Activated Nitriles in Heterocyclic Synthesis: Reaction of Cyanogen Bromide with some Functionally Substituted Enamines

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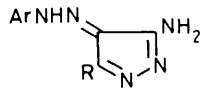
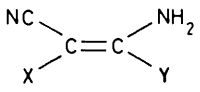
Novel procedures for the synthesis of pyrazolo[4,3-*c*]-1,2,4-triazines and 2-bromopyrimidine derivatives have been developed *via* reaction of cyanogen bromide with some substituted enamines.

Nitriles are versatile reagents that have been extensively utilized in heterocyclic synthesis.[1,2] We have previously reported several syntheses of azoles and azines utilizing the reaction of the readily obtainable enamine derivatives (**1a**—**f**) and (**2a**—**d**) with activated nitriles.[3–5]



(1)



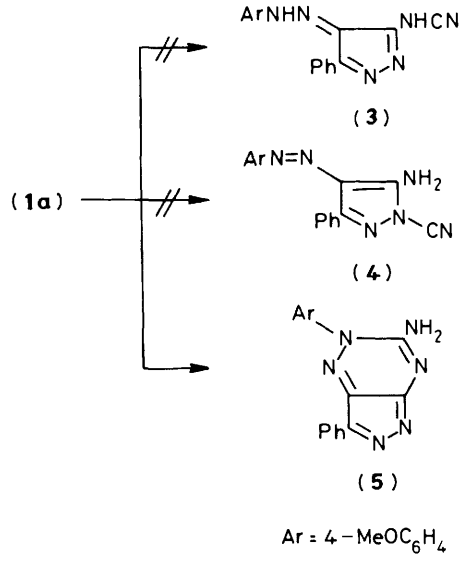
(2)

a; R = Ph, Ar = 4-$MeOC_6H_4$
b; R = OH, Ar = —Ph
c; R = NH_2, Ar = —Ph
d; R = NH_2, Ar = 4-$MeOC_6H_4$
e; R = NH_2, Ar = 2-$NO_2C_6H_4$
f; R = NH_2, Ar = 4-ClC_6H_4

a; X = CO_2Et, Y = CCl_3
b; X = CN, Y = CCl_3
c; X = COPh, Y = CCl_3
d; X = CO_2Et, Y = CH_2CO_2Et

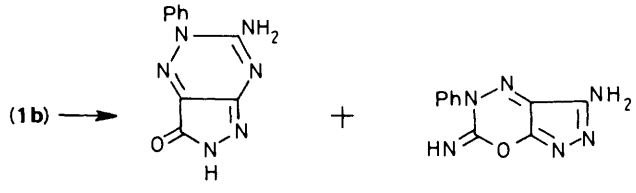
In continuation of this work, we report here the results of our investigation into the reaction of (**1a**—**f**) and (**2a**—**d**) with cyanogen bromide. The investigations have resulted in the development of a novel procedure for the synthesis of pyrazolo[4,3-*c*]-1,2,4-triazines and 2-bromopyrimidine derivatives. The compounds obtained seem promising for further chemical transformations and for biological evaluation studies. Thus, it has been found that compound (**1a**) reacts with cyanogen bromide to afford a product of molecular formula $C_{17}H_{14}N_6O$ in high yield. Three isomeric structures were considered for this product. Structures (**3**) and (**4**) could be readily eliminated on the basis of the i.r. spectrum, which revealed the absence of cyano group absorption and the presence of an NH_2 vibration. Thus, structure (**5**) was assigned to this reaction product. Compound (**1b**) reacted similarly to compound (**1a**) with cyanogen bromide, to yield a mixture of two isomeric products. Again structures (**6**) and (**7**) were established for the reaction products on the basis of the i.r. spectra (see Experimental section).

In contrast to (**1a**) and (**1b**), compounds (**1c**—**f**) reacted with cyanogen bromide to yield products with molecular formulae consistent with the reaction of one molecule of each of (**1c**—**f**) with two molecules of CNBr with the elimination of two molecules of hydrogen bromide. The i.r. spectra of the reaction products revealed a CN group absorption in each case. Two structures, (**8**) and (**9**), were considered. Structure (**8**) was assigned to the reaction product on the basis of the ^{1}H-n.m.r. spectrum, which revealed three NH signals each integratable for 1H at δ 5.90, 6.30, and 8.22. These were assigned for the secondary amino NH's at positions (**3**) and (**5**) and for hydrazone NH, respectively. If this compound was the isomer (**9**), amino group absorption would be observed.

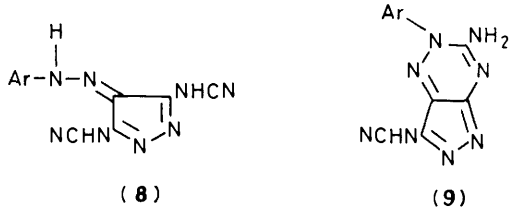


(3) (4) (5)

Ar = 4-$MeOC_6H_4$



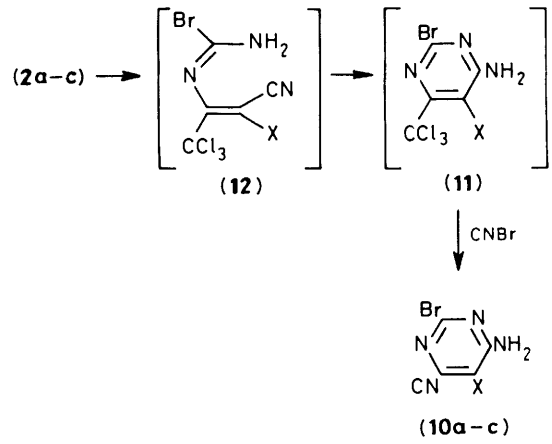
(6) (7)



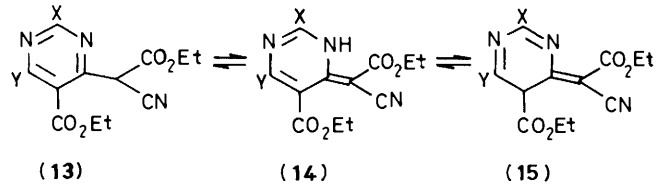
(8) (9)

a; Ar = Ph
b; Ar = 4-$MeOC_6H_4$
c; Ar = 2-$NO_2C_6H_4$
d; Ar = 4-ClC_6H_4

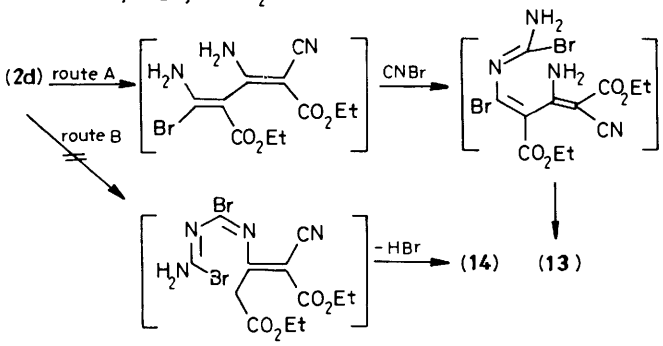
The reaction of (**2a**) with BrCN unexpectedly afforded a product of molecular formula $C_8H_7BrN_4O_2$. Structure (**10a**) was considered for this product. Compound (**10a**) is assumed to be formed *via* the addition of the amino function in (**2a**) to the cyano group in BrCN to yield an adduct (**12**) (see Scheme1) which would readily cyclize into (**11**); the latter then undergoes nucleophilic displacement of the trichloromethyl moiety by the CN group. The addition of the amino function in (**2a**) to the CN



Scheme 1.



(13), (15)a; X = NH_2, Y = Br
b; X = Br, Y = NH_2



Scheme 2.

group of CCl_3CN has recently been observed by us,[3,4] and the ready displacement of the CCl_3 moiety in pyrimidines has recently been reported.[3,6] The formation of (**10a**), however, is a new example for reaction of cyanogen bromide with amines in which addition to the cyano group occurred. Only a few examples of this type of reaction have been reported in the literature.[7] Similarly to (**2a**), compounds (**2b**) and (**2c**) reacted with BrCN to yield the pyrimidine derivatives (**10b**) and (**10c**) respectively. The formation of (**10b**) and (**10c**) is assumed to proceed *via* the same mechanism suggested to account for the formation of (**10a**) from (**2a**) and cyanogen bromide.

Compound (**2d**) also reacted with BrCN, to yield a product of molecular formula $C_{12}H_{13}BrN_4O_4$. ^1H n.m.r. spectroscopy revealed two ester groups and an amino function, and indicated that the active methylene moiety was involved in the reaction. Structure (**13**) or its possible tautomers (**14**) and (**15**) were suggested for this product, and are assumed to be formed *via* either route A or route B (see Scheme 2).

The i.r. spectrum of the reaction product clearly excludes the tautomeric forms (**14**) and (**15**) since the ester group frequencies are higher than would be expected for α, β-unsaturated esters such as those present in (**14**) and (**15**).[8] Carbonyl absorption as well as the presence of a nonchelated amino function in the i.r. spectrum clearly excludes structure (**13b**) as a possibility, because in this case hydrogen bonding of the amino function with the carbonyl group would have been expected.

^{13}C N.m.r. spectroscopy also excludes (**14a**) since this structure does not contain SP^3 carbons, whereas the ^{13}C n.m.r. spectrum revealed a signal at δ 66.45 p.p.m. The ^{13}C n.m.r. spectrum of the product can only be intelligibly interpreted in terms of structure (**13a**). Thus, in addition to the expected signals at δ 13.73, 24.54, 42.27 and 43.05 p.p.m. for two OCH_2Me functions, the CN band at 115.99, and two ester CO functions at 18.4 and 175.6 p.p.m., it revealed four other carbons at δ 164.97 (C-2), 161 (C-4), 138 (C-5) and 150 (C-6) p.p.m. These data are similar to those for unsubstituted pyrimidines,[9] with the exception of the value for C-5 which is appreciably deshielded. This deshielding is due to electron withdrawal by the ester function. Moreover, this low field value indicates that C-6 does not carry an amino function as in this case the shielding effect of the amino group would have counter balanced the deshielding effect of the ester function and a value of around δ 122 p.p.m. would have been found.

Experimental

All melting points are uncorrected. I.r. spectra were recorded in KBr discs using a Pye-Unicam SP-1100 spectrophotometer. ^1H N.m.r. spectra were recorded on a Varian A-60 spectrometer using [$(CD_3)_2SO$] as solvent and tetramethylsilane as internal standard. BrCN was prepared as has been described by Hartman.[10] Elemental analyses (±0.3%) were performed by the microanalytical centre at Cairo University.

Reaction of 3-*Amino*-4-*arylhydrazono*-5-*substituted Pyrazoles* (**1a**) *and* (**1c—f**) *with* BrCN.—To a solution of 0.01 mol each of (**1a**) and (**1c—f**) in ethanol (50 ml), BrCN (2.2 g; 0.02 mol) and 3—4 drops of piperidine were added. The reaction mixture was then refluxed, and after *ca.* 1 h a crystalline precipitate was formed. The period under reflux was extended for a further 2 h, after which time the reaction mixture was allowed to cool to room temperature and the precipitate was collected by filtration, washed several times with water, and recrystallized from the appropriate solvent (see Table).

Reaction of 3-*Amino*-5-*hydroxy*-4-*phenylhydrazonopyrazole* (**1b**) *with* BrCN.—Compound (**1b**) (2.03 g; 0.01 mol) was dissolved in the smallest possible amount of DMF and then ethanol (50 ml) was added. To this solution, CNBr (2.2 g; 0.02 mol) together with 3—4 drops of piperidine as catalyst were added, and the reaction mixture was refluxed for 3 h. The mixture was then allowed to cool to room temperature and the resulting precipitate was filtered off and recrystallized (see Table) to afford a compound which was identified as compound (**6**).

Separation of Compound (**7**).—The mother liquor remaining after filtration of compound (**6**) was evaporated under reduced pressure and then triturated with a little ice, whereupon a red precipitate was formed which was collected by filtration, recrystallized, and identified as (**7**).

Reaction of CNBr *with Compounds* (**2a—d**).—CNBr (2.2 g; 0.02 mol) was added to a solution of each of compounds (**2a—d**) (0.01 mol) in ethanol (50 ml), 3—4 drops of piperidine were added as catalyst and the reaction mixture was heated under reflux for 4—6 h. The solvent was evaporated under reduced pressure and the residue was triturated with cold water. The

Table. Physical data for new compounds.

Compd.	m.p. (°C) (solvent)	Yield (%)	Mol. formula (*M*)	Analysis (%) C	H	N	ν cm^{-1} (selected bands)	δ H
(5)	200 (AcOH)	80	$C_{17}H_{14}N_6O$ (318)	64.0 (64.2)	4.5 (4.4)	26.6 (26.4)	3 200—3 350 (NH_2), 1 680 (C=N), 1 600 (Ar)	3.78 (s, 3 H, Me), 7.12—7.25 (s, 2 H, NH_2), 7.45—7.80 (m, 9 H, ArH), 8.50 (s, 1 H, NH).
(6)	>300 (DMF)	46	$C_{10}H_8N_6O$	52.5 (52.6)	3.6 (3.5)	36.9 (36.8)	3 450—3 250 (NH_2), 1 720 (CO), 1 640 (C=N)	5.63 (s, 1 H, NH), 7.76—8.0 (m, 7 H, ArH and NH_2).
(7)	175 (EtOH)	42	$C_{10}H_8N_6O$ (228)	52.5 (52.6)	3.7 (3.5)	37.0 (36.8)	3 380—3 180 (NH_2 and NH), 1 630 (C=N)	5.60 (s, 1 H, NH), 7.13—7.52 (m, 7 H, Ar and NH_2
(8a)	225 (EtOH)	78	$C_{11}H_8N_8$ (252)	52.5 (52.4)	3.1 (3.2)	44.5 (44.4)	3 350, 3 400 (NH), 2 200 (C=N)	7.20—7.80 (m, 5 H, ArH), 5.9 (s, 1 H, NH), 6.3 (s, 1 H, NH), 8.22 (s, 1 H, hydrazone NH)
(8b)	150 (EtOH)	84	$C_{12}H_{10}N_8O$ (282)	51.0 (51.1)	3.6 (3.5)	40.0 (39.7)		
(8c)	241 (DMF)	85	$C_{11}H_7N_9O_2$ (297)	44.5 (44.4)	2.6 (2.4)	42.3 (42.4)	Satisfactory i.r. and ^{1}H-n.m.r. spectra have been obtained.	
(8d)[a]	235 (AcOH)	86	$C_{11}H_7ClN_8$ (286.5)	46.0 (46.1)	2.5 (2.4)	39.1 (39.1)		
(10a)[b]	94 (EtOH)	63	$C_8H_7BrN_4O_2$ (271)	35.2 (35.4)	2.8 (2.6)	20.6 (20.7)	3 450, 3 380 (NH_2), 1 780 (ester CO), 2 200 (C=N)	1.3 (t, 3 H, CH_3), 3.41 (q, 2 H, CH_2), 9.5 (s, 2 H, NH_2).
(10b)[c]	95 (MeOH)	75	$C_6H_2BrN_5$ (224)	32.0 (32.1)	1.0 (0.9)	31.1 (31.3)		
(10c)[d]	147 (EtOH)	71	$C_{12}H_7BrN_4O$ (303)	47.2 (47.5)	2.5 (2.3)	18.5 (18.5)	Satisfactory spectra have been obtained.	
(13)[e]	85 (EtOH)	87	$C_{12}H_{13}BrN_4O_4$ (357)	40.5 (40.3)	3.5 (3.6)	15.8 (15.7)	3 400, 3 300 (NH_2), 2 200 (C=N), 1 760 and 1 750 (two ester CO)	1.30 (t, 6 H, two Me), 4.21—4.50 (q, 4 H, two CH_2), 5.5. (s, 1 H, CH), 7.82 (s, 2 H, NH_2).

[a] Cl %: Found, 12.5; Calc., 12.4. [b] Br %: Found, 29.5; Calc., 29.5. [c] Br %: Found, 35.5; Calc., 35.7. [d] Br, %: Found, 26.0; Calc., 26.4. [e] Br %: Found, 22.5; Calc., 22.4.

solid product so formed was then filtered off, washed several times with cold water, and then recrystallized (see Table).

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