NITRILES IN HETEROCYCLIC SYNTHESIS: NOVEL SYNTHESES OF BENZO[g]IMIDAZO-[1,2-c]PYRIMIDINES AND BENZO[g]IMIDAZO[1,2-a]PYRIDINE DERIVATIVES

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Abstract- Novel syntheses of benzo[g]imidazo[1,2-c]pyrimidines and benzo[g]imidazo[1,2-a]pyridine derivatives utilising 2-(2-benzimidazolyl)-acetonitrile as starting component is reported.

The utilities of cyano compounds in organic synthesis are now receiving a considerable interest[1,2]. As a part of our program aiming to develop new efficient procedures for synthesis of fused heterocyclic nitrogen compounds utilising readily obtainable nitrile containing intermediates, we have previously reported several new approaches for synthesis of condensed heterocycles utilising 2-cyanomethylazolyl[3,4] and 2-cyanomethylazinyl[5] derivatives as starting material. In conjunction of this work we report here novel synthesis of benzo[g]imidazo[1,2-c]pyrimidine and benzo[g]imidazo[1,2-a]pyridine derivatives utilising the ready obtainable 2-cyanomethylbenzimidazole derivatives 1 as starting material. Compound 1 reacted with trichloroacetonitrile to yield the adduct 2. Compound 2 condensed with ethyl orthoformate to yield a product which can be formulated as 3 or 4. Structure 3 could be established for the reaction product based on ^{1}H NMR which revealed two downfield protons at δ 8.50 and 10.20 ppm respectively which assigned for H-9 and H-1 in 3. Deshielding of these protons is interpreted in terms of wanderwal effects. Similar assumption was made to account for the deshielding of H-1 and H-10 in phenantherene[6]. If the reaction product was 4 it would be difficult to account for the existence of two protons at δ less than 8.0 ppm.

Compound 1 reacted with 2-thiophenecarboxaldehyde or with 2-furanecarboxaldehyde, orange condensation products were obtained. They rearranged, readily in acidic media into isomeric yellow products. These products were thought to be the Z and E forms of the acrylonitrile derivatives 5. However, careful inspection of the ^{1}H NMR spectra of these products revealed that the orange product is the imminium-ylide 6, whereas the yellow product is the ylidene derivative 5, which exists as an equilibrium mixture of the Z and E forms. The ^{1}H NMR spectrum of the yellow product 5b shows a singlet at δ 6.88 ppm, integrated to three protons and assigned to 5-H, 6-H and 7-H, a broad signal at δ 7.22-7.74 ppm, integrated for four protons, assignable to the thiophene ring protons and the ylidene CH, a doublet signal at δ 7.92 ppm, integrated to one proton, assignable to 4-H and a lowfield signal at δ 8.78 ppm, assignable to the ring imino group proton. On the other hand, the ^{1}H NMR spectrum of 6b shows the azomethine proton signal, as a singlet located at δ 8.45 ppm and shows also two downfield doublets at δ 7.77 ppm and 7.99 ppm, assignable to the 4-H and 6-H protons, respectively. The anisotropic effect of the azomethine linkage causes deshielding of the 6-H, whose signal, therefore, appears at a lower field, in comparison with that of the same proton in 5b[6].

Treatment of 5b or 6b with malononitrile in ethanolic piperidine yields 9b. A possible isomer 11, which can be ruled out by ^{1}H NMR spectral analysis. The spectrum reveals a lowfield signal, located at δ 8.45 ppm, assignable to the amino protons and to the 9-H. The latter proton is deshielded by the amino group, an effect which is known in similar systems as reported in the literature[7]. The formation of 9 from 5 is assumed to proceed via addition of malononitrile to the double bond in 5. In case of highly active methylenes like malononitrile we postulate the formation of the intermediate 7. This Micheal adduct then either cyclises to give the intermediate dihydropyridine derivative 8, which is oxidised under reaction conditions to yield 9 or it is oxidised before cyclisation. However, oxidation after cyclisation seems to be most likely, and similar proposal made by other groups[8].

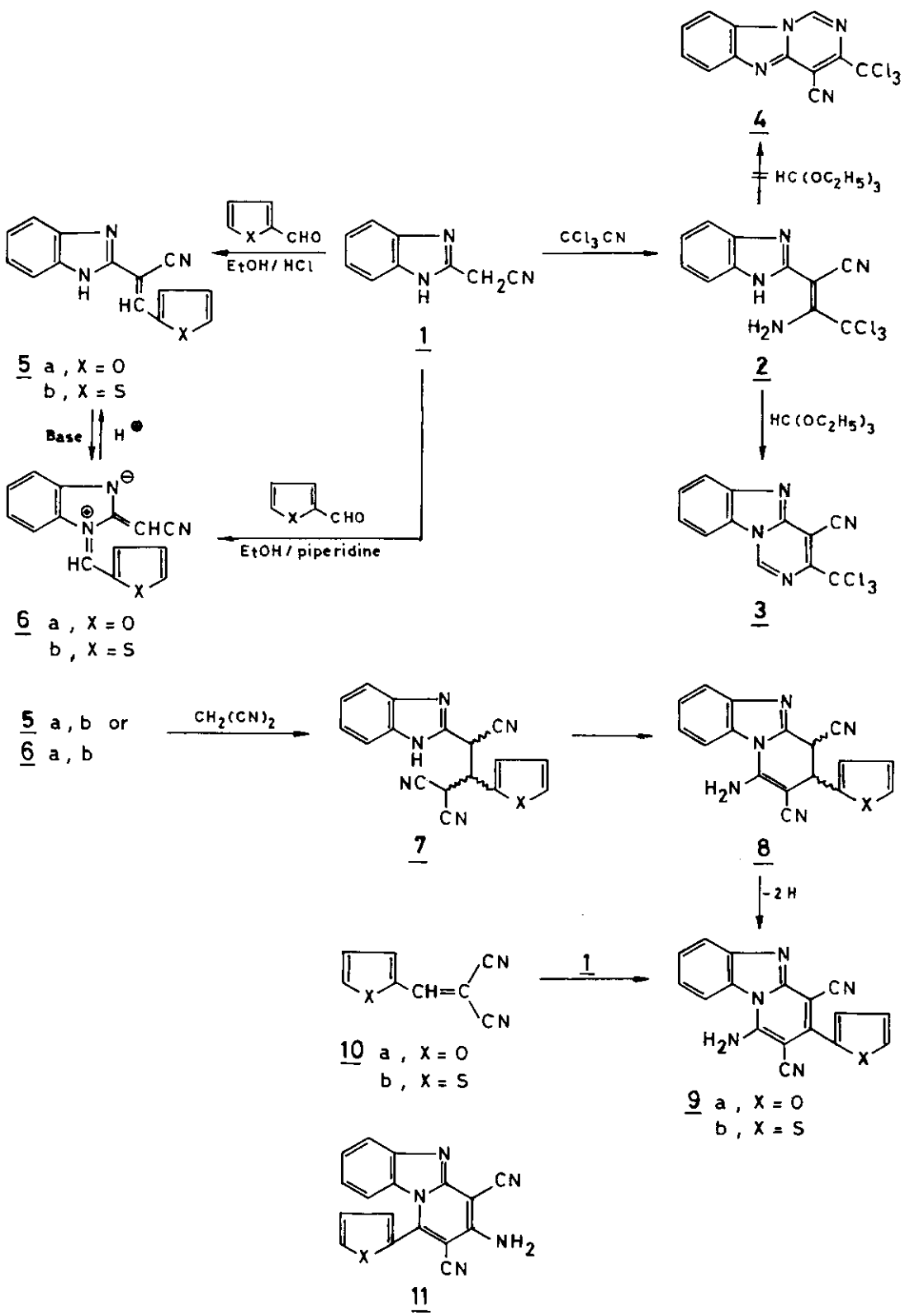
4
HC(OC2H5)3
CCl3CN
1
2
HC(OC2H5)3
3
EtOH/HCl
5 a, X = O
b, X = S
Base
H⊕
6 a, X = O
b, X = S
EtOH/piperidine
5 a, b or
6 a, b
CH2(CN)2
7
8
-2H
10 a, X = O
b, X = S
1
9 a, X = O
b, X = S
11

Table 1: List of compounds 2; 3; 5a,b; 6a,b and 9a,b

Compound*	Solvent of cryst.	Colour	Mp (°C)	Yield (%)	Mol. formula	M^+ m/e
2	MeOH	yellow	192-93	75	$C_{11}H_7N_4Cl_3$	301
3	MeOH	yellow	233-35	80	$C_{12}H_5N_4Cl_3$	310,311
5a	EtOH	yellow	182	82	$C_{14}H_9N_3O$	235
5b	EtOH	yellow	185	70	$C_{14}H_9N_3S$	251
6a	EtOH	orange	192	70	$C_{14}H_9N_3O$	235
6b	EtOH	orange	212	70	$C_{14}H_9N_3S$	251
9a	EtOH	yellow	293-95	60	$C_{17}H_9N_5O$	299
9b	EtOH	yellow	300	60	$C_{17}H_9N_5S$	315

* Satisfactory elemental analysis for all the newly synthesised compounds were obtained.

Table 2: Spectroscopic data for compounds listed in Table 1

Compound	IR (cm^{-1}) (Selected bands)	^1H NMR δ (ppm)
2	3450, 3300 (NH_2 and NH); 2220(CN); 1600(δ NH and δ NH_2)	7.20(m,3H,benzimidazole 5,6,7-H); 7.60(s,br,3H,NH_2 and benzimidazole 4-H); 12.20(s,1H,NH)
3	2220(CN)	7.60(m, 2H, benzimidazole 7,8-H); 8.00(m, 1H, benzimidazole 6-H); 8.50(m, 1H, benzimidazole 9-H); 10.20(d, 1H, CH)
5a	3400, 3220(NH); 2220(CN); 1600(δ NH)	
5b	3390, 3295(NH); 2220(CN); 1615(C=N and δ NH)	6.88(s, 3H, benzimidazole 5,6,7-H); 7.22-7.74(m, 4H, thiophene and ylidene CH protons); 7.92(dd, 1H, benzimidazole 4-H); 8.78(s,1H, NH)

Compound	IR (cm^{-1}) (Selected bands)	^1H NMR δ (ppm)
6a	2220 (CN); 1615 (C=N)	
6b	2220 (CN); 1600 (C=N)	7.08-7.20 (m, 4H, benzimidazole 5,7-H and thiophene 3,4-H); 7.57 (m, 2H, ylidene CH and thiophene 5-H); 7.77 (1H, benzimidazole 4-H); 7.99 (dd, 1H, benzimidazole 6-H); 8.50 (s,1H, azomethine proton)
9a	3320, 3310 (NH_2); 2215 (CN); 1610 (C=N and δ NH_2)	6.80 (dd, 1H, furan 3-H); 7.20 (m, 3H, benzimidazole 6,7,8-H); 7.60 (dd, 1H, furan 4-H); 7.80 7.80 (dd, 1H, furan 5-H); 8.20 (d, 3H, NH_2 and benzimidazole 9-H)
9b	3310, 3200 (NH_2); 2222 (CN); 1615 (C=N and δ NH_2)	7.10 (dd, 1H, thiophene 3-H); 7.20 (m, 3H, benzimidazole 6,7, 8-H); 7.80 (m, 2H, thiophene 4,5-H); 8.45 (d, 3H, NH_2 and benzimidazole 9-H)

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