218. Reactions with Carbo(heterylhydrazonoyl) Halides. I. Chemistry of Carbo(3-phenylpyrazol-5-yl-hydrazonoyl) Chlorides

by **Mohamed Rifaat Hamza Elmoghayar, Mohamed Hilmy Elnagdi, Mohamed Kamal Ahmed Ibrahim** and **Mohamed Mohamed Mohamed Sallam**

Chemistry Department, Faculty of Science, Cairo University, Giza, A. R. Egypt.

(9. V. 77)

Summary

The Carbo(3-phenylpyrazol-5-yl-hydrazonoyl) halides **1a,b** react with active methylene compounds to yield the 1-(3-phenylpyrazol-5-yl)-pyrazole derivatives **2a–k** (*Scheme 1*). The acyclic intermediates **3a,b** could be isolated from reaction of **1a,b** with acetylacetone, thus establishing the substitution mechanism for these reactions.

Compounds **1a,b** reacted with carbon disulfide, phenyl isothiocyanate, methyl cyanide, and with *p*-chlorobenzaldehyde to yield the corresponding heterocyclic derivatives **5–8**, respectively (*Scheme 2*).

The behaviour of compounds **2** with hydrazine hydrate is reported.

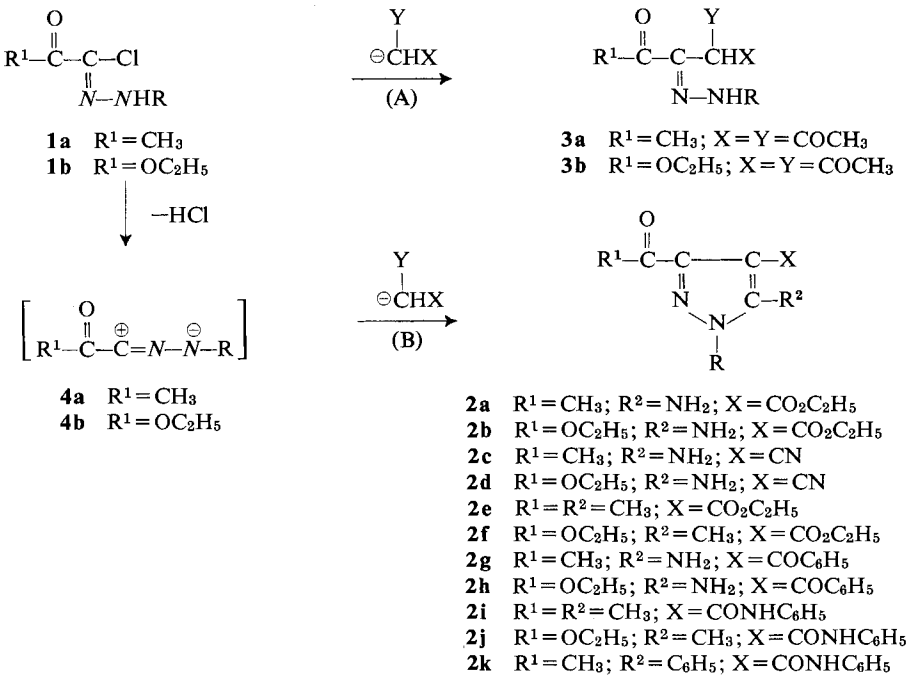
In spite of recent interest in the synthetic potentialities of carboaryl-hydrazonoyl halides [1], very little attention has been paid to the chemistry and synthetic potentialities of their heterocyclic analogues. We have already described the synthesis of carbo(3-phenylpyrazol-5-yl-hydrazonoyl) chlorides and their conversion into pyrazolo-[1,5-*c*]-1,2,4-triazoles and pyrazolo[1,5-*c*]-*as*-triazines [2]. We now report further results. When the carbo(3-phenylpyrazol-5-yl-hydrazonoyl) chlorides **1a,b** were allowed to react with an ethanolic solution of ethyl cyanoacetate, the aminopyrazole derivatives **2a,b** were obtained. The structures assigned to these products were based on the analytical data and the absence of an absorption band for the cyano group in the IR. spectra.

Similarly, compounds **1a,b** reacted with malononitrile, ethyl acetoacetate, benzoylacetonitrile, acetoacetanilide and benzoylacetanilide in ethanolic sodium ethoxide to yield the corresponding pyrazole derivatives **2c–k**. When **1a,b** reacted with acetylacetone, however, the corresponding acyclic condensation products **3a,b** were obtained.

The reaction of **1a,b** with active methylene compounds may proceed *via* two routes (*cf. Scheme 1*). The carbanion of the active methylene compounds might attack the carbohydrazonoyl halides **1a,b** to give acyclic intermediates which then undergo cyclisation under the basic reaction conditions (A). Alternatively (B), dehydrochlorination of **1a,b** may occur to yield resonance-stabilized nitrilimine intermediates **4a,b**, which might then react with the carbanion of the active methylene compound to yield the final products **2a–k**.

Scheme 1

R = 3-Phenylpyrazol-5-yl



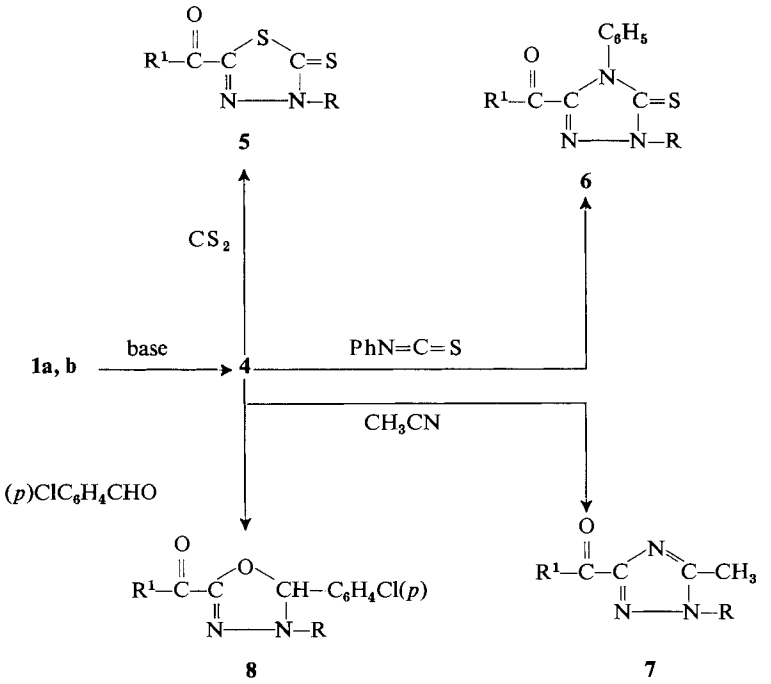
The substitution sequence A seems more likely, since we isolate and identify the acyclic intermediates in the reaction of **1a,b** with acetylacetone. Moreover, compounds **1a,b** were recovered almost unchanged after reaction with ethanolic sodium ethoxide alone. This observation does not exclude completely the nitrilimine mechanism, since there is a possibility of equilibrium between **1a,b** and the nitrilimines **4a,b** in ethanolic sodium ethoxide solution, shifted towards the final products in the presence of the active methylene compounds. The products **2a–k** could also be obtained when **1a,b** were heated with active methylene compounds in pyridine. The formation of **2a–k** under these experimental conditions can be interpreted in terms of the intermediacy of nitrilimines.

In order to throw more light on the mechanism of the reaction of **1a,b** with the carbanions of active methylene compounds, the reaction of **1a,b** with a variety of dipolar reagents was investigated. Thus, when both compounds were allowed to react with carbon disulfide, phenyl isothiocyanate, acetonitrile, and *p*-chlorobenzaldehyde in ethanolic sodium ethoxide solution, they were recovered almost unchanged. However, heating **1a,b** with these reagents in pyridine yielded addition products **5–8** (*cf. Scheme 2*). The structures proposed for compounds **5–8** are based on elemental analysis, spectral data, and analogy to the well established behaviour of nitrilimines in similar reactions [3].

That **1a,b** failed to react with dipolar reagents in ethanolic sodium ethoxide solution but reacted readily with the same reagents in refluxing pyridine might be

Scheme 2

R = 3-Phenylpyrazol-5-yl



evidence for the substitution reaction suggested for the reaction of **1a,b** with active methylene compounds.

Continuing our work for novel syntheses of fused pyrazoles (anti-inflammatory agents [4]), we synthesized some of these compounds from **2**. To our knowledge this route has never been reported. Compounds **2b,d,f,h** react with hydrazine hydrate to yield the pyrazolo[3,4-*d*]pyridazine derivatives **9a–d** (*Scheme 3*). On the other hand, compounds **2a,c,e,g** with hydrazine hydrate under the same conditions undergo acetyl cleavage, and the acyclic hydrazine derivatives **10a–d** (*Scheme 3*) were obtained. The ready cleavage of the acetyl group on treatment of compounds **2a,c,e,g** with hydrazine hydrate is similar to the ready cleavage of 4-acetylpyrazol-5-one and 5-anilino-4-pyrazoles under basic conditions [5].

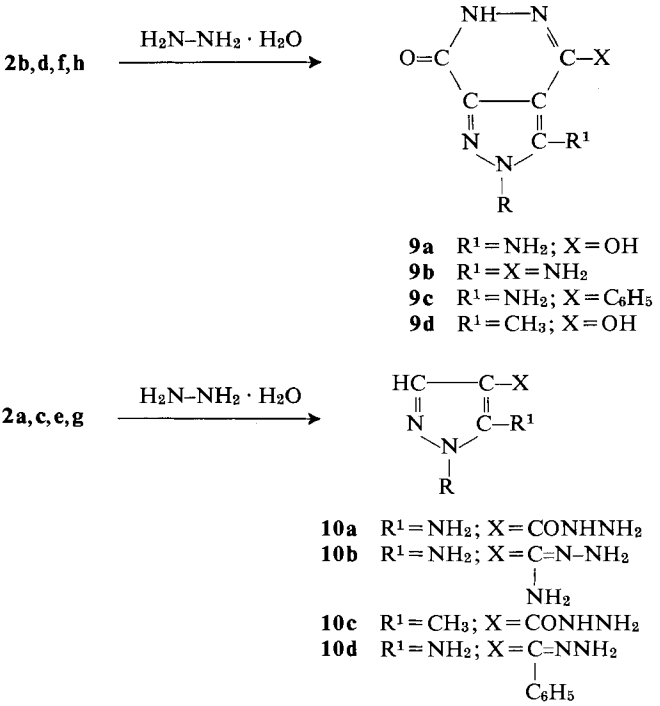
Experimental part

All melting points are uncorrected. IR. spectra were measured on a *Perkin Elmer* 337 spectrophotometer.

Reaction of **1a,b** *with active methylene compounds.* To a solution of sodium ethoxide (20 ml ethanol, 0.25 g Na) was added a suspension of the appropriate active methylene compound (0.1 mol) and **1a** or **1b** (0.1 mol) in ethanol (10 ml). The reaction mixture was kept overnight at RT., then poured into ice/water (50 ml) and acidified by dil. HCl-solution. The reaction product was collected by filtration and crystallized from ethanol (*cf. Table 1*).

Scheme 3

R = 3-Phenylpyrazol-5-yl



9a $R^1 = NH_2$; X = OH
9b $R^1 = X = NH_2$
9c $R^1 = NH_2$; $X = C_6H_5$
9d $R^1 = CH_3$; X = OH

10a $R^1 = NH_2$; $X = CONHNH_2$
10b $R^1 = NH_2$; $X = C(=NH_2)-NH_2$
10c $R^1 = CH_3$; $X = CONHNH_2$
10d $R^1 = NH_2$; $X = C(=NNHC_6H_5)$

4-(3-Phenylpyrazol-5-yl)-3-substituted-Δ^2-4-thiapyrazoline-5-thiones (**5a,b**). Carbon disulfide (2.0 ml) was added to a solution of **1a** or **1b** (0.1 mol) in pyridine (25 ml), and the mixture was heated under reflux for 2 h. The solvent was removed *in vacuo* and the residue triturated with water. The solid product was collected and recrystallized: **5a** (83%), light brown crystals from ethanol, m.p. 175°.

$C_{13}H_{10}N_4OS_2$	Calc.	C 51.66	H 3.34	N 18.54	S 21.02%
(302.24)	Found	,, 51.60	,, 3.30	,, 18.54	,, 21.00%

5b (90%), yellow crystals from ethanol, m.p. 130°.

$C_{14}H_{12}N_4O_2S_2$	Calc.	C 50.60	H 3.64	N 16.86	S 19.24%
(332.27)	Found	,, 50.50	,, 3.64	,, 16.71	,, 19.06%

4-Phenyl-1-(3-phenylpyrazol-5-yl)-3-substituted-Δ^2-1,2,4-triazoline-5-thiones (**6a,b**). Compounds **1a,b** were treated with phenyl isothiocyanate under the conditions described for reaction of **1a,b** with carbon disulfide. The products were crystallized from ethanol.

6a (83%), brown crystals, m.p. 121°.

$C_{19}H_{15}N_5OS$	Calc.	C 63.15	H 4.18	N 19.38	S 8.84%
(361.35)	Found	,, 63.25	,, 4.00	,, 19.15	,, 8.90%

6b (81%), brown crystals, m.p. 138°.

$C_{20}H_{17}N_5O_2S$	Calc.	C 61.37	H 4.38	N 17.90	S 8.16%
(391.38)	Found	,, 62.04	,, 4.10	,, 17.90	,, 7.95%

5-Methyl-1-(3-phenylpyrazol-5-yl)-3-substituted-1,2,4-triazoles (**7a,b**). Compounds **1a,b** were treated with acetonitrile under the conditions described for reaction of **1a,b** with carbon disufilde. The products were crystallized from ethanol.

Table 1. *Condensation products of* **1a,b** *with active methylene compounds*

Compound	M.p. (°)	Yield (%)	Formula	Analysis (%)		Calc. Found
				C	H	N
2a	260	70	$C_{17}H_{17}N_5O_3$	60.17 60.10	5.01 5.00	20.64 20.45
2b	110	70	$C_{18}H_{19}N_5O_4$	58.53 58.76	5.14 5.07	18.97 19.00
2c	200	85	$C_{15}H_{12}N_6O$	61.64 61.44	4.1 4.4	28.76 28.60
2d	216	85	$C_{16}H_{14}N_6O_2$	59.64 59.54	4.35 4.30	26.08 25.89
2e	190	75	$C_{18}H_{18}N_4O_3$	63.9 63.9	5.32 5.30	16.56 16.26
2f	248	75	$C_{19}H_{20}N_4O_4$	60.00 59.70	4.71 4.66	16.47 16.14
2g	195	80	$C_{21}H_{17}N_5O_2$	67.92 68.22	4.58 4.40	18.86 18.95
2h	148	70	$C_{22}H_{19}N_5O_3$	65.83 65.45	4.74 4.51	17.45 17.33
2i	185	88	$C_{22}H_{19}N_5O_2$	68.57 68.29	4.93 4.75	18.18 18.00
2j	128	75	$C_{23}H_{21}N_5O_3$	66.5 66.2	5.06 5.00	16.99 16.66
2k	145	80	$C_{27}H_{21}N_5O_2$	72.48 72.51	4.69 4.90	15.65 15.49
3a	212	60	$C_{17}H_{18}N_4O_3$	62.56 62.2	5.56 5.34	17.17 17.00
3b	265	65	$C_{18}H_{20}N_4O_4$	60.67 61.06	2.62 2.50	15.73 16.00

7a (85%), pale yellow crystals from ethanol, m.p. 176°.

$C_{14}H_{13}N_5O$ (267.28) Calc. C 62.91 H 4.90 N 26.20% Found C 62.27 H 4.87 N 26.00%

7b (76%), yellow crystals, m.p. 260°.

$C_{15}H_{15}N_5O_2$ (297.31) Calc. C 60.59 H 5.09 N 23.56% Found C 61.00 H 4.92 N 23.45%

5-p-Chlorophenyl-1-(3-phenylpyrazol-5-yl)-3-substituted-Δ²-4-oxapyrazolines (**8a,b**). Compounds **1a,b** were treated with *p*-chlorobenzaldehyde under the conditions described for reaction of **1a,b** with carbon disulfide. The products were crystallized from ethanol.

8a (86%), brown crystals, m.p. 215°.

$C_{19}H_{15}ClN_4O_2$	Calc.	C 62.2	H 4.1	N 15.27	Cl 9.68%
(366.5)	Found	,, 62.7	,, 3.9	,, 15.41	,, 9.60%

8b (90%), yellow crystals, m.p. 243°.

$C_{20}H_{17}ClN_4O_3$	Calc.	C 64.95	H 4.60	N 15.15	Cl 9.60%
(396.5)	Found	,, 64.60	,, 4.51	,, 15.30	,, 9.43%

Reaction of compounds **2** *with hydrazine hydrate.* A suspension of **2** (0.1 mol) in ethanol (50 ml) was treated with hydrazine hydrate (5.0 ml, 99%). The reaction mixture was heated under reflux for 2 h, then evaporated *in vacuo* and the residue triturated with water. The solid (**9** or **10**) was collected and recrystallized (*cf. Table 2*).

Table 2. *Reaction products of compounds* **2** *with hydrazine hydrate*

Compound	M.p. (°)	Yield (%)	Formula	Analysis (%)		Calc. Found
				C	H	N
9a	250	85	$C_{14}H_{11}N_7O$	54.3	3.5	33.44
				54.3	3.4	32.98
9b	>250	85	$C_{14}H_{12}N_8O$	54.54	3.80	36.36
				53.90	3.76	36.12
9c	115	60	$C_{15}H_{12}N_6O_2$	58.44	3.92	27.26
				58.39	3.87	27.19
9d	172	80	$C_{17}H_{15}N_7O$	61.25	4.53	29.43
				61.00	4.70	29.8
10a	165	80	$C_{13}H_{13}N_7O$	55.12	4.59	34.62
				55.4	4.28	34.26
10b	176	85	$C_{13}H_{14}N_8$	55.30	5.00	39.70
				55.16	5.40	39.60
10c	>250	75	$C_{14}H_{14}N_6O$	59.50	5.00	29.77
				59.58	4.90	29.53
10d	135	80	$C_{19}H_{17}N_7$	66.45	4.99	28.56
				66.40	5.12	28.39

REFERENCES

[1] *D. Pocar, L. M. Rossi & R. Stradi*, Synthesis *1976*, 684; *L. Garanti, A. Sala & G. Zecchi*, Synthetic Commun. *6*, 269 (1976); *K. Pilgram & R. D. Skiles*, J. org. Chemistry *41*, 3392 (1976); *A. S. Shawali, H. M. Hassaneen, M. Sami & H. M. Fahham*, J. heterocycl. Chemistry *13*, 1137 (1976).

[2] *M. H. Elnagdi, M. R. H. El-Moghayar, E. M. Kandeel & M. K. A. Ibrahim* (submitted for publication).

[3] *R. Huisgen, R. Grashey, M. Seidel, H. Knupfer & R. Schmidt*, Liebigs Ann. Chem. *658*, 169 (1962).

[4] *M. H. Elnagdi*, Tetrahedron *30*, 2791 (1974); *M. H. Elnagdi, D. H. Fleita & M. R. H. El-Moghayar*, Tetrahedron *31*, 63 (1975); *M. H. Elnagdi, M. M. M. Sallam & M. A. M. Illias*, Helv. *58*, 1944 (1975); *M. H. Elnagdi, M. R. H. El-Moghayar, E. A. Hafez, D. H. Felita & S. M. Fahmy*, J. org. Chemistry *41*, 3781 (1976); *M. H. Elnagdi, E. M. Kandeel, E. M. Zayed & Z. E. Kandeel*, J. heterocycl. Chemistry (in press); *M. H. Elnagdi, S. H. Fahmy, E. M. Zayed & M. A. M. Illias*, Z. Naturforsch. *31*, 795 (1976).

[5] *D. E. Warrall*, J. Amer. chem. Soc. *45*, 3092 (1923); *M. H. Elnagdi, E. M. Zayed, S. M. Fahmy & S. A. Amer*, Gazz. chim. Ital. (in press).