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COPPER-CATALYZED ARYLATION OF TETRAZOLE-5-THIONES UPON CONVECTION HEATING AND MICROWAVE ACTIVATION CONDITIONS

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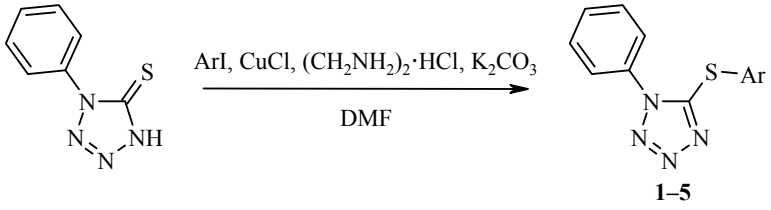
The arylation of 1-phenyltetrazole-5-thione using a series of iodobenzene derivatives in the presence of cuprous chloride and a ligand such as ethylenediamine. It was shown that the use of microwave activation permitted shortening of the reaction time, increasing yields and simplification of the reaction products isolation.

Keywords: aryl iodide, cuprous chloride, ethylenediamine, tetrazole-5-thione, arylation, microwave activation.

The most promising approach to the preparation of 1,5-disubstituted tetrazoles is functionalization of the side chain of a suitable substrate. Until recently, the synthesis of 1-substituted 5-arylsulfanyltetrazoles was carried out by the direct arylation of mercapto group with corresponding fluoro- or chlorodinitrobenzenes [1], electrolytic reaction with dihydroxybenzenes [2], or the nucleophilic substitution of the functional group at the tetrazole ring carbon atom by means of a corresponding thiol [3]. However, these and other methods suitable for the preparation of 1-substituted 5-arylsulfanyltetrazoles are not general in scope or require complicated multistep procedures.

Catalytic arylation of corresponding tetrazole-5-thiones is the most attractive method for preparation of 1-substituted 5-arylsulfanyltetrazoles. Thus, Niu et al. [4] have arylated 1-methyltetrazole-5-thione using iodobenzene. This reaction was carried out in the presence of catalytic amounts of cuprous salts and 1,10-phenanthroline as a ligand at 120°C in DMF during 10 h.



1–5

1 Ar = 2,4,6-$Me_3C_6H_2$; **2** Ar = 4-MeC_6H_4; **3** Ar = 4-$MeOC_6H_4$; **4** Ar = 4-$O_2NC_6H_4$; **5** Ar = Ph

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TABLE 1. Reaction Time and Yields in the Arylation Reaction Using Convection Heating and under MWA Conditions

Compound	Reaction time, h	Yield using convection heating, %	Yield under MWA conditions, %
1	2.0	52	76
2	1.5	60	99
3	2.5	38	90
4	2.0	36	95
5	1.5	42	80

In a continuation of a study of methods for the preparation of functionally-substituted tetrazoles, we have investigated the arylation of 1-phenyltetrazole-5-thione by aryl iodides in the presence of cuprous salts with thermal heating and in microwave activation (MWA) conditions. We have found that the corresponding *S*-aryltetrazoles **1-5** were formed upon the arylation using substituted aryl iodides in the presence of 20 mol% CuCl and ethylenediamine as the ligand in DMF at 85°C.

Microwave activation has a great effect on the course of this reaction. The yields are 20-50% greater than with convection heating at the same reaction time. The reaction times and yields are given in Table 1. The amount of tar formation is markedly reduced using MWA so that isolation of the reaction products is much more convenient.

The use of 1,10-phenanthroline as the ligand did not lead to a significant change in the reaction product yields.

Thus, the arylation of 1-substituted tetrazole-5-thiones in the presence of cuprous salts under microwave activation conditions can be seen today as the most convenient method for the preparation of 5-thioaryl-tetrazoles.

TABLE 2. Spectral Characteristics of Compounds **1-5**

Compound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)
1	3430, 3057, 3025, 2966, 2919, 2903, 1596, 1499, 1460, 1436, 1413, 1388, 1300, 1274, 1237, 1175, 1090, 1074, 1017, 974, 848, 761, 688, 562	7.65-7.75 (5H, m, H Ph); 7.06 (2H, s, H-3,5 Ar); 2.30 (6H, s, 2,6-CH_3); 2.27 (3H, s, 4-CH_3)
2	3445, 3106, 3069, 3046, 3022, 1595, 1501, 1493, 1464, 1416, 1389, 1277, 1241, 1180, 1091, 1061, 1041, 1013, 811, 763, 696, 686, 536	7.50-7.75 (5H, m, H Ph); 7.44 (2H, d, *J* = 8.0, H Ar); 7.25 (2H, d, *J* = 8.0, H Ar); 2.32 (3H, s, CH_3)
3	3432, 3017, 2976, 2934, 2829, 1589, 1571, 1492, 1456, 1419, 1408, 1389, 1288, 1254, 1241, 1175, 1087, 1075, 1023, 1007, 976, 826, 771, 690, 555	7.65-7.70 (5H, m, H Ph); 7.52 (2H, d, *J* = 8.8, H Ar); 7.01 (2H, d, *J* = 8.8, H Ar); 3.79 (3H, s, CH_3)
4	3437, 3092, 3063, 1595, 1576, 1519, 1499, 1462, 1419, 1388, 1346, 1332, 1313, 1276, 1245, 1094, 1062, 1010, 981, 853, 758, 746, 694, 685, 560	8.22 (2H, d, *J* = 9.0, H Ar); 7.65-7.73 (7H, m, H Ar)
5	3440, 3067, 1593, 1500, 1474, 1462, 1440, 1413, 1401, 1390, 1277, 1241, 1090, 1073, 1058, 1013, 1000, 973, 759, 706, 696, 687, 555, 537	7.65-7.68 (5H, m, H 1-Ph); 7.53-7.55 (2H, m, H 5-Ph); 7.43-7.46 (3H, m, H 5-Ph)

TABLE 3. Physicochemical Characterictics of Compounds **1-5**

Compound	Empirical formula	Found, % / Calculated, %			Mp, °C
		C	H	N	
1	$C_{16}H_{16}N_4S$	64.75 / 64.84	5.30 / 5.44	18.81 / 18.90	135-136
2	$C_{14}H_{12}N_4S$	62.60 / 62.66	4.47 / 4.51	20.87 / 20.88	81-82
3	$C_{14}H_{12}N_4OS$	59.01 / 59.14	4.13 / 4.25	19.78 / 19.70	87-88
4	$C_{13}H_9N_5O_2S$	52.10 / 52.17	3.09 / 3.03	23.15 / 23.40	140-141
5	$C_{13}H_{10}N_4S$	61.34 / 61.40	3.93 / 3.96	22.02 / 22.03	129-130

EXPERIMENTAL

The IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer using KBr pellets. The ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer (400 MHz) in DMSO-d_6. The elemental analysis was carried out on a LECO CHNS-932 analyzer. The microwave-assisted reactions were carried out in a Milestone MicroSynth reactor. The purity and identity of the samples obtained were monitored by thin-layer chromatography on Silufol UV-254 plates.

1,3,5-Trimethyliodobenzene was prepared according to Liu et al. [5] and 1-phenyltetrazole-5-thione was prepared according to Lieber and Ramachandran [6].

1-Phenyl-5-(phenylsulfanyl)-1*H*-tetrazole (5). K_2CO_3 (1.93 g, 14.0 mmol), cuprous chloride (0.11 g, 1.1 mmol), and ethylenediamine hydrochloride (0.15 g, 1.1 mmol) were added to a solution of 1-phenyl-tetrazole-5-thione (1.00 g, 5.6 mmol) and iodobenzene (1.20 g, 5.9 mmol) in DMF (15 ml). The reaction mixture was stirred for 2 h at 85°C under microwave activation conditions (100 W), cooled to 20°C, and poured into water (50 ml). The precipitate formed was filtered off. Yield 1.15 g (80%).

The reaction of 1-phenyltetrazole-5-thione with iodobenzene upon convection heating was carried out analogously. After pouring into water, the reaction product was extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate, and evaporated. The residue was subjected to column chromatography to give 0.60 g (42%) tetrazole **5**.

Products **1-4** were synthesized analogously. The yields, melting points, spectral data, and elemental analyses data for compounds **1-5** are given in Tables 2 and 3.

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