REACTIONS OF 4-AMINO-5-(4,6-DIMETHYL-2-PYRIMIDINYL)-2,3-DIHYDRO-1,2,4-TRIAZOLE-3-THIONE WITH *C*-ELECTROPHILES

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Abstract : The title 1,2,4-triazole-3-thione **2** reacted with ethyl bromoacetate in ethanol in the presence of sodium ethoxide to form S-alkyl derivative **3** and its cyclocondensation product - 3-(4,6-dimethyl-2-pyrimidinyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6(5*H*)-one (**4**), whereas with 4-chloroacetoacetate under similar conditions only corresponding cyclocondensation product **5a** was isolated. Reaction of **2** with ω-bromoacetophenone gave 6-hydroxy-3-(4,6-dimethyl-2-pyrimidinyl)-6,7-dihydro-6-phenyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazinium bromide (**6**), which under treatment with sodium hydroxide was converted into corresponding 1,3,4-thiadiazine **5b**. Heating **2** with ethyl orthoformate or 4-chlorobenzaldehyde afforded 4-(methylidene)amino substituted derivatives **7a,b**. Condensation of **2** with benzoic acid in phosphorus oxychloride gave 3-(4,6-dimethyl-2-pyrimidinyl)-6-phenyl-[1,2,4-triazolo][3,4-*b*][1,3,4]thiadiazole (**8**). Reaction of **2** with acetic anhydride yielded triacetylderivative **9**.

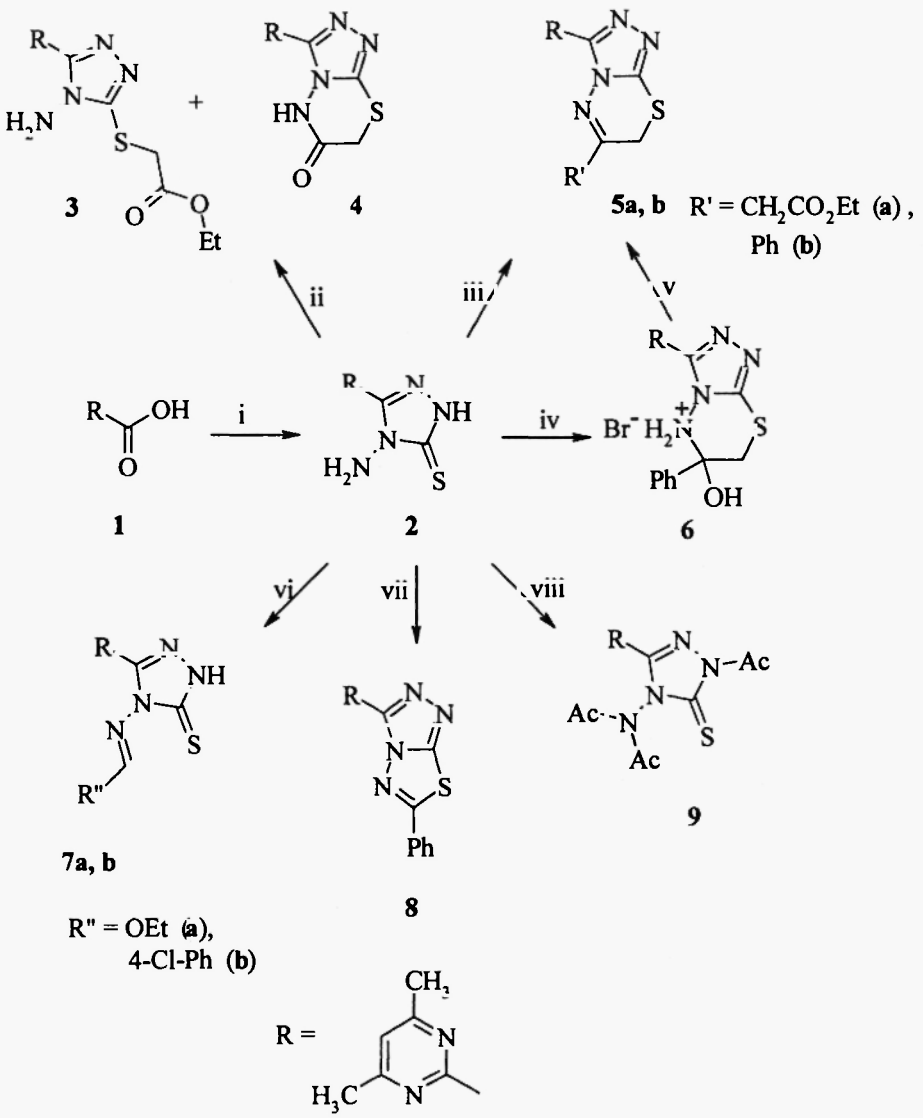
Introduction

A number of biologically active compounds contain in their structure functionalized azole and azine moieties. 1,2,4-Triazoles are of considerable interest on account of the diverse range of biological properties. Many of them show antimicrobial[1-3], antitubercular[4], anticancer[5] activities. 1,2,4-Triazole derivatives were reported to exhibit plant protecting properties[3, 6, 7].

5-Substituted 4-amino-1,2,4-triazole-3-thiones, their S-alkyl derivatives and fused 1,2,4-triazoles exhibit antibacterial, fungicidal[8], antimicrobial[9-12], hypotensive or CNS depressive[13] activity. Our earlier studies involved heterocyclic compounds containing pyrimidine and 1,2,4-triazole fragments[14-16] in their structure. In this context the goal of this work was to study reactions of 4-amino-5-(4,6-dimethyl-2-pyrimidinyl)-2,3-dihydro-1,2,4-triazole-3-thione (**2**) with *C*-electrophiles, capable to react at C_5 of pyrimidine ring or at S-, N_2-atom and NH_2-group of a triazole ring.

Results and Discussion

We have recently reported the synthesis of 4-amino-5-(4,6-dimethyl-2-pyrimidinyl)-2,3-dihydro-1,2,4-triazole-3-thione (**2**) by the reaction of 5-(4,6-dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2(3*H*)-thione with hydrazine hydrate in dioxane or butanol at reflux[17]. In the present study we developed new more convenient procedure for the synthesis of triazolethione **2**. According to this approach 4,6-dimethyl-2-pyrimidinecarboxylic acid (**1**) was fused with thiocarbohydrazide (145-146°C). The proposed procedure is more simple and shorter than that previously reported, however the yield of analytically pure **2** was not high (33%). The triazole ring of 4-amino-5-(4,6-dimethyl-2-pyrimidinyl)-2,3-dihydro-1,2,4-triazole-3-thione (**2**) has three reaction centers sensitive to electrophilic attack, i.e., S- or N_2-atom and NH_2-group.



Reagents and conditions: i: $(NH_2NH)_2CS$, Δ; ii: $BrCH_2CO_2Et$, anh. EtOH, EtONa, Δ; iii: $ClCH_2COCH_2CO_2Et$, anh. EtOH, EtONa, Δ; iv: $BrCH_2COPh$, anh. EtOH, Δ; v: NaOH, Δ; vi: $CH(OEt)_3$, Δ (a), 4-ClPhCHO, gl. AcOH (b), Δ; vii: $PhCO_2H$, $POCl_3$, Δ; viii: Ac_2O, Δ.

Scheme-1

Reaction of triazolethione **2** with ethyl bromoacetate was carried out in anh. ethanol in the presence of sodium ethoxide. S-Alkyl derivative **3** and its cyclocondensation product - 3-(4,6-dimethyl-2-pyrimidinyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6(5*H*)-one (**4**) were isolated in this reaction. Treatment of **2** with ethyl 4-chloroacetoacetate in similar conditions afforded the cyclic 1,2,4-triazolo[3,4-b][1,3,4]thiadiazine derivative **5a**. Triazolethione **2** reacted with ω-bromoacetophenone in anh. ethanol at reflux to give 6-

hydroxy-3-(4,6-dimethyl-2-pyrimidinyl)-6,7-dihydro-6-phenyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazinium bromide (**6**). The latter under treatment with sodium hydroxide was transformed to 3-(4,6-dimethyl-2-pyrimidinyl)-6-phenyl-7*H*-[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazine **5b**. Heating of **2** with an excess of ethyl orthoformate at reflux yielded **7a**. Condensation of **2** with 4-chlorobenzaldehyde in glacial acetic acid gave 4-[(4-chlorophenyl)methylidene]amino]-5-(4,6-dimethyl-2-pyrimidinyl)-2,3-dihydro-1,2,4-triazole-3-thione (**7b**). According to the data of ^{1}H NMR spectrum the structure of **7b** consists of a mixture of isomers E/Z in ratio 4:1. In the reaction of triazolethione **2** with benzoic acid, using an excess of phosphorus oxychloride at reflux, the appropriate 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivative **8** was formed. Full acetylation of NH- and NH_2-group was achieved by heating triazolethione **2** in acetic anhydride at reflux to afford **9**.

The structures of new compounds **3-9** were substantiated by their elemental and spectral data. In the ^{1}H NMR spectra of **3**-6 singlets of SCH_2 group protons are observed in a wide ranging scale of 3.21-4.35 ppm. It should be noted, that for cyclic thiadiazine structures **4** and **5a** the SCH_2 group protons appear at 3.21-3.8 ppm, whereas for S-alkyl derivative **3** the analogous signal is observed at 4.17 ppm and for compounds **5b**, 6 the corresponding peaks are downfield shifted to 4.3-4.35 ppm. Also the signals of $^+NH_2$ and OH group protons of 6 were observed at 5.5 ppm. The **7a,b** show characteristic for triazole ring NH proton downfield signals at 13.94-14.42 ppm and chemical shifts of N=CH protons at 8.58, 9.41 ppm respectively. The IR spectrum of 6 displayed characteristic absorption bands for $^+$NH group at 3077 and 1510 cm^{-1} and OH - at 3335 cm^{-1}. In the IR spectra of **7a,b** and **9** the absorption bands at 1347-1268 cm^{-1} were attributed to C=S group.

Experimental

Melting points were determined in open capillaries and are uncorrected.

IR spectra were run in KBr discs or nujol mulls (**5b**, 6, **7a**, **8**, **9**) on a Perkin Elmer FT spectrophotometer Spectrum BX II (ν, cm^{-1}). ^{1}H NMR spectra were recorded on a Varian Unity Inova (300 MHz) in DMSO-d_6 or Bruker AC-300 spectrometer in DMSO-d_6+CCl_4 solutions (**5b**, **6**, **7a**, **8**, **9**). Chemical shifts are expressed in δ, ppm, relative TMS. All reactions and purity of the synthesized compounds were monitored by TLC on Silica gel 60 F_{254} plates (Merck), in the system methanol-ethyl acetate (1:3), visualized by UV light. Abbreviations: triazole – tr, pyrimidine – pyr, oxadiazole – ox.

4-Amino-5-(4,6-dimethyl-2-pyrimidinyl)-2,3-dihydro-1,2,4-triazole-3-thione (**2**). A mixture of 4,6-dimethyl-2-pyrimidinecarboxylic acid (**1**) (0.76 g, 5 mmol) and thiocarbohydrazide (0.53 g, 5 mmol) was fused for 0.5 h (145-146°C). Then the content was dissolved in methanol at reflux and filtered off. The filtrate was cooled, the precipitate was filtered off to yield **2**, 0.37 g (33%), mp 239-240°C. IR: ν 3207 (NH_2), 2920 (NH tr), 1595 (C=C, C=N), 1344 cm^{-1} (C=S). ^{1}H NMR: δ 2.55 (6H, s, 4-, 6-CH_3), 6.41 (2H, s, NH_2), 7.47 (1H, s, 5-H pyr), 14.15 m.d. (1H, s, NH tr). Ref.[17]: mp 239-240°C.

Alkylation of 4-amino-5-(4,6-dimethyl-2-pyrimidinyl)-2,3-dihydro-1,2,4-triazole-3-thione (2) with ethyl bromoacetate

Ethyl {[4-amino-5-(4,6-dimethyl-2-pyrimidinyl)-1,2,4-triazol-3-yl]sulfanyl}acetate (3) and 3-(4,6-dimethyl-2-pyrimidinyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6(5*H*)-one (4). A suspension of triazolethione **2** (0.3 g, 1.35 mmol) and sodium ethoxide, prepared from sodium (0.03 g, 1.35 mmol) and anh. ethanol (5 ml), was heated at reflux for 15 min. Then ethyl bromoacetate (0.23 g, 1.35 mmol) was added dropwise and the mixture was refluxed under stirring for 0.5 h. The solution was concentrated to 4 ml, cooled to 0°C and the precipitate was filtered off to give compound **4**. The residual filtrate was evaporated to dryness in vacuo. The resinous residue was dissolved in chloroform and filtered off. Ether was added to the filtrate and the precipitate formed was filtered off to give compound **3**.

3: yield 0.23 g (55%), mp 70°C (chloroform/ether). IR: ν 3276 (NH_2), 1742 (C=O), 1595 (C=C), 1539 cm^{-1} (C=N). ^1H NMR: δ 1.23 (3H, t, *J*=7.2 Hz, $CH_2\underline{CH_3}$), 2.54 (6H, s, 4-, 6-CH_3), 4.15 (2H, k, *J*=7.2 Hz, $\underline{CH_2}CH_3$), 4.17 (2H, s, SCH_2), 6.52 (2H, s, NH_2), 7.39 ppm (1H, s, 5-H pyr). Anal. Calcd. for $C_{12}H_{16}N_6O_2S$ (308.36): C 46.74; H 5.23; N 27.25. Found: C 46.36; H 5.37; N 27.46.

4: yield 0.12 g (34%), mp 245°C. IR: ν 3389 (NH), 1703 (C=O). ^1H NMR: δ 2.53 (6H, s, 4-, 6-CH_3), 3.21 (2H, s, CH_2), 7.34 (1H, s, 5-H pyr). Anal. Calcd. for $C_{10}H_{10}N_6OS$ (262.29): C 45.79; H 3.84; N 32.04. Found: C 45.87; H 3.67; N 31.98.

Ethyl [3-(4,6-dimethyl-2-pyrimidinyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl]acetate (5a). A suspension of triazolethione **2** (0.24 g, 1.08 mmol) and sodium ethoxide, prepared from sodium (0.025 g, 1.08 mmol) and anh. ethanol (5 ml), was heated at reflux for 15 min. Then ethyl 4-chloroacetoacetate (0.178 g, 1.08 mmol) was added dropwise, the mixture was refluxed under stirring for 2 h and filtered off. The filtrate was cooled, the precipitate was filtered off, washed with ether and recrystallized to give 0.18 g (51%) of **5a**, mp 160-161°C (ethyl acetate). IR: ν 1730 (C=O), 1636 (C=C), 1583 (C=N), 738 cm^{-1} (C-S-C). ^1H NMR: δ 1.19 (3H, t, *J*=7.2 Hz, $CH_2\underline{CH_3}$), 2.53 (6H, s, 4-, 6-CH_3), 3.79 (2H, s, CH_2), 4.02 (2H, s, $\underline{CH_2}CO$), 4.14 (2H, k, *J*=6.9 Hz, $\underline{CH_2}CH_3$), 7.43 m.d. (1H, s, 5-H pyr). Anal. Calcd. for $C_{14}H_{16}N_6O_2S$ (332.38): C 50.59; H 4.85; N 25.28. Found: C 50.92; H 5.01; N 25.57.

3-(4,6-Dimethyl-2-pyrimidinyl)-6-phenyl-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine (5b). Salt 6 (0.2 g, 0.48 mmol) was stirred with 5% NaOH (3 ml) at room temperature for 10 min. The precipitate was filtered off, washed with water, dried and recrystallized to give 0.12 g (80%) of **5b**, mp 184-185°C [ethanol-water (1:1)]. IR: ν 1588 (C=N), 1537 (C=C), 694 cm^{-1} (C-S-C). ^1H NMR: δ 2.58 (6H, s, 4-, 6-CH_3), 4.3 (2H, s, CH_2), 7.25 (1H, s, 5-H pyr), 7.49 (3H, m, Ph), 8.0 ppm. (2H, m, Ph). Anal. Calcd. for $C_{16}H_{14}N_6S$ (322.39): C 59.61; H 4.38; N 26.07. Found: C 59.49; H 4.26; N 26.12.

6-Hydroxy-3-(4,6-dimethyl-2-pyrimidinyl)-6,7-dihydro-6-phenyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazinium bromide (6). To a solution of triazolethione **2** (0.25 g, 1.12 mmol) in anh. ethanol (10 ml) ω-bromoacetophenone (0.22 g, 1.12 mmol) was added and the reaction mixture was refluxed for 2 h. Then the

solvent was evaporated in vacuo and ether was added to the residue. The precipitate was filtered off and recrystallized to give 0.27 g (57%) of **6**, mp 206-207°C (abs. ethanol/ether). IR: ν 3335 (OH), 3182, 1633, 1510 ($^{+}$NH), 1592 (C=C), 688 cm^{-1} (C-S-C). ^{1}H NMR: δ 2.58 (6H, s, 4-, 6-CH_3), 4.35 (2H, s, CH_2), 5.55 (3H, s, $N^{+}H_2$, OH), 7.28 (1H, s, 5-H pyr), 7.49 (3H, m, Ph), 8.0 (2H, m, Ph). Anal. Calcd. for $C_{16}H_{17}BrN_6OS$ (421.32): C 45.61; H 4.07; N 19.95. Found: C 45.76; H 4.07; N 19.86.

4-Ethoxymethylideneamino-5-(4,6-dimethyl-2-pyrimidinyl)-2,3-dihydro-1,2,4-triazole-3-thione (7a). A mixture of triazolethione **2** (0.3 g, 1.35 mmol) and ethyl orthoformate (2 ml) was refluxed for 2 h. The mixture then was cooled and the precipitate was filtered off to give **7a**. The filtrate was evaporated to dryness, worked up with ether, the precipitate was filtered off to give the additional amount of **7a**. The solids were combined and recrystallized from ethanol to yield 0.1 g (27%) of **7a**, mp 212-212.5°C. IR: ν 3176 (NH), 1619 (C=N), 1595 (C=C), 1347 cm^{-1} (C=S). ^{1}H NMR: δ 1.4 (3H, s, CH_3), 2.6 (6H, s, 4-, 6-CH_3), 4.4 (2H, m, CH_2), 7.3 (1H, s, 5-H pyr), 8.58 (1H, s, N=CH), 13.94 ppm (1H, s, NH tr). Anal. Calcd. for $C_{11}H_{14}N_6OS$ (278.34): C 47.47; H 5.07; N 30.19. Found: C 47.23; H 4.99; N 30.42.

4-[(4-Chlorophenyl)methylidene]amino]-5-(4,6-dimethyl-2-pyrimidinyl)-2,3-dihydro-1,2,4-triazole-3-thione (7b). To a solution of triazolethione **2** (0.1 g, 0.45 mmol) in glacial acetic acid (2.5 ml) 4-chlorobenzaldehyde (0.063 g, 0.45 mmol) was added and the mixture was refluxed under stirring for 1h 10 min. Then the reaction mixture was concentrated, the precipitate was filtered off, washed with water and recrystallized to give 0.11 g (71%) of **7b**, mp 210°C (ethanol). IR: ν 3400 (NH), 1594 (C=N), 1534 (C=C), 1268 cm^{-1} (C=S). ^{1}H NMR: δ 2.43 (6H, s, 4-, 6-CH_3), 7.42 (1H, s, 5-H pyr), 7.66 (2H, d, *J*=8.4 Hz, Ph), 7.92 (2H, d, *J*=8.4 Hz, Ph), 8.75 (*E*), 9.41 (*Z*) (1H, s, N=CH), 14.42 ppm (1H, s, NH tr). Anal. Calcd. for $C_{15}H_{13}ClN_6S$ (344.82): C 52.25; H 3.80; N 24.37. Found: C 52.14; H 4.10; N 24.44.

3-(4,6-Dimethyl-2-pyrimidinyl)-6-phenyl-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole (8). A mixture of triazolothione **2** (0.4 g, 1.8 mmol), benzoic acid (0.22 g, 1.8 mmol) and phosphorus oxychloride (10 ml) was heated at reflux for 5 h. Then the solvent was removed in vacuo and the residue was poured onto crushed ice. The precipitate was filtered off, washed with 10% NaOH solution, water and recrystallized to give 0.17 g (42%) of 8, mp 183-184°C [methanol-water (1:1)]. IR: ν 1592 (C=N), 1539 (C=C), 684 cm^{-1} (C-S-C). ^{1}H NMR: δ 2.62 (6H, s, 4-, 6-CH_3), 7.25 (1H, s, 5-H pyr), 7.59 (3H, m, Ph), 7.8 ppm (2H, m, Ph). Anal. Calcd. for $C_{15}H_{12}N_6S$ (308.36): C 58.42; H 3.92; N 27.25. Found: C 58.64; H 3.88; N 27.10.

N-[2-Acetyl-5-(4,6-dimethyl-2-pyrimidinyl)-3-thioxo-2,3-dihydro-1,2,4-triazol-4-yl]diacetamide (9). A mixture of triazolethione **2** (0.13 g, 0.59 mmol) and acetic anhydride (2.5 ml) was heated at reflux for 0.5 h. The solvent (2 ml) was removed by rotary evaporator, the residue was cooled, the precipitate was filtered off, washed with ether and recrystallized to give 0.13 g (65%) of 9, mp 174-175°C (methanol). IR: ν 1758, 1744 (C=O), 1588 (C=N), 1527 (C=C), 1330 cm^{-1} (C=S). ^{1}H NMR: δ 1.9 (3H, s, $COCH_3$). 2.4 (6H, m, 2 $COCH_3$), 2.5 (6H, s, 4-, 6-CH_3), 7.45 ppm (1H, s, 5-H pyr). Anal. Calcd. for $C_{14}H_{16}N_6O_3S$ (348.38): C 48.27; H 4.63; N 24.12. Found: C 48.58; H 4.70; N 24.07.

References

1. N. Ulusoy, A. Gursoy and G. Otuk, Il *Farmaco*, **56**, 947 (2001).
2. S. G. Küçükgüzel, S. Rolas, H. Erdeniz and M. Kiraz, *Eur. J. Med. Chem.*, **34**, 153 (1999).
3. S. Papakostantinou–Garoufalias, N. Pouli, P. Marakos and A. Chytyroglou–Ladas, Il *Farmaco*, **57**, 973 (2002).
4. I. I. Küçükgüzel , S. G. S. Güniz Küçükgüzel, S. S. Rollas and M. M. Kiraz, Bioorg. *Med. Chem. Lett.*, **11**, 1703 (2001).
5. B. S. Holla, K. N. Poajary, B. S. Rao and M. K. Shivananda, *Eur. J. Med. Chem.*, **37**, 511 (2002).
6. G. J. Tanoury, C. H. Senanyake, R. Hett, A. M. Kuhn, D. W. Kessler and S. A. Wald, *Tetrahedron Lett.*, **39**, 6845 (1998).
7. Y. Quesnel, L. Bidois–Sery, J.–M. Poirier and L. Duhamel, *J. Org. Chem.*, **63**, 3793 (1998).
8. Zhang Zi-Yi, Chen Xin, *Acta Chim. Sin.*, **49**, 513 (1991).
9. A. A. El-Barbary, M. Fahmy, M. El-Badawi, K. El-Brembaly and N. R. El-Brollosi, *Rev. Roum. Chim.*, **36**, 619 (1991).
10. A. H. El-Masry, H. H. Fahmy and S.H. A. Abdelwahed, *Molekules*, **5**, 1429 (2000).
11. K. Colonceska-Ragenovic, V. Dimova, V. Kakurinov, D. G. Molnar and A. Buzarovska, *Molekules*, **6**, 815 (2001).
12. N. Dembiras, A. Dembiras, S. A. Karaouglu and E. Celik, *Arkivoc*, **75** (2005).
13. Zhang Zi-yi and Zou Ning, *Chin. J. Chem.*, **13**, 448 (1995); C. A., **122**, 290780f (1995).
14. G. Mekuskiene, P. Gaidelis and P. Vainilavicius, *Pharmazie*, **53**, 94 (1998).
15. P. Vainilavicius, R. Smicius, V. Jakubkiene and S. Tumkevicius, *Monatsh. Chem.*, **132**, 825 (2001).
16. M. M. Burbuliene, V. Jakubkiene, G. Mekuskiene and P. Vainilavicius, *Phosphorus, Sulfur and Silicon*, **178**, 2431 (2003).
17. G. Mekuskiene, J. Dodonova, M. M. Burbuliene and P. Vainilavicius, *Heterocycl. Commun.* Submitted.

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