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TETRAZOLES.
33.* NEW METHOD FOR OBTAINING FUNCTIONALLY SUBSTITUTED TETRAZOLES†

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The interaction of 5-methylsulfonyl-1-phenyltetrazole with C-, N-, and O-nucleophiles at 18-20°C gives high yields of 1-phenyltetrazoles that are functionally substituted on the carbon atom of the heteroring. Prospects are examined for the use of 5-methylsulfonyl-1-phenyltetrazole as a universal synthon in the synthesis of tetrazoles with various types of structure.

One of the most widely used methods for obtaining 1,5-disubstituted tetrazoles is the reaction of substrates containing a -C(X)=N- fragment (where X = Cl, NR_2, OR, SR, etc.) with hydrazoic acid or its salts. Other methods, less important but still rather widely used, include the Schmidt reaction with ketones, 1,3-dipolar cycloaddition of nitriles with aliphatic and aromatic azides, the interaction of carbodiimides with hydrazoic acid, and certain others [2, 3]. However, even though there is a wide choice of methods for the synthesis of 1,5-disubstituted tetrazoles, they all have a common failing: They cannot be used to obtain tetrazoles containing highly reactive and thermally unstable functional groups. At the same time, the creation and rapid commercialization in medical practice of new, highly effective tetrazole-containing antibiotics [4], antihypertensive preparations [5, 6], and antiviral preparations [7] have made it necessary to develop simple and effective methods for obtaining functionally substituted tetrazoles that might be used in the future as synthons in the synthesis of tetrazole-containing substrates with various types of structure. It should be noted that such "practical" research is of extreme interest within the framework of the general problem of the structure vs. reactivity vs. biological activity of tetrazoles.

A solution of the problem of synthesizing functionally substituted tetrazoles can obviously be achieved either by developing direct methods for the preparation of such compounds, by functionalization of substituents in substituted tetrazoles, or by the introduction of substituents containing various functional groups into the tetrazole ring. This last approach is one of the most promising. The fruitfulness of such an approach can be demonstrated in the example of alkylation (or arylation) of tetrazole and 5-substituted tetrazoles. The application of this method, which is widely used in synthetic practice, offers a means for introducing into the tetrazole ring in positions N_1 and N_2, under mild conditions, substituents containing various functional groups [3].

The introduction of substituents into the tetrazole ring is also possible at the carbon atom of the heteroring; however, up to very recently, this method of obtaining substituted tetrazoles has not been given the necessary attention. It is known that by the interaction of 1-R-5-chloro(bromo)tetrazoles with alcoholates and phenolates of alkali metals, 5-alkyl(aryl)oxy-1-R-tetrazoles are formed [3, 8, 9]. It was also shown quite recently that 1-R-5-bromotetrazoles, upon treatment with arylboric acids in the presence of palladium catalysts, are converted smoothly to 1-R-5-aryltetrazoles [10]. Still another method for introducing substituents into the C_5 position of the heteroring is the aminomethylation of 1-substituted tetrazoles [11]. Finally, a method

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†Dedicated to Professor É. Lukevits on the occasion of his 60th birthday.

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TABLE 1. Characteristics of 5-Alkyl(aryl)oxy-1-phenyltetrazoles Ia-s

Compound	mp, °C	PMR spectrum, δ, ppm	Yield, %
Ia	72...73	4,26 (3H, s, CH_3), 7,34...7,70 (5H, m, C_6H_5)*	70
Ib	69...70	1,38 (3H, t, CH_3, J = 6 Hz), 4,42...4,66 (2H, m, CH_2), 7,24...7,68 (5H, m, C_6H_5)*	74
Ic	51	3,04 (1H, m, OH), 3,10 (2H, s, CH_2), 5,04 (2H, s, CH_2), 7,32...7.98 (5H, m, C_6H_5)*	87
Id	34...35	0,92 (3H, t, CH_3, J = 7Hz), 1,62...2,00 (2H, m, CH_2), 4,48 (2H, t, OCH_2, J = 8Hz), 7,24...7,68 (5H, m, C_6H_5)*	87
Ie	81...82	1,41 (6H, d, $2CH_3$, J = 5 Hz), 5,06...5,48 (1H, m, CH), 7,32...7,84 (5H, m, C_6H_5)*	69
If	42...43	0,86 (3H, t, CH_3, J = 8Hz), 1,22...1,88 (4H, m, $(CH_2)_2$), 4,54 (2H, t, CH_2, J = 6Hz), 7,26...7,72 (5H, m, C_6H_5)*	89
Ig	22	0,88 (6H, d, $2CH_3$, J = 7 Hz), 1,90...2,34 (1H, m, CH), 4,30 (2H, d, CH_2, J = 7 Hz), 7,38...7,74 (5H, m, C_6H_5)*	82
Ih	145	5,53 (2H, s, CH_2), 7,36...7,83 (10H, m, arom.)†	95
Ii	109	3,76 (3H, s, CH_3), 7,48...7,98 (9H, m, arom.)†	67
Ij	83...84	2,16 (3H, s, CH_3), 7,06...7,82 (9H, m, arom.)†	92
Ik	124...125	7,24 (5H, s, C_6H_5O), 7,34...7,70 (5H, m, C_6H_5N)†	83
Il	106...107	7,42...8,00 (9H, m, arom.), 9,94 (1H, s, CHO)†	75
Im	93...94	7,48...7,90 (9H, m, arom.)†	88
In	120	7,22...7,96 (9H, m, arom.)†	79
Io	116...117	7,46...8,60 (9H, m, arom.)†	81
Ip	111...112	7,48...8,46 (9H, m, arom.)†	68
Iq	92...93	7,14...7,66 (14H, m, arom.)†	73
Ir	105...106	7,30...8,00 (12H, m, arom.)†	82
Is	135...136	7,40...8,00 (12H, m, arom.)†	88

*In $CDCl_3$.

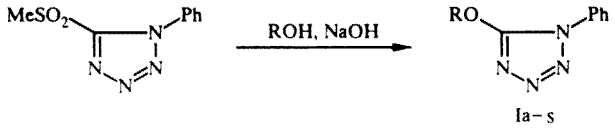
†In $(CD_3)_2CO$.

that has become more and more important recently is the functionalization of tetrazoles by treatment of 1-substituted tetrazoles with n-butyllithium, with subsequent reaction of the resulting lithium derivatives of tetrazoles with electrophilic reagents [12, 13].

We had shown previously that by the interaction of 5-methylsulfonyl-1-phenyltetrazole with alkali metal alcoholates and phenolates under mild conditions, high yields of the corresponding 5-alkyl(aryl)oxy-1-phenyltetrazoles are obtained [14]. This finding suggested that the methylsulfonyl group in 5-methylsulfonyl-1-phenyltetrazole can be replaced by not only the action of O-nucleophiles, but also C- and N-nucleophiles, and hence that this substrate can be used as a convenient and readily accessible synthon in the synthesis of various 1,5-disubstituted tetrazoles.

Here were are presenting new data obtained in a study of the interaction of 5-methylsulfonyl-1-phenyltetrazole with various C-, N-, and O-nucleophiles. In a detailed investigation of the reaction of 5-methylsulfonyl-1-phenyltetrazole with O-nucleophiles, it had been established that in the preparation of 5-alkoxy-1-phenyltetrazoles, it is not necessary to use previously prepared alkali metal alcoholates [14]. We found that the reaction proceeds smoothly when 5-methylsulfonyl-1-phenyltetrazole is treated with a sodium hydroxide solution in the corresponding alcohol; if the 5-methylsulfonyl-1-phenyltetrazole is poorly soluble in the particular alcohol, its solubility in the reaction mixture is increased by adding acetonitrile. The replacement of alkali metal alcoholates by alcohol solutions of sodium hydroxide is a major advantage in terms of ease of preparation; and at the same time, it does not result in any lower yields of the reaction products (Table 1). Under analogous conditions, by the interaction of 5-methylsulfonyl-1-phenyltetrazole with phenols in an alcoholic solution of sodium hydroxide, 5-aryloxy-1-phenyltetrazoles are formed.

Attention is directed to the fact that 5-methylsulfonyl-1-phenyltetrazole manifests higher reactivities in its interaction with alcoholates and phenolates than (for example) 5-chloro-1-phenyltetrazole in reactions with the same reagents [3, 8, 9]. It is highly significant that with the rather broad assortment of reactants that were studied in the present work (Table 1), all

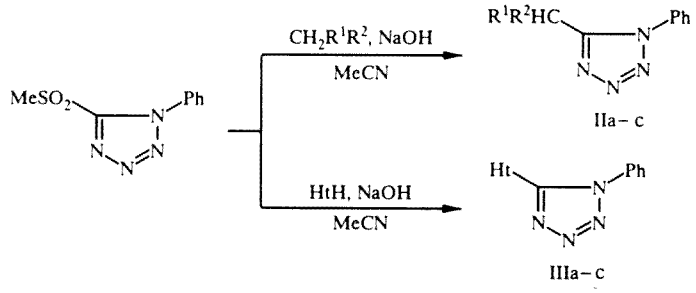


Ia–s

Ia)R = CH_3, b) C_2H_5, c) C_2H_4OH, d) C_3H_7, e) $CH(CH_3)_2$, f) C_4H_9, g) $CH_2CH(CH_3)_2$, h) $C_6H_5CH_2$, i) 2-$CH_3OC_6H_4$, j) 4-$CH_3C_6H_4$, k) C_6H_5, l) 3-$CHOC_6H_4$, m) 4-ClC_6H_4, n) 4-IC_6H_4, o) 3-$NO_2C_6H_4$, p) 4-$NO_2C_6H_4$, q) $C_6H_5C_6H_4$, r) α-naphthyl , s) β-napthyl

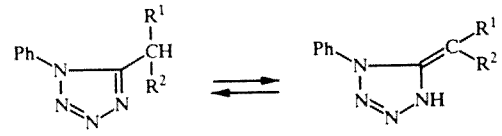
reactions were performed under exactly the same conditions, and not one negative result was obtained. This means that the process obviously proceeds through an S_N2Ar mechanism.

The next important stage in the work was a study of the interaction of 5-methylsulfonyl-1-phenyltetrazole with C- and N-nucleophiles. We also investigated such reagents as malonic acid derivatives, 4-nitrobenzyl cyanide, imidazole, benzimidazole, and benzotriazole. In all cases, mixing of the reagents in acetonitrile in the presence of sodium hydroxide at 18-20°C gave good yields of the corresponding 1,5-disubstituted tetrazoles (Table 2).



II a) $R^1 = CO_2C_2H_5$, $R^2 = CN$, b) $R^1 = R^2 = CN$, c) $R^1 = 4\text{-}NO_2C_2H_5$, $R^2 = CN$;
IIIa) Ht = 1-imidazolyl; b) 1-benzimidazolyl; c) 1-benzotriazolyl.

It should be noted that the tetrazoles IIa-c can exist in two tautomeric forms:



The state of the tautomeric equilibrium depends on the electronic structure of the substituents R^1 and R^2; strongly electronegative substituents are capable of shifting the equilibrium toward the NH-tautomer. Thus, the tetrazoles IIa,b exist in the NH-tautomeric form, the tetrazole IIc in the CH form. This is evidenced by the following facts. In the IR spectra of the tetrazole IIa, we find an absorption band of the carbonyl group at 1670 cm^{-1}, and in the tetrazoles IIa,b absorption bands of nitrile groups at 2205 and 2215 cm^{-1}; in the IR spectrum of the tetrazole IIc, the absorption band of the nitrile group is observed at 2255 cm^{-1}. These data are evidence of conjugation between the π-electron systems of the C=O and C=C bonds in the tetrazole IIa, and between the C=C and C=N bonds in the tetrazoles IIa,b, with no such conjugation in the tetrazole IIc. Still another argument in favor of the proposed structure of the tetrazoles IIa,b and IIc is the fact that in the IR spectra of compounds IIa,b there are absorption bands of NH groups at 3190 and 3200 cm^{-1}, with no such bands in the spectrum of the tetrazole IIc. This same conclusion was reached by other investigators [15-17] after studying the structure of compound IIa and other analogous tetrazoles obtained by different methods.

The extreme ease with which the methylsulfonyl group in 5-methylsulfonyl-1-phenyltetrazole is replaced under the action of C-, N-, or O-nucleophiles suggests that the circle of such reagents can be expanded. To those already studied, we can obviously add S-, Hlg-, and certain other nucleophiles; inclusion of these classes of compounds will broaden the synthetic possibilities of this reaction quite significantly. At the same time, any future successful development of this direction in the chemistry of tetrazoles will be impossible without study of the physicochemical properties of the 5-alkyl(aryl)sulfonyl-1-R-tetrazoles, since hardly any such information is available in the literature [18, 19].

The proposed method for obtaining functionally substituted tetrazoles is distinguished by simplicity and high efficiency; 5-methylsulfonyl-1-phenyltetrazole can be regarded as a universal synthon in the synthesis of tetrazoles with various types of structure.

TABLE 2. Characteristics of 1,5-Disubstituted Tetrazoles IIa-c and IIIa-c

Compound	mp, °C	PMR spectrum, δ, ppm (DMSO)	Yield, %
IIa	187	1,34 (3H, t, CH_3, J = 8Hz), 4,34 (2H, q, CH_2, J = 8Hz), 7,82 (5H, s, C_6H_5)	84
IIb	195	6,80 (2H,s, arom.), 7,57 (3H,s, arom.)	84
IIc	152...153	5,88 (1H, s, CH), 7,22...7,64 (7H, m, arom.), 7,98...8,24 (2H, m, arom.)	95
IIIa	129...130	7,00 (1H, s, CH), 7,16 (1H, s, CH), 7,56 (5H, s, C_6H_5), 7,76 (1H, s, CH)	78
IIIb	102...103	7,16...7,34 (2H,m, arom.), 7,46...7,74 (2H,m, arom.), 7,54 (5H, s, C_6H_5), 7,92 (1H,s, CH)	72
IIIc	127...128	7,50...8,40 (9H, m, arom.)	68

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument in KBr tablets; PMR spectra were recorded on a Bruker WP-200 instrument (200 MHz). The elemental analyses for C, H, and N matched the calculated values.

5-Methoxy-1-phenyltetrazole (Ia). To a solution of 0.14 g (3.5 mmoles) of sodium hydroxide in 15 ml of methanol, 0.72 g (3.2 mmoles) of 5-methylsulfonyl-1-phenyltetrazole was added; the reaction mass was stirred for 3 h at 20°C, 150 ml of water was added, and the resulting precipitate was filtered off and recrystallized from 50% aqueous ethanol. Yield 0.39 g (70%).

Compounds Ib-f were obtained by procedures analogous to that used for Ia.

1-Phenyl-5-phenoxytetrazole (Ik). To a solution of 0.16 g (4 mmoles) of sodium hydroxide and 0.38 g (4 mmoles) of phenol in 20 ml of ethanol, at 18-20°C, 0.67 g (3 mmoles) of 5-methylsulfonyl-1-phenyltetrazole was added; the reaction mass was stirred for 3 h at 20°C, 150 ml of water was added, and the resulting precipitate was filtered off and recrystallized from ethanol. Yield 0.56 g (83%).

Compounds Ii,j,l-s were obtained by procedures analogous to that used for Ik.

5-Benzyloxy-1-phenyltetrazole (Ih). To a solution of 0.77 g (3.4 mmoles) of 5-methylsulfonyl-1-phenyltetrazole and 0.45 g (4.2 mmoles) of benzyl alcohol in 15 ml of acetonitrile, 0.17 g (4.2 mmoles) of sodium hydroxide was added; the reaction mixture was stirred 14 h at 20°C, 200 ml of water was added, and the resulting precipitate was filtered off and recrystallized from ethanol. Yield 0.81 g (95%).

Compound Ig was obtained by a procedure analogous to that used for Ih.

Ethyl(4-hydro-1-phenyl-5-tetrazolylidene)cyanoacetate (IIa). To a solution of 0.58 g (2.6 mmoles) of 5-methylsulfonyl-1-phenyltetrazole and 0.31 g (2.8 mmoles) of ethyl cyanoacetate in 15 ml of acetonitrile, 0.36 g (9 mmoles) of sodium hydroxide was added; the reaction mass was stirred for 8 h at 20°C, 150 ml of water was added, the mixture was acidified with concentrated hydrochloric acid to pH 1, and the resulting precipitate was filtered off and recrystallized from a 1:1 mixture of DMF and chloroform. Yield 0.56 g (84.2%).

Compounds IIb,c were obtained by procedures analogous to that used for IIa.

5-(1-Imidazoyl)-1-phenyltetrazole (IIIa). To a solution of 0.72 g (3.2 mmoles) of 5-methylsulfonyl-1-phenyltetrazole and 0.24 g (3.5 mmoles) of imidazole in 15 ml of acetonitrile, 0.14 g (3.5 mmoles) of sodium hydroxide was added; the reaction mass was stirred for 13 h at 20°C, then diluted with water and extracted with benzene. The solvent was driven off, and the residue was recrystallized from benzene. Yield 0.53 g (78%).

Compounds IIIb,c were obtained by procedures analogous to that used for IIIa.

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