Novel Synthesis of Pyrazolo[5,1-*c*]-1,2,4-Triazoles, Imidazo[1,2-*b*]-pyrazoles, and [1,2,4]-Triazolo[4,3-*a*]benzimidazoles. Reaction of Nitrile Imines with Amino- and Oxo-substituted Diazoles [1]

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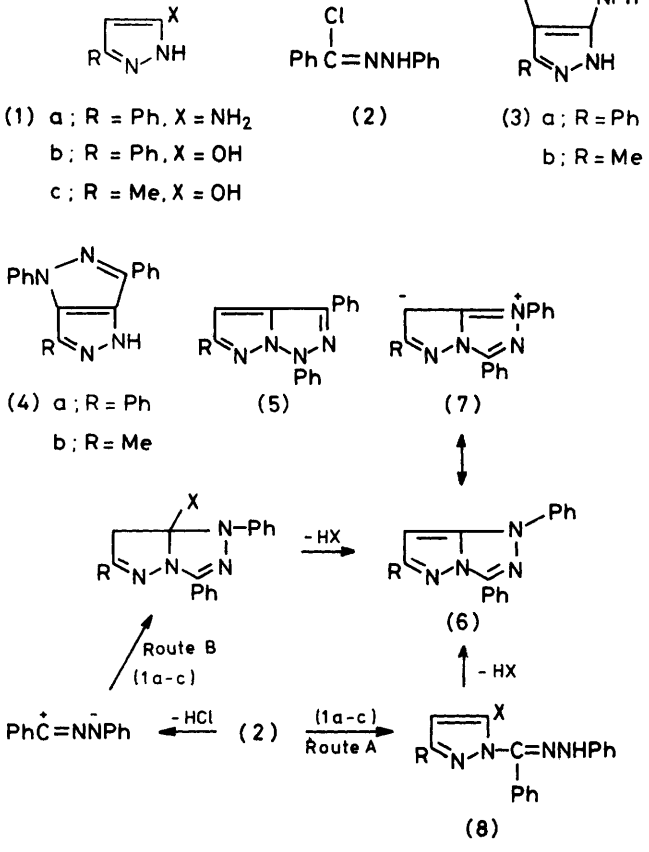
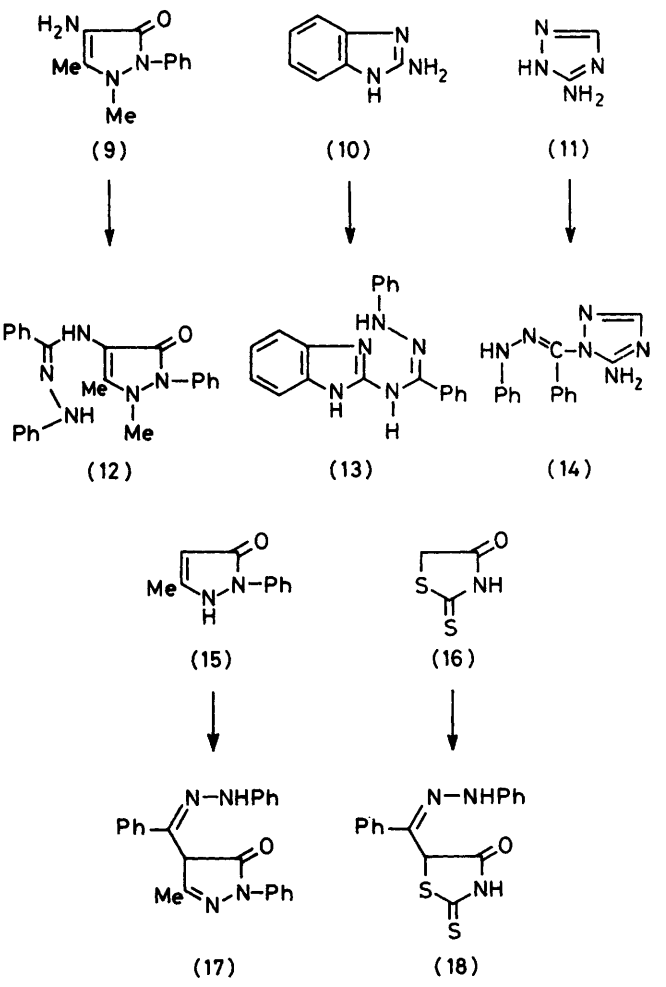
The behaviour of several amino- and hydroxy-diazoles towards nitrile imines and hydrazonoyl halides is reported The results indicate that nitrile imines can add to the double bonds in amino- and hydroxy-heterocyclic derivatives. However, the nature of the end product is dependent on the nitrile imine, the substituent on the heterocyclic ring, and the type of heterocyclic ring.

NITRILE IMINES, usually synthesised *in situ* by base-catalysed elimination of halogeno-acids from hydrazonoyl halides, are reactive intermediates that have found extensive use in heterocyclic synthesis.[2] Their



reactions with aminoazoles and with azolones have not yet been reported.

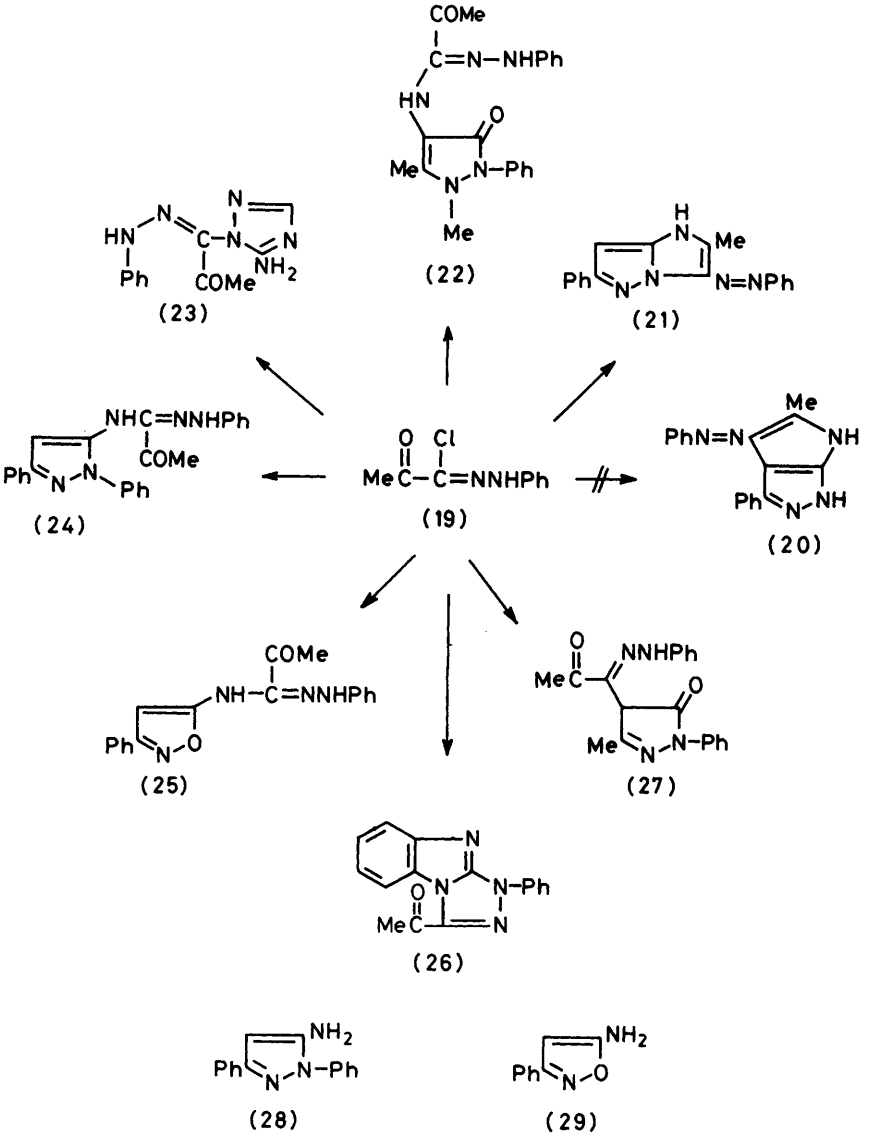
As part of our programme directed towards the development of new, simple procedures for the synthesis of fused azoles [3-5] we have investigated the reaction of nitrile imines with cyclic amidines and with azolones. Thus, 5-amino-3-phenylpyrazole (1a) and *N*-phenylbenzohydrazonoyl chloride (2) reacted in the presence of triethylamine to yield a product with the molecular formula $C_{22}H_{16}N_4$ (M^+ 336). The same product was formed on treatment of compound (2) with 5-hydroxy-3-phenylpyrazole (1b) under the same conditions. Four theoretically possible structures (3)—(6) were



considered for the product. Structures (3a) and (4a) were readily ruled out because of the absence of an NH absorption in the i.r. spectrum of the product, and the appearance of a resonance at δ_H 6.1 for a pyrazole

C(4)–H. Although structure (6) seemed most likely based on mechanistic considerations,[13]C n.m.r. spectroscopy was used to confirm this structure for the product.* Thus, [13]C n.m.r. spectroscopy ([$^2H_6$]DMSO) revealed that all the phenyl carbons were not identical. This observation can only be rationalised in terms of structure (6) since, for compound (5), the 1- and 3-phenyl groups would resonate at almost the same chemical shift.[6] The [13]C n.m.r. spectrum also revealed a signal for the pyrazole C(4) (ring *C*H) at δ_0 79·8 p.p.m., considerably upfield from the region we expected for an sp^2 carbon. A similar resonance has been observed for C(4) of 5-aminopyrazole [7] and can be rationalised by assuming that compound (6) exists, at least in DMSO, as the zwitterion (7). The formation of compound (6) from the reaction of the pyrazole (1a or b) with compound (2) may be assumed to proceed either *via* alkylation of compound (1a, b) and subsequent cyclization (route A) or *via* 1,3-dipolar addition of the generated nitrile imine (route B). It seemed most likely that the reaction proceeds *via* route B since the alkylation sequence would afford acyclic intermediates such as compound (8). Such intermediates could not be detected in the reaction mixture. We have reason to suspect that cyclization of compound (8) into the product (6) cannot take place under these reaction conditions.[8] In fact, the equilibrium of compound (6) back into the starting material (1a, b) and benzoylphenylhydrazine is expected under the reaction conditions.[8]

Similarly to the behaviour of the pyrazoles (1a and b), 3-methyl-5-hydroxypyrazole (1c) reacted with compound (2) under the same experimental conditions to yield the pyrazolo[5,1-*c*]-1,2,4-triazole derivative (6; R = Me) (M^+ 274). This reaction also is assumed to proceed



* In our preliminary communication, structure (3) was mistakenly assigned to this product on the basis of its identical m.p. However, later data on compound (3) (m.s., [1]H n.m.r., and i.r.) showed it was not the product.

Table 1

Products from the reaction of the hydrazonoyl chlorides (2) and (19) with amino- and oxo-substituted diazoles

Compound [a]	Crystallisation solvent	M.p. (°C)	Yield (%)	Molecular formula	Analysis (%) Found (Required) C	H	N
(6; R = Me)	EtOH	100	91	$C_{17}H_{14}N_4$	74.5 (74.5)	4.9 5.1	20.0 20.4)
(6; R = Ph)	Dioxan	192	74	$C_{22}H_{16}N_4$	78.5 (78.6)	4.8 4.8	16.4 16.7)
(12)	EtOH	210	86	$C_{24}H_{23}N_5O$	72.6 (72.5)	6.0 5.8	17.5 17.6)
(13)	$CHCl_3$	236	55	$C_{20}H_{17}N_5$	73.1 (73.4)	5.1 5.2	21.1 21.4)
(14)	$MeCONMe_2$	262	80	$C_{15}H_{14}N_6$	64.8 (64.7	4.8 5.0	30.1 30.2)
(17)	EtOH	200	86	$C_{23}H_{20}N_4O$	75.1 (75.0	5.6 5.4	14.9 15.2)
(18)	EtOH	114	92	$C_{16}H_{13}N_3OS_2$	59.1 (58.7	4.0 4.0	12.7 12.8)
(21)	EtOH	155	66	$C_{18}H_{15}N_5$	72.1 (71.8	5.1 5.0	23.6 23.3)
(22)	EtOH	138	69	$C_{20}H_{21}N_5O_2$	66.4 (66.1	6.1 5.8	19.5 19.4)
(23)	EtOH–$MeCONMe_2$	234	82	$C_{11}H_{12}N_6O$	54.3 (54.1	4.9 4.9	34.3 34.4)
(24)	EtOH	154	76	$C_{24}H_{21}N_5O$	72.6 (72.9	5.3 5.3	17.4 17.7)
(25)	EtOH	188	44	$C_{18}H_{16}N_4O_2$	67.4 (67.5	4.9 5.0	17.2 17.5)
(26)	EtOH	195—196	65	$C_{16}H_{12}N_4O$	69.9 (69.9	4.6 4.3	20.4 20.3)
(27)	EtOH	185	90	$C_{19}H_{16}N_4O$	68.6 (58.3	5.3 5.4	16.5 16.8)

[a] Compounds (6; R = Me, Ph), (12), and (14) are colourless. All others are yellow.

TABLE 2

Selected i.r. and complete ^1H n.m.r. data for the compounds listed in Table 1

Compound	$\nu_{max.}$ cm^{-1}	δ_H
(6; R = Me)	3 050—2 990 (CH and CH_3)	2.05 (3 H, s, Me), 5.66 (1 H, s, CH), and 6.8—8.1 (10 H, m, 2 × Ph)
(6; R = Ph)	3 060—3 000 (CH)	6.1 (1 H, s, CH) and 7.0—7.9 (15 H, m, 3 × Ph)
(12)	3 320 and 3 100 (NH), 1 640 (C=O), and 1 620—1 610 (C=N and C=C)	2.0 (3 H, s, CMe), 2.9 (3 H, s, NMe), 6.66 (15 H, m, 3 × Ph), 8.15 (1 H, s, NH), and 11.2br (1 H, s, NH)
(13)	3 480, 3 390, and 3 200 (NH) and 1 620 (C=N)	6.75—7.60 (total 14 H, m, 2 × Ph and C_6H_4), 8.1 (1 H, s, NH), 8.4 (1 H, s, NH), and 10.4 (1 H, s, NH)
(14)	3 480 and 3 150 (NH) and 1 640 (C=N)	5.9 (2 H, s, NH_2), 7.0—7.4 (10 H, m, 2 × Ph), 7.9 (1 H, s, CH), and 9.9br (1 H, s NH)
(17)	3 200 (NH) and 1 650 (C=O)	2.25 (3 H, s, Me), 5.66 (1 H, s, CH), 6.4—7.7 (15 H, m, 3 × Ph), and 8.05 (1 H, s, NH)
(18)	3 200 (NH) and 1 630 (C=O)	3.5 (1 H, s, CH), 7.5—7.8 (10 H, m, 2 × Ph), and 8.0—8.3br (2 H, s, 2 × NH)
(21)	3 200 (NH)	2.44 (3 H, s, Me), 6.3 (1 H, s, CH), 7.0—7.5 (10 H, m, 2 × Ph), and 12.0br (1 H, s, NH)
(22)	3 360 and 3 100 (NH), 1 670 (acetyl C=O), 1 650 (ring C=O), and 1 610 (C=N)	2.2 (3 H, s, COMe), 2.4 (3 H, s, CMe), 3.1 (3 H, s, NMe), 6.7—7.7 (total 11 H, m, 2 × Ph and NH), and 10.0br (1 H, NH)
(23)	3 380, 3 260, and 3 140 (NH), 1 690 (C=O), and 1 650 (C=N)	2.6 (3 H, s, COMe), 5.9 (2 H, s, NH_2), 7.0—7.9 (total 6 H, m, Ph and CH), and 10.4br (1 H, s, NH)
(24)	3 380 and 3 100 (NH) and 1 670 (C=O)	2.0 (3 H, s, COMe), 5.8 (1 H, s, CH), 6.8—7.2 (5 H, m, 3 × Ph) and 11.0br (2 H, 2 × NH)
(25)	3 240 (NH), 1 670 (C=O), and 1 620 (C=N)	2.55 (3 H, s, COMe), 5.65 (1 H, s, CH), 7.3—8.2 (10 H, m, 2 × Ph), 9.2 (1 H, s, NH), and 10.5br (1 H, s, NH)
(26)	1 690 (C=O) and 1 650 (C=N)	1.75 (3 H, s, COMe) and 7.0—7.8 (total 9 H, Ph and C_6H_4)
(27)	3 400 (NH), 1 690 (acetyl C=O), and 1 660 (ring C=O)	1.66 (3 H, s, CMe), 1.8 (3 H, s, COMe), 5.6 (1 H, s, CH) 7.0—7.8 (10 H, m, 2 × Ph), and 11.2br (1 H, s, NH)

via route B. The isomeric structures (3b) and (4b) were ruled out since the ^{1}H n.m.r. spectrum of the product showed a signal for a pyrazole CH proton at δ 5.66.

The behaviour of several other cyclic amidines and heterocyclic ketones toward compound (2) was investigated. Products resulting from substitution at the heterocyclic active site by the *N*-phenylbenzohydrazonoyl residue were obtained. Thus, from the reaction of compound (2) with 4-aminoantipyrine (9), 2-aminobenzimidazole (10), and 5-amino-1*H*-1,2,4-triazole (11), the amidrazones (12), (13), and (14), respectively were obtained. Alkylation of compounds (10) and (11) may afford ring- or exocyclic aminoalkylated products. The exocyclic aminoalkylated product was assumed to be formed in the reaction of compounds (10) and (2) since the ^{1}H n.m.r. spectrum showed no NH_2 signal at the expected value of δ_H *ca.* 5.9. In contrast, reaction of compounds (12) and (2) afforded a ring-*N*-alkylated product as shown by the NH_2 signal at δ_H 5.9. Two isomeric ring-alkylated products are possible. Again, ^{1}H n.m.r. spectroscopy excludes the *N*(4) alkylated structure since it shows the triazole 3-H at a higher field (δ 7.9) than that expected for *N*(4)-substituted 4-*H*-triazoles (δ *ca.* 9.0). 5-Methyl-2-phenyl-4-pyrazolin-3-one (15) and rhodanine (16) similarly afforded the corresponding hydrazine derivatives (17) and (18), respectively.

The behaviour of *N*-phenylpyruvohydrazonoyl chloride (19) towards aminoheterocycles and hydroxyazoles was also investigated. In contrast to the observed formation of 2 + 3 ⟶ 5 cycloadducts from the reaction compounds (1a) and (2), compound (19) reacted with the pyrazole (1a) to yield a product for which structure (20) or (21) seemed plausible. Structure (20) was, however, readily eliminated on consideration of the ^{1}H n.m.r. data of the product which showed a signal for the pyrazole 4-H. The formation of compound (21) from the reagents (19) and (1a) is similar to that recently reported for the imidazo[1,2-*b*]pyrazole derivative formed from (1a) and benzohydrazonoyl bromides.[9]

In a similar manner to that of the chloride (2), compound (19) reacted with the aminoheterocyclic derivatives (9), (11), (28), and (29) to yield the amidrazones (22)—(25), respectively. However, in contrast to the reaction of 2-aminobenzimidazole (10) with the chloride (2), the cyclic adduct (26) was obtained from reaction of compounds (10) with (19). Although we failed to isolate products from the reaction of compound (1b or c) with the chloride (19), under a variety of conditions, compound (15) reacted smoothly with the chloride (19) to yield the hydrazone derivative (27).

EXPERIMENTAL

M.p.s are uncorrected I.r. spectra (KBr) were recorded with a Pye Unicam SP 1000 spectrophotometer. ^{1}H N.m.r. spectra were obtained on a Varian EM-390 spectrometer at 90 MHz with [$^2H_6$]DMSO as solvent and $SiMe_4$ as internal reference. Analytical data were obtained from the Analytical Data Unit at Cairo University.

Reaction of the Hydrazonyl Chlorides (2) *and* (19) *with Amino- and Oxo-substituted Diazoles.—General procedure.* A suspension of compound (2) or (9) (20 mmol) and the appropriate amino- or oxo-substituted diazole (20 mmol) in ethanol (30 ml) was refluxed with triethylamine (20 mmol) for 3 h and then evaporated to dryness under reduced pressure. The residue was washed with light petroleum (b.p. 40–60 °C), triturated with ethanol, and the resulting solid product was fiiltered off and crystallised from the appropriate solvent (Table 1). Analytical and spectroscopic data are given in Tables 1 and 2.

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