_1 = 2-C_4H_3O) in an 89% yield, m.p. 127-127.5° (benzene) [Lit. 119° (4)].

Anal. Calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.11; H, 5.12; N, 18.50.

Acknowledgment.

The author thanks Mr. Gordon Ginther, Mr. Marvin Tefft and Mr. Raymond Finch for the microanalyses. The aid of Mr.

Table I

Compound No.	X	R	R_1	Yield, %	M.p., °C	Recrystallizing Solvent	Formula	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIa	H	$CH_2C_6H_5$	C_6H_5	55	123-124	Methanol	$C_{21}H_{19}N_3$	80.48	6.11	13.41	80.41	6.14	13.32
IIIb	H	$CH(CH_3)_2$	C_6H_5	88	97.5-98	Aq. Methanol	$C_{17}H_{19}N_3$	76.94	7.22	15.84	76.67	7.19	15.55
IIIc	H	C_6H_5	2-C_4H_3O	58	135.5-136.5	Methanol	$C_{18}H_{15}N_3$	74.72	5.23	14.53	74.96	5.31	14.71
IIId	Cl	C_6H_5	H	50	112-112.5	Methanol	$C_{14}H_{12}ClN_3$	65.24	4.69	16.30 (a)	65.24	4.97	16.42 (a)
IIIe	Cl	$CH_2C_6H_5$	H	40	96.5-97	Methanol	$C_{15}H_{14}ClN_3$	66.30	5.20	13.05 (a)	66.17	5.20	13.11 (a)
IIIf	Cl	C_6H_5	CH_3	52	113.5-114	Methanol	$C_{15}H_{14}ClN_3$	66.30	5.20	13.05 (a)	66.32	5.35	13.25 (a)
IIIg	Cl	C_6H_5	C_6H_5	45	158.5-159.5	2-Propanol	$C_{20}H_{16}ClN_3$	71.96	4.83	10.62 (a)	72.00	4.77	10.77 (a)
IIIh	Cl	$CH_2C_6H_5$	C_6H_5	40	150.5-151.5	2-Propanol	$C_{21}H_{18}ClN_3$	72.51	5.21	10.19 (a)	72.51	5.34	10.28 (a)
IIIi	$OCOCH_3$	C_6H_5	H	50	143-143.5	Methanol	$C_{16}H_{15}N_3O_2$	68.31	5.38	14.94	68.14	5.50	14.88
IIIj	$OCOCH_3$	$CH_2C_6H_5$	H	48	141-142	Methanol	$C_{17}H_{17}N_3O_2$	69.13	5.80	14.23	69.00	5.92	14.50
IIIk	$OCOCH_3$	2-C_5H_4N	C_6H_5	42	230.5-231	Benzene	$C_{21}H_{18}N_4O_2$	70.37	5.06	15.63	70.52	5.13	15.51

(a) Values are for chlorine.

Frederick Abbott for the preparation of chemical intermediates and technical assistance is gratefully acknowledged.

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