Chemistry of Heterocyclic Compounds, Vol. 46, No. 1, 2010

REACTIONS OF HALONITROIMIDAZOLES WITH NUCLEOPHILES (REVIEW)

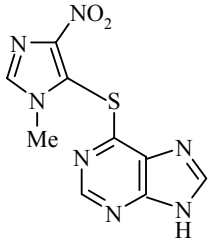
E. V. Aleksandrova[1], A. N. Kravchenko[2], and P. M. Kochergin[3]*

Published data on the reactions of 4(5)-halo-5(4)-nitro- and 2-halo-4(5)-nitroimidazoles with nucleophiles are reviewed and classified.

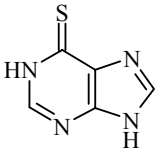
Keywords: amines, halonitroimidazoles, dibromoimidazole, dichloroimidazole, nucleophiles, isomerism.

On account of their chemical stability, high reactivity, and availability 4(5)-halo-5(4)-nitro- and 2-halo-4(5)-nitroimidazoles have proved useful substrates for the study of reactions with O-, S-, N-, C-, and N,O-nucleophiles. The high reactivity of the halogen atom in the series of 4(5)-halo-5(4)-nitroimidazoles is brought about by the presence of the strong electron-accepting NO_2 group at the "*ortho*" position. The activating effect of the NO_2 group also extends to the halogen atom at position 2 of the imidazole ring.

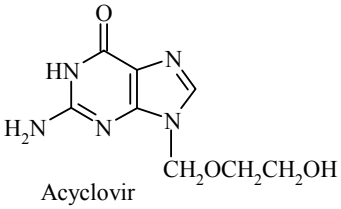
The products from the reactions of halonitroimidazoles with various nucleophiles have found use in fine organic synthesis, especially in the synthesis of heterocycles with a bridging nitrogen atom, biologically active compounds, and medicinal preparation. Thus, 1-methyl-4-nitro-5-(6-purinyl)mercaptoimidazole has found use under the name azathioprine as a medical preparations in the transplantation of vital organs and the treatment of a series of autoimmune diseases [1-4].



Azathioprine



Mercaptopurine



Acyclovir

* To whom correspondence should be addressed, e-mail: oaochls@yandex.ru.

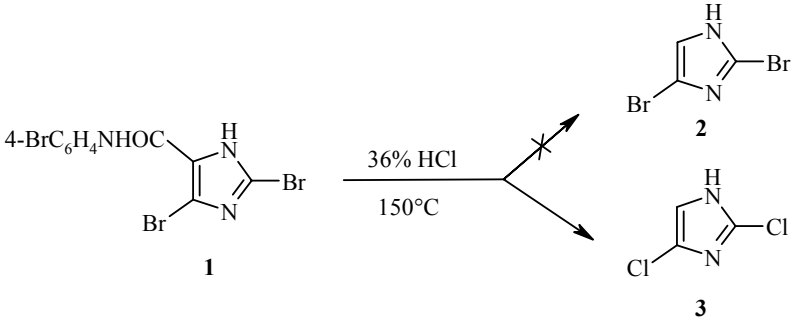
[1]Zaporozhe State University, Zaporozhe 690035, Ukraine.
[2]N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow 119991, Russia.
[3]Center for Drug Chemistry, All-Russian Research Chemical-Pharmaceutical Institute, Moscow 110815, Russia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 3-18, January, 2010. Original article submitted March 22, 2007.

For the creation of azathioprine and also the antileukemic and antiviral agents 6-mercaptopurine and acyclovir the British scientists G. Elion and G. Hitchins were awarded a Nobel prize.

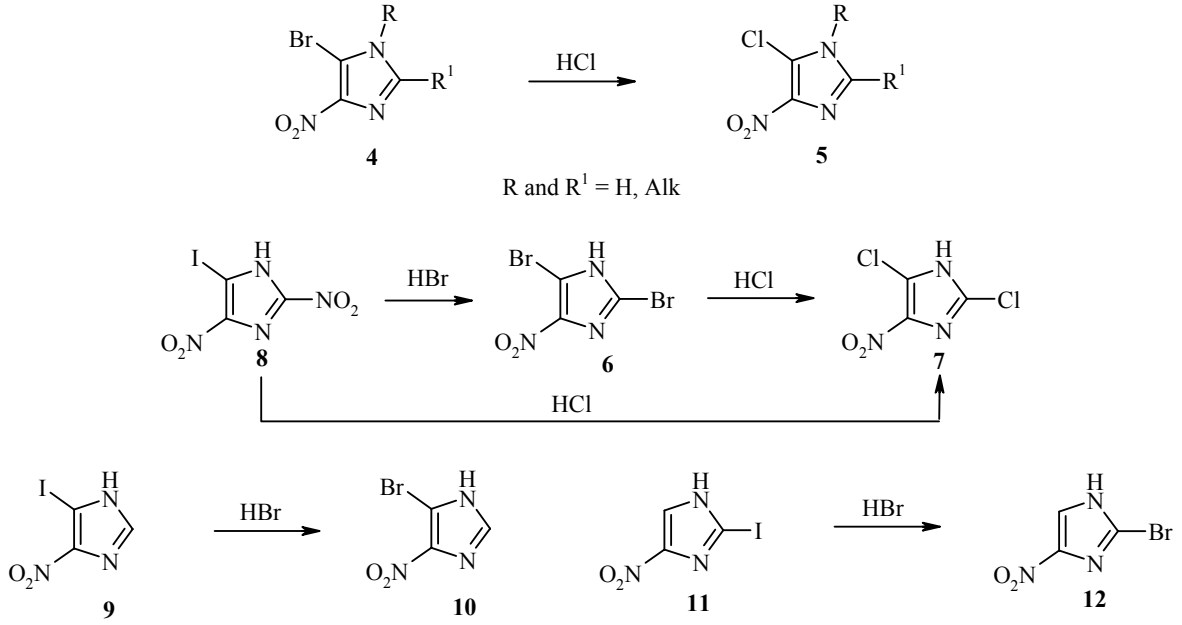
1. Transhalogenation

In the imidazole series the substitution of one halogen atom by another was discovered by accident. During the hydrolysis of the 4-bromoanilide of 2,4(5)-dibromoimidazole-5(4)-carboxylic acid (**1**) in concentrated HCl at 150°C 2,4(5)-dichloroimidazole (**3**) was isolated instead of the expected 2,4(5)-dibromoimidazole (**2**) [5].

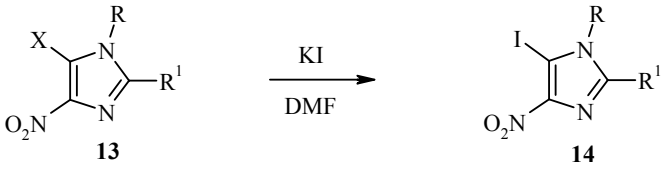


Transhalogenation with concentrated HCl and HBr later began to be used for preparative purposes not only in the production of chloroimidazoles [6] and fluoroimidazoles [7] from the more readily available bromoimidazoles but also for the synthesis of chloronitroimidazoles **5** and **7** [6, 8-12] from bromonitroimidazoles **4** and **6** and iodonitroimidazole **8**. Bromonitroimidazoles **6** [8], **10** [8], and **12** [13] were obtained from the iodonitroimidazoles **8**, **9**, and **11**.

In the case of 5(4)-iodo-2,4(5)-dinitroimidazole (**8**) the NO_2 group at position 2 of the imidazole ring was also replaced by a bromine atom and a clorine atom [8].



A series of 5-iodo-4-nitroimidazoles **14** were obtained by the reaction of 5-chloro(bromo)-4-nitroimidazoles **13** with potassium iodide [14].



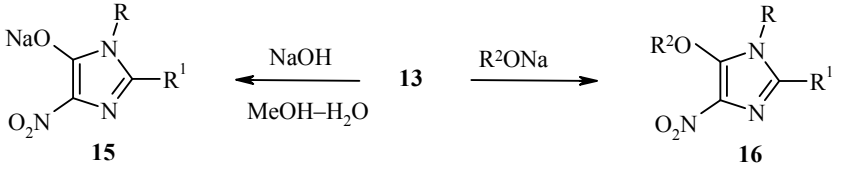
X = Cl, Br; R = H, Alk; R^1 = H, Alk

2. Reactions with O-Nucleophiles

The reaction of 5-halo-4-nitroimidazoles **13** with NaOH leads to the sodium salts of 5-hydroxy-4-nitroimidazoles **15** [14], while the reaction with sodium alcoholates leads to 5-alkoxy-4-nitroimidazoles **16** [12-18].

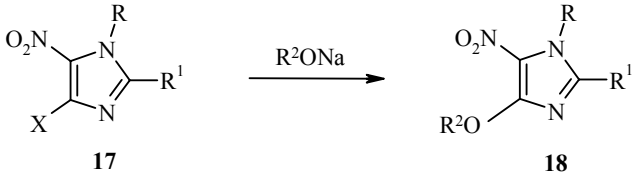
In [19] it was noted that 5-bromo-1,2-dimethyl-4-nitroimidazole, unlike its 4-bromo-5-nitro isomer, does not react with alcoholates, contradicting the experimental data from other authors [12-18].

5-Halo-4-nitroimidazoles **13** also react with phenols [16-18, 20, 21], naphthols [21], 2-hydroxy heterocycles [20], and 8-hydroxyquinoline [21], forming the ethers of 5-hydroxy-4-nitroimidazoles **16**.



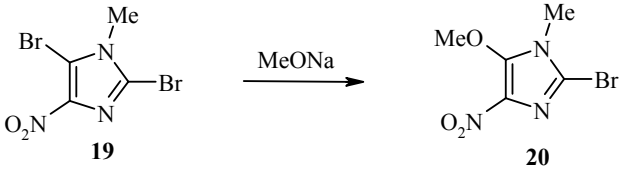
R = H, Alk, CH_2Ar; R^1 = H, Alk; R^2 = Alk, Ar, Het

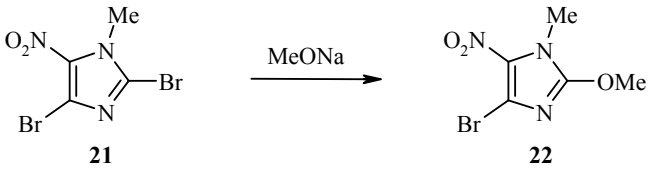
O-Nucleophilic substitution in the reaction of 4-halo-5-nitroimidazoles **17** with sodium alcoholates [19, 22], phenol [22], and 8-hydroxyquinoline [22] takes place in the same way as for 5-halo-4-nitroimidazoles, and the ethers of 4-hydroxy-5-nitroimidazoles **18** are obtained.



X = Cl, Br; R = Alk; R^1 = H, Alk; R^2 = Alk, Ar, Het

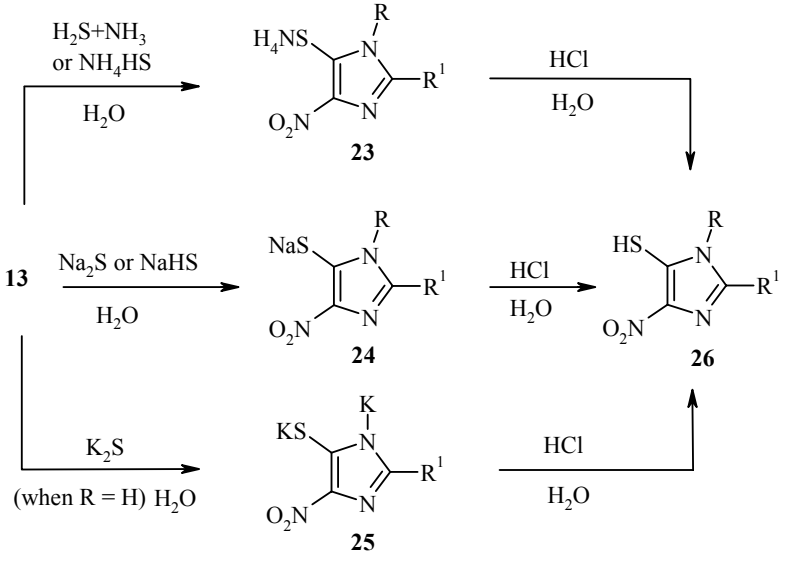
The reaction of 2,5-dibromo-1-methyl-4-nitroimidazole **19** and its 5-nitro isomer **21** with sodium methoxide takes place differently. The 5-methoxy derivative **20** (yield 40%) is obtained in the case of the dibromide **19**, and the 2-methoxy derivative **22** (yield 100%) is obtained in the case of the dibromide **21** [12].





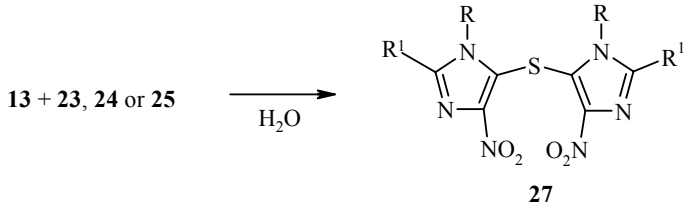
3. Reactions with S-Nucleophiles

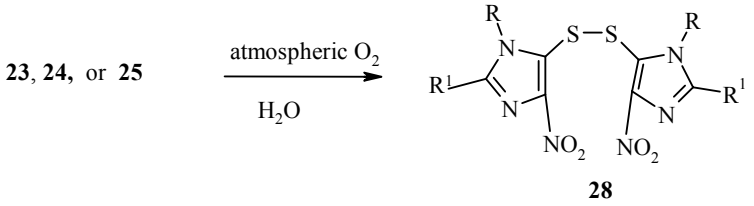
Halonitroimidazoles enter readily into reaction with S-nucleophiles of both inorganic and organic type. Thus, the reaction of 5-halo-4-nitroimidazoles **13** with hydrogen sulfide in aqueous or alcohol solutions of ammonia [23-30], ammonium hydrosulfide [23], sodium sulfide [23], sodium hydrosulfide [31], potassium hydrosulfide [23], and thiourea [23] gave the ammonium, sodium, and potassium salts of 5-mercapto-4-nitroimidazoles **23**-**25**, from which the free 5-mercapto-4-nitroimidazoles **26** were isolated by decomposition with hydrochloric or acetic acid [23-32].



R = H, Alk; R^1 = H, Alk, NO_2

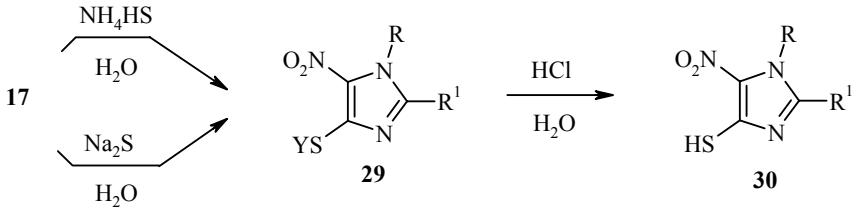
In certain cases the reactions of halonitroimidazoles **13** with ammonium and alkali metal sulfides and hydrosulfides are accompanied by the formation of side products – di(nitroimidazolyl) sulfides **27** and di(nitroimidazolyl) disulfides **28** [23]. The sulfides **27** are obtained as a result of the reaction of the original halonitroimidazoles **13** with the formed salts of nitromercaptoimidazoles **23**-**25** and the disulfides **28** as a result of oxidation of the salts of the nitromercaptoimidazoles **23**-**25** by atmospheric oxygen.





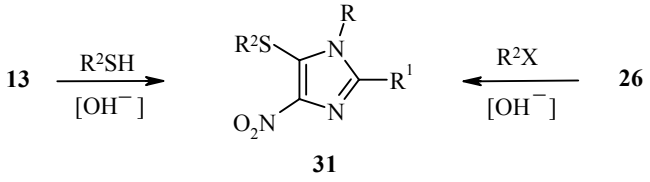
R and R^1 = H, Alk

4-Mercapto-5-nitroimidazoles **30** were synthesized by the reaction of 4-halo-5-nitroimidazoles **17** with hydrogen sulfide [12], ammonium hydrosulfide [23], and sodium sulfide [23].



Y = NH_4, Na; R =Alk; R^1 = H, Alk, CN

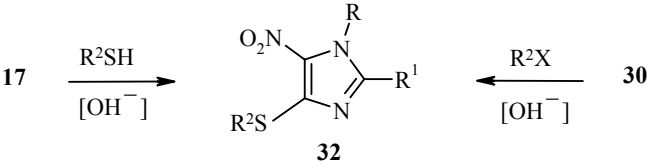
The reaction of 5-halo-4-nitroimidazoles **13** with thiols [17, 20, 23-50] and of 5-mercapto-4-nitroimidazoles **26** with halide compounds [24, 26, 31-36, 38, 39, 47-53] lead to the formation of the thioethers **31**.



R and R^1 = H, Alk; R^2 = Alk, CH_2COOH, Ar, Aralk, Het; X = Cl, Br, I

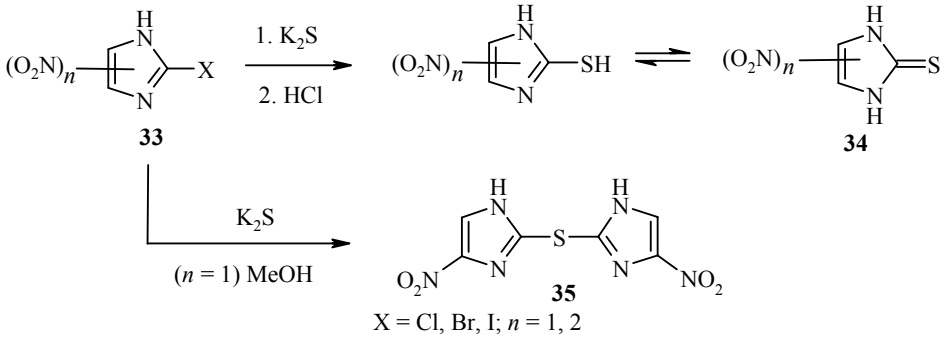
Of the thioethers **31** azathioprine (R = Me, R^1 = H, R^2 = 6-purinyl) [33-36] and the compound with the code C-87 (R = Et, R^1 = Me, R^2 = 2-amino-6-purinyl) [46] have strong immunodepressant activity.

The thioethers **32** were synthesized according to similar schemes by the reactions of 4-halo-5-nitroimidazoles **17** with mercaptans [12, 13, 22, 36, 47, 48, 50] and of 4-mercapto-5-nitroimidazoles **30** with halide compounds [12, 45, 47, 50].

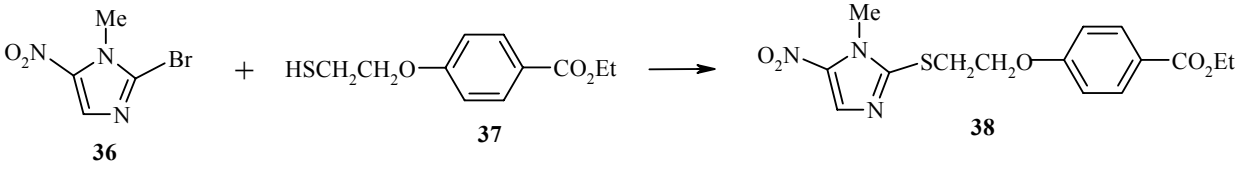


R and R^1 = H, Alk; R^2 = Alk, Ar, CH_2Ar, Het; X = Cl, Br, I

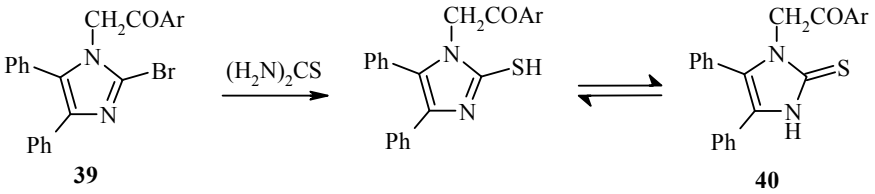
The reaction of 2-halo-4(5)-nitroimidazoles with S-nucleophiles also takes place under mild conditions. In the reaction of 2-halo-4(5)-nitro(4,5-dinitro)imidazoles **33** with potassium sulfide in water the imidazolinethiones **34** were obtained. If this reaction is conducted in methanol the diimidazolyl sulfides **35** are formed [32].



The thioether **38** was obtained by the reaction of 2-bromo-1-methyl-5-nitroimidazole **36** with the thiol **37** [13].

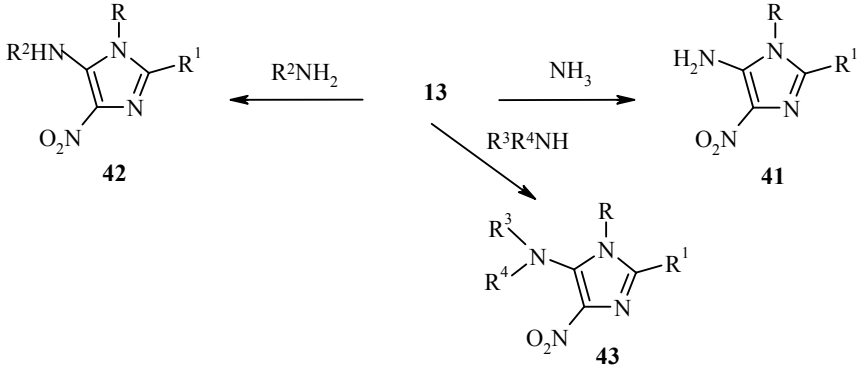


The reaction of 1-aroylmethyl-2-bromo-4,5-diphenylimidazole **39** with thiourea leads to the imidazoline-2-thiones **40** – intermediates in the synthesis of derivatives of imidazo[2,1-*b*]thiazole [54].



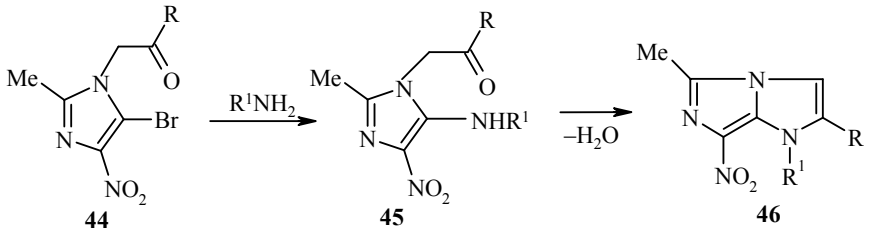
4. Reactions with N-Nucleophiles

5-Halo-4-nitroimidazoles **13** react with ammonia [55], primary [16-18, 21, 56] and secondary [14, 19, 56-58] amines, dialkylaminoalkylamines [16, 17, 20, 56], amino alcohols [19, 59], aminophenols [21], amino acids [60], and heterocyclic compounds containing a free NH group [20, 57]. A large series of 5-amino-4-nitroimidazole derivatives **41**-**43** were synthesized as a result of these reactions.



R = Alk; R^1 = H, Alk; R^2 = Alk, Ar, $(CH_2)_2OH$; R^3 = Alk;
R^4 = Alk; R^3R^4N – secondary acyclic or heterocyclic amine

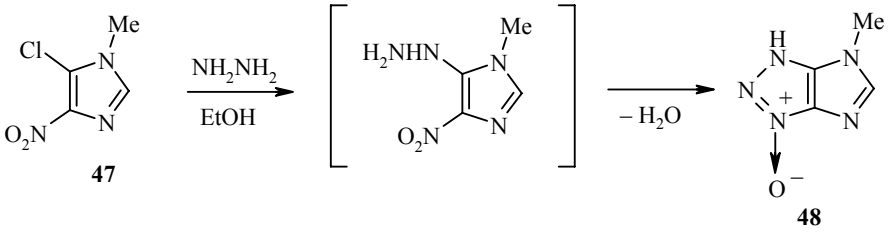
The reaction of 1-acylmethyl-5-bromo-2-methyl-4-nitroimidazoles **44** with amines leads to the formation of derivatives of imidazo[5,1-*a*]imidazole **46**. Under mild conditions it is possible to isolate the intermediate compounds **45** [61, 62].



44 **45** **46**

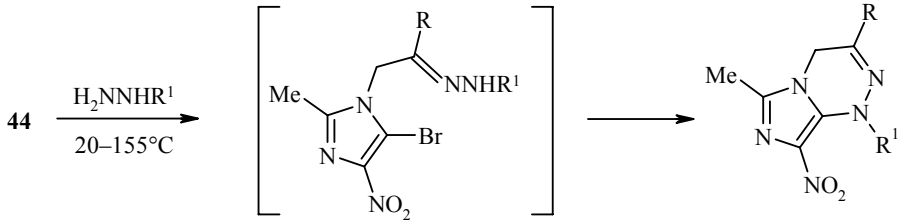
R = Alk, Ar; R^1 = Alk, $(CH_2)_2OH$, Ar, Aralk

In the reaction of 5-chloro-1-methyl-4-nitroimidazole **47** with hydrazine hydrate 1-methylimidazo-[4,5-*d*]triazole N-oxide **48** was obtained [63].

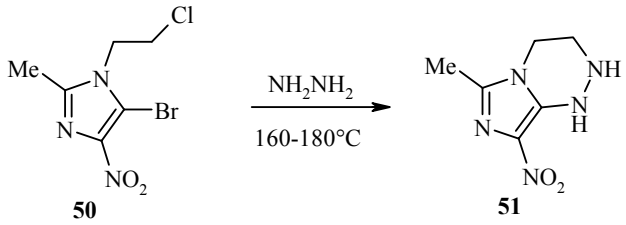


47 **48**

The reactions of 1-acylmethyl-5-bromo-2-methyl-4-nitroimidazoles **44** and 5-bromo-1-(2-chloroethyl)-2-methyl-4-nitroimidazole **50** with hydrazines lead to derivatives of imidazo[5,1-*c*]-1,2,4-triazine **49** and **51** [64, 65].

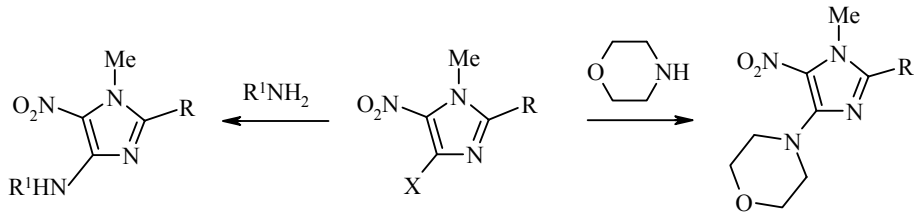


49



50 **51**

4-Halo-5-nitroimidazoles enter into reaction similarly with N-nucleophiles. The reactions of compounds **52** with ammonia [55], amines [14, 19, 22, 58], amino alcohols [19, 59], amino acids [60], and derivatives of imidazole with a free NH group [20, 59] have been described. As a result the substituted 4-amino-5-nitroimidazoles **53** and **54** were obtained.

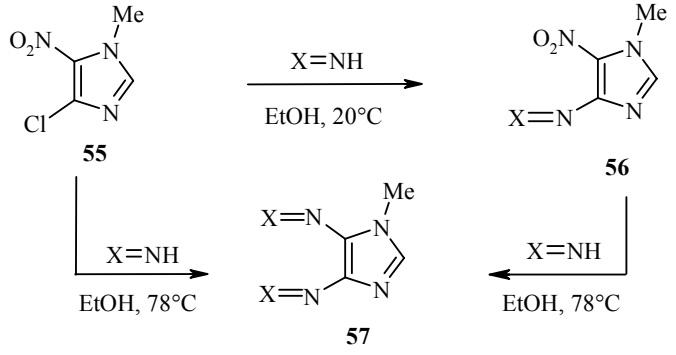


54 **52** **53**

X = Cl, Br, I; R = H, Me; R^1 = H, Alk, Ar, Het, $(CH_2)_2OH$

An unusual reaction with N-nucleophiles, during which not only the halogen atom but also the NO_2 group is substituted by the N-nucleophile fragment, was described in the series of halonitro derivatives of imidazole and 2,2'-diimidazole. Thus, 4,4',5,5'-tetraphenylamino-2,2'-diimidazole was obtained when 4,4'-dibromo-5,5'-dinitro-2,2'-diimidazole was boiled in aniline [66].

In the case of 4-chloro-1-methyl-5-nitroimidazole **55** the substitution of the chlorine atom and NO_2 group by fragments of secondary acyclic amines takes place at a lower temperature (78°C) [14]. As a result derivatives of the almost previously uninvestigated 4,5-diaminoimidazole **57** were obtained.

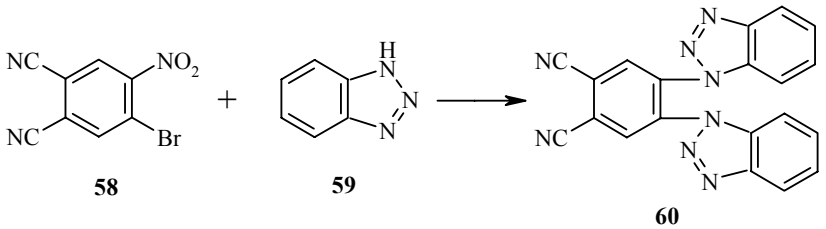


55 **56** **57**

X = $(CH_2)_4$, $(CH_2)_5$, $O(CH_2)_4$

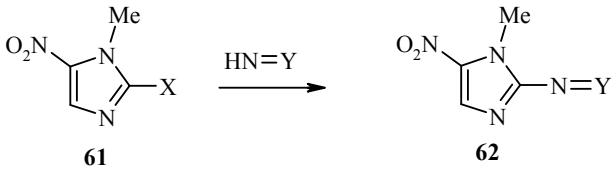
It should be noted that the isomeric compound 5-chloro-1-methyl-4-nitroimidazole **47** reacts with secondary amines at 130-132°C, and the reaction stops at the stage of substitution of the chlorine atom [56].

Recently it was shown that the substitution of the halogen atom and NO_2 group by the N-nucleophile fragment can also occur in the benzene series in the presence of strong electron-withdrawing groups such as CN in the molecule. Thus, 1,2-di(benzotriazolyl)-4,5-dicyanobenzene was obtained in the reaction of 1-bromo-4,5-dicyano-2-nitrobenzene **58** with benzotriazole **59** [67].



58 **59** **60**

In [58, 68] the reactions of 2-halo-4(5)-nitroimidazoles with N-nucleophiles were described. Thus, during the reaction of 2-chloro(bromo)-1-methyl-5-nitroimidazoles **61** with secondary acyclic amines the corresponding 2-amino-substituted 5-nitroimidazoles **62** were obtained [58, 68].

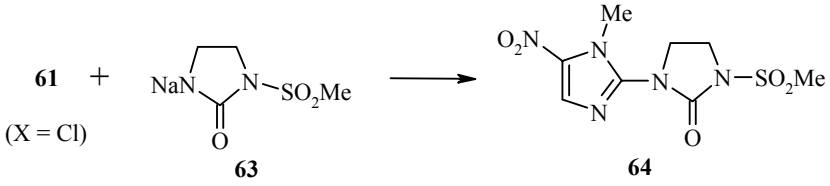


61 **62**

X = Cl, Br; Y = $(CH_2)_5$, $(CH_2)_4O$

The reaction of 2-chloro-1-methyl-4-nitroimidazole with morpholine takes place according to a similar scheme [58].

The diimidazole derivative **64** was synthesized during the reaction of compound **61** (X = Cl) with the sodium salt of imidazolidin-2-one **63** [58].



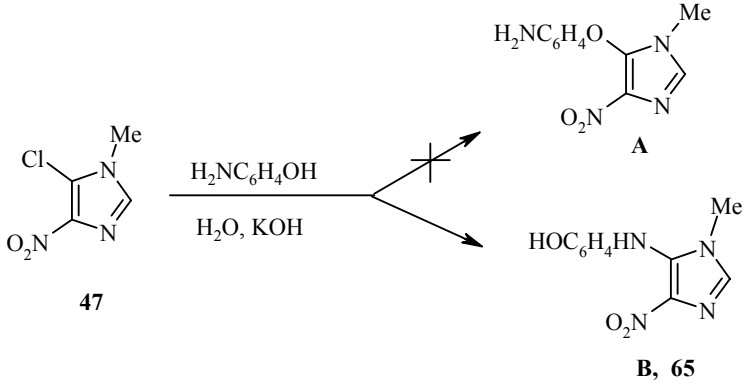
61 (X = Cl) **63** **64**

In [69] there is an extensive range of data on the use of spectral methods to establish the structure of isomeric 1-substituted 4-nitro- and 5-nitroimidazoles, including halonitroimidazoles.

5. Reactions with Ambident N,O-Nucleophiles

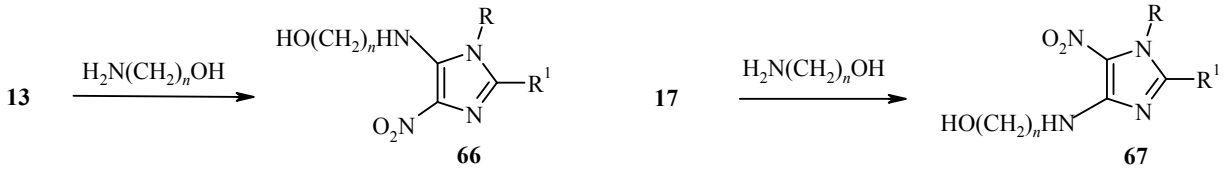
Aminophenols and amino alcohols contain two nucleophilic centers. The reaction of 5-halo-4-nitroimidazoles with these nucleophiles can theoretically therefore take place at the OH and NH_2 groups, leading to the formation of ethers of 5-hydroxy-4-nitroimidazoles (structure **A**), N(5)-substituted 5-amino-4-nitroimidazoles (structure **B**), or their mixture.

In actual fact the reaction of 5-chloro-1-methyl-4-nitroimidazole **47** with 2-, 3-, and 4-aminophenols in an aqueous solution of potassium hydroxide takes place at the more nucleophilic center of the molecule–the NH_2 group, and 5-(hydroxyphenylamino)-1-methyl-4-nitroimidazoles **65** (structure **B**) are formed [21].



47 **A** **B, 65**

5-Halo-4-nitro- and 4-halo-5-nitroimidazoles **13** and **17** react similarly with amino alcohols, leading to the formation of the corresponding 5-(hydroxyalkylamino)-4-nitro- and 4-(hydroxyalkylamino)-5-nitroimidazoles **66** and **67** [19, 59].



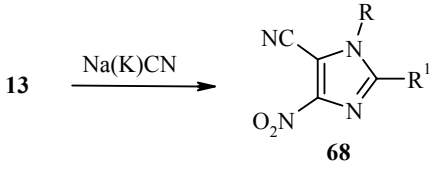
R = Alk; R^1 = H, Alk; *n* = 2, 3

6. Reactions with C-Nucleophiles

The position of the NO_2 group in the molecule of the halonitroimidazoles determines the different behaviors of these compounds toward the cyanides of alkali metals.

The reaction of 5-halo-4-nitroimidazoles **13** with potassium or sodium cyanide in lower alcohols in the presence of the iodides of these metals as catalysts leads to high yields of 5-cyano-4-nitroimidazoles **68** [12, 18, 19, 22, 26, 43, 70-76]. In DMSO this reaction takes place in the absence of the catalyst [12, 73].

Compounds **68** have found use in the synthesis of purine derivatives [77-80].

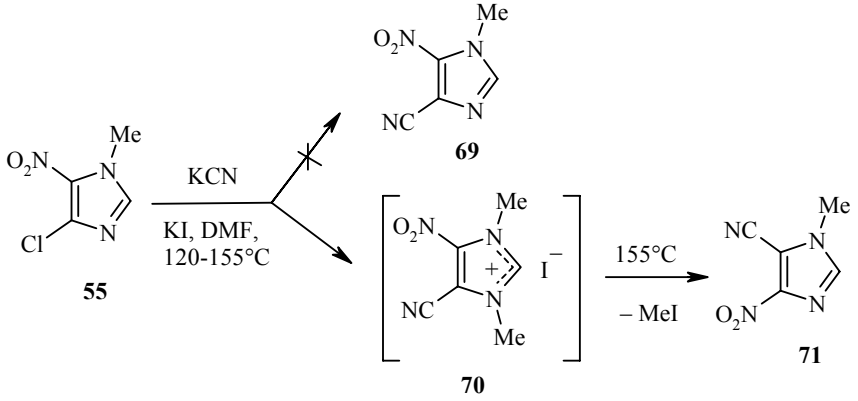


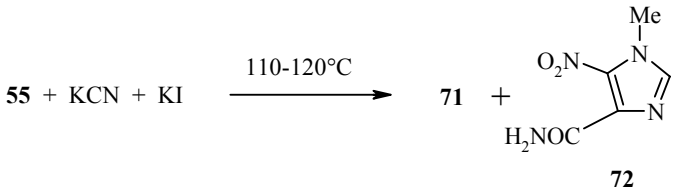
R = Alk, Aralk, ribofuranosyl; R^1 = H, Alk

Exceptions were 4(5)-bromo-5(4)-nitro-, 2,4(5)-dibromo-5(4)-nitro-, and 1-benzyl-2,5-dibromo-4-nitroimidazoles, which according to data in [43] do not react with KCN in the presence of KI when heated in methanol. In our opinion a higher temperature is required for these reactions.

4-Chloro(bromo)-5-nitroimidazoles behave unusually in reaction with potassium cyanide. The reaction does not occur on heating in lower alcohols [18, 19, 22, 43, 70, 71]. In DMF at 120-155°C the isomer 5-cyano-1-methyl-4-nitroimidazole **71** (yield 52%) was formed instead of the expected 4-cyano-1-methyl-5-nitroimidazole **69** [70, 71].

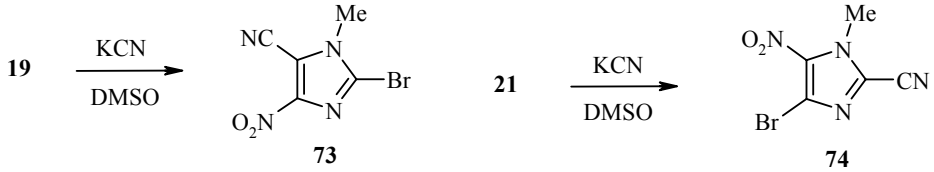
The mechanism of this rearrangement was not established. The authors of [19] suggest that the formation of the quaternary salt **70** is possible in DMF and that its thermal decomposition leads to the formation of **71**. However, such a description of the reaction mechanism does not explain the formation also of 1-methyl-5-nitroimidazole-4-carboxamide **72** (albeit with very small yields) together with compound **71** when chloronitroimidazole **55** is heated at 110-120°C with a mixture of potassium cyanide and iodide in the absence of DMF [70].





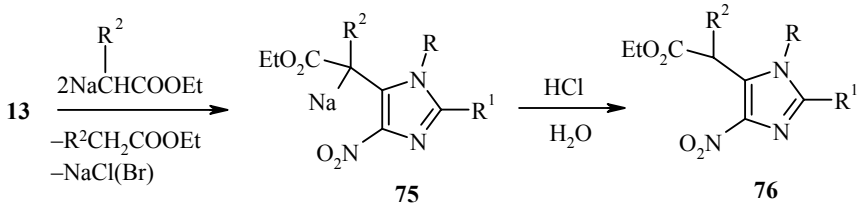
72

The reactions of 2,5-dibromo-1-methyl-4-nitroimidazole **19** and its 5-nitro isomer **21** with KCN in DMSO in the presence of 18-crown-6 ether take place in different ways. As in the case of sodium methoxide, during the reaction of the 4-nitro isomer **19** the bromine atom at position 5 of the imidazole ring is substituted, and 5-cyano-4-nitroimidazole **73** is formed. 2-Cyano-5-nitroimidazole **74** was obtained from the 5-nitro isomer **21** under the same conditions [12].



73 74

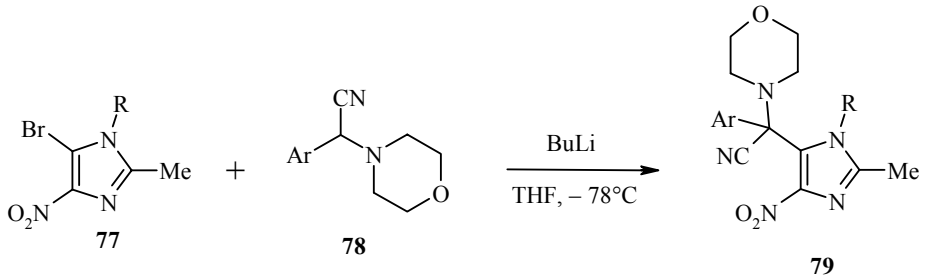
The reaction of 5-halo-4-nitroimidazoles **13** with the sodium salts of CH acids leads to the formation of 4-nitro-5-imidazolyl CH acids **76** [81].



75 76

R = Alk; R^1 = H, Alk; R^2 = COOEt, COMe, CN

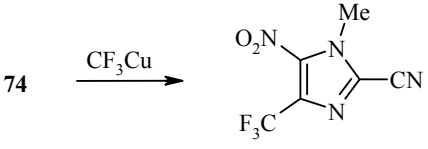
As a result of the reaction of 5-bromo-4-nitroimidazoles **77** with α-arylmorpholylacetonitriles **78** in THF in the presence of butyllithium the corresponding nitriles **79** were obtained [82].



77 78 79

R = COOBu-*t*, CH_2Ph

The reaction of 4-bromo-5-nitroimidazole **74** with trifluoromethylcopper, resulting in the synthesis of 2-cyano-1-methyl-5-nitro-4-trifluoromethylimidazole **80**, was described in [12].



80

REFERENCES

1. M. D. Mashkovskii, *Drugs* [in Russian], 15th edition, Novaya Volna, Moscow (2005).
2. R. P. Baughman and E. E. Lower, *Clin. Immunotherap.*, **67**, 431 (1996).
3. T. Munster and D. E. Furst, *Clin. Exper. Rheumatology*, **17**, 529 (1999).
4. J. N. Stolk, A. M. Boerbooms, R. A. de Abreu, D. G. de Koning, H. J. van Bensekom, W. H. Muller, and L. B. Van de Putte, *Arthritis Rheum.*, **41**, 1858 (1998).
5. H. King and W. O. Murch, *J. Chem. Soc.*, **123**, 621 (1923).
6. A. W. Lutz and S. De Lorenzo, *J. Heterocycl. Chem.*, **4**, 399 (1967).
7. E. C. Coad, Lin Hui, and P. G. Rasmussen, *Tetrahedron*, **55**, 2811 (1999).
8. G. P. Sharnin, R. Kh. Fassakhov, and T. A. Eneikina, *Khim. Geterotsikl. Soedin.*, 1666 (1977). [*Chem. Heterocycl. Comp*., **33**, 1332 (1977)].
9. J. Suwinski, E. Saiwinska, J. Witras, and M. Widel, *Pol. J. Chem*., **56**, 1261 (1982).
10. J. Suwinski, E. Saiwinska, J. Witras, and M. Widel, *Acta Pol. Pharm.*, **43**, 124 (1986).
11. T. J. Benson and B. Robinson, *J. Chem. Soc.*, *Perkin Trans. 1*, 211 (1992).
12. G. Chauviere, C. Viode, and J. Perie, *J. Heterocycl. Chem*., **37**, 119 (2000).
13. J. P. Dickens, R. L. Dyer, B. J. Hamill, T. A. Harrow, R. H. Bible, P. M. Finnegan, K. Hendrick, and Ph. G. Owston, *J. Org. Chem*., **46**, 1781 (1981).
14. P. M. Kochergin, A. M. Tsyganova, V. S. Shlikhunova, and M. A. Klykov, *Khim. Geterotsikl. Soedin.*, 689 (1971). [*Chem. Heterocycl. Comp*., **7**, 648 (1971)].
15. M. A. Iradyan, N. S. Iradyan, and Sh. A. Avetyan, *Arm. Khim. Zh.*, **31**, 435 (1978).
16. A. Mroczkiewicz, *Acta Pol. Pharm.*, **41**, 397 (1984).
17. A. Mroczkiewicz, *Acta Pol. Pharm.*, **41**, 435 (1984).
18. S. Kulkarni, M. R. Grimmett, L. R. Hanton, and J. Simpson, *Aust. J. Chem.*, **40**, 1399 (1987).
19. V. Sunjic, T. Faidiga, M. Japeli, and P. Rema, *J. Heterocycl. Chem.*, **6**, 53 (1969).
20. V. P. Arya, K. Nagarayan, and S. J. Shenoy, *Indian J. Chem.*, **21B**, 1115 (1982).
21. L. A. Reznichenko, R. N. Gireva, P. M. Kochergin, and E. V. Aleksandrova, *Khim. Geterotsikl. Soedin.*, 327 (1998). [*Chem. Heterocycl. Comp.*, **34**, 294 (1998)].
22. K. Shimada, S. Kuriyama, T. Kanazawa, M. Satoh, and S. Toyoshima, *J. Pharm. Soc. Jpn.*, **91**, 221 (1971).
23. P. M. Kochergin, *Khim. Geterotsikl. Soedin.*, 749 (1966). [*Chem. Heterocycl. Comp.*, **2**, 576 (1966)].
24. P. M. Kochergin, A. M. Tsyganova, and E. M. Viktorova, *Khim. Geterotsikl. Soedin.*, Coll. 1, *Nitrogen-Containing Heterocycles* [in Russian], Zinatne, Riga (1967), p. 126.
25. B. Sh. Huang, M. J. Lauzon, and J. C. Parham, *J. Heterocycl. Chem.*, **16**, 811 (1979).
26. M. A. Iradyan, G. M. Stepanyan, A. Kh. Aivazyan, V. S. Merzoyan, Sh. A. Avityan, Z. S. Isakakyan, D. Sh. Manucharyan, N. Kh. Dayan, and B. T. Garibdzhanyan, *Khim.-Farm. Zh.*, **15**, No. 2, 40 (1981).
27. M. A. Iradyan, A. Kh. Aivazyan, V. S. Merzoyan, G. M. Paronikyan, T. P. Sarkisyan, G. M. Stepanyan, F. G. Arsenyan, and B. T. Garibdzhanyan, *Khim.-Farm. Zh.*, **21**, 667 (1987).
28. S. Kulkarni and M. R. Grimmett, *Aust. J. Chem*., **40**, 1415 (1987).
29. M. A. Iradyan, A. Kh. Aivazyan, V. S. Merzoyan, G. M. Stepanyan, F. G. Arsenyan, B. T. Garibdzhanyan, G. M. Paronikyan, and T. P. Sarkisyan, *Khim.-Farm. Zh.*, **23**, 411 (1988).
30. A. I. Iradyan, N. S. Iradyan, G. M. Stepanyan, F. G. Arsenyan, G. M. Paronikyan, G. A. Darbinyan, E. V. Kazaryan, and B. T. Garibdzhanyan, *Khim.-Farm. Zh.*, **37**, No. 2, 17 (2003).
31. A. Hasan, C. R. Lambert, and P. C. Stivastava, *J. Heterocycl. Chem.*, **27**, 1877 (1990).
32. V. V. Nurgatin, G. P. Sharnin, V. V. Nurgatina, and B. M. Ginzburg, *Khim. Geterotsikl. Soedin.*, 812 (1982). [*Chem. Heterocycl. Comp*., **18**, 616 (1982)].
33. G. H. Hitchings and G. B. Elion, Brit. Pat. 878646; *Chem. Abstr*., **56**, 15523 (1962).

34. G. H. Hitchings and G. B. Elion, US Pat. 3056785; *Chem. Abstr.*, **58**, 5701 (1963).
35. P. M. Kochergin and I. S. Shmidt, *Med. Prom. SSSR*, No. 8, 6 (1965).
36. P. M. Kochergin and I. S. Shmidt, *Khim. Geterotsikl. Soedin.*, Coll. 1, *Nitrogen-Containing Heterocycles* [in Russian], Zinatne, Riga (1967), p. 130.
37. The Welcome Foundation Ltd., Brit. Pat. 973007; *Ref. Zh. Khim.*, 14N3O3 (1966).
38. H. Schubert, H. Simon, and A. Jumar, *Z. Chem.*, **8**, 62 (1968).
39. A. Mroczkiewicz, *Acta Pol. Pharm.*, **38**, 379 (1981).
40. S. Puig-Torres, G. E. Martin, S. B. Larson, and S. H. Simonsen, *J. Heterocycl. Chem.*, **21**, 155 (1984).
41. I. Motonobu, S. Masasi, K. Sadamu, and N. Tokuro, Jpn. Pat. 57-38598; *Ref. Zh. Khim.*, 13O187P (1984).
42. S. Balonic, A. Mroczkiewicz, B. Hoffmann, F. Wika, A. Lukowsci, Polish Pat. 128301; *Ref. Zh. Khim.*, 11O151P (1987).
43. B. Iddon, N. Khan, and Bee Lan Lim, *J. Chem. Soc.*, *Perkin Trans. 1*, 1437 (1987).
44. N. Jones and J. L. Maddocks, PCT Int. Appl. WO 9000549; *Chem. Abstr.*, **113**, 145338 (1990).
45. J. G. Buchanan, A. E. McCaid, and R. H. Wightman, *J. Chem. Soc.*, *Perkin Trans. 1*, 955 (1990).
46. P. M. Kochergin, E. V. Aleksandrova, L. S. Tolvinskaya, I. B. Zhukova, B. G. Pukhaliskaya L. Yu. Telegin, and L. A. Pevnitskii, *Khim.-Farm. Zh.*, **34**, No. 11, 9 (2000).
47. P. M. Kochergin, E. V. Aleksandrova, V. S. Korsunskii, and V. S. Shlikhunova, *Khim. Geterotsikl. Soedin.*, 217 (2000). [*Chem. Heterocycl. Comp.*, **36**, 178 (2000)].
48. P. M. Kochergin, E. V. Aleksandrova, V. S. Korsunskii, and V. S. Shlikhunova, *Khim. Geterotsikl. Soedin.*, 221 (2000). [*Chem. Heterocycl. Comp.*, **36**, 182 (2000)].
49. P. M. Kochergin, E. V. Aleksandrova, and V. S. Korsunskii, *Khim. Geterotsikl. Soedin.*, 372 (2000). [*Chem. Heterocycl. Comp*., **36**, 311 (2000)].
50. P. M. Kochergin, E. V. Aleksandrova, V. S. Korsunskii, and V. S. Shlikhunova, *Khim. Geterotsikl. Soedin.*, 538 (2001). [*Chem. Heterocycl. Comp.*, **37**, 490 (2001)].
51. P. M. Kochergin and E. A. Bashkir, *Khim. Geterotsikl. Soedin.*, 754 (1966). [*Chem. Heterocycl. Comp*., **2**, 581 (1966)].
52. P. M. Kochergin and E. A. Bashkir, *Khim. Geterotsikl. Soedin.*, 762 (1966). [*Chem. Heterocycl. Comp.*, **2**, 588 (1966)].
53. P. M. Kochergin, A. M. Tsyganova, and L. M. Viktorova, *Khim. Geterotsikl. Soedin.*, 93 (1967). [*Chem. Heterocycl. Comp.*, **3**, 63 (1967)].
54. I. A. Mazur, P. M. Kochergin, and G. S. Tkachenko, *Khim. Geterotsikl. Soedin.*, 824 (1970). [*Chem. Heterocycl. Comp*., **6**, 763 (1970)].
55. P. M. Kochergin and S. G. Verenikina, *Khim. Geterotsikl. Soedin.*, 765 (1965). [*Chem. Heterocycl. Comp*., **1**, 519 (1965)].
56. P. M. Kochergin and S. G. Verenikina, *Khim. Geterotsikl. Soedin.*, 770 (1965). [*Chem. Heterocycl. Comp*., **1**, 522 (1965)].
57. K. Nagarajan, V. P. Arya, T. George, V. Sudarsanam, R. K. Shan, A. Nagana Goud, S. J. Shenoy, V. Honkan, Y. S. Kulkarni, and M. K. Rao, *Indian J. Chem.* **21B**, 928 (1982).
58. V. Sudarsanam, K. Nagarajan, V. P. Arya, A. P. Kaulgud, S. J. Shenoy, and R. K. Shah, *Indian J. Chem.*, **21B**, 989 (1982).
59. P. M. Kochergin, L. A. Reznichenko, R. N. Gireva, and E. V. Aleksandrova, *Khim. Geterotsikl. Soedin.*, 1346 (1998). [*Chem. Heterocycl. Comp*., **34**, 1142 (1998)].
60. P. M. Kochergin, L. A. Reznichenko, R. N. Gireva, and E. V. Aleksandrova, *Khim. Geterotsikl. Soedin.*, 48 (1999). [*Chem. Heterocycl. Comp*., **35**, 45 (1999)].
61. V. A. Lifanov and P. M. Kochergin, *Khim.-Farm. Zh.*, **27**, No. 12, 59 (1993).

62. P. M. Kochergin and V. A. Lifanov, *Khim. Geterotsikl. Soedin.*, 490 (1994). [*Chem. Heterocycl. Comp.*, **30**, 429 (1994)].
63. A. Kreutzberger, *J. Org. Chem.*, **27**, 886 (1962).
64. M. V. Povstyanoi, M. A. Klykov, N. M. Gorban', and P. M. Kochergin, *Khim. Geterotsikl. Soedin.*, 855 (1975). [*Chem. Heterocycl. Comp.*, **11**, 751 (1975)].
65. M. A. Klykov, M. V. Povstyanoi, and P. M. Kochergin, *Khim. Geterotsikl. Soedin.*, 1540 (1979). [*Chem. Heterocycl. Comp*., **15**, 1237 (1979)].
66. K. Lemstedt and H. Rolker, *Ber.*, **38**, 2955 (1943).
67. I. G. Abramov, A. V. Smirnov, M. B. Abramova, S. A. Ivanovskii, and V. V. Plakhtinskii, *Khim. Geterotsikl. Soedin.*, 1219 (2000). [*Chem. Heterocycl. Comp.*, **36**, 1062 (2000)].
68. G. B. Barlin, *J. Chem. Soc.*, (*B*), 641 (1969).
69. R. Nagarajan, V. Sudarsaman, P. C. Parthsarathy, V. Parya, and S. J. Shenoy, *Indian J. Chem*., **21B**, 1006 (1982).
70. J. Baddiley, J. G. Buchman, F. E. Hardy, and J. Stewart, *J. Chem. Soc.*, 2893 (1959).
71. E. C. Taylor and P. K. Loeffer, *J. Am. Chem. Soc*., **82**, 3147 (1960).
72. N. J. Leonard, K. L. Carravay, and J. P. Helgeson, *J. Heterocycl. Chem*., **2**, 291 (1965).
73. G. E. Trout and P. R. Levy, *Recl. Trav. Chem. Pays-Bas*, **84**, 1257 (1965).
74. R. J. Rousseau, R. K. Robins, and L. B. Townsend, *J. Am. Chem. Soc.*, **90**, 2661 (1968).
75. H. Simon, H. Lettan, H. Schubert, and A. Jumar, *Z. Chem.*, **9**, 58 (1969).
76. L. A. Reznichenko, E. V. Aleksandrova, and P. M. Kochergin, *Khim.-Farm. Zh.*, **34**, No. 8, 30 (2000).
77. J. Sarasin and E. Wegmann, *Helv. Chem. Acta*, **7**, 713 (1924).
78. F. Montequi and D. Plaza, *Anal. Soc. Espani Fizica Quim.*, **24**, 731 (1926).
78. F. Montequi, *Anal. Soc. Espani Fizica Quim.*, **25**, 182 (1927).
80. F. Q. Mann and J. W. Q. Porter, *J. Chem. Soc.*, 751 (1945).
81. P. M. Kochergin, L. A. Reznichenko, R. N. Gireva, and E. V. Aleksandrova, *Khim. Geterotsikl. Soedin.*, 54 (1999). [*Chem. Heterocycl. Comp*., **35**, 51 (1999)].
82. J. D. Albright and D. B. Moran, *J. Heterocycl. Chem.*, **23**, 913 (1986).