REACTIONS OF BENZIMIDAZOLYL-ACETONITRILE AND METHANETHIOL WITH ELECTRON DEFICIENT COMPOUNDS

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Abstract: Addition of 1*H*-benzimidazole-2-acetonitrile 1 and benziimidazole-2-ylmethanethiol 2 to some π-acceptors such as tetracyanoethylene (TCNE), *p*-chloranil (*CHL-p*), *o*-chloranil (CHL-*o*), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), 2,3-dichloro- and 2,3-dicyano-1,4-naphthoquinones (DCHNQ and DCNQ) and dicynomethyleneindane-1,3-dione (CNIND) gave pyrido-, indolo-, naphthoquinopyrrolo-, thiazino-, naphthoquinothiazino[1,2-*a*]benzimidazole as well as pyridazino[1,2-*a*]dibenzimidazole derivatives.

Introduction

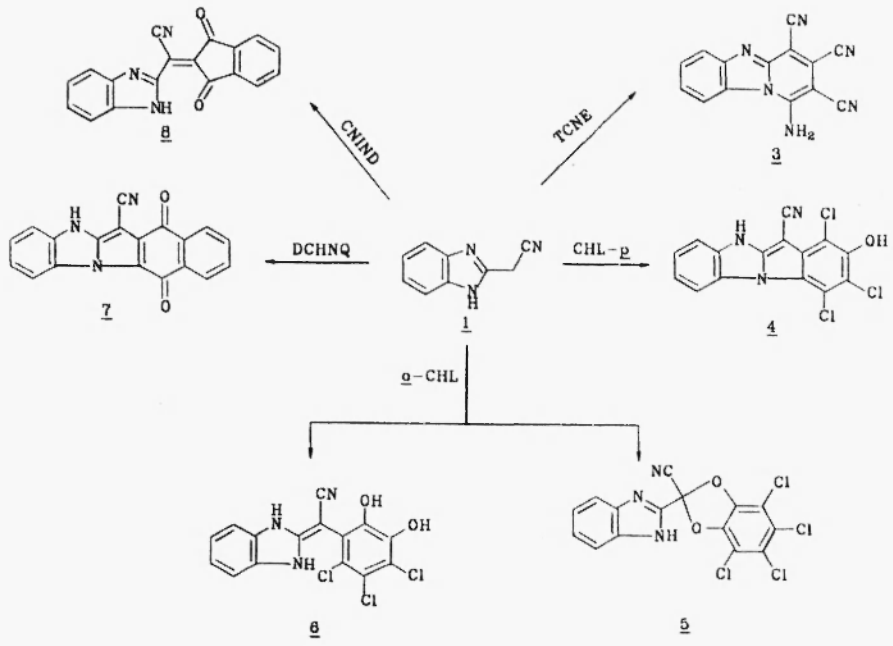
The chemistry of benzimidazole has been of increasing interest, since benzimidazoles are of considerable commercial importance as pharmaceuticals, veterinary anthelmintics and fungicides(1). Several reports were made to synthesize pyrido[1,2-*a*]benzimidazole ring system(2-6) due to the interesting in vitro antibacterial and antifungal potencies associated with some of its substituents(3,7).

In recent years, a number of unexpected and efficient chemical reactions via donor-acceptor interactions have been reported(8-14). Continuing our study of the reactions of π-acceptors with benzimidazole derivatives(11-14); 1H-benzimidazole-2-acetonitrile 1(15) and benzimidazol-2-ylmethanethiol 2(16) were used as donors to investigate and compare their behaviour towards some π-acceptors.

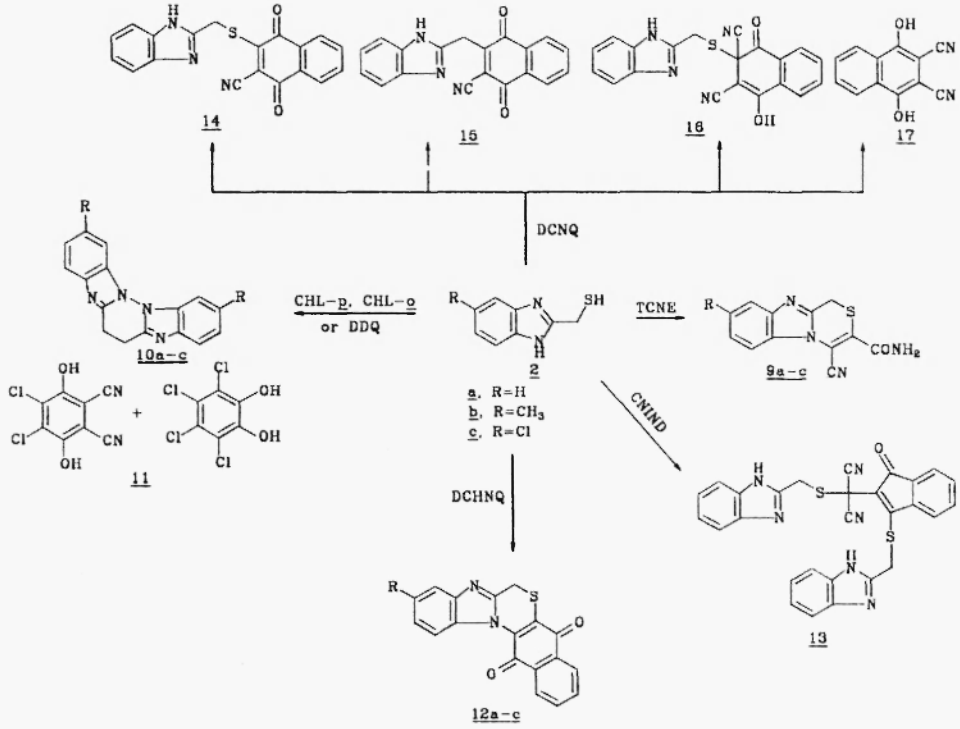
Results and Discussion

Schemes 1 and 2 summarize the interaction of 1 and 2 with π-acceptors. Mixing of a twofold molar amounts of tetracyanoethylene (TCNE) with one mole of each of the donors 1 and 2 in ethyl acetate with admission of air, furnished pyrido[1,2-*a*]benzimidazole derivatives 3 with 1 and dihydrothiazino[1,2-*a*]benzimidazole derivatives 9 with 2a-c. The IR spectra of 9 show absorption bands at 1710-1680, 2220-2210 and 3410-3210 cm^{-1} due to carbonyl group and cyano as well as amino groups respectively. The ^{1}H-NMR spectra of 9 shows among others a singlet at δ 4.12-4.20 ppm corresponding to the thiazino-CH_2 group. The mass spectra of 9 show the expected molecular ion peaks (see Table I).

Indolo[1,2-*a*]benzimidazole derivatives 4 was prepared in high yield by reacting 1 with 2,3,5,6-tetrachloro-1,4-benzoquinone (*CHL-p*), whereas α,α'-(1*H*-benzimidazole-1,3-benzodioxole) acetonitrile derivative 5, and 2-(arylcyanomethylene)-1*H*-benzimidazole derivative 6 were the reaction products of 1 with 3,4,5,6-tetrachloro-1,2-benzoquinone(CHL-*o*). The ^{1}H-NMR spectra of 5 show a broad band at 12.21 ppm due to imidazole-NH proton and confirm the absence of cyanomethylene protons. The disappearance of carbonyl group in the IR spectra and the fragmentation pattern of the mass spectra further confirm the structure of product 5. On the other hand, 2a-c reacted with 1,4- and 1,2-benzoquinones (*CHL-p*, DDQ and CHL-*o*) affording tetrahydropyridazinobenzimidazoles 10 in addition to the dihydroquinones 11. In contrast, 2,3-dichloro-1,4-naphthoquinone (DCHNQ) reacted with 1 and 2 with elimination of two moles of hydrogren chloride to give naphthoquinopyrrolo[1,2-*a*]benzimidazole 7 and nathoquinothiazino[1,2-*a*]benzimidazole derivatives 12. The elemental analysis of 10 showed no evidence of



Scheme 1



9, 10, 12	R
a	H
b	CH_3
c	Cl

Scheme 2

sulfur present in 1a-c or halogen in 10a,b. Further, confirmation of the structure based on the mass spectrum. which exhibited a molecular ion at m/z 260(28%) and a base peak at m/z 130 for 10a (see Tables I and II).

The interaction of CNIND with 1 afforded 1*H*-benzimidazole-2-acetonitrile. α-(methyleneindane-1,3-dionyl) 8 in a similar manner as the reaction of 1 with benzylidenemalononitrile(6,17,18). The condensation product 2(benzimidazol-2-ylmethanethiolyl)-2-[1-(benzimidazol-2-ylmethanethiolyl)-3-oxoindeno-2-yl]malononitrile 13 was formed during the reaction of CNIND with 2. In accordance with the structural relationship between 13 and 2-(1,3-benzothiazol-2-yl)-2-[1-(1,3-benzothiazol-2-yl)-3-oxo-3H-indeno-2-yl]malononitrile derived from 2-mercaptobenzothiazole and CNIND(12), the IR spectrum of 13 show absorption bands at 3420-3280 (imidazole-NH) and 2210 (CN) as well as 1720 cm^{-1} (CO). The ^{1}H-NMR spectrum show a singlet at 4.20 ppm due to methylene group and a broad band at 11.78-11.86 ppm due to imidazole-NH, in addition to the aromatic protons. Furthermore, the structure was established on the basis of mass spectroscopy as well as the elemental analysis.

In a different manner, 2,3-dicyano-1,4-naphthoquinone (DCNQ) interacted with 2 giving a reaction mixture which on chromatographic separation leads to the products 14-17.

Conclusion

From the above findings, it may be concluded that, although compound 1 may act as a bi-functional nucleophile bearing, nucleophilic center at methylene carbon atom as well as the imidazole-NH ring, various reactions performed in the present work showed that, the methylene group is the more active center, as reported in previous work(19,20). On the other hand, the presence of SH group attached to methylene group in compound 2 tends to change the mode of reactions with π-acceptors significantly, with respect to 1. Consequently, interesting and unexpected reaction products were obtained that can not be easily prepared by conventional synthetic methods.

Experimental

Melting points are uncorrected. IR spectra (KBr) were measured on a Shimadzu 470 spectrophotometer. The ^{1}H-NMR spectra were recorded on Bruker AM 200(200 MHz) and the chemical shifts were expressed as δ (ppm) with Me_4Si as the internal standard. Mass spectra were recorded on Finnigan MAT 8430 spectrometer at 70 eV. Microanalyses were performed by microanalytical unit at Cairo University.

Materials: The electron acceptors were prepared(21,22) and purified(12) as reported before. 1*H*-benzimidazole-2-acetonitrile 1 was prepared according to the literature(15). Benzimidazol-2-ylmethanethiol derivatives 2b,c were prepared in a similar procedure described for the preparation of 2a(16).

Reaction of 1H-benzimidazole-2-acetonitrile 1 and benzimidazol-2-ylmethanethiol 2a-c with TCNE: To a stirred solution of TCNE (256 mg, 0.002 mol) in 10 ml of dry ethyl acetate, the benzimidazole derivatives 1 and 2a-c (0.001 mol) in 15 ml of dry ethyl acetate were added dropwise at room temperature. The colour of the reaction mixture was changed from green to reddish-brown. After standing 48h. a reddish-brown crystals were precipitated in case of the reaction of 2a-c with TCNE. The mixture was filtered and the precipitate was washed with 5 ml of cold ethyl acetate. Recrystallization from acetonitrile afforded a pure crystals of 9a-c. On the other hand, the mixture of 1 and TCNE was concentrated and the residue was then chromatographed on thin layer plates using toluene/ethyl acetate (5:1) as eluent to give only one zone contained compound 3, which was recrystallized from ethanol.

Reaction of 1H-benzimidazole-2-acetonitrile 1 and benzimidazole-2-ylmethanethiol 2a-c with CHL-p, CHL-o and DDQ: To a stirred solution of benzoquinones (*CHL-p*, CHL-*o* and DDQ) (0.0015 mol) in 20 ml dry ethyl acetate, the donors *1* and *2a-c* (0.001 mol) in 15 ml dry ethyl acetate was added dropwise at room temperature. In the case of the reaction of 2a-c with the title benzoquinones, the mixture was left standing for 90 min., filtered and the precipitate was washed with cold ethyl acetate several times until the mother liquor became clear. Recrystallization of the precipitate from a suitable solvent afforded 10. The filtrate was concentrated and the residue was purified chromatographically on thin layer plates using toluene/ethyl acetate (5:1) as eluent to give

dihydrobenzoquinone derivatives 11. Whereas, in the case of the reaction of 1 with *CHL-p* and CHL-*o* the reaction mixture was left overnight. Filtered and the precipitate was washed with cold ethyl acetate and recrystallized from acetonitrile to afford 4 with *CHL-p* and 6 with CHL-*o*. The filtrate was chromatographed using toluene/ethyl acetate (10:1) to give compound 5.

Reaction of 1H-benzimidazol-2-acetonitrile 1 and benzimidazol-2-ylmethanthiol derivatives 2a-c with DCHNQ: To a stirred solution of 227 mg (0.001 mol) of DCHNQ in 20 ml dry ethyl acetate, the imidazole derivatives 1 and 2 (0.001 mol) in 15 ml dry ethyl acetate was added at room temperature. Naphthoquinothiazino[1,2-*a*]benzimidazole derivatives 12a-c were precipitated at once in case of reaction of 2 with DCHNQ, filtered and washed with 10 ml of cold ethanol, recrystallized from a suitable solvent to give 12. In case of 1 with DCHNQ the reaction mixture was concentrated and the residue was then chromatographed on thin layer plates using toluene/ethyl acetate (4:1) as eluent to give only one blue zone contained compound 7.

Reaction of 1H-benzimidazole-2-acetonitrile 1 and benzimidazol-2-ylmethanethiol 2a-c with CNIND: A solution of 0.001 mol of the imidazole derivatives 1 and 2 in 15 ml dry ethyl acetate was added to a solution of 416 mg (0.002 mol) CNIND in 20 ml dry ethyl acetate and the reaction mixture was stirred for 5 h. at room temperature. Thereafter, a red crystals of 8 had precipitated after 24 h. in case of 1 with CNIND; whereas in the case of 2 with CNIND a yellow crystals of 13 had precipitated after 72 h. The precipitates were filtered and recrystallized from a suitable solvent to give 8 and 13.

Reaction of benzimidazol-2-ylmethanethiol 2 with DCNQ: To a stirred solution of 416 mg (0.002 mol) DCNQ in 25 ml dry ethyl acetate, the benzimidazol-2-ylmethanethiol 2 (164 mg, 0.001 mol) in 15 ml dry ethyl acetate was added at room temperature. The colour of the reaction mixture changed slowly within 2 h. from green to yellowish-brown. After stirring for 72 h., the reaction mixture was filtered and the precipitate was washed with cold ethyl acetate and recrystallized from appropriate solvent to give 14. The filtrate was concentrated and chromatographed on thin layer plates using toluene/ethyl acetate (7:1) as eluent to give three zones, the fastest migrating one contained compound 15, and the second contained 16; whereas the third zone contained the dihydronaphthoquinone 17. Extraction and recrystallization from a suitable solvent afforded 15 and 16.

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Table I: The ^{1}H-NMR, IR and MS spectral data of compounds 3-10 and 12-16.

Compound	^{1}H-NMR (δ, TMS)*	IR (KBr, cm^{-1})	MS m/z (rel.intensity %)
3	7.23-7.84(m, 3H, Ar-H), 8.50(d, 1H, Ar-H), 8.66(s, br, 2H, NH_2).	3403, 3260(NH_2), 2226, 2209 (CN).	258(M^+, 46), 232 39), 164(58), 91(84), 65(100).
4	7.05-7.95(m, 3H, Ar-H), 8.45(d, 1H, Ar-H), 9.44(s, br, 1H, OH), 12.10(s, br, 1H, imidazole-NH).	3481-3106(OH, NH).	355(8), 353(19), 351(58), 349(M^+, 100), 347(39), 288(18), 252(37), 165(39), 118(52), 91(49).
5	7.22-7.86(m, 3H, Ar-H), 8.48(d, 1H, Ar-H), 12.21(s, br, IH, imidazole-NH).	3405-3173(NH), 2210(CN).	406(2), 404(4), 402(12), 400(M^+, 18), 398(9), 375(11), 347(81), 248(92), 149(100), 118(54).
6	7.10-7.88(m, 3H, Ar-H), 8.49(d, 1H, Ar-H), 9.36(s, br, 2H, 2OH), 12.07(s, br, 2H, imidazole-NH).	3477-3160(OH, NH), 2220(CN).	373(12), 371(46), 369(M^+, 100), 367(38), 283(27), 235(42), 185(24).
7	7.18-7.93(m, 7H, Ar-H), 8.50(d, 1H, Ar-H), 11.97(s, br, 1H, imidazole-NH).	3431-3116(NH), 2184(CN), 1670(CO).	311 (M^+, 100), 283(14), 255(33), 200(12), 176(7), 142(18), 105(26).
8	7.00-7.88(m, 7H, Ar-H), 12.48(s, br, 1H, imidazole-NH).	3418(NH), 1750, 1727, 1705, 1675(CO).	299(M^+, 100), 273(24), 245(51), 126(11), 76(28).
9a	4.18(s, 2H, CH_2), 7.30-7.90(m, 3H, Ar-H), 8.40-8.56(m, 3H, Ar-H and $CONH_2$).	3410-3250(NH_2), 2220(CN), 1710-1690(CO).	256(M^+, 100), 230(18), 202(11), 170(52), 104(22), 90(17).
10a	4.26(s, 4H, $2CH_2$), 7.24-8.48(m, 8H, Ar-H).	2940-2820(Ali-CH), 1620(Ar-C=C).	260(M^+, 28), 130(100), 116(17), 90(32).
12a	4.18(s, 2H, CH_2), 7.40-8.47(m, 8H, Ar-H).	2960-2880(Ali-CH), 1675(CO).	318(M^+, 100), 290(11), 262(19), 164(71), 131(80).
13	4.20(s, 2H, CH_2), 7.10-8.46(m, 12H, Ar-H), 11.78-11.86(br, 2H, imidazole-NH).	3460-3280(NH), 2920(Ali-CH), 2210(CN), 1710(CO).	518(M^+, 61), 454(96), 338(100), 311(54), 163(24), 118(39),104(44), 76(45).
14	3.90(s, 2H, CH_2), 7.14-8.53(m, 8H, Ar-H), 11.79(s, br, 1H, imidazole-NH).	3420-3250(NH), 2930(Ali-CH), 2210(CN), 1680(CO).	345(M^+, 100), 313(17), 259(21), 231(28), 191(16).
15	4.05(s, 2H, CH_2), 7.21-8.52(m, 8H, Ar-H), 11.82(s, br, 1H, imidazole-NH).	3430-3350(NH), 2950(Ali-CH), 2220(CN), 1680(CO).	313(M^+, 100), 287(16), 259(18), 231(8), 117(19).
16	3.95(s, 2H, CH_2), 7.10-8.48(m, 8H, Ar-H), 8.79(s, br, 1H, OH), 11.77(s, br, 1H, imidazole-NH).	3460-3280((OH, NH), 2940(Ali-CH), 2220(CN), 1710(CO).	372(M^+, 12), 345(17), 313(22), 210(100), 183(14).

* All compounds were measured in DMSO-d_6 except compounds 4 and 5 in Acetone-d_6.

Table II: Physical and analytical data of compounds 3-10 and 12-16.

Compound	m.p °C	Yield %	Colour	Solvent of recrystallization	Mol. Formula (M. wt.)	Analysis % Found (Calcd) C	H	N	S	Cl
3	311-313	77	Reddish-brown	Ethanol	$C_{14}H_6N_6$ (258.242)	64.88 (65.11	2.46 2.34	32.68 32.54)		
4	296-298	79	Yellowish-brown	Acetonitrile	$C_{15}H_6Cl_3N_3O$ (350.591)	51.52 (51.39	1.88 1.72	12.11 11.99		30.22 30.34)
5	189-191	36	Colourless	Ethanol	$C_{15}H_5Cl_4N_3O_2$ (401.035)	45.12 (44.93	1.29 1.26	10.31 10.48		35.49 35.36)
6	246-248	42	Grey	Ethanol	$C_{15}H_8Cl_3N_3O_2$ (368.606)	49.12 (48.88	2.24 2.19	11.29 11.40		28.63 28.85)
7	285-287	79	Blue	Methanol	$C_{19}H_9N_3O_2$ (311.299)	73.07 (73.31	3.14 2.91	13.76 13.50)		
8	243-245	76	Red	Acetonitrile	$C_{18}H_9N_3O_2$ (299.288)	72.49 (72.24	2.88 3.03	13.79 14.04)		
9a	255-257	73	Reddish-brown	Acetonitrile	$C_{12}H_8N_4OS$ (256.287)	55.98 (56.24	3.36 3.15	22.11 21.86	12.34 12.51)	
9b	208-210	68	Reddish-brown	Acetonitrile	$C_{13}H_{10}N_4OS$ (270.314)	57.89 (57.76	3.56 3.73	20.58 20.73	12.11 11.86)	
9c	326-328	63	Reddish-brown	Acetonitrile	$C_{12}H\text{-}ClN_4OS$ (290.733)	49.39 (49.58	2.56 2.43	19.46 19.27	10.87 11.03	11.91 12.19)
10a	245-247	69	Yellow	DMF/Ethanol	$C_{16}H_{12}N_4$ (260.298)	74.02 (73.83	4.77 4.65	21.69 21.52)		
10b	240-242	64	Yellow	DMF/Ethanol	$C_{18}H_{16}N_4$ (288.351)	75.26 (74.98	5.84 5.59	19.66 19.43)		
10c	266-268	61	Yellow	DMF/Ethanol	$C_{16}H_{10}Cl_2N_4$ (329.188)	58.64 (58.38	2.81 3.06	16.79 17.02		21.76 21.54)
12a	210-212	88	Pale yellow	Acetonitrile	$C_{18}H_{10}N_2O_2S$ (318.355)	67.74 (67.91	3.26 3.17	8.93 8.80	9.84 10.07)	
12b	278-280	77	Pale yellow	Acetonitrile	$C_{19}H_{12}N_2O_2S$ (332.382)	68.49 (68.66	3.81 3.64	8.61 8.43	9.42 9.65)	
12c	201-203	75	Pale yellow	Methanol	$C_{18}H_9ClN_2O_2S$ (352.800)	61.44 (61.28	2.39 2.57	8.14 7.94	8.83 9.09	9.86 10.05)
13	262-264	64	Yellow	DMF	$C_{28}H_{18}N_6OS_2$ (518.622)	65.06 (64.85	3.36 3.50	16.34 16.20	12.11 12.37)	
14	297-299	29	Colourless	Acetonitrile	$C_{19}H_{11}N_3O_2S$ (345.381)	65.86 (66.07	3.42 3.21	12.36 12.17	9.11 9.28)	
15	235-237	21	Pale yellow	Ethanol	$C_{19}H_{11}N_3O_2$ (313.315)	73.04 (72.84	3.31 3.54	13.59 13.41)		
16	251-253	23	Pale yellow	Ethanol	$C_{20}H_{12}N_4O_2S$ (372.406)	64.66 (64.50	3.12 3.25	14.86 15.04	8.73 8.61)	

Received July 24, 1996