*Chemistry of Heterocyclic Compounds, Vol. 9, No. 9, 1994*

# CYANAMIDES IN HETERODIENE SYNTHESIS (REVIEW)

**D. D. Nekrasov**

*The published data on the participation of cyanamides in heterodiene synthesis as dienophophiles were organized and generalized.*

Cyanamide was first synthesized by S. Cannizzaro and S. Cloez in 1851 [1]. Its N-mono- [2] and N,N-disubstituted derivatives were obtained slightly later [3-5]. Due to their unique chemical properties, the interest in cyanamides has not decreased [6].

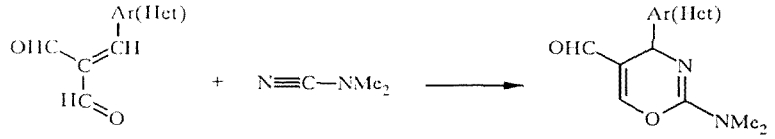
Increasing attention has been focused on cyanamide and its derivatives in the last two decades due to the publication of studies indicating their participation in heterodiene synthesis with inversion of the electronic effect in addends. This comparatively sparsely investigated type of [4 + 2]-cycloaddition [7], in contrast to the classic Diels—Alder reaction in heterodiene synthesis, usually involves cycloaddition of electron-rich dienophiles to electron-deficient dienes.

The published data which consider cyanamides as dienophiles have not previously been generalized. The chemical properties of cyanamides have been touched on in reviews in a fragmentary manner [8-13].

The material is arranged in the present review as a function of the type, number, and combination of heteroatoms in the diene.

## 1-OXA-1,3-BUTADIENES

The 1-oxa-1,3-butadiene system is the backbone of methylene malonaldehydes (I) and acylketenes (II). In the reaction with dimethylcyanamide (boiling in benzene), aldehydes I play the role of $4\pi$ components. 4H-1,3-Oxazines (III) are formed as a result [14].




I III

Ar = 4-$NO_2C_6H_4$, 4-$ClC_6H_4$, Ph; Het = 2- thienyl

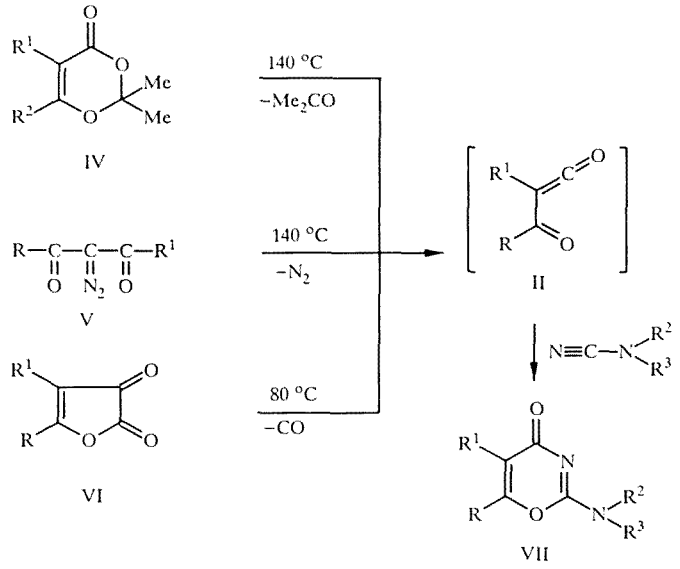
In most cases, acylketenes II are unstable compounds, so that reactions with them are conducted *in situ* (Scheme 1). Thermolysis of 1,3-dioxin-4-ones (IV), 2-diazo-1,3-diketones (V), and 2,3-dihydrofuran-2,3-diones (VI) is the most widely used method of generating them.

The reaction of acylketenes II with cyanamides takes place according to the [4+2]-cycloaddition type with formation of 1,3-oxazin-4-ones (VII). The analysis of the effect of substituents in the dienophile on cycloaddition in [15] showed that this conversion is a Diels—Alder reaction with inversion of the electronic effect in the addends. The most varied oxazinones VII with substituents in positions 2, 5, and 6 were obtained from dioxinones IV [16-19]. Only symmetric diazoketones V [20, 21] are used for preparative purposes, since this excludes formation of isomeric oxazinones. In contrast to dioxinones, only disubsti-

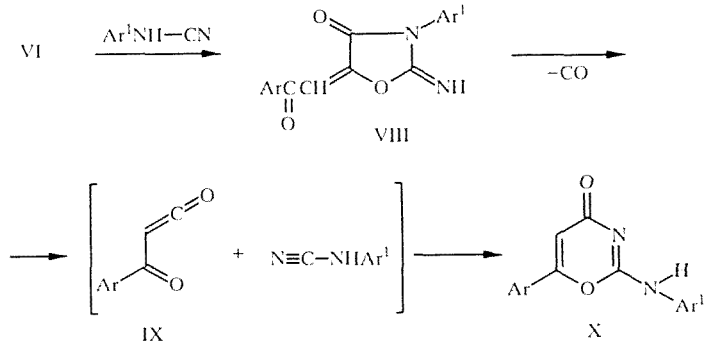
Institute of Industrial Chemistry, Ural Branch, Russian Academy of Sciences, Perm' 614600. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1155-1162, September, 1994. Original article submitted March 28, 1994.

0009-3122/94/3009-0997$12.50 

Scheme 1

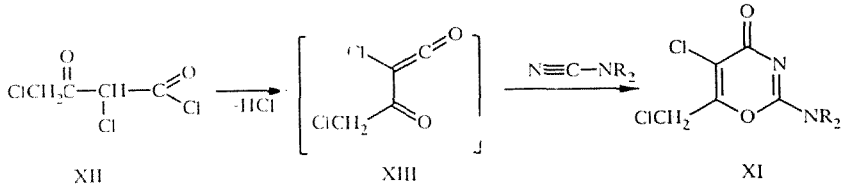


tuted cyanamides react with furandiones [15, 22]. Recyclization of furandiones VI into 2-imino-4-oxazolidones (VIII) takes place in the reaction of arylcyanamides with them [23, 24], and (VIII) are decarbonylated above 140°C with formation of aroylketenes (IX) and the starting cyanamides, subsequently yielding cycloadducts (X) [25, 26].



Ar = Ph, 4-$MeC_6H_4$, 4-$ClC_6H_4$; $Ar^1$= 2-$ClC_6H_4$

Acylketenes are not always formed as intermediates of the reaction. Synthesis of 1,3-oxazin-4-ones (XI) from acid chloride (XII) and disubstituted cyanamides is most probably due to intermediate formation of alkylketene (XIII) [27].



$NR_2$ = $NMe_2$, $N(CH_2CH_2CN)_2$, $N(CH_2)_5$, $N(CH_2)_2O(CH_2)_2$

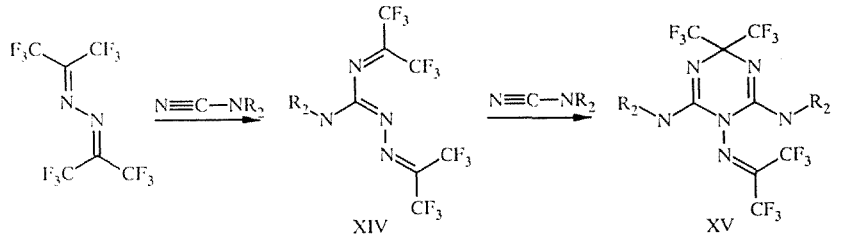
Diketene reacts with cyanamides similar to acylketenes. The corresponding 2-amino-substituted 6-methyl-1,3-oxazin-4-ones are the products of the reaction [28-30].

## 1,3- AND 2,3-DIAZA-1,3-BUTADIENES

The largest number of studies of heterodiene synthesis of cyanamides with azadienes concerns compounds containing a 1,3-diaza-1,3-butadiene system.

Hexafluoroacetonazine reacts with two molecules of dialkylcyanamide. 3,4,6-Triazaocta-2,4,6-triene (XIV) is formed

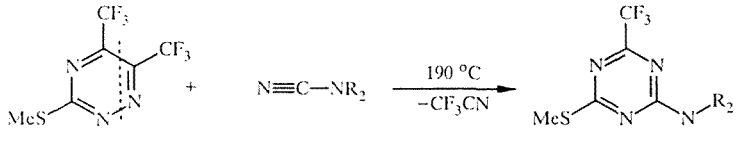
in the first stage, and its 1,3-diazadiene fragment subsequently reacts with a second molecule of cyanamide by [4 + 2]-cycloaddition with formation of 1,4-dihydro-1,3,5-triazine (XV) [31, 32].



XIV XV

$NR_2 = NMe_2,\ NEt_2,\ N(CH_2)_5$

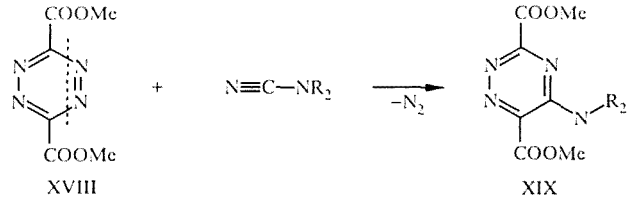
The reaction of electron-poor 1,2,4-triazine (XVI), which contains a 1,3-diazadiene fragment, with electron-rich N-substituted cyanamides is described as [4 + 2]-cycloaddition with inversion of the electronic effect. 1,3,5-Triazines (XVII) are the products of these reactions [33].



XVI XVII

$NR_2 = NMe_2,\ N(CH_2)_4,\ N(CH_2)_5,\ \overline{N(CH_2)_2O(CH_2)_2}$

In addition to 1,2,4-triazines XVI, 1,2,4,5-tetrazines (XVIII) were also involved in the reaction of [4 + 2]-cycloaddition with dialkylcyanamides. In contrast to the former, they contain a 2,3-diaza-1,3-butadiene fragment. This reaction is also an example of reverse diene synthesis which exclusively yields 1,2,4-triazines (XIX) [34].

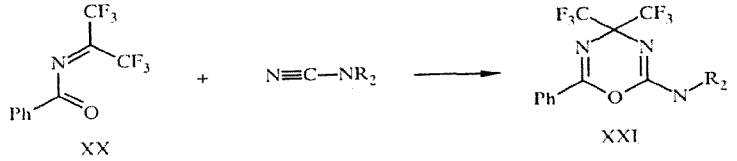


XVIII XIX

$NR_2 = NMe_2,\ N(CH_2)_4,\ N(CH_2)_5,\ \overline{N(CH_2)_2O(CH_2)_2}$

## 1-OXA-3-AZA-1,3-BUTADIENES

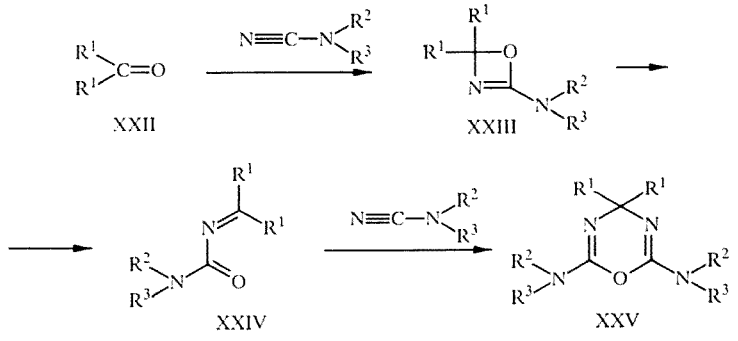
1-Oxa-3-aza-1,3-butadiene (XX) and cyanamides form [4 + 2]-cycloadduct (XXI) [35].



XX XXI

$NR_2 = NH_2,\ NMe_2,\ NEt_2,\ N(CH_2)_4$

In the reaction of perhaloketones (XXII) with cyanamides, an unstable product of [2 + 2]-cycloaddition (XXIII) is initially formed, as in the case of azines. As a result of spontaneous electrocyclic splitting, (XXIII) is converted into 1-oxa-3-aza-1,3-butadiene (XXIV), which subsequently enters into the cycloaddition reaction with a second molecule of cyanamide with formation of 1,3,5-oxadiazine (XXV) [35-37].

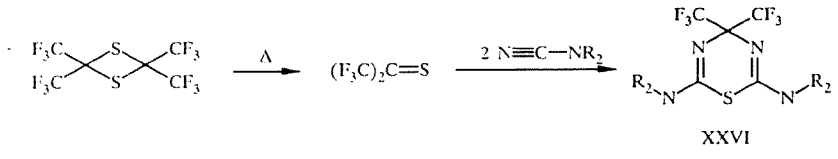


XXII XXIII XXIV XXV

$R^1 = CF_3$, $CF_2Cl$; $NR^2R^3 = NH_2$, $NMe_2$, $NEt_2$, $N(CH_2)_5$

## 1-THIA-3-AZA-1,3-BUTADIENES

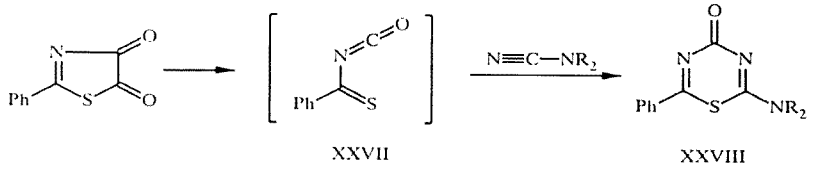
Hexafluorothioacetone, which exists as a dimer, reacts with cyanamides according to a scheme similar to the one shown above for haloketones XXII. The products of the reaction in this case are 4H-1,3,5-thiadiazines XXVI [35].



XXVI

$NR_2 = NMe_2$, $NEt_2$, $N(CH_2)_5$

The 1-thia-3-aza-1,3-butadiene fragment contains thioacyl isocyanate (XXVII), generated in thermolysis of 2-phenyl-thiazoline-4,5-dione. 1,3,5-Thiadiazin-4-ones (XXVIII) are formed as a result of [4 + 2]-cycloaddition of cyanamides to isocyanate XXVII [38].



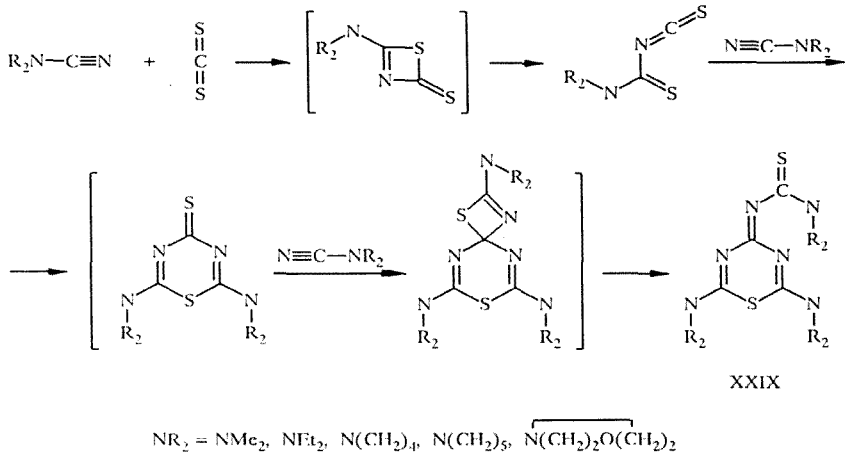
XXVII XXVIII

$NR_2$ (yield, %): $NMe_2$ (83), NMePh (27), $NPh_2$ (4)

An increase in the number of aromatic substituents in the cyanamide decreases the electron density in the dienophile and sharply reduces the yield of thiadiazinones XXVIII. Such a mechanism is observed in diene synthesis with a reverse electronic effect in the addends.

The subsequent reaction of carbon disulfide with three molecules of disubstituted cyanamide under high pressure (500 MPa, 100°C, 20 h) is shown in Scheme 2. The final products are 1,3,5-thiadiazines (XXIX) [39, 40].

Scheme 2



XXIX

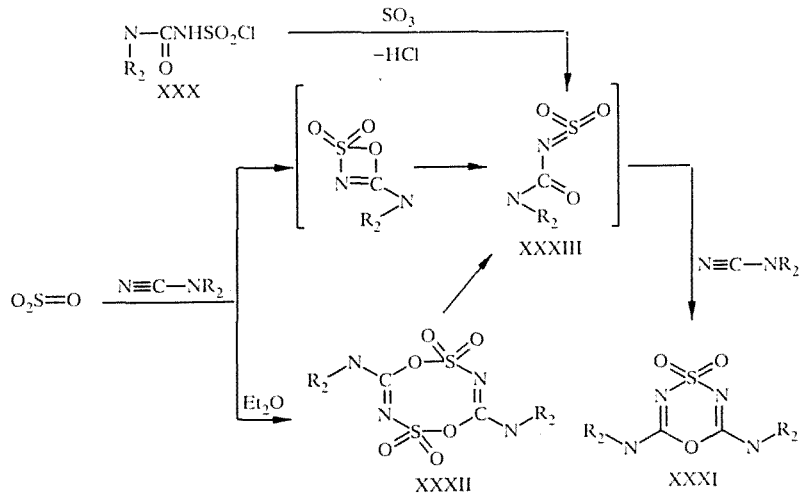
$NR_2$ = $NMe_2$, $NEt_2$, $N(CH_2)_4$, $N(CH_2)_5$, $N(CH_2)_2O(CH_2)_2$

In similar conditions, cycloaddition of O=C=S to dialkylcyanamides yields 1:2 adducts — 2,6-dialkylamino-1,3,5-thiadiazin-4-ones [41].

## OTHER HETERODIENES

1,4,3,5-Oxathiadiazine-4,4-dioxides (XXXI) are formed in the reaction of chlorosulfonylurea (XXX) or sulfur trioxide with cyanamides (Scheme 3) [42, 43].

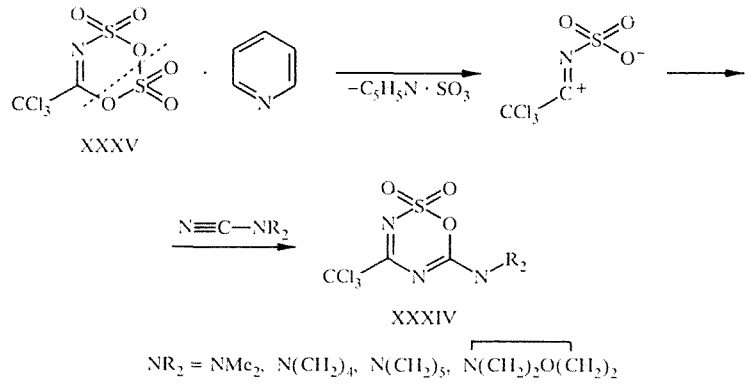
Scheme 3



XXX XXXIII XXXII XXXI

In the presence of ethyl ether, the direction of this reaction changes to formation of stable tetraoxides (XXXII) in the case of sulfur trioxide [44]. In our opinion, oxathiazine dioxides (XXXI) are most probably formed via intermediate generation of heterodiene (XXXIII) with subsequent [4 + 2]-cycloaddition to the cyanamide.

The tetraoxide (XXXV)—pyridine system is not a source of the heterodiene, but of zwitterion particles which react with cyanamides according to the scheme of 1,4-dipolar cycloaddition with formation of 1,2,3,5-oxathiadiazine 2,2-dioxides (XXXIV) and isomeric compounds XXXI [45].



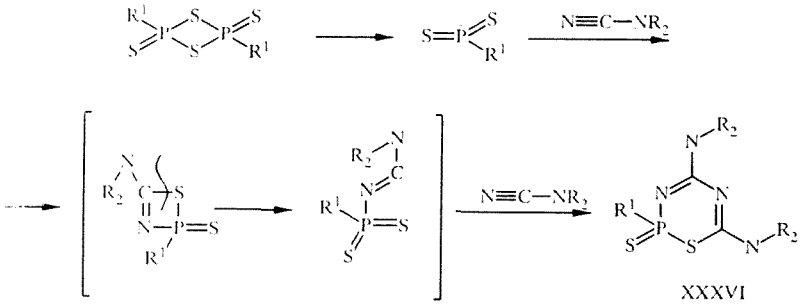
XXXV

XXXIV

$NR_2$ = $NMe_2$, $N(CH_2)_4$, $N(CH_2)_5$, $N(CH_2)_2O(CH_2)_2$

The formation of 1,3,5,2-thiadiazaphosphorine-2-thiones (XXXVI) in the reaction of cyanamides with dithiophosphoric acid anhydride dimer, similar to the reaction with carbon disulfide and sulfur trioxide, can be represented by Scheme 4 [46]:

Scheme 4



XXXVI

## CONCLUSION

The present review demonstrates the promise of using cyanamides in heterodiene synthesis. Their use as dienophiles will allow obtaining previously inaccessible azines containing oxygen, sulfur, and phosphorus instead of nitrogen atoms in the ring. The additional interest in cyanamides in the reaction of [4 + 2]-cycloaddition is because the products formed exhibit biological activity [18, 34, 47, 48].

## REFERENCES


1. V. A. Volkov, E. V. Vonskii, and G. I. Kuznetsova, Chemists [in Russian], Naukova Dumka, Kiev (1984), p. 218.
2. A. Cahouzs and S. Cloez, C.R., **38**, 354 (1854).
3. O. Wallach, Ber., **32**, 1872 (1899).
4. J. V. Braun, Ber., **33**, 1438 (1900).
5. R. H. McKee, Am. Chem. J., **36**, 208 (1906).
6. Dr. S. Weis, Spec. Chem., No. 4, 26, 29, 30 (1984).
7. A. F. Pozharskii, Khim. Geterotsikl. Soedin., No. 1, 3 (1989).
8. L. A. Yanovskaya and G. V. Kryshtal', Khim. Geterotsikl. Soedin., No. 8, 1011 (1991).
9. Yu. S. Andreichikov and S. N. Shurov, Khim. Zh. Ural. Univ., **1**, 49 (1992).
10. Ch. Kaneko, M. Sato, J. Sakaki, and Y. Abe, J. Heterocycl. Chem., **27**, 25 (1990).

11. R. J. Clemens, Chem. Rev., **86**, 241 (1986).
12. V. M. Cherkasov and N. A. Kapran, Khim. Geterotsikl. Soedin., No. 10, 1299 (1992).
13. D. L. Boger, Tetrahedron, **39**, 2869 (1983).
14. Z. Arnold and D. Dvorak, Coll., **50**, 2265 (1985).
15. Yu. S. Andreichikov and D. D. Nekrasov, Zh. Org. Khim., **20**, 1755 (1981).
16. M. Sato, N. Yoneda, and C. Kaneko, Chem. Pharm. Bull., **34**, 621 (1986).
17. M. Sato, N. Kanuma, and T. Kato, Chem. Pharm. Bull., **32**, 106 (1984).
18. Yu. S. Andreichikov, D. D. Nekrasov, M. A. Rudenko, and O. V. Vinokurova, Khim. Geterotsikl. Soedin., No. 9, 1265 (1989).
19. G. Jäger and J. Wenzelburger, Ann., No. 9, 1689 (1976).
20. L. Capuano, H. R. Kirn, and R. Zandler, Chem. Ber., **109**, 2456 (1976).
21. L. Capuano, K. Djokar, N. Schneider, and C. Wamprecht, Ann., **3**, 183 (1987).
22. Yu. S. Andreichikov, D. D. Nekrasov, and S. G. Pitirimova, USSR Inventor's Certificate No. 950,721; Byull. Izobr., No. 25, 87 (1983).
23. Yu. S. Andreichikov and D. D. Nekrasov, Khim. Geterotsikl. Soedin., No. 2, 166 (1985).
24. Yu. S. Andreichikov, D. D. Nekrasov, N. N. Shapet'ko, and Yu. S. Bogachev, USSR Inventor's Certificate No. 1,057,498; Byull. Izobr., No. 44, 102 (1983).
25. Yu. S. Andreichikov and D. D. Nekrasov, Zh. Org. Khim., **1**, 217 (1984).
26. Yu. S. Andreichikov, D. D. Nekrasov, and A. Yu. Konovalov, USSR Inventor's Certificate No. 1,051,084; Byull. Izobr., No. 40, 94 (1983).
27. W. Reid and K. Schopke, Ann., No. 11, 1997 (1986).
28. R. Comper and J. Steffer, Tetrahedron Lett., No. 3, 233 (1973).
29. J. Perronett, P. Cirault, and L. Taliani, J. Heterocycl. Chem., **18**, 433 (1981).
30. T. Kato, T. Chiba, T. Shimizu, and H. Takahashi, Chem. Pharm. Bull., **29**, 862 (1981).
31. K. Burger, F. Hein, and J. Firl, Chem.-Ztg., **103**, 264 (1979).
32. K. Burger, F. Hein, and J. Firl, Z. Naturf., **37**, 361 (1982).
33. G. Zeitz and R. John., Ber., **122**, 1381 (1989).
34. G. Zeitz and W. Overhen, Chem.-Ztg., **103**, 230 (1979).
35. K. Burger and R. Simmert, Ann., No. 5, 982 (1984).
36. K. Burger and R. Simmert, Synthesis, No. 3, 237 (1983).
37. M. E. Hermes and B. A. Braun, J. Org. Chem., **31**, 2568 (1966).
38. J. Goerdeler and R. Weis, Chem. Ber., **100**, 1627 (1967).
39. T. Tsuchiya, M. Yasumoto, J. Shibuya, V. Tagachi, K. Vonemoto, and M. Goto, Chem. Lett., No. 8, 1423 (1990).
40. T. Tsuchiya, M. Yasumoto, J. Shibuya, and M. Goto, J. Chem. Soc., Part 1, No. 4, 1218 (1990).
41. T. Tsuchiya, M. Yasumoto, V. Taguchi, K. Yonemoto, and J. Shibuya, 15th Int. Symp. Org. Chem. Sulfur, Caen, June 28-July 3, 1992, Abstracts, Caen (1992), p. 179.
42. E. Fischer, C. Möller, and G. Rembarz, Z. Chem., **17**, 222 (1977).
43. A. A. Michurin, A. V. Shishulina, A. N. Chernov, and I. A. Verin, Zh. Org. Khim., **28**, 1756 (1992).
44. A. A. Michurin, A. V. Shishulina, A. N. Chernov, and I. A. Verin, Zh. Org. Khim., **27**, 2019 (1991).
45. A. A. Michurin, A. N. Chernov, A. V. Shishulina, and I. A. Verin, Zh. Org. Khim., **27**, 881 (1991).
46. A. Smidpeter and N. Schindler, Angew. Chem., **80**, 1030 (1968).
47. T. Kato, Japanese Patent No. 59-172482, Chem. Abstr., **102**, 95660 (1985).
48. D. D. Nekrasov, Yu. S. Andreichikov, S. N. Shurov, and L. N. Karpova, Scientific Principles of Creation of Chemotherapeutic Agents [in Russian], Ekaterinburg (1993), p. 6.