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One-pot synthesis of disulfide-tethered ionic liquids by the reaction between 4*H*-1,2,4-triazole-3-thiol and α-iodoketones

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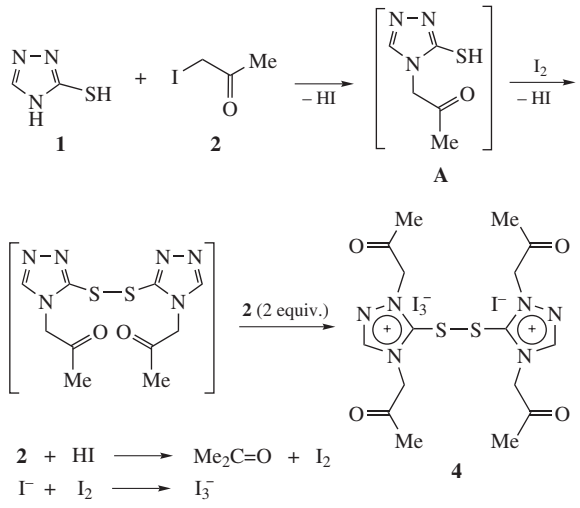
The one-pot reaction of 4*H*-1,2,4-triazole-3-thiol with 1-iodopropan-2-one or 1,3-diiodopropan-2-one proceeds without solvents and basic media to afford a novel family of ionic liquids containing disulfide bridge.

Triazole moiety is not uncommon in drugs,[1] herbicides, fungicides,[2] insecticides and acaricides.[3] Triazoles are valuable precursors for the synthesis of magnetoactive,[4] luminescent,[5] coordination compounds,[6] high-energy compositions,[7] ionic liquids,[8] and antitumor medicines.[9,10]

Classical methods for the S-derivatization of valuable 1,2,4-triazole-3-thiol **1** comprise the use of chloro- or bromomethyl-substituted aliphatic, aromatic, or heteroaromatic compounds.[10,11] For example, S-alkylation with chloromethyl compounds is successfully implemented in the presence of anhydrous potassium carbonate or potassium hydroxide. In the case of bromo analogues, the reaction requires no basic media. The data on alkylation of thiol **1** with 1-iodopropan-2-one and 1,3-diiodopropan-2-one are lacking in the literature.

Earlier we have found that reactivity of iodo ketones in comparison with chloro and bromo analogues in alkylation of azoles is quite specific due to high lability of the C–I bond, ability of the iodomethyl group to be reduced with hydrogen iodide released in the course of the alkylation, and formation of stable triiodide anion or new types of liquid salts.[12] With this assumption, in this work, we have studied the interaction of 1,2,4-triazole-3-thiol **1** with 1-iodopropan-2-one **2** and 1,3-diiodopropan-2-one **3**.

The reaction between 1,2,4-triazole-3-thiol **1** and 1-iodopropan-2-one **2** proceeds at 45 °C in the absence of solvents to deliver bis-salt **4** (Scheme 1),† in one synthetic operation. The obtained experimental data allow us to assume that the reaction represents a domino sequence involving alkylation of triazole **1** with iodo ketone **2** at the pyrrole ring, partial reduction of iodopropanone **2** to acetone with the released hydrogen iodide, oxidation of the SH moiety to disulfide by the delivered iodine and quaternization of the nitrogen pyridine atoms.



Scheme 1

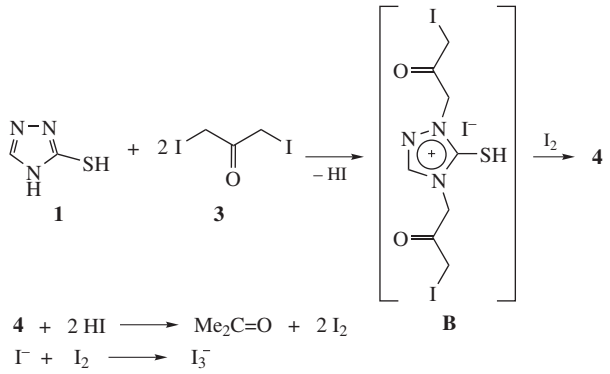
It is known that alkylation of benzotriazole and 1,3-bis(benzotriazolyl)propan-2-one with 1,3-dihalopropan-2-one occurs with the participation of two halomethyl groups of ketone that allows one to synthesize both bis-derivatives and cyclic products with dimethylenecarbonyl bridges.[13,14] However, the interaction between 1,2,4-triazole-3-thiol **1** and 1,3-diiodopropan-2-one **3** is accompanied by reduction of the iodomethyl groups with hydrogen iodide released in the course of alkylation, thus preventing the reaction involving the second iodomethyl moiety (Scheme 2).† Therefore, polyiodide **4** becomes the major reaction product.

† Elemental analysis was performed on an automatic Thermo Scientific Flash 2000 CHNS-analyzer. UV spectra were recorded on a UV-VIS Lambda 35 (MeCN) spectrometer. IR spectra were run on a Vertex 70 instrument (film). ^{1}H, ^{13}C, ^{15}N NMR spectra were measured on a Bruker DPX-400 spectrometer (400.13, 100.61, 40.56 MHz, respectively) in acetone-d_6. Chemical shifts were measured relative to TMS (for ^{1}H and ^{13}C) and nitromethane (for ^{15}N). 2D ^{1}H-^{15}N NMR spectra were recorded using HMBC-gp ^{1}H-^{15}N technique.

Reaction between mercaptotriazole **1** *and α-iodoketones* **2**, **3** *(general procedure)*. Mercaptotriazole **1** was added to α-iodoketone **2**, **3** under argon at 45 °C. The mixture was stirred for 2 h until disappearance of the starting ketones **2**, **3**, diluted with acetone (5 ml) and precipitated with diethyl ether (30 ml). The red oil formed was re-precipitated 3 times (acetone : diethyl ether, 1 : 6) and purified on a chromatographic column (10×500 mm) filled with silica gel MN Kieselgel 60 (0.063–0.2 mm). Acetone was used as an eluent.

*5,5′-Dithiobis[1,4-bis(2-oxopropyl)-4*H*-1,2,4-triazol-1-ium] tetraiodide* **4**. (*a*) From **1** (0.4 g, 4 mmol) and **2** (1.4 g, 8 mmol), 0.63 g (34%) of dark-red oil was obtained (R_f = 0.84, acetone). UV (MeCN, λ_{max}/nm): 210 (I^-), 293, 361 (I_3^-). ^{1}H NMR, δ: 2.32 (s, 12H, Me), 4.44 (s, 8H, NCH_2), 9.46 (s, 2H, H-5). ^{13}C NMR, δ: 27.90 (Me), 42.67 (NCH_2), 143.69 (C-5), 153.74 (C-3), 200.05 (C=O). ^{15}N NMR, δ: –113.8 (N-1), –146.3 (N-2, $^3J_{NH}$ 8.1 Hz), –187.8 (N-4, $^2J_{NH}$ 9.6 Hz). Found (%): C, 19.97; H, 2.14; I, 54.98; N, 9.51; S, 7.40. Calc. for $C_{16}H_{22}I_4N_6O_4S_2$ (%): C, 20.55; H, 2.35; I, 54.38; N, 8.99; S, 6.85.

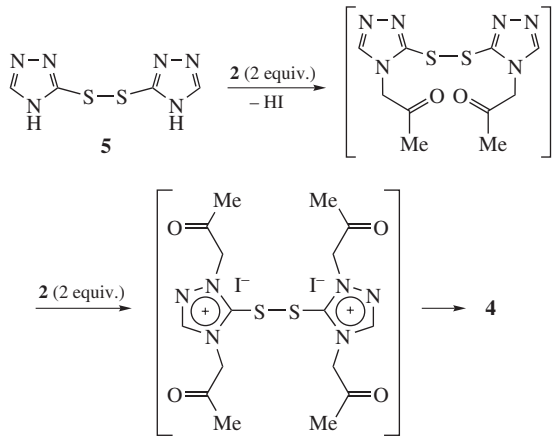
(*b*) From **1** (0.2 g, 2 mmol) and **3** (1.2 g, 4 mmol), 0.28 g (30%) of dark-red oil was obtained (R_f = 0.84, acetone). ^{1}H NMR, δ: 2.39 (s, 12H, Me), 4.48 (s, 8H, NCH_2), 9.50 (s, 2H, H-5). ^{13}C NMR, δ: 27.97 (Me), 42.70 (NCH_2), 143.72 (C-5), 153.80 (C-3), 200.00 (C=O). Found (%): C, 19.88; H, 2.00; I, 54.78; N, 8.51; S, 7.10. Calc. for $C_{16}H_{22}I_4N_6O_4S_2$ (%): C, 20.55; H, 2.35; I, 54.38; N, 8.99; S, 6.85.



Scheme 2

The molecular iodine, formed during the reduction, takes part in oxidation of the mercapto group and generation of triiodide anion of salt **4**.

To verify the results obtained, we have carried out a counter synthesis of liquid salt **4** by the reaction between ditriazolyl disulfide **5** and 1-iodopropan-2-one **2** (Scheme 3).‡ In this case, homogeneity of the medium is reached due to ionic liquid **4**, which is formed in the course of the reaction.



Scheme 3

The structure of salt **4** was proved by elemental analysis, IR, UV, ^{1}H, ^{13}C and ^{15}N NMR techniques. In the ^{1}H and ^{13}C NMR spectra, signals of the CH_2 groups are observed at 4.4 and 42.7 ppm, respectively. The 2D ^{15}N HMBC ^{1}H-^{15}N NMR spectra of the salt show cross-peaks of N-1, N-2, N-4 nitrogen atoms with protons of both the triazole ring and the methylene fragments. In the IR spectra, the carbonyl groups are present in the region of 1737 cm^{-1}. The UV spectra of salt **4** contain absorption bands, which are typical of iodide (210 nm) and triiodide (287 and 362 nm) anions.[15]

‡ *Reaction between 3,3′-dithiobis-4*H*-1,2,4-triazole* **5** *and 1-iodopropan-2-one* **2**. Disulfide **5** (0.2 g, 1 mmol) was added to ketone **2** (0.74 g, 4 mmol) under argon at 45 °C. The reaction mixture was stirred for 2 h at 62 °C until disappearance of compound **2**. Salt **4** was isolated and purified by general procedure to give 0.33 g (32%) of dark-red oil (R_f = 0.84, acetone). ^{1}H NMR, δ: 2.34 (s, 12H, Me), 4.40 (s, 8H, NCH_2), 9.41 (s, 2H, H-5). ^{13}C NMR, δ: 28.05 (Me), 42.77 (CH_2), 143.90 (C-5), 153.95 (C-3), 199.85 (C=O). ^{15}N NMR, δ: –113.8 (N-1), –146.3 (N-2, $^3J_{NH}$ 8.1 Hz), –187.8 (N-4, $^2J_{NH}$ 9.6 Hz). Found (%): C, 20.15; H, 2.12; I, 54.10; N, 8.45; S, 6.55. Calc. for $C_{16}H_{22}I_4N_6O_4S_2$ (%): C, 20.55; H, 2.35; I, 54.38; N, 8.99; S, 6.85.

Compound **5** was synthesized according to the published protocol[16] by mixing the ethanol solution of 1,2,4-triazole-3-thiol **1** (1 g, 10 mmol) and I_2 (5 g, 20 mmol). The reaction course and compounds purity were monitored by TLC using Silufol UV-254 plates (acetone as eluent).

In conclusion, we have discovered a new and convenient access to novel type of ionic liquids possessing two disulfide-tethered azolium moieties. The key steps of the reaction mechanism involve oxidation of the mercapto group and alkylation of the azole nitrogen atoms. The synthesis can be accomplished in one synthetic operation without solvents and basic media.

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References

1 (*a*) A. Foroumadi, S. Mansouri, Z. Kiani and A. Rahmani, *Eur. J. Med. Chem.*, 2003, **38**, 851; (*b*) B. S. Holla, B. Veerendra, M. K. Shivananda and B. Poojary, *Eur. J. Med. Chem.*, 2003, **38**, 759; (*c*) Z.-G. Le, T. Zhong, Z.-B. Xie, X.-X. Lu and X. Cao, *Synth. Commun.*, 2010, **40**, 2525.
2 (*a*) T. P. Kofman, T. F. Uvarova and G. Yu. Kartseva, *Zh. Org. Khim.*, 1995, **31**, 271 (in Russian); (*b*) A. Dzygiel, B. Rzeszotarska, E. Masiukiewicz, P. Cmoch and B. Kamieñski, *Chem. Pharm. Bull.*, 2004, **52**, 192.
3 (*a*) K. Suzuki, T. Kuroda, Y. Miura and J. Murai, *Plant Dis.*, 2003, **87**, 779; (*b*) D. Lafortune, M. Béramis, A.-M. Daubèze, N. Boissot and A. Palloix, *Plant Dis.*, 2005, **89**, 501.
4 E. V. Lider, D. A. Piryazev, A. V. Virovets, L. G. Lavrenova, A. I. Smolentsev, E. M. Uskov, A. S. Potapov and A. I. Khlebnikov, *J. Struct. Chem.*, 2010, **51**, 514 (*Zh. Strukt. Khim.*, 2010, **51**, 532).
5 J. Zhou, X. Liu, Y. Zhang, B. Li and Y. Zhang, *Inorg. Chem. Commun.*, 2006, **9**, 216.
6 (*a*) A. L. Romanyuk, B. L. Litvin, N. I. Ganushchak and R. M. Vishnevskii, *Russ. J. Gen. Chem.*, 2006, **76**, 1834 (*Zh. Obshch. Khim.*, 2006, **76**, 1919); (*b*) X. Meng, U. J. Li, H. Hou, Y. Song, Y. Fan and Y. Zhu, *J. Mol. Struct.*, 2008, **891**, 305.
7 M. S. Pevzner, *Mendeleev Chem. J.*, 1997, **41**, 73 [*Ross. Khim. Zh. (Zh. Ross. Khim. Ob-va im. D. I. Mendeleeva)*, 1997, **41**, 113].
8 (*a*) Y. Gao, H. Gao, C. Piekarski and J. M. Shreeve, *Eur. J. Inorg. Chem.*, 2007, 4965; (*b*) D. Meyer and T. Strassner, *J. Org. Chem.*, 2011, **76**, 305.
9 (*a*) A. Duran, H. N. Dogan and S. Rollas, *Farmaco*, 2002, **57**, 559; (*b*) B. S. Holla, B. Veerendra, M. K. Shivananda and B. Poojary, *Eur. J. Med. Chem.*, 2003, **38**, 759.
10 M. S. R. Murty, K. R. Ram, R. V. Rao, J. S. Yadav, J. V. Rao, R. Pamanji and L. R. Velatooru, *Lett. Drug Des. Discov.*, 2012, **9**, 276.
11 (*a*) L. Labanauskas, E. Udrenaite, P. Gaidelis and A. Brukstus, *Farmaco*, 2004, **59**, 255; (*b*) G. F. Yang, R. J. Lu and X. N. Fei, *Chin. J. Chem.*, 2000, **18**, 435.
12 (*a*) N. O. Yarosh, L. V. Zhilitskaya, L. G. Shagun, I. A. Dorofeev, L. I. Larina and M. G. Voronkov, *Russ. J. Org. Chem.*, 2013, **49**, 475 (*Zh. Org. Khim.*, 2013, **49**, 486); (*b*) N. O. Yarosh, L. V. Zhilitskaya, L. G. Shagun, I. A. Dorofeev, L. I. Larina and M. G. Voronkov, *Russ. J. Org. Chem.*, 2013, **49**, 1546 (*Zh. Org. Khim.*, 2013, **49**, 1567); (*c*) L. G. Shagun, I. A. Dorofeev, N. O. Yarosh, L. V. Zhilitskaya, L. I. Larina and M. G. Voronkov, *Russ. J. Org. Chem.*, 2013, **49**, 1528 (*Zh. Org. Khim.*, 2013, **49**, 1693); (*d*) M. G. Voronkov, N. O. Yarosh, L. V. Zhilitskaya, L. G. Shagun, I. A. Dorofeev and L. I. Larina, *Russ. J. Gen. Chem.*, 2013, **83**, 2057 (*Zh. Obshch. Khim.*, 2013, **83**, 2340); (*e*) M. G. Voronkov, L. G. Shagun, I. A. Dorofeev, L. V. Zhilitskaya, N. O. Yarosh and L. I. Larina, *Russ. Chem. Bull., Int. Ed.*, 2013, **11**, 2261 (*Izv. Akad. Nauk, Ser. Khim.*, 2013, 2554); (*f*) V. A. Shagun, I. A. Dorofeev and L. G. Shagun, *J. Struct. Chem.*, 2013, **54**, 819 (*Zh. Strukt. Khim.*, 2013, **54**, 829); (*g*) L. V. Zhilitskaya, N. O. Yarosh, L. G. Shagun, I. A. Dorofeev and L. I. Larina, *Russ. J. Gen. Chem.*, 2014, **84**, 1754 (*Zh. Obshch. Khim.*, 2014, **84**, 2055).
13 A. R. Katritzky and J. Wu, *Synthesis*, 1994, 597.
14 N. O. Yarosh, L. V. Zhilitskaya, L. G. Shagun and I. A. Dorofeev, *Russ. J. Org. Chem.*, 2014, **50**, 1384 (*Zh. Org. Khim.*, 2014, **50**, 1398).
15 P. Reiller, F. Mercier-Bion, N. Gimenez, N. Barre and F. Miserque, *Radiochim. Acta*, 2006, **94**, 739.
16 M. S. Chernovyants, N. V. Aleshina, I. N. Shcherbakov, Z. A. Starikova, *Russ. J. Gen. Chem.*, 2013, **83**, 986 (*Zh. Obshch. Khim.*, 2013, **83**, 852).

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