NEW SYNTHETIC APPROACH TO PYRAZOLO [3,4-d] PYRIDAZIN-7(6H)-ONE RING SYSTEM

Vittorio Dal Piaz*, Giovanna Ciciani, Maria Paola Giovannoni, and Giovanni Turco
Dipartimento di Scienze Farmaceutiche dell'Università di Firenze, Via Gino Capponi 9, 50121 Firenze, Italy

Abstract-Treatment of 2,6-disubstituted 5-acetyl-4-nitropyridazin-3(2H)-ones (2a-b) with hydrazine or substituted hydrazines in alcoholic medium gives rise in high yields to new 1H- and 2H-pyrazolo[3,4-d]pyridazin-7(6H)-ones (1a-f).

A considerable number of pyrazolo[3,4-d]pyridazin-7(6H)-one derivatives displaying biological activity are reported in the recent literature . Thus type 1 compounds, besides their application in agriculture as herbicides [1], have also been synthesized and tested as analgesic and antinflammatory [2-4] agents. Furthermore pyrazolo[3,4-d]pyridazine C-nucleosides are of interest as analogues of the antitumour antibiotics formycin and showdomycin [5].

The synthetic approaches to title compound 1 have mainly consisted of ring closure of difunctionalized pyrazoles with hydrazine or substituted hydrazines [6,7]. Ring contraction of pyridazinothiadiazines [8,9] and ring transformation of isoxazolopyridazines [10] have also been reported. Recently hydrazinopyridazines have been employed as starting material to obtain the same compounds [11].Less attention has been devoted to the method founded on annelation of suitable disubstituted pyridazines [12,13].

On these grounds we proposed to verify whether the difunctionalized pyridazinones (2 a-b), easily available from isoxazolo[3,4-d]pyridazinones (3 a-b) by treatment with cerium ammonium nitrate (CAN)[14] are able to react with hydrazines to give pyrazolo[3,4-d]pyridazinones through a nucleophilic attack on C-4. In fact the nitro group of 2b is a very good leaving group and easily undergoes the substitution by primary and secondary amines without the acetyl group being affected [15].

Treatment of 2 a-b with hydrazine, methylhydrazine,and phenylhydrazine in alcoholic medium at room temperature smoothly leads to substitution of the nitro group, and pyrazolo[3,4-d]pyridazinones are formed in excellent yields as shown by analytical and spectroscopic data. The structures of 2H-pyrazolo[3,4-d]-pyridazinones (1 a-b) proposed for the products of the reaction between 2 a-b and phenylhydrazine are confirmed by their univocal synthesis starting from ethyl 4-acyl-5-methyl-1-phenylpyrazole-3-carboxylates (4 a-b) [16]; these results allow the hypothesis that the first step in the reaction of 2 a-b with substituted

hydrazines is the substitution of the nitro group by the more nucleophilic nitrogen rather then their attack at the carbonylic carbon. According to this mechanism to compounds obtained from 2a-b and methylhydrazine are assigned the structures 1e-f. This hypotesis was confirmed by the foregoing arguments .The ^{1}H-nmr spectra are consistent with the structures 1e and 1f. Thus, their spectra exhibit signals at 4.32 and 4.40 ppm which are assignable to 1-NCH_3 ; these values being in agreement with the chemical shifts of 1-methyl-1H-pyrazole[4,3-d]pyrimidine-5,7-dione [17,18] and 1-methylpyrazoles with similar chemical environment [19].On the other hand, the signal of pyrazolic NCH_3 for products related to the 2H-pyrazolo[3,4-d]pyridazin-7(6H)-one system is shifted highfield [20] .

Treatment of 2a-b with unsubstituted hydrazine gives compounds whose structures are proved to be 1c-d on the basis of the close similarity of their uv spectra with those of 1e-f; furthermore 1 c-d by treatment with methyl iodide gives 1 e-f in excellent yield. Several physical and spectroscopic data of compounds 1a-f are reported in the Table.

The method described provides a simple and rapid two-step procedure to convert isoxazolo[3,4-d]-pyridazin-7(6H)-ones into the corresponding pyrazolo[3,4-d]pyridazinones with an overall yield of 40-45%. Since the first step of the reaction is the attack of the more nucleophilic nitrogen on C-4, as showed for other nucleophilic reagents [15], the method allow to obtain 1H or 2H-pyrazolopyridazinones using as reagent, methylhydrazine or phenylhydrazine, respectively, as reagents . The direct trasformation of (3) into (1) by hydrazinolysis, previously reported in very few cases [10] , appears unfavourable.In fact treatment of 3b with phenylhydrazine or hydrazine in ethanol affords compound (5) [21] in a 60-80% yield through a reductive opening of the isoxazole ring,whereas the same reaction carried out with hydrazine at reflux for 45 min in the absence of the solvent gives a very complex reaction mixture from which we have isolated by column chromatography and identified (1d) (yield = 5 %), (5) (yield = 9 %) and the 4-cyano-1,5-dimethyl-3-phenylpyrazole (6) (yield = 12 %), arising from base promoted opening of both heterocyclic rings and rearrangement [22] .

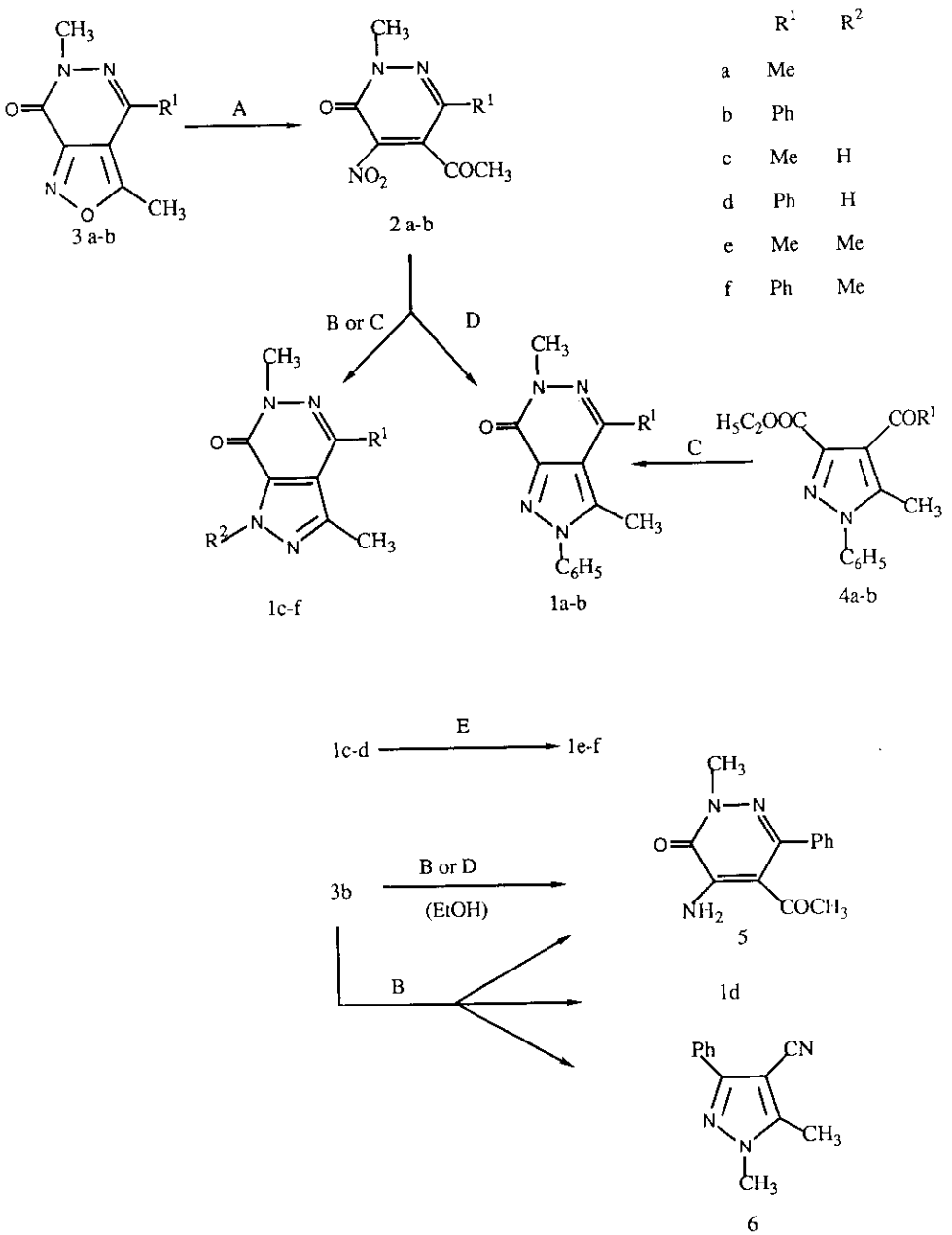
Further studies are in progress to apply these reactions to the synthesis of other hetero-condensed pyridazinones.

EXPERIMENTAL

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Ir spectra were measured for nujol mulls with a Perkin-Elmer 337 spectrophotometer . ^{1}H-Nmr spectra were recorded with either a Varian EM-360 or Perkin-Elmer R32 spectrometer ; chemical shifts are reported in ppm from internal tetramethylsilane, coupling constans in Hz; u v spectra were recorded for solutions in ethanol on a Beckman 25 spectrophotometer. Extracts were dried over sodium sulfate and solvents were removed under reduced pressure. Silica gel plates (Merk F_{254}) and silica gel 60 (Merck 70-230 mesh) were used for analytical t l c and for column chromatography respectively.

General procedure for the synthesis of compounds 1a-f

SCHEME



Reagents : A, CAN ; B, $N_2H_4 \cdot H_2O$; C, $MeNHNH_2$; D, $PhNHNH_2$; E, CH_3I

Table. Main experimental data for compounds 1a-f and 4b

Compd.	mp (°C)	Yield %	Cryst. solvent	Formula	Elemental analysis Calculated / Found C	H	N	ir $\sqrt{}$max (cm^{-1}) nujol	^{1}H-nmr (∂, ppm, $CDCl_3$)	uv λmax nm, (logε)
1a	211-13	81	EtOH	$C_{14}H_{14}N_4O$	66.13 65.98	5.55 5.79	22.03 22.41	1670 (CO)	2.55 (s, 3H, 4-CH_3), 2.67 (s, 3H, 3CH_3),3.80 (s,3H, NCH_3),7.47, (s, 5H, ArH)	
1b[a]	192-94	86	benzene + cycloexane	$C_{19}H_{16}N_4O$	72.13 72.40	5.10 5.18	17.71 17.51	1670 (CO)	2.20 (s, 3H, 3-CH_3), 3.95 (s,3H, NCH_3), 7.57 (s, 10H 2xArH)	
1c[b]	228-29	77	acetone	$C_8H_{10}N_4O$	53.92 54.03	5.66 5.77	31.44 31.26	3400-2500 br (NH) 1660 (CO)	2.61 (s, 3H, 4-CH_3), 2.66 (s, 3H, 3-CH_3), 3.87 (s, 3H, NCH_3)	264 (4.05) 280 sh (3.96)
1d	254-56	89	EtOH	$C_{13}H_{12}N_4O$	64.99 64.80	5.03 5.31	23.32 23.11	3140 (NH) 1660 (CO)	2.18 (s, 3H, 3-CH_3), 3.80 (s, 3H, NCH_3), 7.57 (s, 5H ArH), 14.3 (exch. br. s, 1H, NH)	240 sh (4.28) 276 (4.14)
1e	168-69	83	EtOH	$C_9H_{12}N_4O$	56.24 56.49	6.29 6.12	29.15 29.32	1660 (CO)	2.58 (s,3H, 4-CH_3), 2.60 (s, 3H, 3-CH_3), 3.80 (s, 3H 6-NCH_3), 4.32 (s, 3H, 1-NCH_3)	266 (4.12) 282 sh (4.05)
1f	126-28	86	EtOH	$C_{14}H_{14}N_4O$	66.13 65.97	5.55 5.71	22.03 21.87	1670 (CO)	2.12 (s, 3H, 3-CH_3), 3.87 (s, 3H, 6-NCH_3), 4.37 (s, 3H, 1-NCH_3), 7.52 (s, 5H, ArH)	232 sh (4.37) 280 (4.21)
4b	95	72	EtOH	$C_{20}H_{18}N_2O_3$	71.84 71.92	5.43 5.59	8.38 8.26	1725 (CO) 1650 (CO)	1.51 (t, J=6.5 Hz, 3H, $\underline{CH_3}$-CH_2-), 2.37 (s, 3H, 5-CH_3), 4.03 (q, J=6.5 Hz, 2H,-$\underline{CH_2}$-CH_3), 7.20-8.00 (m, 10H, 2xArH)	

[a]solvent for ^{1}H-nmr : DMSO-d_6

[b]signal of NH in ^{1}H-nmr not evident

To a suspension of 2 (1 mmol) in EtOH (5-7 ml) was added an excess of the appropriate hydrazine (3-5 mmole) and the mixture was stirred at room temperature for 20-40 min. Compounds 1a , 1d and 1e were directly recovered by suction; in the other cases the reaction mixture was diluted with water (100 ml) and extracted with ethyl acetate (3 x 70 ml) . After removal in vacuo of the solvent the crude product was crystallized from the appropriate solvent.

5-Acetyl-4-amino-2-methyl-6-phenylpyridazin-3(2H)-one (5)

a) A mixture of 3b (0.27 g , 1.1 mmol) and hydrazine hydrate (0.5 g , 10 mmol) in EtOH (4 ml) was heated under reflux for 45 min. After cooling the precipitated (5) (0.215 g , yield 80%) was collected and crystallized from EtOH . m p 202-203° C [21].

b) A mixture of 3b (0.1g, 0.4 mmol) and phenylhydrazine (0.18 g, 1.67 mmol) in EtOH (3 ml) was heated under reflux for 10 h. After removal of the solvent, treatment of the residue with ethyl acetate (5 ml) affords (5) (60 mg , yield 60 %) which was purified as above.

Ethyl 4-benzoyl-1-phenyl-5-methylpyrazole-3-carboxylate (4b)

This compound was obtained according to the method described for 4a (reference 7), starting from 1-phenylbutane-1,3-dione (1.62 g, 10 mmole) and N-phenylcarbethoxyhydrazonoyl chloride (2.3 g, 10 mmole) as pale yellow crystals.

Synthesis of 1a-b from 4a-b

Treatment of 4a (0.2 g, 0.73 mmol) in EtOH (1.5 ml) with methylhydrazine (0.15 g, 3.3 mmol) at room temperature affords 1a in 73 % yield. 1b was obtained in a 63 % yield by refluxing a mixture of 4b (0.2 g, 0.6 mmol), methylhydrazine (0.15 g, 3.3 mmol) and EtOH (2 ml) for 90 min. Both compounds are identical with the samples prepared starting from 2a-b and phenylhydrazine.

Methylation of 1c-d

To a stirred suspension of 1c-d (0.5 mmol) and anhydrous potassium carbonate (0.5 mmol) in anhydrous N,N-dimethylformamide (5 ml) methyl iodide (5 mmol) was added dropwise at room temperature. After 30 min the mixture was diluted with water (25 ml) and extracted with ethyl acetate (3x20 ml). Removal of the solvent afforded 1e-f, which were identical with the samples prepared from 2a-b and methylhydrazine.

Hydrazinolysis of 3b

A mixture of 3b (920 mg, 3.8 mmol) and hydrazine hydrate (18 ml, 349.5 mmol) was heated under reflux for 45 min. After dilution with water (150 ml), the suspension was treated with 2N HCl (pH 4.5) and extracted with ethyl acetate (3x80 ml). After removal in vacuo of the solvent, the residue was chromatographated on silica gel (70:30 ethyl acetate-cyclohexane). Compounds (1d) (yield = 5 %), (5) (yield = 9 %) and (6) (yield = 12 %) were isolated and identified by comparison with authentic samples.

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