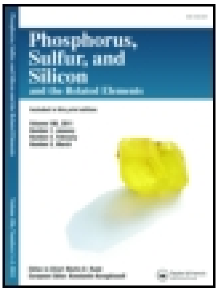

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STUDIES WITH ARYLAMINOMETHYLBENZIMIDAZOLETHIOLS: NOVEL SYNTHESIS OF 1,3-DIAZEPINO- AND 1,2,4-TRIAZEPINO[1,2-a] BENZIMIDAZOLE DERIVATIVES

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The reaction of 3-(*p*-substituted arylaminomethyl)benzimidazole-2-thiols 1a,b with tetracyanoethylene (TCNE) afforded 1,3-diazepino[1,2-a]benzimidazole derivatives 8. 2-Hydrazinobenzimidazole 2 reacted with TCNE and dicyanomethyleneindane-1,3-dione (CNIND) to form 1,2,4-triazepino[1,2-a]benzimidazole derivatives 17 and 18.

Key words: (Arylaminomethyl)benzimidazolethiols, TCNE, CNIND, 1,3-diazepino[1,2-a]benzimidazole.

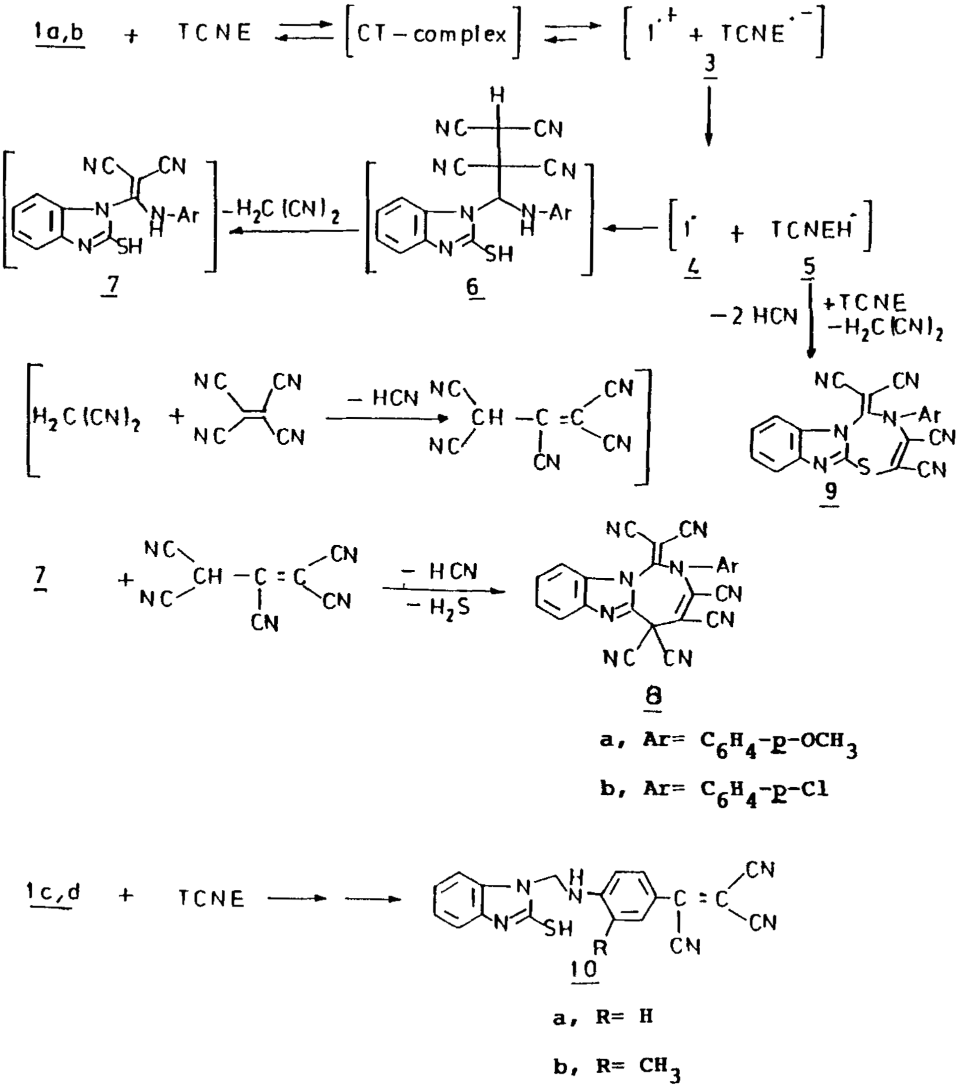
During the course of our long-standing interest in the chemistry of biologically active sulfur compounds,[1–7] we have investigated the behaviour of 2-mercaptobenzimidazole towards π-acceptors[8] due to its physiological activities.[9]

Recently, we have reported that, on mixing aryl 3-aminomethylbenzimidazole-2-thiols with various π-acceptors such as tetracyanoethylene (TCNE) and dicyanomethyleneindane-1,3-dione (CNIND) in dichloromethane, 1,2-dichloroethane, chloroform or ethyl acetate stable charge-transfer (CT) complexes form.[10,11]

In the present paper we report a novel synthesis of 1,3-diazepino- and 1,2,4-triazepino[1,2-a]benzimidazole derivatives utilizing the readily accessible arylaminomethylbenzimidazolethiol 1 and hydrazinobenzimidazole 2 as starting materials.

Mixing of a twofold molar amount of TCNE with one mole of 1a,b in DMF leads to CT-complex which gradually changed to products of chemical reaction (Scheme 1). The unstable CT-complex between 1a,b and TCNE is followed by electron transfer from 1 to TCNE to form TCNE anion radical ($TCNE^{\bullet -}$) in contact with aminomethylbenzimidazolethiol cation radical ($1^{\bullet +}$). The formation of a nitrogen cation radical is followed by transfer of an α-proton to $TCNE^{\bullet -}$ to generate a carbon-centered radical 4 together with $TCNEH^{\bullet}$ 5. These two may combine to give the adduct 6, which eliminates one molecule of malononitrile to form 7. Interestingly, TCNE interacts with malononitrile with elimination of one molecule of HCN giving pentacyanopropene. Reaction of 7 with pentacyanopropene under elimination of a molecule of HCN and another of H_2S gave 1,3-diazepino[1,2-a]benzimidazole derivatives 8.

The structure proof of 8 is based on spectral and analytical data. For example, the ^{1}H-NMR of 8a in ([D_6] DMSO, 300 MHz) clearly indicates the absence of the NH proton attached to aryl group, the SH proton attached to imidazole ring and the CH_2 group, but showed the aromatic hydrogens as well as the substituent group OCH_3. The elemental analysis of 8a showed no evidence of sulfur being present and the gross formula $C_{25}H_{11}N_9O$ was confirmed by the mass spectrum which exhibited a



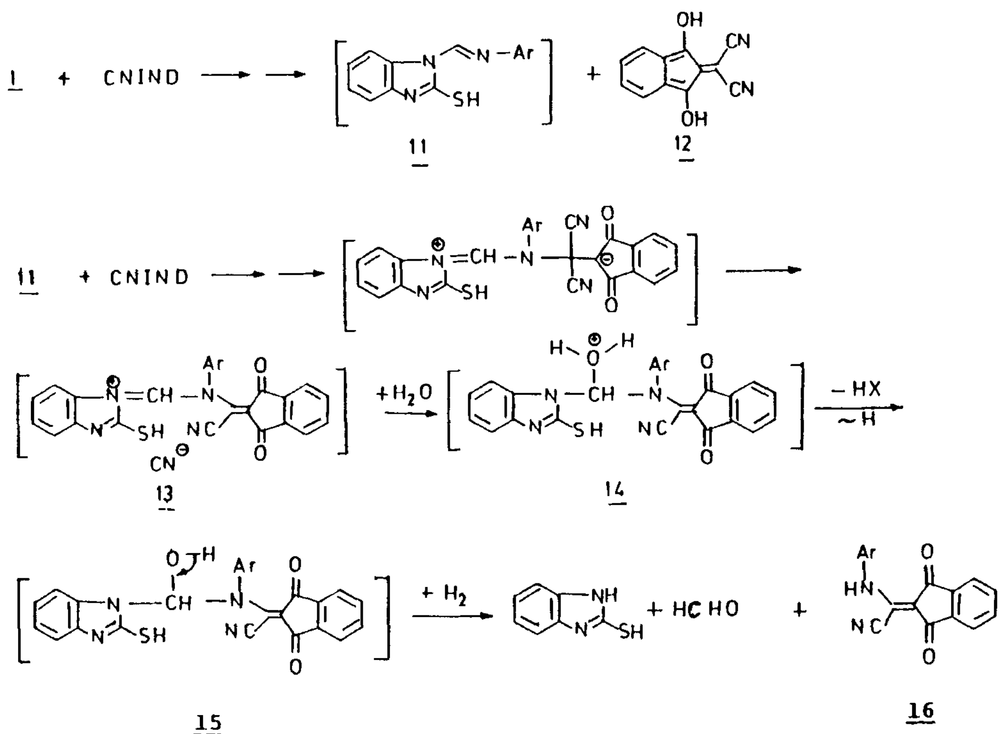
Scheme 1

molecular ion at m/z 453 (M^+, 100%). The IR spectrum showed absorption at 2210 and 1640, 1600 cm^{-1} (CN and ArC=C respectively).

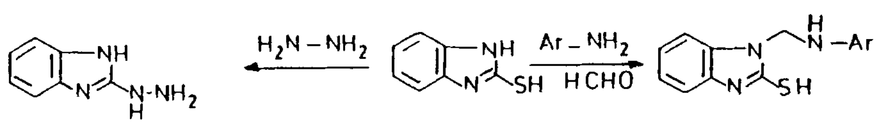
The alternative structure 9 which could reasonably arise as a result of HN-Ar proton abstraction by $TCNE^{\cdot-}$ (Scheme 1) was ruled out on the basis of spectral and analytical data.

The previous findings are supported by the reaction of 1c,d with two moles of TCNE, which afforded the expected tricyanovinylation product 10, in a similar manner to the reaction of TCNE with secondary amines.[12]

In contrast, interaction of 1a–d with CNIND yielded the reduction product 1,3-dihydroxy-,2H-(inden-2-ylidene)malononitrile 12 and 2-mercaptobenzimidazole, in addition to substituted anilino-(1,3-dioxo-2-indanylidene)-acetonitrile 16, as pro-



Scheme 2



2

1

a, Ar= C_6H_4-p-OCH_3

b, Ar= C_6H_4-p-Cl

c, Ar= C_6H_5

d, Ar= C_6H_4-o-CH_3

TCNE CNIND

FIGURE 1

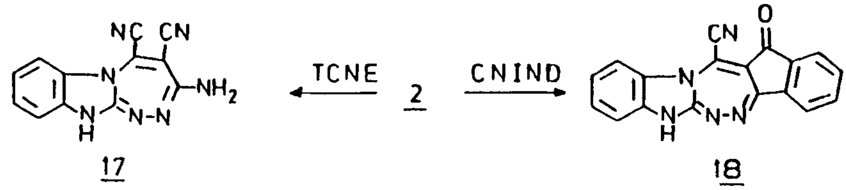


FIGURE 2

posed in Scheme 2. The hydrolysis of Schiff's base 11 (which should generate the formaldehyde and 2-mercaptobenzimidazole as well as the free amine Ar—NH_2, which in turn would attack the CNIND) prior to reaction with CNIND is considered unlikely, because there is no change in 1a–d under the similar conditions, where CNIND is absent.

Fusion of 2-mercaptobenzimidazole with hydrazine hydrate results in formation of 2-hydrazinobenzimidazole 2 (Figure 1). It has been reported that, 2-hydrazinobenzimidazole reacted with a β-diketone to give 2-(3,5-disubstituted-H-pyrazol-1-yl)benzimidazole rather than the triazepinobenzimidazole derivatives.[13] In the present investigation, the interaction of 2 with both TCNE and CNIND in DMF afforded 1,2,4-triazepino[1,2-a]benzimidazole 17 and 1,2,4-indenotriazepino[1,2-a]benzimidazole 18 (Figure 2).

EXPERIMENTAL

All the melting points are uncorrected. The IR spectra were measured with a Shimadzu 470 spectrophotometer (KBr). ^{1}H-NMR spectra were recorded on a Bruker WM 300 instrument with TMS as internal reference. Mass spectra were obtained on a Varian MAT 311 A instrument by EI at 70 eV on direct injection. Combustion analysis was carried out with CHN + O/S elemental analysis in Cairo University.

Materials: Aryl 3-aminomethylbenzimidazole-2-thiols 1a–d were prepared as previously described by us (Figure 1).[10] Analytical and spectroscopic results were also reported for compounds. 2-Hydrazinobenzimidazole 2 was prepared according to literature (Figure 1).[14] Tetracyanoethylene (TCNE) came from Merck. Dicyanomethyleneindane-1,3-dione (CNIND) (Figure 1) was prepared according to the procedure described by Chatterijee.[15] Thin Layer Chromatography (TLC): Air-dry 1-mm layers of silicagel Merck Pf 254 on plates 20 cm by 48 cm were employed for preparative TLC.

1. Reaction of 1a,b with TCNE

To a solution of 256 mg TCNE (0.002 mol) in 10 ml of DMF, the arylaminomethylbenzimidazolethiol 1a,b (0.001 mol) which was dissolved in 10 ml of DMF was added dropwise with stirring at room temperature. The reaction mixture became deep green which turned immediately to brown. After standing 144 hours brown crystals had precipitated. Recrystallization from DMF afforded pure crystals of 8a,b.

8a: Yield 276 mg (61%), m.p. 258–60°C, brown crystals (DMF).—^{1}H-NMR ([D_6]DMSO), δ = 3.87 (s, 3H, OCH_3), 7.05, 7.40 (m, 4H, Ar—H), 7.80–8.10 (m, 4H, Ar—H).—IR (KBr): $\tilde{\nu}$ = 2210 cm^{-1}, 1640, 1610, 1580 (C=N, ArC=C).—MS (70 eV) m/z (%): 453 (M^+, 100), 437 (5), 422 (4), 396 (6), 370 (4), 306 (3), 288 (4), 226 (11), 198 (5), 172 (10), 134 (9), 133 (5), 123 (5), 108 (29), 92 (5).—$C_{25}H_{11}N_9O$ (453.422): Calcd. C 66.22, H 2.45, N 27.80; found C 66.37, H 2.29, N 27.93.

8b: Yield 200 mg (43%), m.p. 318–20°C, brown crystals (DMF).—^{1}H-NMR ([D_6]DMSO), δ = 7.16, 7.59 (m, 4H, Ar—H), 7.78–8.15 (m, 4H, Ar—H).—IR (KBr): $\tilde{\nu}$ = 2205 cm^{-1} (CN), 1635, 1607, 1578 (C=N, ArC=C).—MS (70 eV) m/z (%) = 457/459 (M^+, 100), 423 (18), 397 (5), 371 (8), 307 (11), 288 (4), 75 (63).—$C_{24}H_8ClN_9$ (457.841): Calcd. C 62.96, H 1.76, N 27.53, Cl 7.74; found C 63.12, H 1.89, N 27.36, Cl 7.55.

2. Reaction of 1c,d *with TCNE*

A solution of 1c,d (0.001 mol) in 10 ml of DMF was added to a solution of TCNE, 256 mg (0.002 mol). The reaction mixture became deep green which turned immediately to reddish brown. The solvent was concentrated. The obtained reddish brown residue was dissolved in acetone and chromatographed on TLC using cyclohexane/ethyl acetate (4:1) as eluent to give only one zone which was characterized by an orange color. The zone was extracted with acetone and recrystallized from a suitable solvent to afforded the pure crystals 10.

10a: Yield 233 mg (65%), m.p. 263–65°C, orange crystals (Ethanol).—^{1}H-NMR ([D_6]DMSO) δ = 5.37 (s, br, 1H, SH), 5.66 (s, 2H, CH_2), 6.92–7.54 (m, 9H, Ar—H, NH).—IR (KBr): $\tilde{\nu}$ = 3392 cm^{-1} (NH), 2218 (CN), 1610, 1586 (ArC=C).—$C_{19}H_{12}N_6S$ (356.404): Calcd. C 64.03, H 3.39, N 23.58, S 9.00; found C 63.86, H 3.55, N 23.69, S 9.14.

10b: Yield 214 mg (58%), m.p. 277–79°C, orange crystals (Ethanol).—^{1}H-NMR ([D_6]DMSO) δ = 2.21 (s, 3H, CH_3), 5.39 (s, br, 1H, SH), 5.74 (s, 2H, CH_2), 6.83–7.44 (m, 8H, Ar—H, NH).—IR (KBr): $\tilde{\nu}$ = 3407 cm^{-1} (NH), 2224 (CN), 1607, 1570 (ArC=C).—MS (70 eV) m/z (%): 219 (91), 192 (48), 165 (48), 150 (100), 138 (15), 122 (10), 106 (23).—$C_{20}H_{14}N_6S$ (370.431): Calcd. C 64.85, H 3.81, N 22.69, S 8.65, found C 65.07, H 3.66, N 22.78, S 8.48.

3. Reaction of 1a–d *with CNIND*

To a stirred solution of 416 mg (0.002 mol) of CNIND in 15 ml of DMF, the arylaminomethylbenzimidazolethiol 1 was added with stirring for 3 hours. The reaction mixture was left for 168 hours, and the color changed from green to yellowish brown. The solvent was evaporated and the residue was dissolved in acetone, chromatographed on TLC using cyclohexane/ethyl acetate (4:1) as eluent to afford three zones. The fastest migrating zone contained 2-mercaptobenzimidazole (18–22%). The second zone which was characterized with yellow color contained substituted anilino-(1,3-dioxo-2-indanylidene)-acetonitrile 16 (31–39%). The third zone contained 1,3-dihydroxy-2H-(inden-2-ylidene)malonodinitrile 12 (22–25%).[16]

16a: *p*-Methoxyanilino-(1,3-dioxo-2-indanylidene)-acetonitrile, yield 118 mg (39%), m.p. 201–203°C (lit. 202°C).[17]

16b: *p*-Chloroanilino-(1,3-dioxo-2-indanylidene)-acetonitrile, yield 112 mg (36%), m.p. 211–213°C (lit. 214°C).[17]

16c: Anilino (1,3-dioxo-2-indanylidene)-acetonitrile, yield 93 mg (34%), m.p. 215–217°C (lit. 214–215°C).[17]

16d: 2-Methylanilino-(1,3-dioxo-2-indanylidene)-acetonitrile, yield 91 mg (31%), m.p. 181–183°C (lit. 182°C).[18]

4. Reaction of 2 *with TCNE and CNIND*

To a stirred solution of TCNE or CNIND (0.002 mol) in 15 ml of DMF, the hydrazinobenzimidazole 2 (0.001) in 10 ml of DMF was added dropwise at room temperature. After standing for 72 hours, crystals of triazepino[1,2-a]benzimidazole derivatives 17 and 18 were precipitated. Recrystallization from appropriate solvent gave compounds 17 and 18.

17: Yield 189 mg (76%), m.p. 333–335°C, pale yellow crystals (DMF).—^{1}H-NMR ([D_6]DMSO) δ = 7.34–8.10 (m, 4H, Ar—H), 8.76 (s, br, 2H, NH_2), 12.10 (s, br, 1H, imidazole-NH).—IR (KBr) $\tilde{\nu}$ = 3365–3140 cm^{-1} (NH_2, NH), 2254, 2235 (CN), 1643, 1626, 1597 (C=N, ArC=C).—MS (70 eV) m/z (%) = 249 (M^+, 100), 222 (17), 208 (4), 197 (7), 184 (4), 170 (3), 145 (7), 132 (37), 118 (38), 105 (19), 90 (14).—$C_{12}H_7N_7$ (249.234): Calcd. C 57.83, H 2.83, N 39.34; found C 57.66, H 2.96, N 39.18.

18: Yield 258 mg (83%), m.p. 325–327°C, yellow crytals (DMF).—^{1}H-NMR ([D_6]DMSO) δ = 7.28–8.20 (m, 8H, Ar—H), 12.24 (s, br, 1H, imidazole-NH).—IR (KBr). $\tilde{\nu}$ = 3423–3130 cm^{-1} (NH), 2246 (CN), 1683 (CO), 1610, 1587 (C=N, ArC=C).—MS (70 eV) m/z (%) = 311 (M^+, 100), 283 (16), 255 (5), 230 (6), 207 (8), 195 (6), 179 (5), 155 (5), 133 (10), 105 (10).—$C_{18}H_9N_5O$ (311.302): Calcd. C 69.45, H 2.91, N 22.50; found C 69.63, H 2.76, N 22.67.

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