A ONE STEP SYNTHESIS OF BENZIMIDAZO[2,1-*c*][1,2,4]TRIAZOLE DERIVATIVES USING HYDRAZONOYL HALIDES

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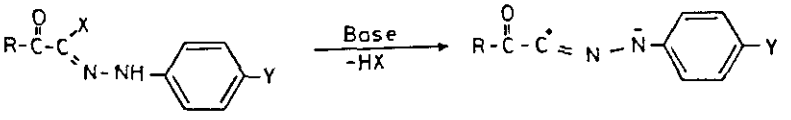
Abstract - A synthesis of benzimidazo[2,1-*c*][1,2,4]triazole derivatives (**9**) has been accomplished from the reaction of hydrazonoyl halides (**1**) with 2-methylmercaptobenzimidazole (**6**) in chloroform in the presence of triethylamine.

Hydrazonoyl halides (**1**) represent a unique class of compounds which undergo base catalysed 1,3-elimination reaction to give nitrilimines (**2**). The latter are versatile synthetic intermediates



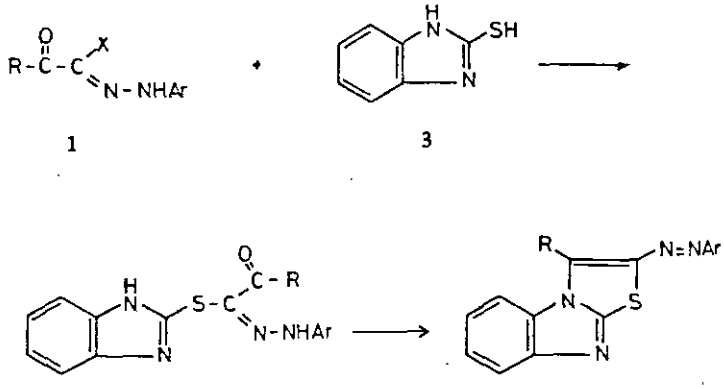
1 2

R/Y/X a, OC_2H_5/H/Cl b, OC_2H_5/CH_3/Cl c, CH_3/H/Cl
d, CH_3/CH_3/Cl e, C_6H_5/H/Br f, C_6H_5/CH_3/Br
g, 2-thienyl/H/Br h, 2-thienyl/CH_3/Br i, C_6H_5NH/H/Cl
j, C_6H_5NH/CH_3/Cl k, 2-naphthyl/H/Br l, 2-naphthyl/CH_3/Br

specially useful for 1,3-dipolar cycloaddition reactions that have been employed in the synthesis of numerous heterocycles.[1-8] However, the cycloaddition reactions of **2** with 2-methylmercaptobenzimidazole (**6**) have not yet been reported. In this paper, we wish to report the results of the study of the cycloaddition of nitrilimines (**2**) with **6**. The aim of the present study is on one hand to report a synthesis of the title compounds and on the other hand to prepare compounds that might have biological activity. In addition, this investigation

indicates that 2-mercaptobenzimidazole (3) exhibits different behaviour from its S-methyl analogs (6) towards nitrilimines (2).

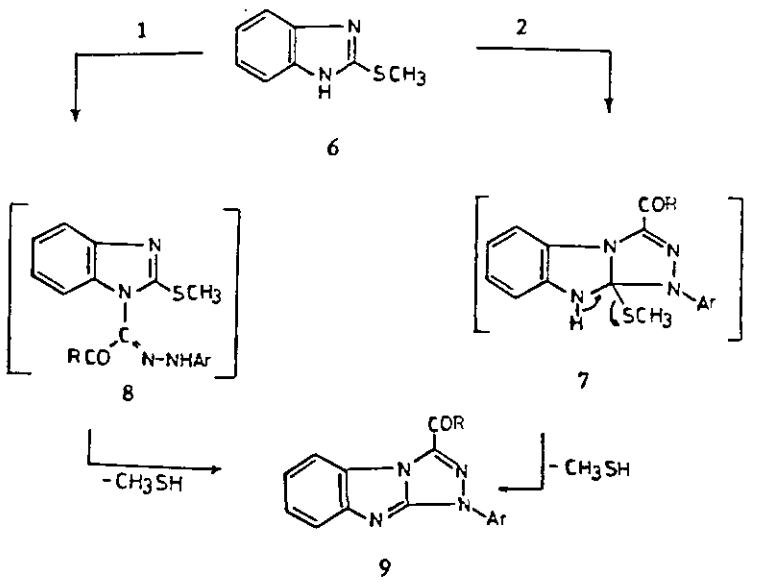
Recently, it was reported that α-ketohydrazonoyl halides (1) react with 2-mercaptobenzimidazole (3) to give the corresponding substitution products (4), which are cyclized in the presence of *p*-toluenesulfonic acid to give 5[9] (Scheme 1). In our laboratory, treatment of α-ketohydrazonoyl halides (1) with 2-methylmercaptobenzimidazole (6) in chloroform in the presence of triethyl-



Scheme 1

amine afforded benzimidazo[2,1-*c*][1,2,4]triazole derivatives (9) in moderate yield (Scheme 2). The latter products (9) resulted *via* thermal elimination of methyl mercaptan from the corresponding cycloadducts (7), formed from 1,3-dipolar cycloaddition of 2 to C=N double bond of the imidazole ring (Scheme 2). The formation of 9 can also explained by the stepwise path involving substitution to give acyclic hydrazone (8). Cyclization of the latter is completed by elimination of methyl mercaptan. All attempts to isolate the open-chain arylhydrazones (8) were unsuccessful. The reactions were regioselective and in each case only one regioisomeric compound was formed (as indicated by tlc). The regiochemical result was found to be independent on the nature of the solvent. Thus, when the reaction of **1a** with **6** was carried out in chloroform, acetonitrile or ethanol, compound (9a) was the exclusive product. The structures of the products (9) were inferred from their elemental analyses and spectral data. Thus, the infrared spectrum of 9a as an example, shows a carbonyl band at 1715 cm^{-1} assignable to an ester carbonyl group. The ^1H nmr spectrum of 9a exhibited no signal

due to the protons of S-methyl and NH groups, but it shows signals at δ 1.5 (t, J = 7 Hz, 3H), 4.6 (q, J = 7 Hz, 2H) and 7.2-8.5 (m, 9H) ppm assignable to ester and aromatic protons. Also, it shows the following m/z 306, 278, 233, 167 and 129 peaks in its mass spectrum which confirms its structure.



R/Ar a, OC_2H_5/C_6H_5 b, $OC_2H_5/C_6H_4CH_3$-p c, CH_3/C_6H_5
d, $CH_3/C_6H_4CH_3$-p e, C_6H_5/C_6H_5 f, $C_6H_5/C_6H_4CH_3$-p
g, 2-thienyl/C_6H_5 h, 2-thienyl/$C_6H_4CH_3$-p i, C_6H_5NH/C_6H_5
j, $C_6H_5NH/C_6H_4CH_3$-p k, 2-naphthyl/C_6H_5 l, 2-naphthyl/$C_6H_4CH_3$-p

Scheme 2

Antimicrobial Activity

The biological effect of these compounds were studied on some selected bacteria. The results reveal that compounds (**9a**) and (**9b**) highly affected the bacteria; while compounds (**9c**, **9d**, and **9j**) showed a moderate inhibiting action on these species. Most of the compounds showed a moderate bacteriocidal action on *Staphylococcus* species.

Different effects on some species of bacteria are shown in Table 1 . On the other hand, these compounds were shown to have no effect on the following species of bacteria:*Erwinia carato-vora var. caratovora, Erwinia caratovora var. citrullis, Mycobacterium phlei, Escheri-*

chia coli, Pseudomonas, and proteus vulgaris.

Table 1 Antimicrobial Activity

Tested organism	9a	9b	9c	9d	9e	9f	9g	9h	9i	9j	9k	9l
Staphylococcus aureus	+++	+	-	+++	-	-	-	-	-	+++	--	-
Bacillus cereus	+	+++	+	-	-	-	-	-	-	-	-	+++
Bacillus subtilis	+	++	-	-	-	-	-	-	-	-	-	-
Pseudomonas aeruginosa	-	+	-	-	-	-	+	-	-	-	-	-
Micrococcus luteus	+	-	-	-	-	++	-	+	-	+	+	+
Serratia marcescens	+++	+	+++	+	-	-	-	-	-	-	-	+

All the above species of bacteria were kindly provided from the culture collection of Microbiological Research Center [MIRCEN], Cairo, Egypt.

EXPERIMENTAL

Melting points were determined on a Gallenkamp electrothermal melting point apparatus and are uncorrected. Infrared spectra (KBr) were recorded on a Pye Unicam Sp-300 IR spectrophotometer. ^{1}H Nmr spectra were recorded on a Varian Gemeni 200 and Varian EM 390 spectrometers for solution in deuterated chloroform or dimethyl sulfoxide-d_6 using tetramethylsilane as an internal standard. Mass spectra were recorded on a GCMS-QP 1000 Ex Shimadzu, Japan. Elemental analyses were carried out at microanalytical laboratory, University of Cairo, Giza, Egypt. The hydrazonoyl halides **(1a,b)**,[10] **(1c,D)**,[11] **(1e,f)**,[12] **(1g,h)**,[13] **(1i,j)**[14] and **(1k,l)**[15] were prepared as previously described.

Preparation of benzimidazo[2,1-*c*][1,2,4]triazole derivatives (9). General Method. To a solution of 2-methylmercaptobenzimidazole **(6)** (0.8 g, 5 mmol) and the appropriate hydrazonoyl halides **(1)** (5 mmol) in chloroform (40 ml) was added triethylamine (0.7 ml, 5 mmol) at room temperature. The reaction mixture was refluxed till the hydrazonoyl halides disappeared (3-4

h) as indicated by tlc analysis. The solvent was evaporated and the residue was treated with methanol. The solid was collected and crystallized from suitable solvent to give the corresponding benzimidazo[2,1-*c*][1,2,4]triazole derivatives **(9)**.

Compound **(9a)** had mp 150°C (ethanol), (73 %); δ ($CDCl_3$) 1.6 (t, J = 7 Hz, 3H), 4.6 (q, J = 7 Hz, 2H), 7.2-8.5 (m, 9H) ppm; υ (KBr) 1715 (C=O) cm^{-1}. Ms m/z 306, 278, 233, 167, 129. Anal. Calcd for $C_{17}H_{14}N_4O_2$: C, 66.7; H, 4.6; N, 18.3. Found: C, 66.5; H, 4.4; N, 18.0.

Compound **(9b)** had mp 165°C (ethanol); (70 %); δ ($CDCl_3$) 1.6 (t, J = 7 Hz, 3H), 2.2 (s, 3H), 4.5 (q, J = 7 Hz, 2H), 7.2-8.5 (m, 8H) ppm; υ (KBr) 1715 (C=O) cm^{-1}. Anal. Calcd for $C_{18}H_{16}N_4O_2$: C, 67.5; H, 5.0; N, 17.5. Found: C, 67.3; H, 5.1; N, 17.4.

Compound **(9c)** had mp 162°C (ethanol); (70 %); δ ($CDCl_3$) 2.3 (s, 3H), 7.0-8.3 (m, 9H) ppm; υ (KBr) 1700 (C=O) cm^{-1}. Ms m/z 276, 233, 157, 118, 71, 43. Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.6; H, 4.4; N, 20.3. Found: C, 69.4; H, 4.3; N, 20.5.

Compound **(9d)** had mp 218-220°C (acetic acid); (67 %); δ ($CDCl_3$) 2.2 (s, 3H), 2.3 (s, 3H), 7.1-8.4 (m, 8H) ppm; υ (KBr) 1700 (C=O) cm^{-1}. Ms m/z 290, 247, 220, 116, 89, 65, 43. Anal. Calcd for $C_{17}H_{14}N_4O$: C, 70.3; H, 4.9; N, 19.3. Found: C, 70.5; H, 4.8; N, 19.4.

Compound **(9e)** had mp 207-208°C (acetic acid); (69 %); δ ($CDCl_3$) 7.1 - 8.3 (Ar-H) ppm; υ (KBr) 1660 (C=O) cm^{-1}. Ms m/z 388, 233, 105, 55. Anal. Calcd for $C_{21}H_{14}N_4O$: C, 74.5; H, 4.2; N, 16.6. Found: C, 74.6; H, 4.3; N, 16.4.

Compound **(9f)** had mp 198°C (acetic acid); (75 %); δ ($CDCl_3$) 2.2 (s, 3H), 7.1-8.4 (m, 13H) ppm; υ (KBr) 1660 (C=O) cm^{-1}. Anal. Calcd for $C_{22}H_{16}N_4O$: C, 75.0; H, 4.6; N, 15.9. Found: C, 74.8; H, 4.4; N, 16.0.

Compound **(9g)** had mp 272°C (acetic acid); (70 %); δ (DMSO-d_6) 6.9-8.3 (Ar-H) ppm; υ (KBr) 1640 (C=O) cm^{-1}. Ms m/z 344, 233, 220, 111. Anal. Calcd for $C_{19}H_{12}N_4OS$: C, 66.3; H, 3.5; N, 16.3; S, 9.3. Found: C, 66.4; H, 3.6; N, 16.4; S, 9.2.

Compound **(9h)** mp 256°C (acetic acid); (70 %); δ (DMSO-d_6) 2.2 (s, 3H), 7.1-8.4 (m, 11H) ppm; υ (KBr) 1650 (C=O) cm^{-1}. Ms m/z 358, 247, 220, 179, 137, 111. Anal. Calcd for $C_{20}H_{14}N_4OS$: C, 67.0; H, 3.9; N, 15.6; S, 8.9. Found: C, 67.2; H, 3.8; N, 15.5; S, 9.0.

Compound **(9i)** had mp 202°C (acetic acid); (65 %); δ ($CDCl_3$) 7.0-8.4 (m, Ar-H) ppm; υ (KBr) 1670 (C=O) , 3280 (NH) cm^{-1}. Ms m/z 253, 233, 77. Anal. Calcd for $C_{21}H_{15}N_5O$: C, 71.4; H, 4.3; N, 19.8. Found: C, 71.1; H, 4.2; N, 19.9.

Compound **(9j)** had mp 160°C (ethanol); (74 %); δ ($CDCl_3$) 2.2 (s, 3H), 7.1-8.5 (m, 14H) ppm; υ (KBr) 1570 (C=O), 3280 (NH) cm^{-1}. Anal. Calcd for $C_{22}H_{17}N_5O$: C, 71.9; H, 4.7; N, 19.1. Found: C, 72.0; H, 4.5; N, 19.2.

Compound **(9k)** had mp 164°C (acetic acid); (70 %); δ ($CDCl_3$) 7.0-8.4 (m, 15H), 9.0 (s, 1H) ppm; υ (KBr) 1650 (C=O) cm^{-1}. Ms m/z 388, 320, 272, 257, 181, 155, 127, 100, 60. Anal. Calcd for $C_{25}H_{16}N_4O$: C, 77.3; H, 4.2; N, 14.4. Found: C, 77.1; H, 4.3; N, 14.6.

Compound **(9l)** had mp 180°C (acetic acid); (73 %); δ ($CDCl_3$) 2.3 (s, 3H), 7.0-8.4 (m, 14H), 9.0 (s, 1H) ppm; υ (KBr) 1650 (C=O) cm^{-1}. Anal. Calcd for $C_{26}H_{18}N_4O$: C, 77.6; H, 4.5; N, 13.9. Found: C, 77.7; H, 4.6; N, 14.0.

Method used for testing the antibacterial action. 20 Ml of nutrient agar medium were poured in each sterile Petri dish (10 cm in diameter). Each plate has incubated by 2 ml of bacterial suspension containing 10^8 cells/ml. Discs containing 100 mg of different compounds were placed on the surface of the agar. The plates were incubated for 48 h at 28°C. The results were recorded and tabulated (Table 1).

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