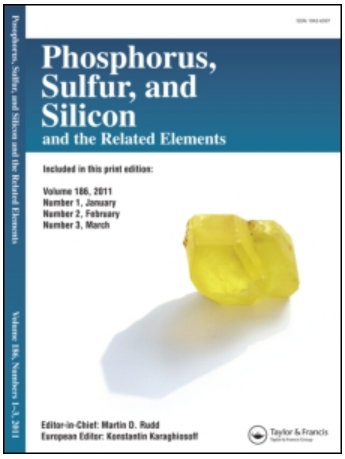

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Synthesis of Thiazinobenzimidazole Derivatives in a Solventless System Under Microwave Irradiation

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A series of thiazino [3,2-a] benzimidazole derivatives were synthesized in a solventless system under microwave irradiation in a very short time and in excellent yields.

Keywords Benzimidazole; microwave irradiation; solventless system; thiazinobenzimidazole

Benzimidazole derivatives exhibit antibacterial activity,[1,2] act as hypoglycaemic agents,[3] and more over are indicated as being associated with a particularly wide range of biological propertiès, including antitumor,[4] antiviral, and antitubercular activity.[5] These compounds are an important class of nitrogen- and sulfur-containing heterocycles and they constitute useful intermediates in organic synthesis.[6]

The microwave-enhanced chemical reactions[7] have gained popularity over the usual homogeneous and heterogeneous reactions as they can be conducted rapidly and pure products are obtained in high yields in a solvent-free condition. Organic solvents are not only expensive, they are also hazardous and flammable.[8]

We are interested in the chemistry of heterocyclic compounds containing nitrogen and sulfur atoms.[9] We are also interested in microwave-assisted organic reactions in a solventless system.[10] As part of a research program on the synthesis of a heterocyclic system containing nitrogen and sulfur in a solventless system under microwave irradiation and with a view to extending the synthetic utility of dialkyl

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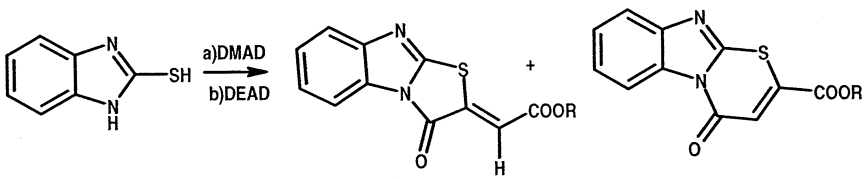
acetylendicarboxylate,[11] we have investigated the addition of the latter to 2-mercapto benzimidazole under microwave irradiation in a solventless system.

In 1978, McKillop and his co-workers[12] reported that benzimidazole-2-thione **1** reacted with DMAD in either methanol or acetic acid to give mixtures of two 1:1 molar-MeOH adducts. One adduct was identified as **2a** by X-ray crystallography but the other adduct, which was not isolated, was tentatively assigned structures **3a**.

In 1981, Acheson et al.[13] have found that thione **1** and DMAD reacted in wet and dry acetonitrile to give only **2a** and in dry methanol to give only **3a.**

We have investigated the addition of DMAD or DEAD to 2-mercapto benzimidazole under microwave irradiation in solventless system.

The reactions were simply conducted by mixing of **1** with dialkyl acetylenedicarboxylat (R = Me or Et) in a beaker and placing the beaker in a microwave oven for a short period of time. The progress of the reaction was monitored by TLC using ethanol and ethyl acetate as an eluent. Our product showed the same physical and spectroscopic data as given for **3a** in the literature[13] (Scheme 1). We also used diethyl acetylene dicarboxylate to obtain the different substituted methyl-2-oxo-2H-thiazino[3, 2-a] benzimidazole-4-carboxylate. **3b**.[13]

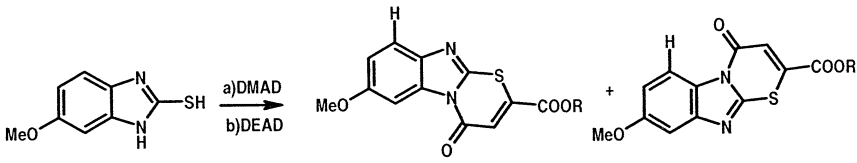


1 **2a** **3a R = Me** **3b R = Et**

SCHEME 1

Reaction of 5-methoxy benzimidazole-2-thione **4** with DMAD in either hot methanol or a solventless condition under microwave irradiation gave a mixture of two isomers that showed closely moving spots in TLC (ethanol: ethyl acetate) which could be separated chromatographically. These compounds were identified as methyl-7-methoxy-2-oxo-2H-thiazino[3, 2-a]benzimidazole-4-carboxylate, **5a**, and methyl-8-methoxy-2-oxo-2H-thiazino[3, 2-a]benzimidazole-4-carboxylate, **6a** (Scheme 2).

In 1H-NMR spectra of **5a**, 9-H (7.58 δ) is more shielded than 6-H of **6a** (8.32 δ, near to C=O).



4

5a R = Me (44%)
5b R = Et (35%)

6a R = Me (56%)
6b R = Et (65%)

SCHEME 2

EXPERIMENTAL

The melting points were obtained using an Electrothermal IA 9100 Digital Melting Point apparatus. The IR spectra were recorded on a 4300 Shimadzu spectrometer. ^{1}HNMR spectra were recorded on a 500 MHz spectrometer using TMS as internal standard.

SYNTHESIS OF THIAZINO[3,2-a]BENZIMIDAZOLE

General Procedure

Compound **1** and **4** (1 mol) was mixed with DMAD or DEAD (1 mol) thoroughly in a beaker; the beaker was placed in a microwave oven for 5 min. The progress of reaction was monitored by TLC using ethanol: ethyl acetate (3:1) as an eluent. The mixture of two isomers was separated chromatographically (ethanol: ethyl acetate 3:1). **3a**, **3b**, **5a**, **5b**, **6a**, and **6b** were crystallized from a suitable solvent. The selected physical and spectroscopic data are given below.

METHYL-2-OXO-2H-THIAZINO[3,2-a]BENZIMIDAZOLE-4-CARBOXYLATE 3a

Mp = 172°C yellow micro needles from MeOH, (Lit[13] 172.5–173°C) yield 90%. ^{1}H-NMR ($CDCl_3$)δ 4.05 (s, 3H, OMe), 7.45 (m, 1H, benzen hydrogen), 7.52 (s, 1H, =CH), 7.55 (m, 1H, benzene hydrogen), 7.81 (d, J = 7.8, 1H, benzenhydrogen), 8.58 (d, J = 7.9, 1H, benzen hydrogen, near of CO). IR (KBr): 3035, 2910, 1731, 1691, 1580, 1470, 1430, 1354, 1256, 1184, 1108, and 755 cm^{-1}. MS, m/z; M^+, 260 (100), 201 (25), 174 (21), 129 (15), 90 (7.2), 77 (4), 63 (5), 39 (4).

ETHYL-2-OXO-2H-THIAZINO[3,2-a]BENZIMIDAZOLE-4-CARBOXYLATE 3b

Mp = 135°C, yellow micro needles from EtOH, (Lit[13].135–137°C) yield 87%. ^{1}H-NMR ($CDCl_3$)δ 1.45 (t, J = 7.1, 3H, Me), 4.50 (q, J = 7.1, 2H, CH2), 7.46 (m, 2H, benzen hydrogen), 7.49 (s, 1H, = CH), 7.82 (d, J = 5.3, 1H, benzene hydrogen), 8.59 (d, J = 5, 1H, benzene hydrogen). IR (KBr): 3060, 2976, 2361, 1726, 1689, 1586, 1521, 1477, 1438, 1363, 1298, 1251, 1186, 1101, 1033, 977, 756 cm^{-1}.

METHYL-7-METHOXY-2-OXO-2H-THIAZINO[3,2-a]-BENZIMIDAZOLE-4-CARBOXYLATE 5a

Mp = 223°C, Orange micro needles, from MeOH yield 44%. ^{1}H-NMR ($CDCl_3$)δ 3.87 (s, 3H, OMe), 4.01 (s, 3H, OMe), 7.05 (d, J = 8.6, 1H, benzene hydrogen), 7.38 (s, 1H, =CH), 7.58 (d, J = 8.6, 1H, benzene hydrogen), 7.98 (s, 1H, benzene hydrogen). IR (KBr): 3060, 2923, 2853, 1733, 1691, 1617, 1477, 1433, 1366, 1292, 1249, 1194, 1148, 1114, 1020, 923, 760 cm^{-1}. MS, m/z; M^+, 290 (100), 275 (57), 247 (7), 207 (35), 159 (11), 44 (17), 28 (92).

ETHYL-7-METHOXY-2-OXO-2H-THIAZINO[3,2-a]-BENZIMIDAZOLE-4-CARBOXYLATE 5b

Mp = 126°C, Orange powder from EtOH, yield 35%. ^{1}H-NMR ($CDCl_3$)δ 1.38 (t, J = 8.5, 3H, Me), 3.88 (s, 3H, OMe), 4.37 (q, J = 8.5, 2H, OCH_2), 6.89 (d.d, J = 8.6, 1.6, 1H, benzene hydrogen), 7.16 (d, J = 1.6, 1H, benzene hydrogen), 7.18 (s, 1H, =CH), 7.80 (d, J = 8.6, 1H, benzene hydrogen). IR (KBr): 3030, 1729, 1682, 1609, 1578, 1501, 1428, 1384, 1312, 1195, 1145, 1024 cm^{-1}. MS, m/z; M,$^+$ 304 (100), 298 (13), 276 (34), 261 (43.75), 203 (7), 189 (13), 159 (13), 85 (8), 69 (5), 53 (6), 32 (4).

METHYL-8-METHOXY-2-OXO-2H-THIAZINO[3,2-a]-BENZIMIDAZOLE-4-CARBOXYLATE 6a

Mp = 140°C, orange micro needles from MeOH, yield 56%. ^{1}H-NMR ($CDCl_3$)δ 3.85 (s, 3H, OMe), 4.01 (s, 3H, OMe), 6.97 (d, J = 8.6, 1H, benzen hydrogen), 7.16 (s, 1H, benzene hydrogen), 7.42 (s, 1H, =CH), 8.32 (d, 8.6, 1H, benzen hydrogen). IR (KBr): 3098, 3049, 2947, 2828, 1729, 1690, 1621, 1517, 1475, 1433, 1386, 1323, 1281, 1196, 1138, 1099, 1021, 932, 865, 752, 711, 628 cm^{-1}. MS, m/z; M^+, 290 (100), 275 (57), 247 (7), 207 (35), 159 (11), 44 (17), 28 (92).

ETHYL-8-METHOXY-2-OXO-2H-THIAZINO[3,2-a]-BENZIMIDAZOLE-4-CARBOXYLATE 6b

Mp = 139°C, orange micro needles from EtOH, yield 65%. ^{1}H-NMR ($CDCl_3$)δ 1.45 (t, J = 7.1, 3H, Me), 3.92 (s, 3H, OMe), 4.49 (q, J = 7.1, 2H, CH_2)7.07 (d.d, J = 8.9, 2.2, 1H, benzene hydrogen), 7.25 (d, 2.2, 1H, benzene hydrogen), 7.5 (s, 1H, =CH), 8.43 (d, J = 8.9, 1H, benzene hydrogen). IR (KBr): 3035, 2960, 1697, 1690, 1576, 1463, 1424, 1362, 1291, 1242, 1193, 1145 cm^{-1}. MS, m/z; M,$^+$ 304 (100), 290 (19), 261 (25), 241 (8), 224 (35), 209 (22), 189 (12), 159 (23), 94 (5), 77 (8), 43 (9).

CAUTION

Although we did not have any accident, the use of a microwave oven in an efficient hood is highly recommended.

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