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# Reaction of 3-azidoisoxazoles with active methylene compounds

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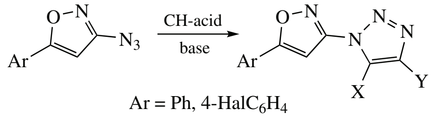
**3-Azidoisoxazoles react with various active methylene compounds (malononitrile, ethyl cyanoacetate and ethyl acetoacetate) in the presence of base to give hybrid isoxazole–triazole molecules in good to nearly quantitative yields.**



Ar = Ph, 4-Hal$C_6H_4$
X = Me, $NH_2$    Y = CN, COOEt

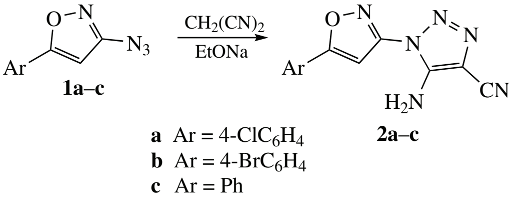
Triazoles, in particular, fluorine-containing ones, some of which were obtained recently,[1,2] are valuable compounds in medicinal chemistry. Broad spectrum of biological activity of 1,2,3-triazoles promotes development of their synthesis.[3–7] Organic azides may be considered as an important source for construction of 1,2,3-triazole ring. Apart from azide–alkyne cycloaddition[8] known for organic azides, they also react with active methylene compounds to afford functionalized triazoles.[9–14]

On the other hand, isoxazoles are useful scaffolds for development of new drugs with low toxicity.[15] To this, creating hybrid molecules containing both isoxazole and other heterocycle in their structure, *e.g.* 1,2,3-triazole scaffold is underway.[16–21]

Recently we reported the synthesis of azidoisoxazoles from sodium azide[22] and dichlorovinyl ketones,[23] which proceeded through unusual cyclization of the intermediate diazidoethenes.[24] The present work was focused on the reaction of azidoisoxazoles with various active methylene compounds to afford new representatives of multi-decorated isoxazole-substituted 1,2,3-triazoles.

First, the reaction of azidoisoxazoles **1a–c** with malononitrile in the presence of sodium ethoxide as a base was studied. As expected, new derivatives **2a–c** were obtained in high yields (Scheme 1). It is worth of attention that NMR spectra of compounds **2a–c** contain two sets of signals. The characteristic band of CN group at 2200–2240 $cm^{-1}$ was also split in some cases.

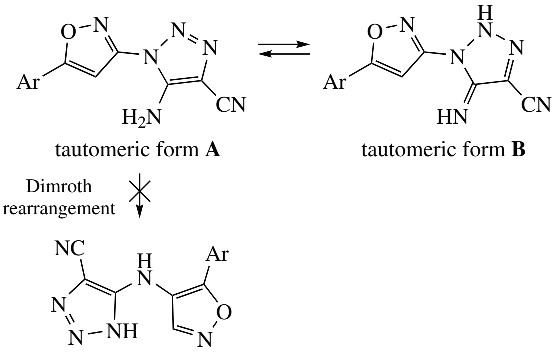
Initially, we proposed that Dimroth rearrangement might occur (Scheme 2), however the chemical shifts of isoxazole carbon atoms for $^{13}C$ NMR spectra were not in accordance with that proposal. Alternatively, one might suppose the coexistence of regioisomers, which was not yet in a good agreement with known mechanism for such transformations.[21] Most probably, we observed two tautomeric forms affected by some specific factors, *e.g.*, the presence of moisture (see Scheme 2).



Scheme 1

To get deeper insight into the examined reaction, azidoisoxazoles **1a–c** were reacted with other active methylene compounds such as dimethyl malonate, ethyl cyanoacetate and ethyl acetoacetate (Scheme 3) in the presence of sodium ethoxide (potassium *tert*-butoxide was also suitable for this purpose). Clean transformation was observed in the cases of ethyl cyanoacetate and ethyl acetoacetate to give products **3a–c** and **4a**,**b** in excellent yields as white or off-white crystalline powders.[†] However, the reaction with dimethyl malonate failed even upon reflux at 80 °C.

As expected, NMR spectra of products **3** look like those for compound mixture.[3] Note that heating of solution in DMSO-$d_6$ at 60 °C led to substantial evolution of $^1H$ NMR spectra (see Online Supplementary Materials). To our surprise, NMR spectra of



Scheme 2

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[†] *General procedure for the synthesis of compounds* **2a–c**, **3a–c** *and* **4a**,**b**. Sodium hydride (0.525 mmol, 21 mg of 60% dispersion in mineral oil) was carefully added to 10 ml of absolute ethanol. To a resulted solution of sodium ethoxide, a solution of the corresponding active methylene compound (0.525 mmol) in ethanol (1 ml) was added dropwise, and the resulting mixture was chilled to –20 °C. A solution of azidoisoxazole **1** (0.5 mmol) in ethanol (5 ml) was then added dropwise. The mixture was stirred at –20 °C for 30 min, allowed to reach the room temperature and then acidified with acetic acid to pH 6. The precipitate was filtered off and washed with cold ethanol and diethyl ether. The combined filtrates were concentrated and worked up to give additional crop of the product.

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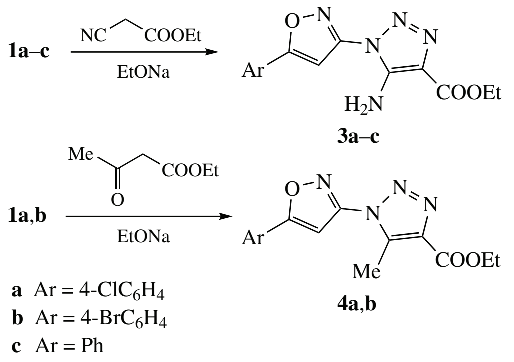

**Scheme 3**

compounds **4** contain two different forms as well, which are most probably rotational isomers. Indeed, in the spectra recorded at 60 °C only one form was observed, whereas subsequent cooling down recovered two forms again. Very poor solubility of compounds **3** and **4** should be taken into account when recording $^{13}$C and $^{15}$N NMR spectra. To unambiguously confirm the structure of products **4**, a single-crystal X-ray analysis of compound **4b** was performed (Figure 1).[‡]

These results additionally proved our proposal about existence of tautomeric forms of prepared compounds **2**–**4** and explained the added complexity of their NMR and IR spectra.

In conclusion, 3-azidoisoxazoles were found to react smoothly with various active methylene compounds in the presence of EtONa to give the corresponding products in excellent yields, which exist in tautomeric forms making their spectra more complex. The obtained isoxazole–triazole hybrids may be of interest for bioorganic chemistry due to their potential biological activity and they also may be considered as prospective ligands for metallocomplex catalysis.[28]

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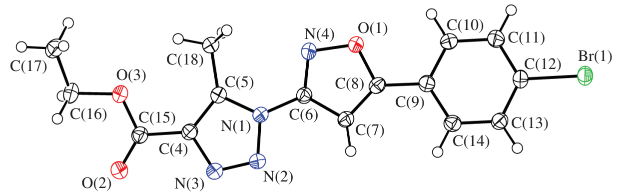

**Figure 1** Ellipsoid plot drawing for compound **4b** with 50% probability.

*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.09.017.

## References

1 V. M. Muzalevskiy, M. N. Mamedzade, V. A. Chertkov, V. A. Bakulev and V. G. Nenajdenko, *Mendeleev Commun.*, 2018, **28**, 17.
2 Y. A. Rozin, J. Leban, W. Dehaen, V. G. Nenajdenko, V. M. Muzalevskiy, O. S. Eltsov and V. A. Bakulev, *Tetrahedron*, 2012, **68**, 614.
3 Z. Chen, Z. Liu, G. Cao, H. Li and H. Rena, *Adv. Synth. Catal.*, 2017, **359**, 202.
4 M. Teci, M. Tilley, M. A. McGuire and M. G. Organ, *Org. Process Res. Dev.*, 2016, **20**, 1967.
5 S. Brand, E. J. Ko, E. Viayna, S. Thompson, D. Spinks, M. Thomas, L. Sandberg, A. F. Francisco, S. Jayawardhana, V. C. Smith, C. Jansen, M. De Rycker, J. Thomas, L. MacLean, M. Osuna-Cabello, J. Riley, P. Scullion, L. Stojanovski, F. R. C. Simeons, O. Epemolu, Y. Shishikura, S. D. Crouch, T. S. Bakshi, C. J. Nixon, I. H. Reid, A. P. Hill, T. Z. Underwood, S. J. Hindley, S. A. Robinson, J. M. Kelly, J. M. Fiandor, P. G. Wyatt, M. Marco, T. J. Miles, K. D. Read and I. H. Gilbert, *J. Med. Chem.*, 2017, **60**, 7284.
6 D. B. Ramachary, A. B. Shashank and S. Karthik, *Angew. Chem., Int. Ed.*, 2014, **53**, 10420.
7 D. G. Brooke, E. M. van Dam, C. K. W. Watts, A. Khoury, M. A. Dziadek, H. Brooks, L.-J. K. Graham, J. U. Flanagan and W. A. Denny, *Bioorg. Med. Chem.*, 2014, **22**, 1029.
8 N. V. Sokolova and V. G. Nenajdenko, *RSC Adv.*, 2013, **3**, 16212.
9 A. Zdzienicka, D. Schols, G. Andrei, R. Snoeck and I. Głowacka, *Phosphorus Sulfur Silicon Relat. Elem.*, 2015, **190**, 2207.
10 N. T. Pokhodylo, O. Ya. Shyyka, R. D. Savka and M. D. Obushak, *Russ. J. Org. Chem.*, 2018, **54**, 1090 (*Zh. Org. Khim.*, 2018, **54**, 1083).
11 V. A. Mamedov, V. N. Valeeva, L. A. Antokhina, G. M. Doroshkina, A. V. Chernova and I. A. Nuretdinov, *Chem. Heterocycl. Compd.*, 1993, **29**, 607 (*Khim. Geterotsikl. Soedin.*, 1993, 710).
12 S. N. Mikhailychenko, A. A. Chesniuk, L. D. Koniushkin, S. I. Firgang and V. N. Zaplishny, *Chem. Heterocycl. Compd.*, 2004, **40**, 1162 (*Khim. Geterotsikl. Soedin.*, 2004, 1343).
13 I. G. Dmitrieva, L. V. Dyadyuchenko, V. D. Strelkov and E. A. Kaigorodova, *Chem. Heterocycl. Compd.*, 2008, **44**, 1267 (*Khim. Geterotsikl. Soedin.*, 2008, 1556).
14 H. H. Abbas Temerik, M. I. Younes and S. A. Metwally, *Coll. Czech. Chem. Commun.*, 1993, **58**, 3017.
15 A. Sysak and B. Obmińska-Mrukowicz, *Eur. J. Med. Chem.*, 2017, **137**, 292.
16 Q. Chen, F. Liu, F. Xu and C. Yang, *J. Heterocycl. Chem.*, 2008, **45**, 77.
17 Y. J. Rao and A. Srinivas, *J. Heterocycl. Chem.*, 2014, **51**, 1675.
18 Z. Najafi, M. Mahdavi, M. Safavi, M. Saeedi, H. Alinezhad, M. Pordeli, S. K. Ardestani, A. Shafiee, A. Foroumadi and T. Akbarzadeh, *J. Heterocycl. Chem.*, 2015, **52**, 1743.
19 T.-F. Niu, M.-F. Lv, L. Wang, W.-B. Yi and C. Cai, *Org. Biomol. Chem.*, 2013, **11**, 1040.
20 K. C. Coffman, T. P. Hartley, J. L. Dallas and M. Kurth, *ACS Comb. Sci.*, 2012, **14**, 280.
21 V. P. Krivopalov and O. P. Shkurko, *Russ. Chem. Rev.*, 2005, **74**, 339 (*Usp. Khim.*, 2005, **74**, 369).
22 K. Banert, in *Organic Azides – Syntheses and Applications*, eds. S. Bräse and K. Banert, John Wiley & Sons, Chichester, 2010, pp. 115–166.
23 P. S. Lemport, I. V. Smolyar, V. N. Khrustalev, V. A. Roznyatovsky, A. V. Popov, V. A. Kobelevskaya, I. B. Rozentsveig and V. G. Nenajdenko, *Org. Chem. Front.*, 2019, **6**, 335.
24 A. V. Shastin, B. D. Tsyrenova, P. G. Sergeev, V. A. Roznyatovsky, I. V. Smolyar, V. N. Khrustalev and V. G. Nenajdenko, *Org. Lett.*, 2018, **20**, 7803.
25 T. G. G. Battye, L. Kontogiannis, O. Johnson, H. R. Powell and A. G. W. Leslie, *Acta Crystallogr., Sect. D: Biol. Crystallogr.*, 2011, **67**, 271.
26 P. R. Evans, *Acta Crystallogr., Sect. D: Biol. Crystallogr.*, 2006, **62**, 72.
27 G. M. Sheldrick, *Acta Crystallogr., Sect. C*, 2015, **71**, 3.
28 D. Dheer, V. Singh and R. Shankar, *Bioorg. Chem.*, 2017, **71**, 30.

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[‡] *Crystallographic data*. Crystals of **4b** ($C_{15}H_{13}BrN_4O_3$, $M$ = 377.19) are triclinic, space group $P\bar{1}$, at 100(2) K: $a$ = 6.3358(13), $b$ = 7.4548(15) and $c$ = 16.165(3) Å, $\alpha$ = 87.49(3)°, $\beta$ = 87.94(3)°, $\gamma$ = 80.18(3)°, $V$ = = 751.3(3) Å$^3$, $Z$ = 2, $d_{\text{calc}}$ = 1.667 g cm$^{-3}$, $\mu$ = 3.545 mm$^{-1}$, $F$(000) = 380. A total of 13210 reflections were collected (3421 independent reflections, $R_{\text{int}}$ = 0.041, 2$\theta$ = 61.52°). The final $R_1$ = 0.028 for 3279 observed reflections with $I > 2\sigma(I)$, $wR_2$ = 0.073 for all data, $S$ = 1.074, crystal size 0.15×0.10×0.03 mm. The measurements were performed on the ‘Belok’ beamline ($\lambda$ = 0.78790 Å) of the National Research Center ‘Kurchatov Institute’ (Moscow, Russian Federation) using a Rayonix SX165 CCD detector. The data were indexed and integrated using the utility iMOSFLM from the CCP4 program suite[25] and then scaled and corrected for absorption using the Scala program.[26] The structure was solved by the direct methods and refined by full-matrix least square technique on $F^2$ with anisotropic displacement parameters for all non-hydrogen atoms. The hydrogen atoms were placed in calculated positions and refined within the riding model with fixed isotropic displacement parameters [$U_{\text{iso}}$(H) = = 1.5$U_{\text{eq}}$(C) for the methyl groups and 1.2$U_{\text{eq}}$(C) for the other groups]. All calculations were carried out using the SHELXTL program suite.[27]

CCDC 1920479 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.