PHASE-TRANSFER CATALYSIS IN THE CHEMISTRY OF TETRAZOLES

**G. I. Koldobskii, Yu. E. Myznikov,
A. B. Zhivich, V. A. Ostrovskii,
and V. S. Poplavskii**

In this review we discuss results obtained in the development of methods for the synthesis of tetrazoles and tetrazolium salts together with studies of alkylation, acylation, and imidoylation of tetrazole and 5-substituted tetrazoles under conditions of phase-transfer catalysis.

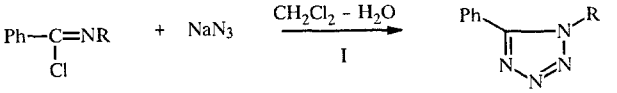
Developments in the chemistry of the tetrazoles in the last decade has greatly facilitated the wide use of these compounds in medicine [1, 2], biochemistry [3, 4], agriculture [5], and photography, and particularly as components in information recording systems [6-9]. On a theoretical level, there is undoubted interest in the results of studies of the electronic structure [10-12], acid–base properties [13, 14], and tautomerism [15] together with the reactivity [16, 17] and thermal stability of tetrazoles [18-20].

These achievements became possible through the use of the newest physico-chemical and synthetic methods in the study of the tetrazoles and the development of routes for their preparation. Among these new, highly effective, synthetic methods is phase-transfer catalysis the use of which in the chemistry of tetrazoles forms the subject of the present review.

PREPARATION OF 1,5-DISUBSTITUTED TETRAZOLES

The most widely used method for the preparation of 1,5-disubstituted tetrazoles is the reaction of imidoyl chlorides with hydrazoic acid or inorganic azides [16, 17]. In the first case solutions of hydrazoic acid, which are highly dangerous to handle, are used in such solvents as methylene chloride or benzene [21]. In the second case, the reaction is carried out with sodium azide in DMF [22] or in an aqueous buffer [23]. Although this latter method is quite straightforward, it always yields a mixture of amide and tetrazole which are difficult to separate. This difficulty can be successfully overcome by the use of a phase-transfer catalyst; it is then possible to use more accessible and cheaper solvents such as methylene chloride or chloroform.

The reaction is carried out in a two-phase system of organic solvent and water at 20-25°C in the presence of 2,3-diphenyl-5-butyltetrazolium bromide I; tetrazoles are formed in yields of 87-92% [24, 25].



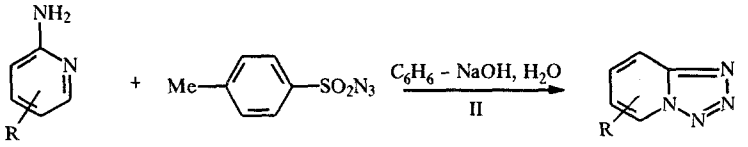
R = Me , Et, *p*-$MeOC_6H_4$, *p*-MeC_6H_4, Ph, *p*-BrC_6H_4, *p*-ClC_6H_4, *м*-$NO_2C_6H_4$

In cases where readily hydrolysable imidoyl chlorides are used in the preparation of tetrazoles the reaction is carried out under homogeneous conditions in methylene chloride, dichloroethane, or chloroform. 2,3-Diphenyl-5-butyl- or 2,3,5-triphenyltetrazolium azides are used as reagents; they differ from tetrabutylammonium azide [26] in having a high thermal stability and in being non-hygroscopic and freely soluble in the listed solvents [25, 27]. The original method for preparing

Saint Petersburg Technological Institute, Saint Petersburg 198013. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 754-761, June, 1992. Original article submitted January 6, 1992.

 0009-3122/92/2806-0626$12.50

annelated tetrazoles from 2-aminopyridine and *p*-toluene sulfonazide under phase-transfer catalysis was given in [28]. The reaction was carried out in benzene–aqueous sodium hydroxide and benzyltriethylammonium chloride II was used as catalyst.

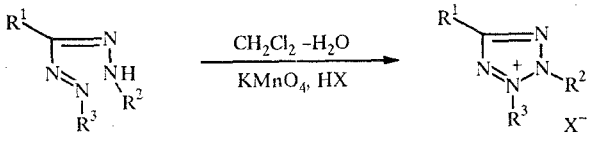


R=H, 4-Me, 5-Me

Repeated attempts to prepare 5-substituted tetrazoles from nitriles and sodium azide under conditions of phase-transfer catalysis did not lead to the desired result in spite of wide variations in the reaction conditions and the use of different types of phase-transfer catalyst. The reason for this lack of success seems to be that the formation of 5-substituted tetrazoles from nitriles proceeds via a 1,3-dipolar addition mechanism [29] and not through the formation of an azidoimine as was previously supposed [30].

PREPARATION OF 2,3,5-TRISUBSTITUTED TETRAZOLIUM SALTS

Practically the only method for the preparation of 2,3,5-substituted tetrazolium salts is the oxidation of 1,3,5-trisubstituted formazans [8]. A wide variety of oxidants have been used in carrying out this reaction: oxides of nitrogen, nitrous acid, mercury salts, lead tetraacetate, silver nitrite, chlorine, bromine, and several other reagents [8]. However, because of the unsatisfactory reproducibility of the results of the oxidation it is difficult to give preference to one or another of the listed variants. The problem was successfully resolved when phase-transfer catalysis was used for the oxidation of formazans [25, 27, 31-35]. It has been shown for an extensive range of formazans that in the oxidation of these compounds by potassium permanganate in a two-phase system organic solvent–water tetrazolium salts are formed in yields of 70-87%.

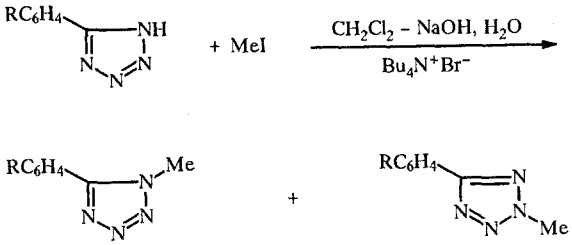


R^1 = Alk, Ar; R^2 = Ph; R^3 = Ar

An essential feature of this reaction is that oxidation of the formazan will take place in the absence of phase-transfer catalyst. The tetrazolium hydroxide, which is formed in the first stage of the reaction by the oxidation of formazan at the phase interface, plays the part of the catalyst in this process. The tetrazolium hydroxide is then transferred into the bulk of the aqueous phase where tetrazolium permanganate is formed by ion-exchange with the permanganate anion. Alternatively, the ion exchange may take place at the interface. The remainder of the process takes place under the general scheme for phase-transfer catalysed reactions. It should be added that when preparing tetrazolium salts which have a high sensitivity to bases it is desirable to use hydrochloric acid (5% max) as the aqueous phase. Finally, it should be noted that in the oxidation of triarylformazans in two phase organic solvent–water systems, in addition to potassium permanganate such reagents as nitrous acid [35] and thionyl chloride [36] can be used.

ALKYLATION OF TETRAZOLE AND 5-SUBSTITUTED TETRAZOLES

The alkylation of tetrazole and 5-substituted tetrazoles has been studied in some detail [37-41]. On the basis of a detailed analysis of the kinetic data it was concluded that the alkylation of 5-substituted tetrazoles proceeds in two stages. The rate and selectivity of this reaction depend on the electronic structure of the substituents at the 5-position of the tetrazole ring, the nature of the alkylating reagent, the counterion if a salt of tetrazole is undergoing alkylation, and the properties of the reaction medium. The first communication on the alkylation of tetrazoles under conditions of phase-transfer catalysis appeared at the beginning of the 1980s with a study of tetrazole, 5-methyltetrazole and a large number of 5-aryltetrazoles by methyl iodide and dimethyl sulfate [31, 42]:



R = *p*-MeO, *p*-Me, H, N_3, *p*-Br, *m*-Cl, *p*-NO_2

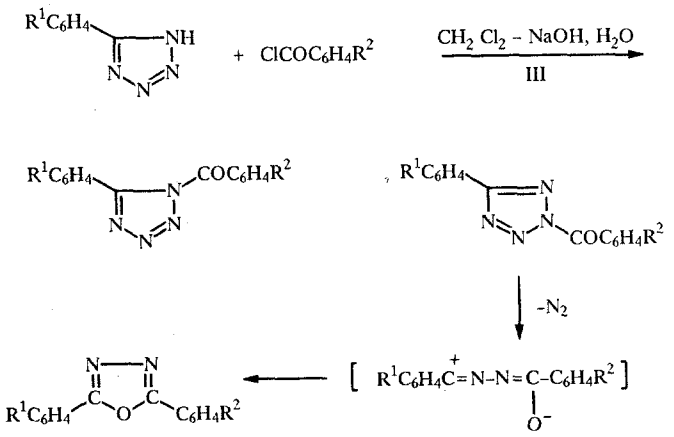
It has been suggested that the use of phase-transfer catalysis will lead to a considerable shift in the selectivity of the process. However, it is found that the ratio of N_1 to N_2 isomers formed in the alkylation of tetrazoles is practically the same under homogeneous and phase-transfer conditions. It has been established that the reason for this lies in the peculiarity of the structure of tetrazole salts in which the tetrabutyl-ammonium cation is located over the plane of the tetrazole ring. With such a salt structure, attack by the ion pair of the alkylating agent occurs at the side of the tetrazole ring opposite to the cation. This means that the steric hindrance resultinng from the large dimensions of the tetrabutyl-ammonium cation have no effect on the selectivity of the alkylation and this is supported by the experimental results given in [42].

Recently the alkylation of tetrazole by 1,2-dibromoethane and 1-chloro-2-(pyrazol-1-yl)ethane has been studied in the two-phase system benzene–aqueous sodium hydroxide in the presence of tetrabutylammonium bromide [43]. The selectivity of this reaction is not discussed but on the basis of the results of ^1H and ^{13}C NMR spectroscopy it is considered that under these conditions 1,2-bis(tetrazol-2-yl)ethane and 1-(pyrazol-1-yl)-2-(tetrazol-2-yl)ethane are formed respectively.

In conclusion, it should be noted that use of phase-transfer catalysis in the alkylation of tetrazoles, although it does not result in a change in the selectivity of the reaction, does however have great potential in so far as it makes it possible to prepare a wide range of disubstituted tetrazoles under mild conditions usinng simple and accessible reagents and solvents.

ACYLATION OF 5-SUBSTITUTED TETRAZOLES

Acylation of 5-substituted tetrazoles is a simple and effective method for preparing 2,5-disubstituted-1,3,4-oxadiazoles of different structures. The reaction is carried out at high temperature in the presence of organic bases and in the majority of cases the yields of oxadiazoles are high [16, 17]. Until very recently it was considered that in the acylation of 5-substituted tetrazoles under homogeneous conditions, generally in solution in pyridine, an unstable 2-acyltetrazole is formed in the first stage of the reaction and this recyclizes at the higher temperature with the loss of a molecule of nitrogen to form the corresponding 2,5-disubstituted-1,3,4-oxadiazole [44]. In a study of the acylation of 5-substituted tetrazoles under phase-transfer conditions, however, it was found that the earlier concept of the mechanism of this reaction was too simple [45-47]. It was established that in the acylation of substituted 5-aryltetrazoles by aromatic acid chlorides in a two-phase methylene chlorine–water system in the presence of tetrabutylammonium bromide III or 2,3,5-triphenyltetrazolium chloride, not one but two isomeric compounds were formed – 1-acyl- and 2-acyltetrazoles – and these were isolated and identified.



On subsequent heating of the mixture of 1-acyl- and 2-acyltetrazoles to 80-100°C these compounds rearrange to the corresponding 2,5-disubstituted-1,3,4-oxadiazoles. Thus, it has been shown that oxadiazoles are formed not only from 2-acyl tetrazoles, as assumed previously, but also from the 1-acyl derivatives. The mechanism of these transformations can be represented by the following scheme. In the thermolysis of 2-acyl-tetrazoles, in the first stage of the reaction an acylnitrilimine is formed as a result of rupture of the tetrazole ring and this then cyclizes to form the oxadiazole.

The formation of oxadiazoles from 1-acyltetrazoles proceeds via isomerization to the 2-tetrazole and then as indicated above. These results are of importance for an understanding of the mechanism of the conversion of 5-substituted tetrazoles into oxadiazoles and provide a basis for considering that, independently of the acylation conditions, 1-acyl- and 2-acyltetrazoles are formed in the first stage of the reaction and thermolysis of these leads to the same product.

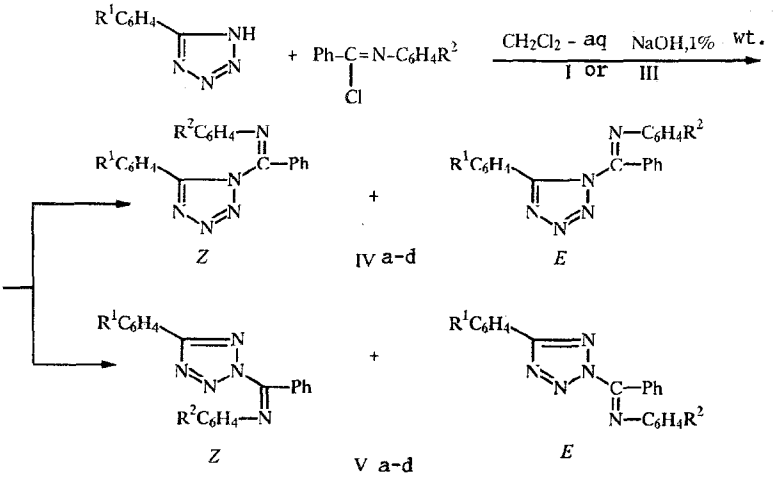
It should also be mentioned that N-acyltetrazoles have a high reactivity towards various nucleophilic substrates.

It has been shown that 1-benzoyl and 2-benzoyl-5-phenyltetrazoles are mild and effective acylating agents in reactions with compounds having a mobile hydrogen atom – aliphatic and aromatic alcohols, aromatic amines, benzimidazoles, benzotriazoles, and several others [47]. In comparison with N-benzoylimidazole [48] and N,N′-carbonyldiimidazole [49], widely used at present as acylating agents, 1-benzoyl- and 2-benzoyl-5-phenyltetrazoles have considerable advantages. The synthesis of these compounds is distinguished by its exceptional simplicity. N-benzoyltetrazole exceeds N-acylimidazoles in terms of reactivity and displays a quite high selectivity with respect to primary and secondary hydroxy and amino groups. Finally, it should be emphasized that the use of N-benzoyltetrazole is especially effective when the reactants and products are sensitive to acids and alkalis and also when they have poor thermal stability.

IMIDOYLATION OF 5-SUBSTITUTED TETRAZOLES

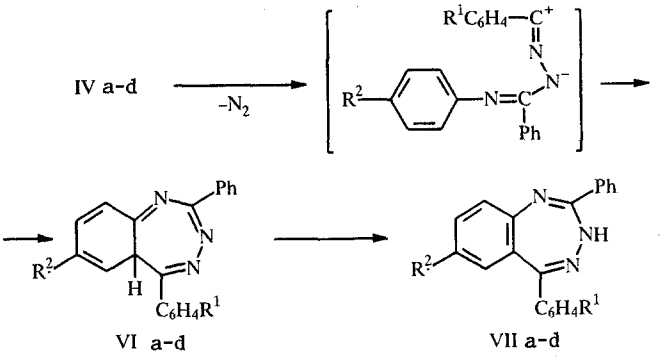
Among the numerous and varied transformations of 5-substituted tetrazoles, the reactions of these compounds with imidoyl chlorides has at present been insufficiently studied. It has been shown from several examples that in the reaction of 5-substituted tetrazoles with imidoyl chlorides in pyridine at elevated temperatures, 3,4,5-trisubstituted-1,2,4-triazoles are formed [50]. Since the publication of these results over thirty years ago, it has been considered that imidoylation and acylation of 5-substituted tetrazoles proceed by the same mechanism. On this basis it has been assumed that the unstable 2-imidoyltetrazole is formed in the first stage of the reaction and this, as the result of thermal decomposition and the elimination of a molecule of nitrogen, is converted into an imidoyl-nitrilimine. Subsequent cyclization of the imidoylnitrilimine leads to a 1,2,4-triazole. Application of phase-transfer catalysis to this reaction makes it possible to define more closely the mechanism of the imidoylation of 5-substituted tetrazoles and simultaneously opens up new, unexpected possibilities in the synthesis of heterocyclic structures that were previously difficult of access.

In the imidoylation of 5-substituted tetrazoles in a two-phase system methylene chloride-water in the presence of catalyst III not only 2-imidoyl-tetrazoles but also the isomeric 1-imidoyltetrazoles are formed [51]. In addition, it was found that the 1-imidoyl- and 2-imidoyltetrazoles IVa-d and Va-d so prepared were found in the form of Z- and E-isomers, i.e., the reaction of 5-substituted tetrazoles with imidoyl chlorides takes place nonstereospecifically.



IV, V a R^1 = H, R^2 = H; b R^1 = H, R^2 = *p*-Me; c R^1 = H, R^2 = *p*-Cl; d R^1 = *p*-Br, R^2 = H

On heatinng a mixture of isomeric 1-imidoyl- and 2-imidoyltetrazoles at 85-120°C in the absence of solvent or in such solvents as toluene, m-xylene, or dioxane, besides the expected 3,4,5-trisubstituted-1,2,4-triazoles, 3H-1,3,4-benzotriazepines are formed. So unusual a course for the reaction can be explained as follows. The imidoylnitrilimine which is formed by thermolysis of the 2-imidoyl-5-aryltetrazole is converted, as a result of intramolecular electrophilic attack at the α-carbon of the N-aryl group of the imidoyl fragment, into the intermediate 5aH-1,3,4-benzotrizepine VIa-d and this then isomerizes into the 3H-1,3,4-benzotriazepine VIIa-d.



Conversion of 1-imidoyl-5-aryltetrazoles into triazepines takes place via their isomerization into 2-imidoyl-5-aryltetrazoles. Such a route for the formation of triazepines was recently supported by studies of the thermolysis of 1-imidoyl-5-dimethylaminotetrazoles prepared by an indirect route [52].

Finally, it should be noted that tetrazolium salts are catalysts for phase-transfer catalysis and in terms of catalytic activity they are not inferior to tetrabutylammonium bromide while being at the same time considerably superior to this widely used catalyst in their thermal stability. The use of tetrazolium salts in various phase-transfer catalyzed reactions is described in [53].

As can be seen from the material collected above, over the last seven or eight years there has been marked progress in the study of the reactions of tetrazoles under phase-transfer conditions and there is every reason to conclude that further studies in this direction will begin a new, significant stage in the development of the chemistry of these compounds.

LITERATURE CITED

1. W. Durckheimer, J. Blumbach, R. Lattrel, and K. H. Scheunemann, Angew. Chem. Int. Ed., No. 3, 183 (1985).
2. M. D. Mullican, R. J. Sorenson, D. T. Connor, D. O. Thueson, J. A. Kennedy, and M. C. Conroy, J. Med. Chem., **34**, 2186 (1991).
3. A. N. Markaryan, Ya. V. Voznyi, B. B. Dzantiev, and A. M. Egorov, Bioorg. Khim., **13**, 263 (1987).
4. N. N. Karpyshev, Usp. Khim., **57**, 1546 (1988).
5. V. M. Ostrovskaya, I. A. D'yakonova, and T. D. Nikolaeva, Zh. Vses. Khim. Ova, **30**, 585 (1985).
6. S. Rokutanda, A. Tsuchida, and Y. Shigemitsu, Japanese Patent 90 287346 (1990); Chem. Abs., **115**, 18522 (1991).
7. Y. Ishida and M. Ohashi, Japanese Patent 90 280140 (1990); Chem. Abs., **115**, 18528 (1991).
8. A. B. Zhivich, G. I. Koldobskii, and V. A. Ostrovskii, Khim. Geterotsikl. Soedin., No. 12, 1587 (1991).
9. T. Habu, N. Mil, K. Kuge, H. Manto, and Y. Takamuki, J. Imaging Science, **35**, 202 (1991).
10. V. A. Ostrovskii, N. S. Panina, G. I. Koldobskii, B. V. Gidaspov, and I. Yu. Shirobokov, Zh. Org. Khim., **15**, 844 (1979).
11. E. Fos, J. Vilarrasa, and J. Fernandez, J. Org. Chem. **50**, 4894 (1985).
12. I. Jano, J. Phys. Chem., **95**, 7694 (1991).
13. V. A. Ostrovskii and G. I. Koldobskii, Weak Organic Bases [in Russian], Leningrad University Press, Leningrad (1990), p. 98.
14. G. I. Koldobskii, V. A. Ostrovskii, and B. V. Gidaspov, Khim. Geterotsikl. Soedin., No. 5, 579 (1988).
15. G. I. Koldobskii, V. A. Ostrovskii, and B. V. Gidaspov, Khim. Geterotsikl. Soedin., No. 7, 867 (1980).
16. R. N. Buttler, Adv. Heterocycl. Chem., **21**, 323 (1977).

17. G. I. Koldobskii, V. A. Ostrovskii, and V. S. Poplavskii, Khim. Geterotsikl. Soedin., No. 10, 1299 (1981).
18. A. I. Lesnikovich, O. A. Ivashkevich, V. A. Lyutsko, G. V. Printsev, K. K. Kovalenko, P. N. Gaponik, and S. V. Levchik, Termochim. Acta, **145**, 195 (1989).
19. A. I. Lesnikovich, O. A. Ivashkevich, G. V. Printsev, P. N. Gaponik, and S. V. Levchik, Termochim. Acta, **171**, 207 (1990).
20. A. I. Lesnikovich, G. V. Printsev, O. A. Lvashkevich, P. N. Gaponik, and V. A. Shandakov, Termochim. Acta, **184**, 221 (1991).
21. E. K. Harvill, R. H. Herbst, E. C. Schreiner, and C. W. Roberts, J. Org. Chem., **15**, 622 (1950).
22. P. K. Kadaba, J. Org. Chem., **41**, 1073 (1976).
23. J. Vaughan and P. A. S. Smith, J. Org. Chem., **23**, 1909 (1958).
24. I. V. Nikonova, G. I. Koldobskii, A. B. Zhivich, and V. A. Ostrovskii, Zh. Obshch. Khim., **61**, 1483 (1991).
25. I. V. Nikonova, G. I. Koldobskii, A. B. Zhivich, and V. A. Ostrovskii, Zh. Obshch. Khim., **61**, 2104 (1991).
26. R. Imhif, D. W. Lander, and J. M. Muchowski, J. Org. Chem., **42**, 3709 (1977).
27. A. B. Zhivich, Preparation, Properties and Uses of 2,3,5-Triaryl-tetrazolium Salts [in Russian], Dissertation, Leningrad (1988).
28. B. Stanovik, M. Tisler, D. Gabrijelcic, M. Kundver, and J. Zmitek, J. Heterocycl. Chem., **16**, 1567 (1979).
29. I. E. Titova, V. S. Poplavskii, G. I. Koldobskii, V. A. Ostrovskii, V. D. Nikolaev, and G. B. Erusalimski, Khim. Geterotsikl. Soedin., No. 8, 1086 (1986).
30. W. G. Finnegan, R. A. Henry, and R. Lofquist, J. Am. Chem. Soc., **80**, 3908 (1958).
31. T. F. Osipova, Reactions of Tetrazoles under Conditions of Phase Transfer Catalysis [in Russian], Dissertation, Leningrad (1984).
32. T. F. Osipova, G. I. Koldobskii, V. A. Ostrovskii, and Yu. E. Myznikov, Khim. Geterotsikl. Soedin., No. 6, 841 (1985).
33. A. B. Zhivich, G. I. Koldobskii, and V. A. Ostrovskii, Zh. Org. Khim., **24**, 225 (1988).
34. A. B. Zhivich, Yu. E. Myznikov, G. I. Koldobskii, and V. A. Ostrovskii, Zh. Obshch. Khim., **58**, 1906 (1988).
35. S. A. Belyakov, Zh. Org. Khim., **26**, 217 (1990).
36. S. A. Belyakov, Zh. Org. Khim., **25**, 2252 (1989).
37. M. L. Shpak, V. A. Ostrovskii, I. Yu. Shirobokov, G. I. Koldobskii, and B. V. Gidaspov. Zh. Org. Khim., **14**, 2444 (1978).
38. I. Yu. Shirobokov, V. A. Ostrovskii, and G. I. Koldobskii, Zh. Org. Khim., **15**, 839 (1979).
39. I. Yu. Shirobokov, V. A. Ostrovskii, and G. I. Koldobskii, Zh. Org. Khim., **16**, 788 (1980).
40. V. A. Ostrovskii, I. Yu. Shirobokov, and G. I. Koldobskii, Zh. Org. Khim., **17**, 146 (1981).
41. V. S. Poplavskii, I. E. Titova, V. A. Ostrovskii, and G. I. Koldobskii, Zh. Org. Khim., **18**, 1981 (1982).
42. T. F. Osipova, V. A. Ostrovskii, G. I. Koldobskii, and G. B. Erusalimskii, Zh. Org. Khim., **20**, 398 (1984).
43. J. Torres, J. L. Lavandera, P. Cabildo, R. M. Claramunt, and J. Elguero, J. Heterocycl. Chem., **25**, 771 (1988).
44. R. Huisgen, J. Sauer, H. J. Sturm, and J. H. Markgraf, Chem. Ber., **93**, 2106 (1960).
45. T. F. Osipova, G. I. Koldobskii, and V. A. Ostrovskii, Zh. Org. Khim., **20**, 1119 (1984).
46. T. F. Osipova, G. I. Koldobskii, and V. A. Ostrovskii, Zh. Org. Khim., **20**, 2468 (1984).
47. Yu. E. Myznikov, G. I. Koldobskii, I. N. Vasil'eva, and V. A. Ostrovskii, Zh. Org. Khim., **24**, 1550 (1988).
48. L. Fieser and M. Fieser, Reagents for Organic Synthesis, Wiley, New York (1967).
49. L. Fieser and M. Fieser, Reagents for Organic Synthesis, Wiley, New York (1967).
50. R. Huisgen, J. Sauer, and M. Seidel, Chem. Ber., **93**, 2885 (1960).
51. G. I. Koldobskii, I. V. Nikonova, A. B. Zhivich, V. A. Ostrovskii, and V. S. Poplavskii, Zh. Obshch. Khim., **62**, 194 (1992).
52. P. F. Lindey, G. V. Boyd, and G. A. Nicolaou, Acta Cryst., **C46**, 1693 (1990).
53. G. I. Koldobskii, A. B. Zhivich, and V. A. Ostrovskii, Zh. Obshch. Khim., **62**, 3 (1992).