NEW FUNCTIONALIZED PYRAZOLES FROM ISOXAZOLOPYRIDAZINONES*

Vittorio Dal Piaz and Giovanna Ciciani
Dipartimento di Scienze Farmaceutiche dell'Università di Firenze, Via Gino Capponi 9, 50121 Firenze, Italy

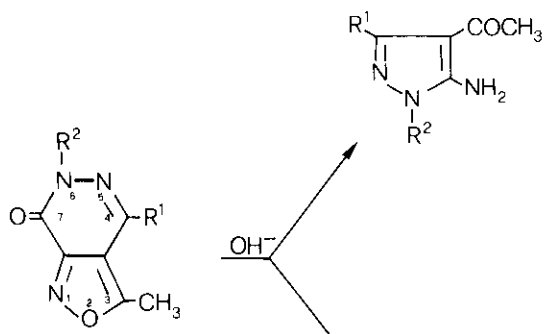
Stefano Chimichi
Centro di Studio del CNR sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni, presso l'Istituto di Chimica Organica dell'Università, Via Gino Capponi 9, 50121 Firenze, Italy

Abstract-Treatment of 3-methylisoxazolo[3,4-d]pyridazin-7(6*H*)-ones (1a-d) with dilute NaOH affords in good yields new pyrazole derivatives which can be regarded as building blocks for condensed heterocycles with potential biological activity.

Previous papers from our laboratory have dealt with the conversion of 3-(2-substituted ethenyl)isoxazolopyridazinones into 5*H*-1,2-diazepinones which under acidic conditions undergo ring transformation into pyrazoles.[1,2] We wish to call further attention here to the synthesis of new pyrazoles containing *o*-functional groups, promising intermediates to formation of condensed heterocycles with potential biological activity,[3-5] by alkaline hydrolysis of 3-methylisoxazolo[3,4-d]pyridazin-7(6*H*)-ones.

Conversion of compounds 1a-d into pyrazoles was effectively performed in basic medium but the nature of the obtained products is strictly correlated to the substituents at position 4 and 6 of the pyridazine ring.

SCHEME 1



	R^1	R^2
1a	Ph	H
1b	Ph	Me
1c	Ph	Ph
1d	Me	Ph

	R^1	R^2
2	Ph	Ph
3	Me	Ph

	R^1	R^2	R^3
4	Ph	H	CN
5	Ph	Me	CN
6	Ph	Me	$CONH_2$
7	Me	Ph	CN
8	Me	Ph	$CONH_2$

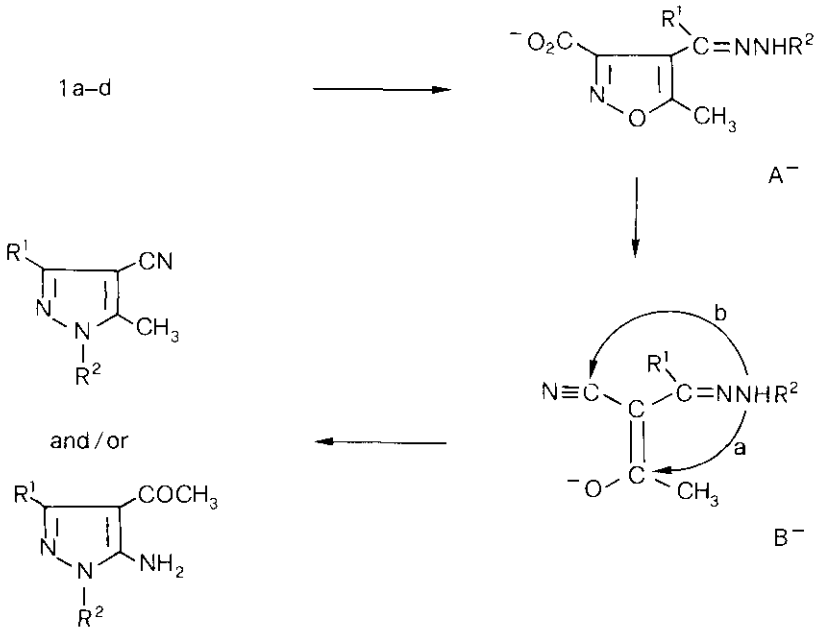
Thus, treatment of compounds 1a-b (R^1=Ph, R^2=H or Me) with dilute sodium hydroxide afforded regiospecifically the 4-cyanopyrazoles 4 and 5, respectively, whereas the isoxazolopyridazinone 1c, with $R^1 = R^2$ = Ph, gave as the sole product and in good yield (82%) the amino-ketone 2. Finally, compound 1d (R^1= Me, R^2= Ph) afforded mainly the pyrazole 3 (65%), with minor amounts of derivatives 7 and 8. Assigned structures for the new pyrazoles (2-6,8) were supported by their chemical and spectroscopic properties (see Table and Experimental) and elemental analysis data. In particular, for compounds 2,4, and 5, ^{1}H- and ^{13}C-nmr analysis of the crude reaction mixtures showed no traces of the alternative products.

Table 1. ^{1}H- and ^{13}C-nmr data ($CDCl_3$)

Compound	*^{1}H-nmr (δ: ppm)*	*^{13}C-nmr (δ: ppm)*
2	*1.99(s,3H,$COCH_3$),6.10(exch. br s,2H,NH_2),7.30-7.80 (m,10H,2xArH_5)*	*29.0(q,$CO\underline{CH_3}$),105.0(s,C-4),123.9,128.0,128.1, 128.6,129.4,129.6(d,C-arom.),133.8(s,C-ipso, 3-Ph),137.0(s,C-ipso,N-Ph),150.0(s,C-5/C-3), 152.9(s,C-3/C-5),194.0(s,CO)*
3	*2.42(s,3H,$COCH_3$/3-CH_3),2.49 (s,3H,3-CH_3/$COCH_3$),6.09 (exch. br s,2H,NH_2),7.35-7.60(m,5H,ArH_5)*	*15.6(q,3-CH_3),29.0(q,$CO\underline{CH_3}$),104.9(s,C-4),123.6 (d,C-o/m),127.75(d,C-p),129.5(d,C-m/o),136.9 (s,C-ipso),148.6(s,C-3/C-5),150.2(s,C-5/C-3), 193.05(s,CO)*
4	*2.40(s,3H,CH_3),7.32-7.60 (m,3H,ArH_3,m/p),7.73-8.00 (m,2H,ArH_2,o),11.03(exch. br s,1H,NH)*	*10.9(q,5-CH_3),89.5(s,C-4),114.5(s,CN),126.5 (d,C-o/m),129.0(d,C-m/o),129.8(d,C-p),130.0 (s,C-ipso),150.0(s,C-5/C-3),151.7(s,C-3/C-5)*
5	*2.39(s,3H,C-CH_3),3.80(s, 3H,N-CH_3),7.21-7.59(m,2H, ArH_2,o),7.80-8.09(m,3H, ArH_3,m/p)*	*10.5(q,5-CH_3),36.6(q,N-CH_3),89.3(s,C-4),115.0 (s,CN),126.8(d,C-o/m),128.6(d,C-m/o),128.9(d, C-p),130.8(s,C-ipso),146.5(s,C-3),151.45(s,C-5)*
6	*2.60(s,3H,C-CH_3),3.83(s, 3H,N-CH_3),5.38(exch. br s,2H,NH_2),7.30-7.70(m,5H, ArH_5)*	*10.8(q,5-CH_3),36.0(q,N-CH_3),111.6(s,C-4),128.65 (d,C-o,m),129.1(d,C-p),132.8(s,C-ipso),143.6 (s,C-5),149.5(s,C-3),166.0(s,CO)*
8	*2.51(s,6H,2xCH_3),5.75 (exch. br s,2H,NH_2), 7.45(s,5H,ArH_5)*	*12.2(q,5-CH_3),14.0(q,3-CH_3),113.6(s,C-4),125.4 (d,C-o/m),128.3(d,C-p),129.0(d,C-m/o),138.6(s, C-ipso),142.75(s,C-5),147,5(s,C-3),166.6(s,CO)*

A probable pathway for the ring closure to pyrazoles may be depicted as a process in which the unstable ion (A^-) decarboxylates with ring opening, as reported for 3-unsubstituted isoxazoles in alkaline medium,[6] giving rise to a reactive *cis*-cyanoenolate ion (B^-). This intermediate eventually gives the pyrazoles by intramolecular nucleophilic attack of the 1-NH group on the carbonyl carbon (route a) and/or on the cyano group (route b).

SCHEME 2



Attemps to synthesize pyrazolopyrimidines and -pyridines starting from compounds 2 and 3 are now in progress and will be shortly reported.

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 spectrometer. ^{1}H-nmr spectra were recorded with either a Varian EM-360 or a Perkin-Elmer R32 spectrometers and ^{13}C-nmr spectra with a Varian FT-80A instrument; chemical shifts are reported in ppm from internal tetramethylsilane. Extracts were dried over sodium sulfate and solvents were removed under reduced pressure. Silica-gel plates (Merck F_{254}) were used for analytical and preparative t.l.c..
Compounds 1a-d were prepared as reported in Ref. 7 and 8.
All the new compounds gave satisfactory (± 0.3%) microanalytical data (C,H,and N).

General Procedure for Hydrolysis of Compounds 1a-d

A mixture of 1a-d (2 mmoles), 2-4N NaOH (25 ml), and EtOH (10 ml) was refluxed for 2-6 h. After dilution with H_2O the reaction mixture was filtered or exhaustively extracted with chloroform.

4-Acetyl-5-amino-1,3-diphenylpyrazole (2): (y 82%); white crystals, mp 154°C (from cyclohexane); ir 3380 and 3280 (NH_2), 1620 cm^{-1} (CO).

4-Acetyl-5-amino-3-methyl-1-phenylpyrazole (3): (y 65%); yellow oil which was purified by preparative layer chromatography ($CHCl_3$); ir 3400 and 3310 (NH_2), 1630 cm^{-1} (CO); [picrate, mp 163°C (from ethanol)].

4-Cyano-5(3)-methyl-3(5)-phenylpyrazole (4): (y 70%); pale yellow crystals, mp 155°C (from benzene); ir 3240 br (NH) and 2240 cm^{-1} (CN).

4-Cyano-1,5-dimethyl-3-phenylpyrazole (5): hydrolysis of 1b gives compound 5 as the main product (yield 72%) which was separated by preparative t.l.c. with $CHCl_3$-CH_3OH (10:1 v/v) as eluent; white crystals, mp 107°C (from ciclohexane); ir 2220 cm^{-1} (CN). Treatment of compound 5 with H_2SO_4 (80%) for 42 h at 105°C afforded 1,5-dimethyl-3-phenylpyrazole-4-carboxylic acid, mp 197°C (from H_2O) [lit.[9] mp 197-198°C (from EtOH/H_2O)].

1,5-Dimethyl-3-phenylpyrazole-4-carboxamide (6): i) compound 6 is obtained (yield 9%) as by-product from the hydrolysis of 1b; ii) treatment of compound 5 with H_2SO_4 (96%) at 65°C for 2.5 h afforded the amide 6 (yield 67%); white crystals, mp 181°C (from H_2O); ir 3360 and 3170 (NH_2), 1640 cm^{-1} (CO).

4-Cyano-3,5-dimethyl-1-phenylpyrazole (7): compound 7 was obtained as by-product from the hydrolysis of 1d (yield 10%), mp 90°C (from EtOH/H_2O) [lit.[10] mp 90°C (from EtOH/H_2O)].

3,5-Dimethyl-1-phenylpyrazole-4-carboxamide (8): compound 8 was obtained as by-product from the hydrolysis of 1d (yield 10%); white crystals, mp 188°C (from ciclohexane); ir 3380 and 3190 (NH_2), 1640 cm^{-1} (CO).

ACKNOWLEDGEMENT

We are grateful for the excellent technical assistance of Miss Sandra Gallori

REFERENCES AND NOTES

• Dedicated to Prof. C. Musante on the tenth anniversary of his death.

1. V. Dal Piaz, G. Ciciani, A. Costanzo, G. Auzzi, and S. Chimichi, Heterocycles, 1984, 22, 1741.
2. G. Ciciani, V. Dal Piaz, and S. Chimichi, Heterocycles, in press.
3. R.E. Orth, J. Pharm. Sci., 1968, 57, 537.
4. W.E. Kirkpatrick, T. Okabe, I.W. Hillyard, R.K. Robins, A.T. Dren, and T. Novinson, J. Med. Chem.,1977, 20, 386.

5. P.G. Baraldi, D. Simoni, V. Periotto, S. Manfredini, and M. Guarneri, Synthesis, 1984, 148.
6. N.K. Kochetkov and S.D. Sokolov, Adv. Heterocycl. Chem., 1963, 2, 365.
7. G. Renzi and V. Dal Piaz, Gazz. Chim. Ital., 1965, 95, 1478.
8. G. Renzi and S. Pinzauti, Il Farmaco Ed. Sc., 1969, 24, 885.
9. C.A. Rojahn, Chem. Ber., 1926, 59, 607.
10. C. Musante, Gazz. Chim. Ital., 1939, 69, 523.

Received, 22nd October, 1984