Reactions with Heterocyclic Diazonium Salts: Novel Synthesis of Pyrazolo[4,3-*c*]pyridazines and of Pyrazolo[4,3-*c*]pyrazoles

By **Mohamed Hilmy Elnagdi, Hassan Attia Elfahham, Mohamed Rifaat Hamza Elmoghayar, Kamal Usef Sadek, and Galal Eldin Hamza Elgemeie**, Department of Chemistry, Faculty of Science, Minia University, Minia and Cairo University, Giza, A.R. Egypt

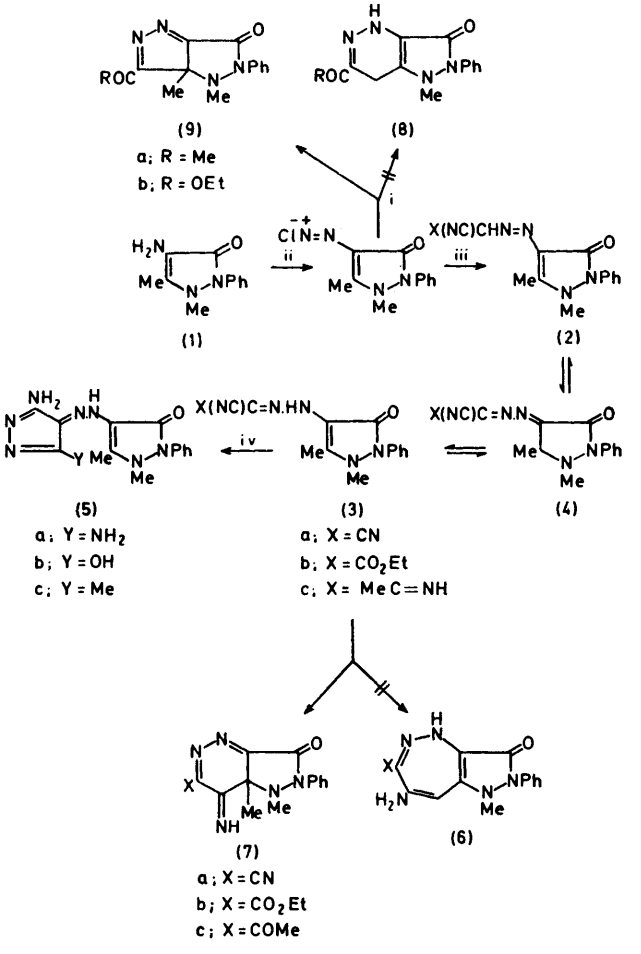
Diazotised 4-amino-1,5-dimethyl-2-phenylpyrazol-3(2*H*)-one (1) coupled with active methylene nitriles to yield the corresponding cyanohydrazones (3a—c) and (11). Compounds (3a—c) afforded the 4-(3-aminopyrazol-4-ylidenehydrazino)-1,5-dimethyl-2-phenylpyrazol-3(2*H*)-ones (5a—c) on treatment with hydrazine hydrate, and cyclised to give the pyrazolo[4,3-*c*]pyridazines (7a—c) on treatment with ethanolic hydrochloric acid. The hydrazone (11) cyclised to give the pyridazin-6-one derivative (12) when boiled under reflux in ethanol. Diazotised pyrazolone (1) coupled with 3-chloropentane-2,4-dione and with ethyl 2-chloro-3-oxobutanoate to yield the pyrazolo[4,3-*c*]pyrazole derivatives (9a and b).

CONTINUING our interest in the synthesis of azoles and of fused azoles as both potential CNS regulants and antimetabolites in purine biochemical reactions,[1,2] we investigated the possible utility of the products obtained by coupling diazotised 4-amino-1,5-dimethyl-2-phenylpyrazol-3(2*H*)-one (1) with active methylene reagents for the synthesis of new pyrazole and fused pyrazole derivatives. The work has resulted, in addition to the syntheses of several new pyrazole derivatives, in new routes for the syntheses of pyrazolo[4,3-*c*]pyridazines and pyrazolo[4,3-*c*]pyrazoles.

The coupling reactions of diazotised pyrazolone (1) with β-diketones, β-ketoesters, and phenols are reported to afford the corresponding hydrazone derivatives.[3] It has now been found that the diazotised compound (1) also couples with malononitrile, ethyl cyanoacetate, and 3-aminocrotononitrile. Although the products can be formulated as the azo-derivatives (2), the hydrazones (3), or the azine derivatives (4), it was readily established that they had the hydrazone structure on the basis of both their i.r. spectra, which revealed in each case a highly conjugated C=N band, and their ^{1}H n.m.r. spectra which indicated the absence of a CH_3CH signal expected for the azine form. Similarly to the reported[4,5] behaviour of the aryl analogues, compounds (3a—c) reacted with hydrazine hydrate to yield the corresponding aminopyrazole derivatives (5a—c).

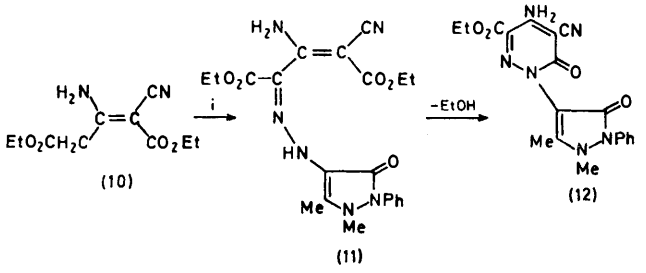
Attempted cyclization of the hydrazone (3a) to give pyrazolo[4,3-*c*]diazepine in boiling ethanolic hydrochloric acid resulted in the formation of a colourless product, the analytical data and the molecular-weight (by mass spectra) of which agreed well with the proposed pyrazolo[4,3-*c*]diazepine structure (6). Although the i.r. spectrum of the product supported the assignment, the ^{1}H n.m.r. spectrum revealed two different methyl protons indicating that the methyl group at C-3 was not involved in the cyclization. The pyrazolo[4,3-*c*]pyridazine structure (7a) was therefore suggested for the reaction product. Similarly, compounds (3b and c) cyclised under the same conditions to give the pyrazolo[4,3-*c*]pyridazine derivatives (7b and c). As far as we know this is the first intramolecular cyclization of this type to be reported for 3-pyrazoline derivatives.

Diazotised aromatic amines and diazotised aminoheterocyclic derivatives have been reported to couple with 3-chloropentane-2,4-dione and with ethyl 2-chloro-3-oxobutanoate to yield hydrazonyl chloride derivatives which serve as excellent precursors for the syntheses of nitrile imines.[6] Attempted coupling of diazotised pyrazolone (1) with both the above reagents, with



Reagents: i, ClCH(COR)·COMe; ii, $NaNO_2$–HCl; iii, XCH_2CN, EtOH–NaOAc; iv, $NH_2·NH_2·H_2O$

the aim of synthesising the corresponding hydrazonyl chlorides, afforded products with molecular formulae corresponding to the loss of hydrogen chloride from the hydrazonyl chloride intermediate. Two structures, (8) and (9), seemed possible for these products. The pyrazolo[4,3-*c*]pyrazole structure (9) was established for the reaction products on the basis of their ^{1}H n.m.r.



Reagent i, diazotised pyrazolone (1)

spectra which revealed two methyl signals at δ 2.5 and 3.2. The formation of compound (9) on coupling diazotised pyrazolone (1) with 3-chloropentane-2,4-dione and with ethyl 2-chloro-3-oxobutanoate is assumed to proceed *via* the elimination of HCl, under the coupling reaction conditions, from the hydrazonyl chloride intermediate to form the corresponding nitrile imine which then undergoes intramolecular cyclization to give final, isolatable products.

Diazotised pyrazolone (1) also coupled with the ethyl cyanoacetate dimer (10) to yield the arylhydrazone derivative (11) which cyclised readily, even in boiling protic organic solvents, *e.g.* ethanol, to yield the pyrazol-4-ylpyridazine derivative (12).

EXPERIMENTAL

All m.p.s are uncorrected. I.r. spectra were recorded (KBr) on a Pye Unicam SP-1100 spectrophotometer. ^{1}H N.m.r. spectra were measured in Me_2SO on a EM-360-60 MHz n.m.r. spectrometer and chemical shifts are expressed as δ p.p.m. Micro-analytical data (C, H, N) were obtained from the Micro-analytical Data Unit at Cairo University.

Coupling of Diazotised 4-Amino-1,5-dimethyl-2-phenylpyrazol-3(2H)-one (1) with Active Methylene Reagents.—A solution of the diazotised 4-aminopyrazol-3(2*H*)-one (10 mmol) in the appropriate quantity of hydrochloric acid and sodium nitrite was added to a solution of the appropriate active nitrile (10 mmol) in ethanol (100 ml) and sodium acetate (1 g). The reaction mixture was left for 2 h at room temperature and then poured into water. The solid product was filtered off, washed several times with water and crystallised from the appropriate solvent. The arylhydrazone derivatives (3a, c) and (11) are listed in Table 1 and i.r. and ^{1}H n.m.r. data of these hydrazones are listed in Table 2.

5-Substituted-4-(3-aminopyrazol-4-ylidenehydrazino)-1,5-dimethyl-2-phenylpyrazol-3(2H)-ones (5a—c).—A solution of each of (3a)—(3c) (10 mmol) in ethanol (30 ml) was treated with hydrazine hydrate (0.9 ml). The reaction mixture was refluxed for 3 h and then left to cool to room temperature. The solid product was filtered off and crystallised from the appropriate solvent (*cf.* Table 1).

6-Substituted-7-imino-1,7a-dimethyl-2-phenylpyrazolo[4,3-c]pyridazin-3(2H)-ones (7a—c).—A solution of each of (3a)—(3c) (10 mmol) in ethanol (20 ml) was treated with concentrated hydrochloric acid (3 ml; 37.5%). The reaction mixture was heated under reflux for 2 h and then evaporated under reduced pressure. The remaining product was triturated with water and neutralised by addition of ammonium hydroxide. The solid product was filtered off and crystallised from the appropriate solvent. Reaction products (7a—c) are listed in Tables 1 and 2.

TABLE 1

Compound	Solvent (Colour)	M.p. (°C)	Yield (%)	Mol. formula (Mol. weight)	Found / Required (%) C	H	N	M^+
(3a)	EtOH (Yellow)	145	70	$C_{14}H_{12}N_6O$ (280.28)	60.2 / 60.0	4.3 / 4.3	29.8 / 30.0	
(3b)	EtOH (Orange)	178	66	$C_{16}H_{17}N_5O_3$ (327.34)	58.9 / 58.7	5.0 / 5.2	21.1 / 21.4	
(3c)	EtOH–Dioxan (Yellow)	254—256	68	$C_{15}H_{16}N_6O$ (296.33)	60.3 / 60.8	5.5 / 5.4	28.0 / 28.4	
(5a)	(Yellow)	280—282	90	$C_{14}H_{16}N_8O$ (312.33)	53.9 / 53.8	4.7 / 5.1	35.5 / 35.9	312
(5b)	AcOH (Yellow)	241	85	$C_{14}H_{15}N_7O_2$ (313.31)	53.3 / 53.7	5.2 / 4.8	31.6 / 31.3	
(5c)	DMF (Yellow)	270—272	81	$C_{15}H_{17}N_7O$ (311.33)	58.3 / 57.9	5.2 / 5.5	31.3 / 31.5	
(7a)	EtOH–DMF (Colourless)	258—260	78	$C_{14}H_{12}N_6O$ (280.28)	60.3 / 60.0	4.6 / 4.3	29.7 / 30.0	280
(7b)	EtOH–DMF (Colourless)	228—230	45	$C_{16}H_{17}N_5O_3$ (327.34)	58.7 / 58.7	5.5 / 5.2	21.1 / 21.4	327
(7c)	(Colourless)	264—266	73	$C_{15}H_{15}N_5O_2$ (297.31)	60.2 / 60.6	5.1 / 5.1	23.2 / 23.6	297
(9a)	EtOH (Pale yellow)	222—224	74	$C_{14}H_{14}N_4O_2$ (270.28)	62.4 / 62.2	5.3 / 5.2	20.5 / 20.7	270
(9b)	EtOH (Yellow)	190—192	53	$C_{15}H_{16}N_4O_3$ (300.31)	60.1 / 60.0	5.0 / 5.4	18.3 / 18.7	300
(11)	EtOH (Yellow)	136	91	$C_{21}H_{24}N_6O_5$ (440.45)	56.9 / 57.3	5.5 / 5.5	18.7 / 19.1	440
(12)	EtOH–DMF (Yellow)	284—286	84	$C_{19}H_{18}N_6O_4$ (394.38)	57.7 / 57.9	4.5 / 4.6	21.0 / 21.3	394

TABLE 2

I.r. and ^{1}H n.m.r. data for the compounds listed in Table 1

Compound	I.r. (cm^{-1}) (selected bands)	^{1}H N.m.r. δ (p.p.m.)
(3a)	3 450 (NH), 2 230 and 2 220 (two CN), 1 675 (ring CO)	2.60 (s, 3 H, 3-Me), 3.2 (s, 3 H, 2-Me), 7.3—7.5 (m, 5 H, Ph), and 12.2 (br s, NH)
(3b)	3 300 (NH), 2 235 (CN), 1 680 (ester CO), and 1 660 (ring CO)	1.30 (t, 3 H, Me), 2.58 (s, 3 H, 3-Me), 3.16 (s, 3 H, 2-Me), 4.41 (q, 2 H, CH_2), 7.33—7.5 (m, 5 H, Ph), and 12.8 (br s, 1 H, NH)
(3c)	3 460, 3 330, 3 220 and 3 080 (NH), 2 200 (conjugated CN), 1 650 (CO), and 1 620 (C=N)	2.44 and 2.55 (s, each for 3 H, 4-Me and exocycl.-Me), 3.16 (s, 3 H, 2-Me), 7.3—7.5 (m, 5 H, Ph), and 7.7—8.0 (br, 2 H, NH)
(5a)	3 480 and 3 400 (NH_2), 3 200—2 700 (chelated NH), 1 660—1 640 (ring CO and NH_2), and 1 620 (C=N)	Insoluble
(5b)	3 440 and 3 340 (NH_2), 3 200—2 500 (NH and OH), 1 670—1 660 (ring CO), and 1 625 (C=N)	Insoluble
(5c)	3 480, 3 400, and 3 300 (NH_2), 1 650 (ring CO), and 1 625 (C=N)	Insoluble
(7a)	3 230 (NH), 2 240 (CN), 1 660 (CO), and 1 620 (C=N)	2.4 (s, 3 H, Me), 3.24 (s, 3 H, Me), 4.5 (br s, 1 H, NH), and 7.2—7.4 (m, 5 H, Ph)
(7b)	3 450—3 200 and 3 100 (NH), 1 740 (ester CO), 1 650 (ring CO), and 1 620 (C=N)	1.18 (t, 3 H, Me), 2.2 s, 3 H, Me), 3.18 (s, 3 H, Me), 3.9 (br s, 1 H, NH), 4.16 (q, 2 H, CH_2), and 7.2—7.4 (m, 5 H, Ph)
(7c)	3 500—3 400 and 3 100 (NH), 1 690 (acetyl CO), 1 650 (ring CO), and 1 630 (C=N)	Insoluble
(9a)	3 400—3 200 (NH), 1 665—1 645 (acetyl CO), and 1 625 (C=N)	2.3 (s, 3 H, Me), 2.5 (s, 3 H, COMe), 3.16 (s, 3 H, NMe), and 7.3—7.6 (m, 5 H, Ph)
(9b)	3 400 (NH), 1 690 (ester CO), and 1 650 (C=N)	1.33 (t, 3 H, Me), 2.33 (s, 3 H, Me), 3.0 (s, 3 H, 2-Me), 4.3 (q, 2 H, CH_2), and 7.2—7.5 (m, 5 H, Ph)
(11)	3 420—3 100 (NH_2 and NH), 2 230 (CN), 1 730, 1 690 (unconjugated and conjugated ester CO), 1 660 (ring CO), and 1 625 (C=N)	1.3 (t, 6 H, Me), 2.16 (s, 3 H, Me), 3.2 (s, 3 H, Me), 4.30 (q, 4 H, CH_2), 7.2—7.5 (m, 5 H, Ph), and 8.25 (br s, 2 H, NH_2)
(12)	3 400 and 3 300—3 240 (NH_2), 2 230 (CN), 1 730 (ester CO), 1 700 (pyridazine CO), and 1 640 (pyrazoline CO)	1.25 (t, 3 H, Me), 2.26 (s, 3 H, Me), 3.18 (s, 3 H, Me), 4.20 (q, 2 H, CH_2), 7.2—7.5 (m, 5 H, Ph), and 8.25 (br s, 2 H, NH_2)

1,6a-*Dimethyl*-2-*phenylpyrazolo*[4,3-c]*pyrazol*-3(2H)-*ones* (9a and b).—A solution of diazotised pyrazolone (1) [prepared from 10 mmol of compound (1) as described above] was added to a solution of 3-chloropentane-2,4-dione or of ethyl 2-chloro-3-oxobutanoate (10 mmol) in ethanol (30 ml) containing anhydrous sodium acetate (3 g). The reaction mixture was stirred for 2 h and then evaporated at 100 °C (bath temp.). The reaction product was triturated with water, and the solid product, so formed, was filtered off and crystallised from the appropriate solvent. Compounds (9a and b) are listed in Tables 1 and 2.

[1/830 *Received*, 27*th May*, 1981]

REFERENCES

[1] M. H. Elnagdi and H. Wamhoff, *Chem. Lett.*, 1981, 415.
[2] M. H. Elnagdi, M. R. H. Elmoghayar, H. A. Elfahham, M. M. M. Sallam, and H. H. Alnima, *J. Heterocycl. Chem.*, 1980, **17**, 209.
[3] G. T. Morgan and J. Reilly, *J. Chem. Soc.*, 1913, **103**, 808.
[4] M. H. Elnagdi and S. O. Abdoula, *J. Prakt. Chem.*, 1973, **315**, 1009.
[5] M. H. Elnagdi, M. R. H. Elmoghayar, and D. H. Fleita, *Tetrahedron*, 1975, **31**, 63.
[6] A. S. Shawali and C. Parkanyi, *J. Heterocycl. Chem.*, 1980, **17**, 833.