Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2020, **30**, 180–182

Mendeleev Communications

Trifluoroacetyl substituted pyrazolotriazines: synthesis and pathways of formation

Elena V. Sadchikova,[a,b] Daria L. Alexeeva[a] and Valentine G. Nenajdenko*[c]

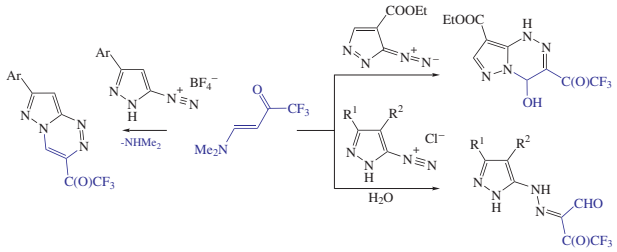
[a] *Institute of Chemical Engineering, Ural Federal University, 620002 Ekaterinburg, Russian Federation. E-mail: e.v.sadchikova@urfu.ru*

[b] *Ural State Medical University, 620028 Ekaterinburg, Russian Federation*

[c] *Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation. Fax: +7 495 932 8846; e-mail: nenajdenko@gmail.com*

DOI: 10.1016/j.mencom.2020.03.016

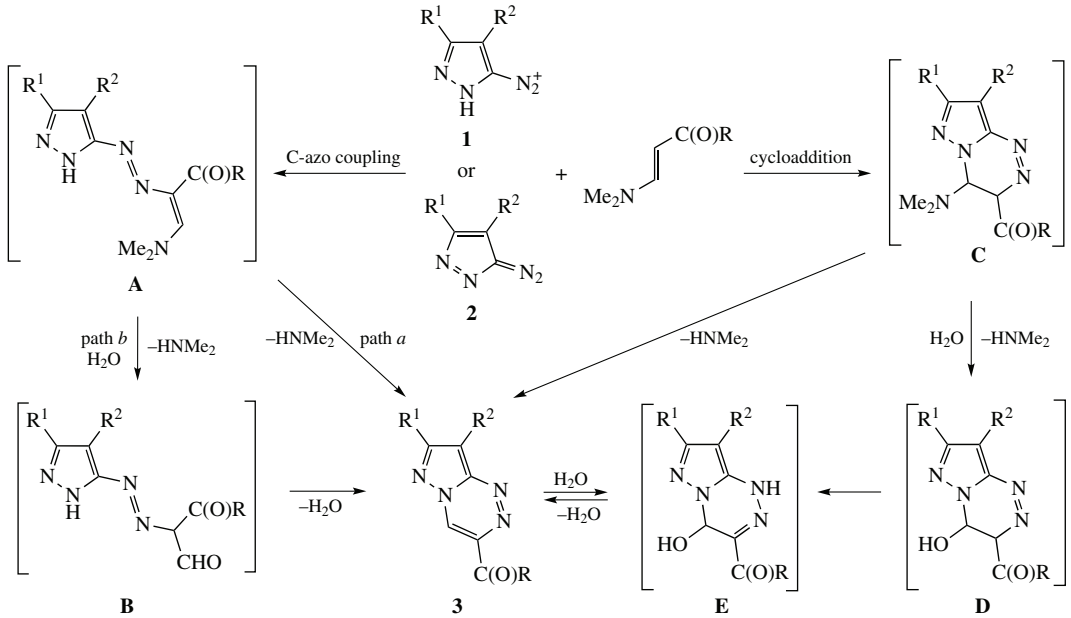
The reaction of 4-dimethylamino-1,1,1-trifluorobut-3-en-2-one with 3-arylpyrazole-5-diazonium salt in MeCN affords 7-aryl-3-(trifluoroacetyl)pyrazolo[5,1-*c*][1,2,4]triazines. The transformation of relative 5-diazopyrazoles leads to 4-hydroxy-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine derivatives, while the reaction in acidic aqueous solution results in 4,4,4-trifluoro-3-oxo-2-(pyrazol-5-ylhydrazono)-butanals.



Keywords: pyrazoles, diazo compounds, diazonium salts, enones, pyrazolo[5,1-*c*][1,2,4]triazines, trifluoromethyl group.

β-Amino α,β-enones with dual nature of nucleophilic enamines and electrophilic enones are utilized as building blocks for the synthesis of a wide range of heterocycles.[1] One of their notable transformations is the reaction with diazonium salts affording after final hydrolysis the corresponding 2-arylhydrazono-2-oxopropanals[2] suitable for further synthesis of various diazines.[3] The known reactions of pyrazole-5-diazonium salts **1** or diazopyrazoles **2** with amino enones bearing aliphatic,[4(a),(b)] aromatic[4(a),(c),(d)] or heteroaromatic[5–9] substituents result in 3-substituted pyrazolo[5,1-*c*][1,2,4]triazines **3** (Scheme 1). Due to the structural similarity with purines, these products can act as purine metabolites and thus revealed antimicrobial, antiviral, antidiabetic and antitumor activities.[10]

The mechanism of the reaction of pyrazole-5-diazonium salts **1** or diazopyrazoles **2** with amino enones still demands to be investigated. Since all attempts to isolate acyclic intermediates had failed,[4(a)] it was suggested that the reaction proceeded *via* [4+2] cycloaddition to form intermediates **C**–**E** (see Scheme 1). An alternative proposed mechanism comprised C-azo coupling with formation of intermediate **A** as a key step. Subsequent intramolecular cyclization (path *a*)[5(a),7,9] or hydrolysis to intermediate formyl derivative **B** and its cyclization (path *b*)[4(a),5(b),6(c)] can explain the formation of product **3**. However, none of the proposed intermediates has been isolated and/or characterized to support these mechanisms.

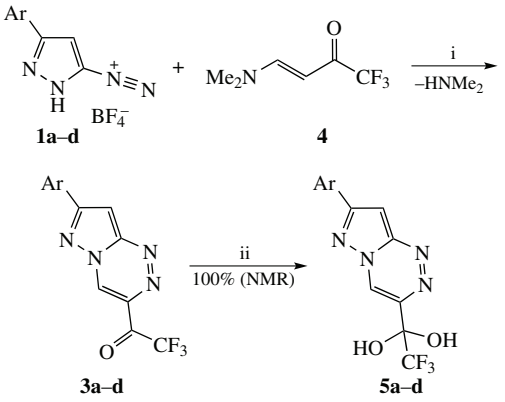


Scheme 1

No examples of α,β-unsaturated trifluoromethyl ketones with participation in these transformations have been reported in spite of the fact that they represent good building blocks for the synthesis of various fluorinated heterocyclic derivatives.[11] At present, the chemistry of organofluorine compounds is one of the most rapidly developing areas of organic chemistry.[12,13]

We have developed preparative syntheses and investigated properties of some pyrazole-5-diazonium salts **1** and 5-diazopyrazoles **2**.[14–17] It was found that different substitution pattern in pyrazole ring resulted in various products of 5-aminopyrazoles diazotization, namely either of type **1** or **2**. In this work, the reaction of the diazotization products with 4-dimethylamino-1,1,1-trifluorobut-3-en-2-one[18] **4** has been investigated.

In fact, pyrazole-5-diazonium tetrafluoroborates **1a–d** react with amino enone **4** at room temperature in dry acetonitrile for 1–2 h to form pyrazolo[5,1-*c*][1,2,4]triazines **3a–d** in 62–73% isolated yields (Scheme 2). Compounds **3a–d** turned to be moisture-sensitive and rapidly converted to the corresponding geminal diols **5a–d** in the presence of traces of water from any medium. A model hydration of ketone **3a** resulted in diol **5a** in 94% yield. In the recording of IR spectra, we observed only diols **5** having broad adsorption bands at 3000–3400 cm^{-1} and no adsorption within the carbonyl region.

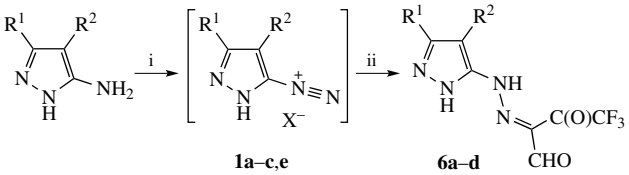


a Ar = Ph (68%)
b Ar = 4-$MeOC_6H_4$ (70%)
c Ar = 4-ClC_6H_4 (73%)
d Ar = 4-MeC_6H_4 (62%)

Scheme 2 *Reagents and conditions*: i, MeCN, room temperature, 1–2 h; ii, H_2O.

^{1}H NMR spectra of compounds **3a–d** contain no signals of dimethylamino group but contain singlets for aromatic C^4 and C^8 atoms at 9.22–9.26 and 7.88–8.07 ppm, respectively. For hydrates **5a–d**, the heterocyclic proton is shifted upfield by ~0.2 ppm. As well, a broadened signal for the protons of the two hydroxyl groups appears at 8.02–8.07 ppm and vanishes after addition of CD_3COOD. The ^{13}C NMR spectra of diols **5a–d** contain quadruplets for the $C(OH)_2$ moiety and the CF_3 group at 91.6–91.8 and 123.0–127.1 ppm, respectively, whereas the signals for the trifluoroacetyl fragment in ketone **3b** are observed at 180.8 and 128.0 ppm. In the ^{19}F NMR spectra, the CF_3 group resonates at –70.2 to –71.6 ppm for ketones **3a–d** and at –81.7 to –82.2 ppm for diols **5a–d**.

We attempted to develop a one-pot version of this reaction in water since the diazotization stage is typically carried out under aqueous conditions. Herein, pyrazole-5-diazonium salts **1a–c**,**e** were obtained from the corresponding 5-aminopyrazoles. The subsequent addition of amino enone **4** to these *in situ* obtained diazonium salts resulted in the corresponding hydrazones **6a–d** in 52–61% total yields (Scheme 3) instead of anticipated bicyclic



X = Cl, BF_4^-

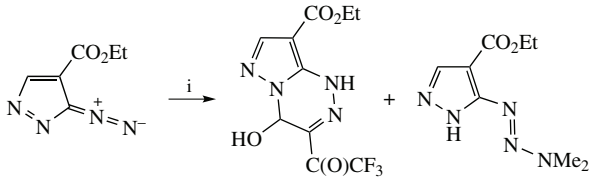
6a R^1 = Ph, R^2 = H (58%)
6b R^1 = 4-$MeOC_6H_4$, R^2 = H (57%)
6c R^1 = 4-ClC_6H_4, R^2 = H (61%)
1e, **6d** R^1 = H, R^2 = CO_2Et (52%)

Scheme 3 *Reagents and conditions*: i, $NaNO_2$ aq., HCl or HBF_4, 0–5 °C; ii, $Me_2NCH{=}CHC(O)CF_3$ **4**, room temperature, 30–36 h.

compounds **5**. ^{1}H NMR spectra of compounds **6a–d** contain broad singlets for the NH fragments of the pyrazole ring and the hydrazone group at 12.98–13.03 and 8.72–9.12 ppm, which disappear upon addition of CD_3COOD. Signals of the trifluoromethyl group in the ^{19}F NMR spectra are observed at –77.5 to –77.8 ppm.

We performed monitoring of the reaction to detect compound **3b** using a TLC and ^{1}H NMR spectroscopy. According to NMR data, intermediate **A** (see Scheme 1) was observed in the reaction mixture along with products **3b** and **6b**. These data confirm that bicyclic derivatives **3** are formed stepwise. At the first step, C-azo coupling of pyrazole-5-diazonium salts **1** takes place with formation of azo intermediate **A**. Next, the enamino fragment is hydrolyzed to formyl group affording intermediate **B** identical to hydrazones **6a–d** obtained under acidic aqueous reaction conditions. The high rate of this hydrolysis can be explained by the additional acceptor group present in the molecule. At the final step, intermediate **B** undergoes an intramolecular cyclization with the formation of pyrazolo[5,1-*c*][1,2,4]triazines **3**.

A different outcome was achieved in examination of the reaction of ethyl 5-diazopyrazole-4-carboxylate **2′** with amino enone **4** in acetonitrile. Four products were detected in the reaction mixture, however, we succeeded to isolate only two of them, namely compounds **7** and **8** in 57 and 33% yields, respectively (Scheme 4).



Scheme 4 *Reagents and conditions*: i, $Me_2NCH{=}CHC(O)CF_3$ **4**, MeCN, room temperature, 24 h.

Note that ^{1}H NMR spectra of the reaction mixture did not provided any evidence for the formation of hydrazone **6d** even in trace amount. Most probably, the reaction of compounds **2′** and **4** proceeds as cycloaddition with intermediates **C** and **D** (see Scheme 1). The rate of this process is essentially low, which causes the formation of by-product **8** resulting from the *N*-azo coupling of diazopyrazole **2′** with dimethylamine. The structure of triazene **8** was confirmed by spectral data and an alternative synthesis[19] *via* the reaction of diazopyrazole **2′** with dimethylamine. On the other hand, an NMR monitoring in DMSO-d_6 at room temperature of the cyclization of compound **6d** into **7** for eight days revealed the slow course of this process, namely **6d/7** ratio was approached only 1 : 2 to the end of the experiment. At the same time, no dehydration of compound **7b** into product of type **3** was detected.

In summary, the comparative examination of the reactivity of pyrazole-5-diazonium salts **1** and 5-diazopyrazoles **2** with respect to fluorine-containing amino enone **4** revealed that the form of the diazo reactant had a significant impact on both the reaction rate and the structure of the products. The results obtained allowed us to elucidate the mechanism of these processes.

V.G.N. acknowledges support of the Russian Science Foundation (grant no. 18-13-00136) for the synthesis of starting amino enone.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.03.016.

References

1 (*a*) P. Lue and J. V. Greenhill, in *Advances in Heterocyclic Chemistry*, ed. A. R. Katritzky, Elsevier, 1996, vol. 67, pp. 207–343; (*b*) A.-Z. A. Elassar and A. A. El-Khair, *Tetrahedron*, 2003, **59**, 8463; (*c*) H. M. Gaber, M. C. Bagley, Z. A. Muhammad and S. M. Gomha, *RSC Adv.*, 2017, **7**, 14562.

2 (*a*) F. Al-Omran, M. M. A. Khalik, A. Abou-Elkhair and M. H. Elnagdi, *Synthesis*, 1997, 91; (*b*) V. Macháček, A. Lyčka, P. Šimůnek and T. Weidlich, *Magn. Reson. Chem.*, 2000, **38**, 293; (*c*) H. Jiang and S. Zhu, *J. Fluorine Chem*., 2008, **129**, 40; (*d*) A.-A. Alnajjar, M. M. Abdelkhalik, A. Al-Enezi and M. H. Elnagdi, *Molecules*, 2009, **14**, 68.

3 (*a*) M. M. Abdel-Khalik, S. M. Agamy and M. H. Elnagdi, *Synthesis*, 2001, 1861; (*b*) I. A. Abdelhamid, M. A. Nasra and M. H. Elnagdi, *Synlett*, 2009, 3237.

4 (*a*) M. A. Al-Shiekh, A. M. S. El-Din, E. A. Hafez and M. H. Elnagdi, *J. Chem. Res.*, 2004, 174; (*b*) S. Al-Mousawi, M. M. Abdelkhalik, E. John and M. H. Elnagdi, *J. Heterocycl. Chem*., 2003, **40**, 689; (*c*) S. M. Agamy, *J. Chem. Res.*, 2001, 349; (*d*) F. Al-Omran and A. A. El-Khair, *J. Chem. Res.*, 2006, 6.

5 (*a*) H. A. Abdel-Aziz, N. A. Hamdy, A. M. Farag and I. M. I. Fakhr, *J. Heterocycl. Chem*., 2008, **45**, 1033; (*b*) M. R. Shaaban, T. S. Saleh and A. M. Farag, *Heterocycles*, 2009, **78**, 699.

6 (*a*) A. O. Abdelhamid, *J. Heterocycl. Chem*., 2009, **46**, 680; (*b*) N. A. Kheder, *Heterocycles*, 2009, **78**, 1281; (*c*) W. S. Hamama, M. A. Berghot, E. A. Baz and M. A. Gouda, *Arch. Pharm.*, 2011, **344**, 710.

7 (*a*) A. O. Abdelhamid, S. A. Shokry and S. M. Tawfiek, *J. Heterocycl. Chem*., 2012, **49**, 116; (*b*) A. O. Abdelhamid, A. A. Fahmi and A. A. M. Alsheflo, *Eur. J. Chem*., 2012, **3**, 129.

8 (*a*) A. S. Shawali, *J. Adv. Res*., 2012, **3**, 185; (*b*) A. O. Abdelhamid, A. A. Fahmi and K. N. M. Halim, *Synth. Commun.*, 2013, **43**, 1101.

9 (*a*) I. H. El Azab and K. M. Khaled, *Russ. J. Bioorg. Chem*., 2015, **41**, 421; (*b*) N. A. Abdelriheem, Y. H. Zaki and A. O. Abdelhamid, *Chem. Cent. J*., 2017, **11**, 53; (*c*) S. M. H. Sanad and A. E. M. Mekky, *J. Heterocycl. Chem*., 2018, **55**, 836.

10 (*a*) W. M. Al-Adiwish, M. I. M. Tahir, A. Siti-Noor-Adnalizawati, S. F. Hashim, N. Ibrahim and W. A. Yaacob, *Eur. J. Med. Chem*., 2013, **64**, 464; (*b*) V. L. Rusinov, E. N. Ulomskii, O. N. Chupakhin and V. N. Charushin, *Russ. Chem. Bull*., *Int. Ed*., 2008, **57**, 985 (*Izv. Akad. Nauk, Ser. Khim*., 2008, 967); (*c*) V. L. Rusinov, I. M. Sapozhnikova, A. M. Bliznik, O. N. Chupakhin, V. N. Charushin, A. A. Spasov, P. M. Vassiliev, V. A. Kuznetsova, A. I. Rashchenko and D. A. Babkov, *Arch. Pharm*., 2017, **350**, e1600361; (*d*) S. Cascioferro, B. Parrino, V. Spanò, A. Carbone, A. Montalbano, P. Barraja, P. Diana and G. Cirrincione, *Eur. J. Med. Chem*., 2017, **142**, 328.

11 (*a*) S. V. Druzhinin, E. S. Balenkova and V. G. Nenajdenko, *Tetrahedron*, 2007, **63**, 7753; (*b*) V. G. Nenajdenko and E. S. Balenkova, *ARKIVOC*, 2011, (**i**), 246.

12 L. V. Politanskaya, G. A. Selivanova, E. V. Panteleeva, E. V. Tretyakov, V. E. Platonov, P. V. Nikul'shin, A. S. Vinogradov, Ya. V. Zonov, V. M. Karpov, T. V. Mezhenkova, A. V. Vasilyev, A. B. Koldobskii, O. S. Shilova, S. M. Morozova, Ya. V. Burgart, E. V. Shchegolkov, V. I. Saloutin, V. B. Sokolov, A. Yu. Aksinenko, V. G. Nenajdenko, M. Yu. Moskalik, V. V. Astakhova, B. A. Shainyan, A. A. Tabolin, S. L. Ioffe, V. M. Muzalevskiy, E. S. Balenkova, A. V. Shastin, A. A. Tyutyunov, V. E. Boiko, S. M. Igumnov, A. D. Dilman, N. Yu. Adonin, V. V. Bardin, S. M. Masoud, D. V. Vorobyeva, S. N. Osipov, E. V. Nosova, G. N. Lipunova, V. N. Charushin, D. O. Prima, A. G. Makarov, A. V. Zibarev, B. A. Trofimov, L. N. Sobenina, K. V. Belyaeva, V. Ya. Sosnovskikh, D. L. Obydennov and S. A. Usachev, *Russ. Chem. Rev*., 2019, **88**, 425.

13 (*a*) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, 2nd edn., Wiley-VCH, 2013; (*b*) *Fluorine in Heterocyclic Chemistry*, ed. V. Nenajdenko, Springer, 2014, vols. 1, 2; (*c*) *Fluorinated Heterocycles* (*ACS Symposium Series*, Book 1003), eds. A. A. Gakh and K. L. Kirk, 1st edn., American Chemical Society, 2009; (*d*) *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*, ed. V. A. Petrov, John Wiley & Sons, Inc., Hoboken, NJ, 2009; (*e*) V. P. Reddy, *Organofluorine Compounds in Biology and Medicine*, Elsevier, Amsterdam, 2015.

14 D. L. Alexeeva, E. V. Sadchikova, N. N. Volkova, I. V. Efimov, J. Jacobs, L. Van Meervelt, W. Dehaen and V. A. Bakulev, *ARKIVOC*, 2016, (**iv**), 114.

15 D. L. Alekseeva, V. Yu. Rakhimova, A. S. Minin, A. V. Belousova and E. V. Sadchikova, *Chem. Heterocycl. Compd*., 2018, **54**, 1145 (*Khim. Geterotskl. Soedin*., 2018, **54**, 1145).

16 E. V. Sadchikova, D. L. Alexeeva and V. G. Nenajdenko, *Mendeleev Commun.*, 2019, **29**, 653.

17 E. V. Sadchikova and V. S. Mokrushin, *Russ. Chem. Bull*., *Int. Ed*., 2005, **54**, 354 (*Izv. Akad. Nauk, Ser. Khim*., 2005, 348).

18 A. V. Sanin, V. G. Nenajdenko, K. I. Smolko, D. I. Denisenko and E. S. Balenkova, *Synthesis*, 1998, 842.

19 M. K. Spassova and E. V. Golovinski, *Arzneim. Forsch*., 1977, **27**, 758.

Received: 20th November 2019; Com. 19/6061