CHEMISTRY LETTERS, pp. 295-298, 1986.

SYNTHESIS AND UNAMBIGUOUS ASSIGNMENT OF STRUCTURE TO PYRANO[4,3-c]PYRAZOL-4(1H)-ONES AND -4(2H)-ONES

Albert CANTOS, Pere DE MARCH, Marcial MORENO-MAÑAS,* Anna PLA, Francisco SANCHEZ-FERRANDO, and Albert VIRGILI

Departamento de Química Orgánica, Universidad Autónoma de Barcelona, Bellaterra, Barcelona, Spain

A clean synthesis of pyranopyrazolones is described. The reactions of 4-chloro-3-(1-chlorovinyl)-6-methyl-2-pyrone with arylhydrazines give pyrano[4,3-c]pyrazol-4(2H)-ones as the only identified products. However, the isomeric pyrano[4,3-c]pyrazol-4(1H)-ones have been isolated when alkylhydrazines were used. Unambiguous assignment of structure could be achieved by homonuclear $^{1}H\{^{1}H\}$ NOE determinations.

A substituted 6,7-dihydropyrano[4,3-c]pyrazol-4(1H)-one has been found to possess analgesic activity.[1] However, references concerning 4(2H)-ones and 4(1H)-ones in this series (3 and 4 respectively) are scarce, probably due to the difficult accessibility of these compounds. Perkin in 1884 described the reaction of dehydroacetic acid, 1, with phenylhydrazine, but no structure was proposed for the resulting product.[2] Later, Stollé[3] and Benary[4] studied the reactions between the same starting materials under different experimental conditions, two products being isolable. Also, the same products were formed starting from the phenylhydrazone of 1. One of them was 3,6-dimethyl-1-phenylpyrano[4,3-c]pyrazol-4(1H)-one, 4a (R = C_6H_5). It should be mentioned that Benary[4] proposed structure 4a for a product of mp 158 °C, which was incorrectly formulated by Stollé.[3] Much more recently, a French group[5] studied again the different products arising from 1 (and related pyrones) and phenylhydrazine, correcting also a structural assignment which appeared in an older report.[6] No examples of compounds 3 were mentioned in the above literature. However, a Russian group reported the reaction between the methyl

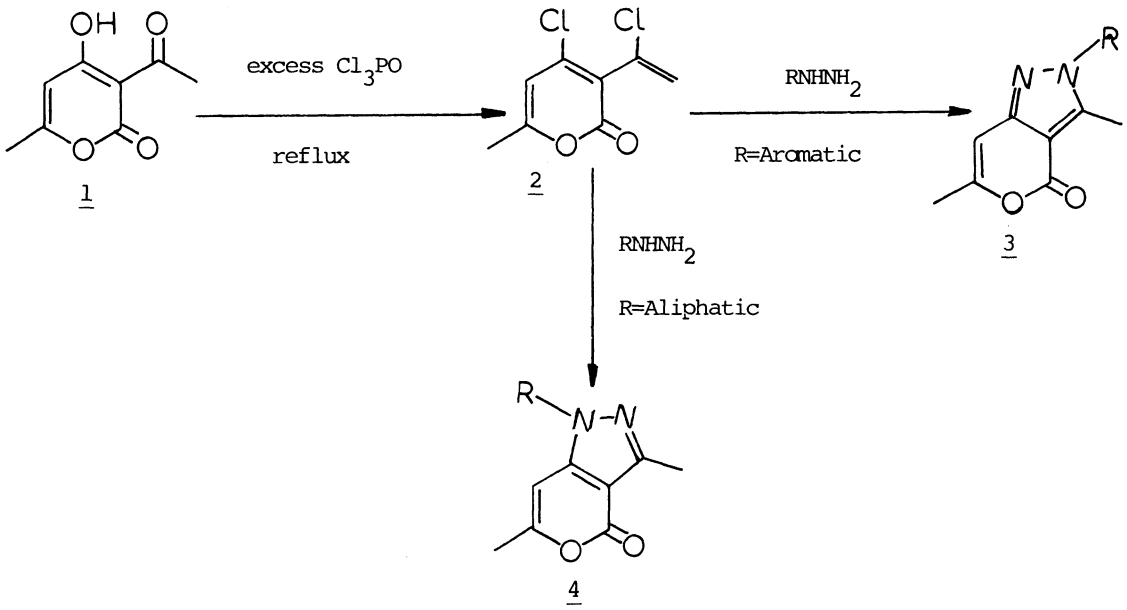

Table 1. Reaction Conditions for the Preparation of Compounds 3 and 4

Product	R	Mp/°C	Preparation method				
			Solvent	Temp	Time/h	Ratio 2:$RNHNH_2$	Yield/%
3a	C_6H_5	209-10[a]	DME	refl.	54	1:4.9[b]	53[a]
3b	4-ClC_6H_4	179-82	MeOH	refl.	91	1:3.1[c]	83
3c	4-Me-C_6H_4	172-3	MeOH	refl.	66	1:3.2[c]	58
3d	2-pyridyl	154-5	MeOH	refl.	39	1:3.1[b]	33
3e	3-CF_3-C_6H_4	156-7	MeOH	refl.	66	1:3.2[b]	76
4f	H	192-4	EtOH	refl.	1.75	1:4.1[d]	21
4g	CH_3	152-4	DME	r.t.	20	1:3.1[b]	40
4h	$HOCH_2CH_2$	144-6	MeOH	r.t.	40	1:3.6[b]	81

a) Lit,[7,8] mp 210 °C, yield: 25%.
b) Aryl- or alkylhydrazine as free base was used.
c) The arylhydrazine hydrochloride was treated in methanol with sodium acetate (1.2 equiv.), and the resulting solution was dropwise added over 2 in methanol.
d) Hydrazine hydrate (98%) was used.

ether of 1 and phenylhydrazine to produce 3,6-dimethyl-2-phenylpyrano[4,3-c]pyrazol-4(2H)-one, 3a.[7,8] Since in our hands the methyl ether of 1 is not very stable and the reactions of 1 with phenylhydrazine are quite complex, we were interested in finding a general method to prepare pyrano[4,3-c]pyrazol-4-ones and also in an

analytical method for the unambiguous assignment of their structures.

A method for the regioselective preparation of 3,5-disubstituted isoxazoles from β-substituted enones by controlling the location of the more nucleophilic center in the hydroxylamine molecule has been described.[11] We have found that the reaction of 1 with phosphorus oxychloride affords 4-chloro-3-(1-chlorovinyl)-6-methyl-2-pyrone, 2, [12] mp 100 °C, in which the C(4) carbon atom is much more electrophilic than the first carbon atom of the chain at C(3).

Table 2. Homonuclear NOE enhancements in pyrano[4,3-c]pyrazol-4-ones 3 and 4 [a]

	Irradiated protons		Enhanced protons		
Compound	Numbering	δ/ppm	Numbering	δ/ppm	η/%
3a	C_3-Me	2.8	H_{Ar}	7.5	5.3
3b	C_3-Me	2.8	H_{Ar}	7.5	5.0
3c	H_{Ar}	7.3	C_3-Me	2.75	2.5
3d	C_3-Me	3.1	none[b]		
	H_7	6.25	C_6-Me	2.3	1.6
3e	C_3-Me	2.8	H_{Ar}	7.6-7.8	4.8
4g	N_1-Me	3.9	H_7	6.15	4.4
4h	H_7	6.2	N_1-CH_2	4.1	1.7

a) Determined on 10 mM solutions of pyrano[4,3-c]pyrazol-4-ones in $CDCl_3$, using the differential technique described elsewhere.[9]

b) Results obtained using the heteronuclear NOE difference technique[10] confirm the constitution proposed for this compound. We think that the lack of homonuclear NOE on any pyridine proton can be due to a preferred conformation in which the pyranopyrazole N(1) and the pyridine N(1') are anti.

The dichloropyrone 2 reacts with aromatic hydrazines to afford 2-aryl-3,6-dimethylpyrano[4,3-c]pyrazol-4(2H)-ones, 3a-e, in reasonable yields. When aliphatic hydrazines were used, the isomeric 1-alkyl-3,6-dimethylpyrano[4,3-c]pyrazol-4(1H)-ones, 4g-h, were isolated, which is compatible with the higher nucleophilicity of the substituted nitrogen atom in alkylhydrazines.

Product 4f was not amenable to NOE determinations, but its constitution was unambiguously determined by its UV spectrum (215 nm, $\log \varepsilon = 4.33$ and 255 nm, $\log \varepsilon = 3.79$) as compared with those of 4g (218 nm, $\log \varepsilon = 4.40$ and 258 nm, $\log \varepsilon = 4.01$) and 4h (218 nm, $\log \varepsilon = 4.38$ and 259 nm, $\log \varepsilon = 3.80$).

Unambiguous assignment of structure for the fused heterocyclic systems 3 and 4

was achieved by means of homonuclear $^{1}H\{^{1}H\}$ NOE determinations as indicated in Table 2.

Correct elemental analyses were secured for all new compounds described in this report.

Financial support from "Comisión Asesora de Investigación Científica y Técnica" through project no. 2014/83 and a generous gift of dehydroacetic acid from LONZA A.G. (Basel) are gratefully acknowledged. We also thank generous funding from "Fundación María Francisca de Roviralta", which allowed the purchase of the NMR spectrometer, and "Direcció General d'Ensenyament Universitari", Generalitat de Catalunya, for the NMR data system.

References

1) S. Gelin, B. Chantegrel, and C. Deshayes, J. Heterocyclic Chem., 19, 989 (1982).

2) W.H. Perkin and C. Bernhart, Ber., 17, 1522 (1884).

3) R. Stollé, Ber., 38, 3023 (1905).

4) E. Benary, Ber., 43 1070 (1910).

5) S. Gelin, B. Chantegrel, and A.I. Nadi, J. Org. Chem., 48, 4078 (1983).

6) V.K. Makesh and R.S. Gupta, Indian J. Chem., 12, 570 (1974).

7) A.A. Akhrem, A.M. Moiseenkov, F.A. Lakhvich, V.I. Kadentsev,and O.S. Chizhov, Izv. Akad. Nauk SSSR, Ser. Khim., 1970, 1206.

8) A.A. Akhrem, A.M. Moissenkov, F.A. Lakhvich, and C.P. Smulski, Izv. Akad. Nauk SSSR, Ser. Khim., 1971, 1098.

9) M.R. Cuberes, M. Moreno-Mañas, and F. Sánchez-Ferrando, Magn. Reson. Chem., 23, 814 (1985).

10) F. Sánchez-Ferrando, Magn. Reson. Chem., 23, 185 (1985); C. Cativiela and F. Sánchez-Ferrando, Magn. Reson. Chem., 23, 1072 (1985).

11) C. Kashima, N. Yoshiwara, S. Shirai, and Y. Omote, Chem. Lett., 1982, 1455.

12) This constitution, confirmed by spectroscopic and analytical data, should be given to the "Dehydracetchlorid" reported by F. Feist; Ber., 25, 340 (1892); see also Beilsteins Handbuch der Organischen Chemie, H 17, 562 (1933).

(Received November 28, 1985)