DOI 10.1007/s10593-019-02484-8

Chemistry of Heterocyclic Compounds **2019**, *55*(4/5), 478–480

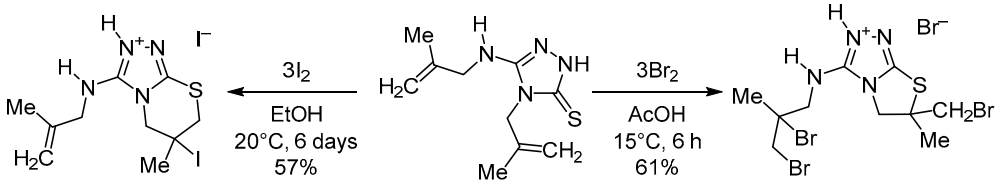
Peculiarities of 4-methallyl-5-methallylamino-1,2,4-triazole-3-thione halogenation

Maksym M. Fizer[1], Mikhailo V. Slivka[1]*, Vasil G. Lendel[1]

[1] *Uzhhorod National University,*
53/1 Fedyntsia St., Uzhhorod 88000, Ukraine; e-mail: mikhailo.slivka@uzhnu.edu.ua

Published in Khimiya Geterotsiklicheskikh Soedinenii,
2019, *55*(4/5), 478–480

Submitted February 27, 2019
Accepted March 27, 2019



Bromination and iodination of 4-methallyl-5-methallylamino-1,2,4-triazole-3-thione lead to the annulation of five- and six-membered thiazaheterocycles, respectively. The usage of halogen excess does not give the product of 5-methallylamino group cyclization – the product of the bromine addition was isolated.

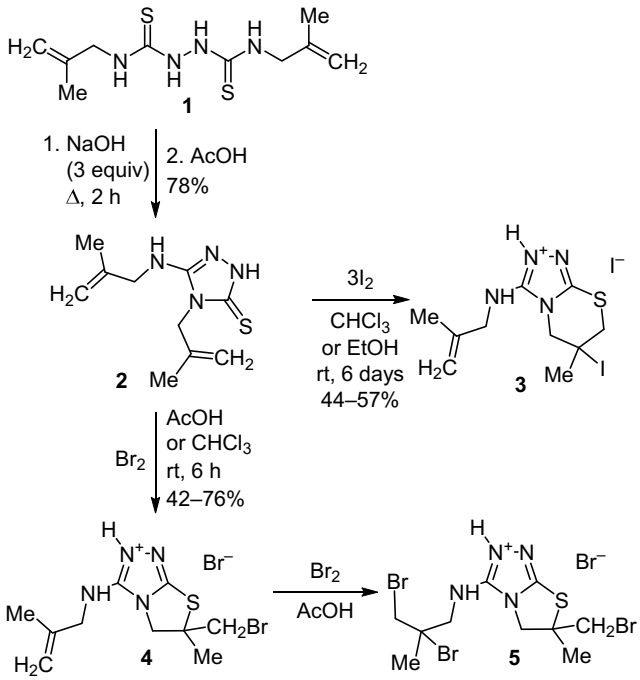
Keywords: [1,3]thiazolo[2,3-*c*][1,2,4]triazole, 1,2,4-triazole, [1,2,4]triazolo[3,4-*b*][1,3]thiazine, electrophilic cyclization, halogenation.

Electrophilic heterocyclization is a highly efficient and direct route to the condensed heterocycles.[1,2] The main advantage of this technique is the possibility of annulation of partially hydrated heterocycles: hydropyrimidine and imidazoline,[3] hydropyrazine,[4] hydropyran and hydrofuran,[5] thiazoline,[6–8] hydrothiazine,[8–11] oxazoline.[12,13] Moreover, the presence of several alkenyl groups and appropriate nucleophilic centers gives one-step access to polycyclic systems.[14] Considering many aspects, we have to note that intramolecular electrophilic cyclization of alkenyl-substituted azaheterocycles has become a powerful synthetic tool for annulation of a partially hydrated five- or six-membered rings. Scientific interest for such systems is related to the wide range of their biological activities.[15]

Intensive investigations in the field of fused triazole chemistry[16–18] have led to the development of regioselective methods that allow to annulate partly hydrated pyrimidine or triazoline moieties to 1,2,4-triazole ring through halogenation of 4(5)-allyl-substituted 1,2,4-triazole-3-thiones.[14,19] It was established that the use of low concentrations of initial reagents is the key for regioselectivity of the process.

In the present work, we wish to report our investigation of peculiarities of halogenation (with bromine or iodine) of 4-methallyl-5-methallylamino-1,2,4-triazole-3-thione under mild reaction conditions. Starting dimethallyl-substituted 1,2,4-triazole was synthesized according to the modified procedure described for diallyl analogs.[20] Thus, the reaction of double excess of methallyl isothiocyanate[21] with hydrazine hydrate in EtOH has led to the corresponding bisthiourea **1**, that under basic conditions forms dimethallyltriazole **2** (Scheme 1).

Scheme 1



Considering that triazole **2** contains two different methylallyl substituents and three nucleophilic centers, which can participate in electrophilic heterocyclization, several reaction pathways are theoretically possible: cyclization of 4-methallyl substituent on nitrogen 5-NH with formation of imidazo[2,1-*c*][1,2,4]triazole-3-thione; cyclization of 4-methallyl substituent on sulfur C=S with annulation of [1,3]thiazolo[2,3-*c*][1,2,4]triazole system; cyclization of 5-methallylamino fragment on highly nucleophilic nitrogen N-1[22] with production of imidazo[2,1-*b*]-[1,2,4]triazole-3-thione (Scheme 1). Moreover, the formation of six-membered analogs or the products of halogen addition to the double bond is possible.

The iodination of triazole **2** goes with unexpected annulation *via* the sulfur atom of six-membered thiazine cycle to form compound **3** (Scheme 1). Evidence of the formation of a six-membered cycle instead of a five-membered cycle is the signal of the iodo-substituted carbon C-6 at 38.84 ppm in ^{13}C NMR spectra of compound **3**. Opposite, the primary carbon of CH_2I group is located upfield: 3.87 ppm (in ^{13}C NMR spectrum),[11] 10.4–10.6 ppm (in ^{1}H NMR spectrum).[14]

The addition of bromine to triazole **2** in AcOH or $CHCl_3$ under various reaction conditions selectively leads to the cyclization of 4-methallyl fragment on the sulfur atom with the formation of five-membered thiazoline moiety **4**. Such regioselectivity is in total agreement with the literature data.[23,24] The maximum yield is observed using AcOH as a solvent and carrying out the process at 15°C.

Further bromine action on salt **4** leads to the bromination of exocyclic methallylamino group without annulation of additional diazocycle. This is in full agreement with the behavior of a previously described similar allyl-substituted derivative.[14] However, the absence of cyclization of similar allylamino-1,3,4-thiadiazoles is known.[25] Such a low reactivity of intermediate electrophile group (bromonium cation) and the nitrogen atom in position 1 of triazole system can be explained by steric hindrance of the methyl group and by blocking of the nucleophilic triazole nitrogen atom at first position through the protonation, which was established by X-ray diffraction study of similar 5-amino-3-mercapto-1,2,4-triazole.[22] Trying of additional iodination of salts **3**, **4** was not successful – starting materials were isolated. The bromination of salt **3** was accompanied by iodine release, obviously through a redox reaction, however, we could not obtain individual products.

In an attempt to run cyclization of product **5**, we have tried to use different bases with hope to deprotonate the triazole moiety and thus increase its nucleophilicity. However, using of NaOH, Na_2CO_3, AcONa, Et_3N, and DIPEA did not lead us to the desired products. In the last two cases, salt **5** was recovered, whereas when sodium salts were used we could not isolate individual substances, only mixtures with uninterpretable NMR spectra.

In conclusion, we have found a few peculiarities of the halogenation of 4-methallyl-5-methallylamino-1,2,4-triazole-3-thione: (a) the methallyl fragment in position N-4 of triazole ring is more reactive; (b) the sulfur atom is the most reactive nucleophilic center in 5-amino-1,2,4-triazole-3-thione; (c) iodination leads to the annulation of six-membered dihydrothiazine cycle, whereas in the case of bromination, thiazoline ring was formed; (d) bromination of exocyclic methallyamino fragment does not lead to cyclization – addition of bromine to the double bond takes place.

Experimental

^{1}H NMR spectra (300 MHz) were recorded on a Varian VXR-300 instrument, while ^{13}C NMR spectra (126 MHz) on a Bruker Avance DRX spectrometer in DMSO-d_6. TMS was used as internal standard for ^{1}H NMR spectra and DMSO-d_6 signal (39.50 ppm) in the case of ^{13}C NMR spectra. Mass spectra were recorded on a Shimadzu GCMS-QP2010 Ultra gas chromato-mass spectrometer with EI ionization (70 eV). Elemental analysis was performed on an Elementar vario MICRO cube analyzer. Melting points were determined on a Boetius micro hot stage.

***N*,*N*'-Bis(2-methylallyl)hydrazine-1,2-dicarbothioamide (1)** was synthesized according to a described procedure,[17] from hydrazine hydrate (0.02 mol) and methallyl isothiocyanate (0.04 mol). Yield 4.2 g (82%), white flakes, mp 188–189°C. ^{1}H NMR spectrum, δ, ppm: 1.66 (6H, s, $2CH_3$); 4.03 (4H, s, $2CH_2N$); 4.74 (2H, s, *trans* CH_2=); 4.78 (2H, s, *cis* CH_2=); 8.03 (2H, br. s, $2N\underline{H}CH_2$); 9.35 (2H, s, NH–NH). Found, %: C 46.54; H 7.11; N 21.45; S 24.66. $C_{10}H_{18}N_4S_2$. Calculated, %: C 46.48; H 7.02; N 21.68; S 24.81.

4-(2-Methylallyl)-5-[(2-methylallyl)amino]-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (2) was synthesized according to a described procedure[15] from bisthiourea **1** (0.05 mol). Yield 8.72 g (78%), colorless needles, mp 116–117°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.67 (3H, s, CH_3); 1.70 (3H, s, CH_3); 3.66 (2H, d, *J* = 5.7, $C\underline{H}_2NH$); 3.67 (1H, s, *cis* CH_2=); 4.40–4.47 (3H, m, CH_2N, *trans* CH_2=); 4.78 (1H, s, *trans* CH_2=); 4.79–4.85 (2H, m, *cis* CH_2=); 6.55 (1H, t, *J* = 6.0, NH); 13.02 (1H, br. s, 4-NH). Mass spectrum, *m*/*z* (I_{rel}, %): 224 $[M+H]^+$ (100). Found, %: C 53.66; H 7.32; N 24.85; S 14.12. $C_{10}H_{16}N_4S$. Calculated, %: C 53.54; H 7.19; N 24.98; S 14.29.

6-Iodo-6-methyl-3-[(2-methylallyl)amino]-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3]thiazin-2-ium iodide (3). Solid iodine (3.43 g, 13.5 mmol) was added to a solution of compound **2** (1.0 g, 4.5 mmol) in EtOH or $CHCl_3$ (50 ml), and the reaction mixture was maintained at room temperature for 6 days. The resulting dark-yellow precipitate of compound **3** was filtered off, washed with Et_2O, and dried on air. Yield 1.22 g (57%, from EtOH), 0.95 g (44%, from $CHCl_3$), yellow powder, mp 107–108°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.72 (3H, s, CH_3); 2.18 (3H, s, CH_3); 3.22 (1H, d, *J* = 13.3, CH_2S); 3.49 (1H, d, *J* = 13.4, CH_2S); 3.74 (2H, d, *J* = 5.6, $C\underline{H}_2NH$); 3.93 (1H, d, *J* = 13.5, $C\underline{H}_2N$); 4.29 (1H, d, *J* = 13.6, $C\underline{H}_2N$); 4.80 (1H, s, *trans* CH_2=); 4.88 (1H, s, *cis* CH_2=); 6.36 (1H, t, *J* = 5.8, $N\underline{H}CH_2$). Signal of 1-N^+H proton in triazole cycle is overlapped with the signal of water (3.42 ppm). ^{13}C NMR spectrum, δ, ppm: 20.7 (CH_3); 32.6 (CH_3); 38.8 (C-6); 41.3 (C-7); 48.4 (CH_2NH); 57.3 (C-5); 110.8 (CH_2=); 138.3 (C); 142.7 (C-8a); 154.8 (C-3). Mass

spectrum, *m*/*z* (I_{rel}, %): 350 $[M+H-HI]^+$ (100). Found, %: C 25.36; H 3.62; N 11.53; S 6.61. $C_{10}H_{16}I_2N_4S$. Calculated, %: C 25.12; H 3.37; N 11.72; S 6.71.

6-(Bromomethyl)-6-methyl-3-[(2-methylallyl)amino]-5,6-dihydro[1,3]thiazolo[2,3-*c*][1,2,4]triazol-2-ium bromide (4). A solution of triazole **2** (1.00 g, 4.5 mmol) in AcOH or $CHCl_3$ (20 ml) was treated with a solution of bromine (0.23 ml, 4.5 mmol) in AcOH or $CHCl_3$ (10 ml), and the reaction mixture was maintained at room temperature for 6 h. The obtained precipitate of compound **4** was filtered off, washed with Et_2O, and dried on air. Yield 1.30 g (76%, from AcOH), 0.72 g (42%, from $CHCl_3$), white powder, mp 115–116°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.72 (3H, s, CH_3); 2.01 (3H, s, CH_3); 3.45 (1H, d (second peak is overlapped with the water signal), CH_2Br); 3.58 (1H, d, *J* = 13.4, CH_2Br); 3.74 (2H, d, *J* = 5.7, C<u>H</u>$_2$NH); 4.06 (1H, d, *J* = 13.6, CH_2N); 4.27 (1H, d, *J* = 13.6, CH_2N); 4.81 (1H, s, *trans* CH_2=); 4.89 (1H, s, *cis* CH_2=); 6.35 (1H, t, *J* = 5.8, N<u>H</u>CH_2). ^{13}C NMR spectrum, δ, ppm: 20.8 (CH_3); 30.1 (CH_3); 38.6 (CH_2Br); 48.4 (CH_2NH); 54.9 (C-6); 59.1 (C-5); 110.7 (CH_2=); 138.0 (C); 143.0 (C-7a); 155.5 (C-3). Mass spectrum, *m*/*z* (I_{rel}, %): 302 $[M(^{79}Br)+H-HBr]^+$ (100), 304 $[M(^{81}Br)+H-HBr]^+$ (100). Found, %: C 31.48; H 4.42; N 14.45; S 8.18. $C_{10}H_{16}Br_2N_4S$. Calculated, %: C 31.27; H 4.20; N 14.59; S 8.35.

6-(Bromomethyl)-3-[(2,3-dibromo-2-methylpropyl)-amino]-6-methyl-5,6-dihydro[1,3]thiazolo[2,3-*c*][1,2,4]-triazol-2-ium bromide (5). Triazole **2** (1.00 g, 4.5 mmol) or salt **4** (1.00 g, 2.6 mmol) was treated with a solution of bromine (0.47 ml, 9.1 mmol) in AcOH (20 ml) or with a solution of bromine (0.14 ml, 2.7 mmol) in AcOH (10 ml), respectively. The resulting yellow reaction mixture was maintained at room temperature for 6 h until it became colorless. The solvent was evaporated under reduced pressure, and obtained gummy product was triturated few times with the Me_2CO–Et_2O, 1:2 mixture until the white powder was obtained. The target compound **5** was filtered off, washed with Et_2O, and dried on air. Yield 1.49 g (61%, from triazole **2**), 1.05 g (74%, from salt **4**), white powder, mp 144°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.83 (3H, s, CH_3); 1.87 (3H, s, CH_3); 3.85 (2H, d, *J* = 6.6, C<u>H</u>$_2$NH); 4.09 (2H, s, CH_2Br); 4.09–4.20 (3H, m, CH_2N, CH_2Br); 4.51 (1H, d, *J* = 11.8, CH_2N); 9.20 (1H, t, *J* = 6.3, N<u>H</u>CH_2). ^{13}C NMR spectrum, δ, ppm: 25.5 (CH_3); 28.0 (CH_3); 41.7 (CH_2Br); 42.5 (CH_2Br); 53.0 (C-6); 53.9 (CH_2NH); 67.1 (CH_2N); 67.7 (C); 149.9 (C-7a); 153.5 (C-3). Mass spectrum, *m*/*z* (I_{rel}, %): 460 $[M(^{79}Br,^{79}Br,^{79}Br)+H-HBr]^+$ (35), 462 $[M(^{79}Br,^{79}Br,^{81}Br)+H-HBr]^+$ (100), 464 $[M(^{79}Br,^{81}Br,^{81}Br)+H-HBr]^+$ (100), 466 $[M(^{81}Br,^{81}Br,^{81}Br)+H-HBr]^+$ (35). Found, %: C 22.01; H 3.12; N 10.12; S 5.65. $C_{10}H_{16}Br_4N_4S$. Calculated, %: C 22.08; H 2.97; N 10.30; S 5.89.

References

1. Rodriguez, F.; Fananas, F. J. In *Handbook of Cyclization Reactions*; Ma, S., Ed.; Wiley-VCH: New York, 2010, Vol. 2. p. 951.
2. Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937.
3. Dyachenko, I. V.; Vas'kevich, R. I.; Vas'kevich, A. I.; Polovinko, V. V.; Vovk, M. V. *Russ. J. Org. Chem.* **2018**, *54*, 436. [*Zh. Org. Khim.* **2018**, *54*, 431.]
4. Kim, D. G. *Chem. Heterocycl. Compd.* **2007**, *43*, 1591. [*Khim. Geterotsikl. Soedin.* **2007**, 1877.]
5. Vas'kevich, A. I.; Vovk, M. V. *Russ. J. Org. Chem*. **2017**, *53*, 270. [*Zh. Org. Khim.* **2017**, *53*, 271.]
6. Korol, N. I.; Slivka, M. V. *Chem. Heterocycl. Compd.* **2017**, *53*, 852. [*Khim. Geterotsikl. Soedin.* **2017**, *53*, 852.]
7. Kut, M.; Fizer, M.; Onysko, M.; Lendel, V. *J. Heterocycl. Chem.* **2018**, *55*, 2284.
8. Slivka, M.; Korol, N.; Rusyn, I.; Lendel, V. *Heterocycl. Commun*. **2015**, *21*, 397.
9. Dyachenko, I. V.; Vas'kevich, R. I.; Vas'kevich, A. I.; Shishkina, S. V.; Vovk, M. V. *Russ. J. Org. Chem.* **2016**, *52*, 745. [*Zh. Org. Khim.* **2016**, *52*, 755.]
10. Onysko, M.; Filak, I.; Lendel, V. *Heterocycl. Commun*. **2017**, *23*, 309.
11. Il'inykh, E. S.; Kim, D. G.; Kodess, M. I.; Matochkina, E. G.; Slepukhin, P. A. *J. Fluorine Chem.* **2013**, *149*, 24.
12. Osheko, K. Yu.; Kim, D. G.; El'tsov, O. S.; Shtukina, T. S. *Russ. J. Org. Chem.* **2018**, *54*, 1406. [*Zh. Org. Khim.* **2018**, *54*, 1390.]
13. Khripak, S. M.; Plesha, M. V.; Slivka, M. V.; Yakubets, V. I.; Krivovyaz, A. A. *Russ. J. Org. Chem.* **2004**, *40*, 1705. [*Zh. Org. Khim.* **2004**, *40*, 1749.]
14. Fizer, M.; Slivka, M.; Rusanov, E.; Turov, A.; Lendel, V. *J. Heterocycl. Chem.* **2015**, *52*, 949.
15. Küçükgüzel, Ş. G.; Çıkla-Süzgün, P. *Eur. J. Med. Chem.* **2015**, *97*, 830.
16. Gümüş, M. K.; Gorobets, N. Yu.; Sedash, Y. V.; Chebanov, V. A.; Desenko, S. M. *Chem. Heterocycl. Compd.* **2017**, *53*, 1261. [*Khim. Geterotsikl. Soedin.* **2017**, *53*, 1261.]
17. Bhatt, A.; Singh, R. K.; Kant, R. *Chem. Heterocyc. Compd.* **2018**, *54*, 1111. [*Khim. Geterotsikl. Soedin.* **2018**, *54*, 1111.]
18. Kulikov, A. S.; Epishina, M. A.; Fershtat, L. L.; Makhova, N. N. *Chem. Heterocyc. Compd.* **2018**, *54*, 669. [*Khim. Geterotsikl. Soedin.* **2018**, *54*, 669.]
19. Fizer, M. M.; Slivka, M. V.; Lendel, V. G. *Chem. Heterocycl. Compd.* **2013**, *49*, 1243. [*Khim. Geterotsikl. Soedin.* **2013**, 1331.]
20. Khripak, S. M.; Slivka, M. V.; Zborovskii, Yu. L.; Staninets, V. I.; Yakubets, V. I. *Scientific Bulletin of the Uzhhorod University* (*Series Chemistry)* [In Ukrainian] **2000**, *5*, 89.
21. Fizer, M. *Synlett* **2013**, 2019.
22. Fizer, M.; Slivka, M.; Mariychuk, R.; Baumer, V.; Lendel, V. *J. Mol. Struct.* **2018**, *1161*, 226.
23. Kochikyan, T. V.; Samvelyan, M. A.; Petrosyan, A. M.; Langer, P. D. *Russ. J. Org. Chem.* **2015**, *51*, 1469. [*Zh. Org. Khim.* **2015**, *51*, 1499.]
24. Khripak, S. M.; Slivka, M. V.; Vilkov, R. V.; Usenko, R. N.; Lendel, V. G. *Chem. Heterocycl. Compd.* **2007**, *43*, 781. [*Khim. Geterotsikl. Soedin.* **2007**, 922.]
25. Fizer, M.; Slivka, M.; Baumer, V.; Lendel, V. *Heterocycl. Commun.* **2016**, *22*, 79.