

Reaction of α -Bromo Enones with 1,2-Diamines. Cascade Assembly of 3-(Trifluoromethyl)piperazin-2-ones via Rearrangement

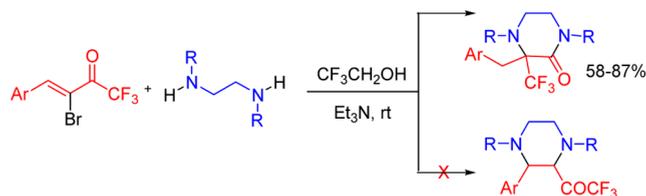
Alexander Yu. Rulev,^{*,†} Vasily M. Muzalevskiy,[‡] Evgeniy V. Kondrashov,[†] Igor A. Ushakov,[†] Alexey R. Romanov,[†] Victor N. Khrustalev,[§] and Valentine G. Nenajdenko^{*,‡}

A. E. Favorsky Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, Irkutsk 664033, Russia, Department of Chemistry, Lomonosov Moscow State University, 119899 Moscow, Russia, A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Moscow 119991, Russia

rulev@irioch.irk.ru; nen@acylium.chem.msu.ru

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ABSTRACT



A facile one-pot synthesis of 3-trifluoromethylated piperazin-2-ones has been achieved by the treatment of trifluoromethyl 2-bromo enones with N,N' -disubstituted ethylenediamines in trifluoroethanol. The mechanism of this unexpected reaction is discussed in terms of multistep processes involving formation of captodative aminoenone as a key intermediate. The unique influence of trifluoromethyl group on the reaction path was demonstrated.

Piperazine is a privileged structure for medicinal chemistry, and this heterocyclic subunit is incorporated as a crucial structural motive in several top-selling drugs. As a result, approximately 10% of all modern drugs contain piperazine or pyrazine fragments (Figure 1). For example, Abilify (aripiprazole), Seroquel (quetiapine), and Zyprexa (olanzapine) are very popular modern antipsychotics. These three drugs alone had near \$15 billion in worldwide sales in 2011.¹ It should be emphasized that very wide types of physiological activity have been demonstrated for piperazine derivatives including antineoplastics, DPP-IV inhibitors (diabetes treatment), drugs for erectile dysfunction treatment, antibiotics, angiogen-II antagonists. Therefore, development of new approaches to piperazine core

synthesis is a top priority task for modern synthetic chemistry.

At the same time, much attention has been paid to the synthesis of fluorinated heterocycles.² It is not surprising because it is well recognized that the incorporation of fluorine atoms or perfluoroalkyl groups into bioactive molecules leads to the dramatic modification of its physical and chemical properties, increased biological activity, and significantly improves metabolic stability. Therefore,

(2) For recent reviews, see: (a) *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*; Petrov, V. A., Ed.; Wiley: Hoboken, 2009; 515 pp. (b) *Fluorinated Heterocycles*; Gakh, A. A., Kirk, K. L., Eds.; ACS Symposium Series; Oxford University Press/American Chemical Society: Washington, D.C., 2009; 360 pp. (c) Muzalevskiy, V. M.; Nenajdenko, V. G.; Shastin, A. V.; Balenkova, E. S.; Haufe, G. *Synthesis* **2009**, 3905. (d) Schlosser, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432. (e) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214. (f) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004; 308 pp. (g) Muzalevskiy, V. M.; Shastin, A. V.; Balenkova, E. S.; Haufe, G.; Nenajdenko, V. G. *Synthesis* **2009**, 3905. (h) Serdyuk, O. V.; Muzalevskiy, V. M.; Nenajdenko, V. G. *Synthesis* **2012**, 2115.

[†] A. E. Favorsky Institute of Chemistry.

[‡] Lomonosov Moscow State University.

[§] A. N. Nesmeyanov Institute of Organoelement Compounds.

(1) McGrath, N. A.; Brichacek, M.; Njardarson, Jon T. *J. Chem. Educ.* **2010**, *87*, 1348.

incorporation of fluorine (usually CF₃ group or fluorine atom(s)) is a powerful tool of modern drug design and drug discovery.³

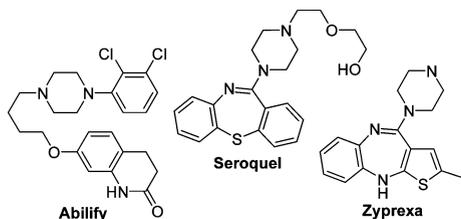


Figure 1. Some piperazine-derived drugs.

α,β -Unsaturated carbonyl compounds (enones, enals, esters) are classical scaffolds for reactions with nucleophiles and binucleophiles. They have been studied intensively for the synthesis of various carbo- and heterocyclic systems.⁴ CF₃ enones are of special interest because they are very valuable building blocks for the preparation of various trifluoromethylated heterocycles.⁵ The reactivity of CF₃ enones often differs significantly from nonfluorinated analogues in exhibiting the unique role of fluorine. For example, we have found unusual reaction of α -bromoalkenyl trifluoromethyl ketones with secondary amines leading easily to captodative carbonyl-bearing aminoalkenes which are readily transformed into indenol derivatives⁶ in contrast to their nonfluorinated analogues.⁷ On the other hand, the captodative formyl(amino)alkenes undergo surprising transformations upon treatment with mono- and binucleophiles.⁸

Considering the significance of both the trifluoromethyl group and piperazine moiety, we decided to investigate the reaction of trifluoromethyl α -bromo enones with symmetrically substituted ethylenediamines as a short pathway to trifluoroacetylated piperazines.

(3) Selected publications: (a) Filler, R.; Kobayashi, Y.; Yagulpolskii, L. M. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, 1993. (b) *Fluorine-Containing Amino Acids. Synthesis and Properties*; Kukhar, V. P., Soloshonok, V. A., Eds.; John Wiley & Sons: Chichester, 1995. (c) Hiyama, V. A. *Organofluorine Compounds: Chemistry and Properties*; Springer-Verlag: Berlin, 2000; Chapter 5, pp 137–182. (d) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3.

(4) For reviews, see: (a) Rulev, A. Yu. *Russ. Chem. Rev.* **1998**, *67*, 279. (b) De Kimpe, N.; Verhé, R. *The Chemistry of α -Haloketones, α -Haloaldehydes and α -Haloamines*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1988. For examples, see: (c) Rulev, A. Yu.; Maddaluno, J. *J. Phys. Org. Chem.* **2002**, *15*, 590. (d) Rulev, A. Yu.; Azad, S.; Kotsuki, H.; Maddaluno, J. *Eur. J. Org. Chem.* **2010**, 6423.

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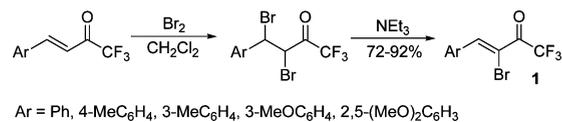
(6) Rulev, A. Yu.; Ushakov, I. A.; Nenajdenko, V. G.; Balenkova, E. S.; Voronkov, M. G. *Eur. J. Org. Chem.* **2007**, 6039. Rulev, A. Yu.; Ushakov, I. A.; Nenajdenko, V. G. *Tetrahedron* **2008**, *64*, 8073.

(7) Rulev, A. Yu. *Russ. Chem. Rev.* **2002**, *71*, 195.

(8) (a) Rulev, A. Yu.; Larina, L. I.; Keiko, N. A.; Voronkov, M. G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1567. (b) Rulev, A. Yu.; Larina, L. I.; Voronkov, M. G. *Tetrahedron Lett.* **2000**, *41*, 10211. (c) Rulev, A. Yu.; Larina, L. I.; Voronkov, M. G. *Russ. J. Gen. Chem.* **2001**, *71*, 1891. (d) Rulev, A. Yu.; Larina, L. I.; Voronkov, M. G. *Molecules* **2001**, *6*, 892. (e) Rulev, A. Yu.; Novokshonov, V. V.; Chuvashov, Yu. A.; Fedorov, S. V.; Larina, L. I. *Mendeleev Commun.* **2003**, 23.

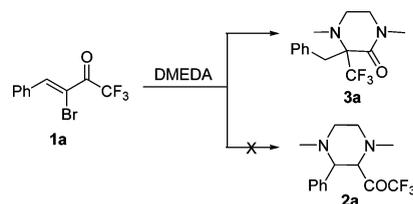
Starting bromo enones **1a–e** were prepared in high yields from α,β -unsaturated CF₃ ketones by the classical bromination–dehydrobromination sequence without isolation of the intermediate dibromo derivatives (Scheme 1).⁶

Scheme 1. Synthesis of Starting Bromo Enones **1a–e**



First, the model reaction of enone **1a** with *N,N'*-dimethylethylenediamine (DMEDA) was investigated. We envisioned that this reaction proceeds as a cascade Michael addition–nucleophilic substitution process to give trifluoroacetylated piperazine **2**. However, the reaction of enone **1a** with DMEDA surprisingly afforded compound **3a**, having a skeleton of 3-(trifluoromethyl)piperazin-2-one.

Table 1. Reaction of Enone **1a** with DMEDA



| entry | solvent | base | yield ^a (%) |
|-------|--|-------------------|------------------------|
| 1 | Et ₂ O | DMEDA | 42 |
| 2 | Et ₂ O | Et ₃ N | 51 |
| 3 | EtOH | Et ₃ N | 25 |
| 4 | (CF ₃) ₂ CH(OH) | Et ₃ N | 19 |
| 5 | CF ₃ CH ₂ OH | Et ₃ N | 84 |
| 6 | Pyridine | Et ₃ N | 8 |
| 7 | DMSO | Et ₃ N | 18 |
| 8 | DMF | Et ₃ N | 18 |
| 9 | acetone | Et ₃ N | 30 |
| 10 | CH ₂ Cl ₂ | Et ₃ N | 20 |
| 11 | THF (–20 °C) | Et ₃ N | 36 |
| 12 | THF | Et ₃ N | 59 |
| 13 | MeCN | Et ₃ N | 50 |
| 14 | Et ₃ N | Et ₃ N | 6 |
| 15 | PhH | Et ₃ N | 24 |
| 16 | H ₂ O | Et ₃ N | 0 |

^a ¹⁹F NMR yields (rt, 48 h).

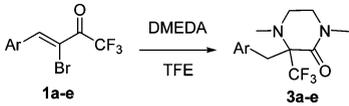
Deep structural changes are observed for the product **3a** having the trifluoromethyl group migrated in the adjacent position. This type of compounds is a rare type of heterocycles which is difficult to prepare. To the best of our knowledge only two approaches to CF₃ substituted piperazines (based on the trifluoropyruvic acid derivatives⁹ or

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corresponding aldehydes¹⁰) have been described so far in the literature.

To find optimal reaction conditions, we performed the reaction in solvents of a different nature and polarity (Table 1). One can see that the yield depends very significantly on the solvent used. Finally, trifluoroethanol was found to be the solvent of choice providing highest yield of the product.

Table 2. Reaction of Enones **1a–e** with DMEDA

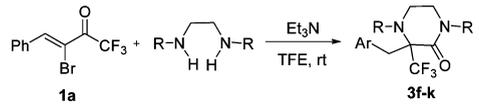


| entry | Ar | product 3 (yield, %) ^a |
|-------|--|--|
| 1 | Ph | 3a (80) |
| 2 | 4-MeC ₆ H ₄ | 3b (78) |
| 3 | 2,5-(MeO) ₂ C ₆ H ₃ | 3c (58) |
| 4 | 3-MeC ₆ H ₄ | 3d (75) |
| 5 | 3-MeOC ₆ H ₄ | 3e (73) |

^a Isolated yield.

Such an unusual skeletal rearrangement took place in the case of other enones **1b–e** as well, giving piperazin-2-ones **3b–e** in good to high isolated yields (Table 2). The reaction proceeds smoothly under mild conditions (room temperature, without any catalyst). The best results were obtained when triethylamine was used as an acceptor of HBr instead of an excessive amount of DMEDA.

Table 3. Reactions of **1a** with Symmetric *N,N'*-Disubstituted Ethylenediamines



| entry | R | yield of product 3 ^a (%) |
|-------|------------------------------------|--|
| 1 | Et | 3f , 75 (77) |
| 2 | <i>i</i> -Pr | 3g , 87 (90) |
| 3 | Bn | 3h , 79 (87) |
| 4 | cyclohexyl | 3i , 85 (92) |
| 5 | allyl | 3j , 83 (93) |
| 6 | MeOCH ₂ CH ₂ | 3k , 79 (85) |

^a Isolated yield (yield determined by ¹⁹F NMR).

Motivated by the importance of the development of an original approach to unique piperazinones **3**, we next investigated the scope of the reaction. For this purpose, bromo enone **1a** was treated with various symmetric *N,N'*-disubstituted ethylenediamines.

These binucleophiles were easily prepared by the reactions of 1,2-dibromoethane with the corresponding aliphatic amines¹¹ or by using reductive amination of benzaldehyde with ethylenediamine.¹² We have found that the reaction also proceeded effectively as well with the formation of trifluoromethylated piperazinones **3f–k**. The best yields of piperazinones **3f–k** were obtained for the more bulky cyclohexyl and isopropyl substituents (Table 3).

The structure of unexpected heterocycles **3a–k** was assigned on the basis of multinuclear 1D (¹H, ¹³C, ¹⁵N, ¹⁹F) and 2D NMR and IR spectroscopy, mass spectrometry, and elemental analysis. Thus, both ¹H and ¹³C NMR spectra revealed the absence of any signals in the region of olefinic protons or carbons. In contrast, a pair of diastereotopic protons was observed at 3.00–3.55 ppm in the ¹H NMR spectra, confirming the presence of the ArCH₂ moiety connected to an asymmetric carbon. The carbonyl group resonated as a singlet (not a quadruplet expected for trifluoroacetyl piperazine **2**) at 163–165 ppm that is characteristic for amides. The quadruplet at ~70 ppm (*J* = 20 Hz) confirmed the presence of quaternary carbon center adjacent to trifluoromethyl group. The peaks of two nitrogen atoms appeared at ca. –355 and –270 ppm, pointing to the presence of amine and amide functions. Finally, the structure of piperazinones **3** was unambiguously confirmed by X-ray diffraction analysis of compound **3g** (Figure 2).

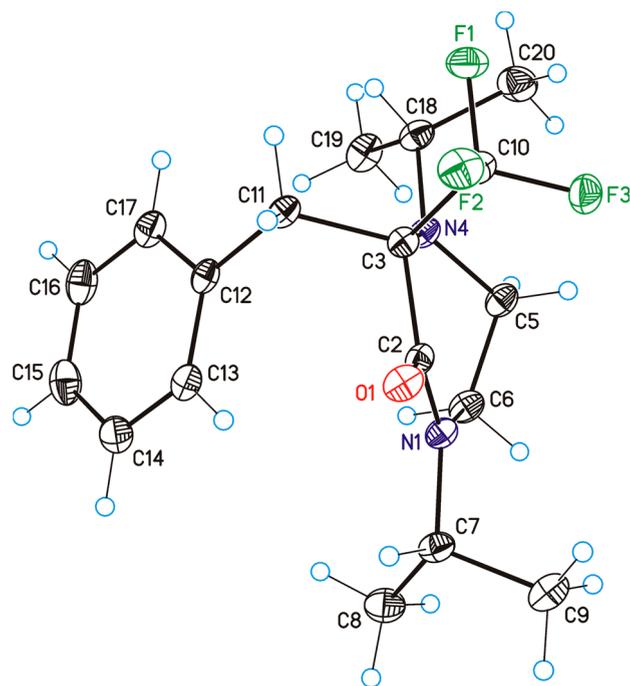


Figure 2. X-ray crystal structure of **3g**.

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In order to understand the mechanism of these unusual transformations, we have monitored the reaction of α -bromo enone **1b** with DMEDA by NMR. Thus, the ^{19}F NMR spectrum of the reaction mixture registered after stirring of enone **1b** and DMEDA for 1.5 h at room temperature showed the presence of one principal intermediate ($\delta = -80.3$ ppm) and the final heterocycle **3b** ($\delta = -66.4$ ppm). The ^1H NMR spectrum contained only one singlet in the field of the olefinic protons ($\delta = 5.92$ ppm). In the ^{13}C NMR spectrum instead of the quadruplet of the carbonyl carbon atom the signal of quaternary carbon atom $\text{C}(\text{OH})\text{CF}_3$ (quartet, $\delta = 86.9$ ppm, $J = 30.1$ Hz) appeared. Finally, ^{15}N NMR spectrum showed the presence of two types of amine nitrogens ($\delta = -332.8$ and -342.6 ppm). These data allow us to conclude that the principle intermediate of the cascade transformations has the structure of piperazinol **5**. As the reaction progresses, the intensity of all peaks of the intermediate **5** decreases, while the intensity of characteristic signals of final product **3** increases. Finally, only piperazinone **3** was isolated in good yield by column chromatography from the reaction mixture. These facts indicate clearly that the intermediate **5** is the precursor of the piperazinone **3**.

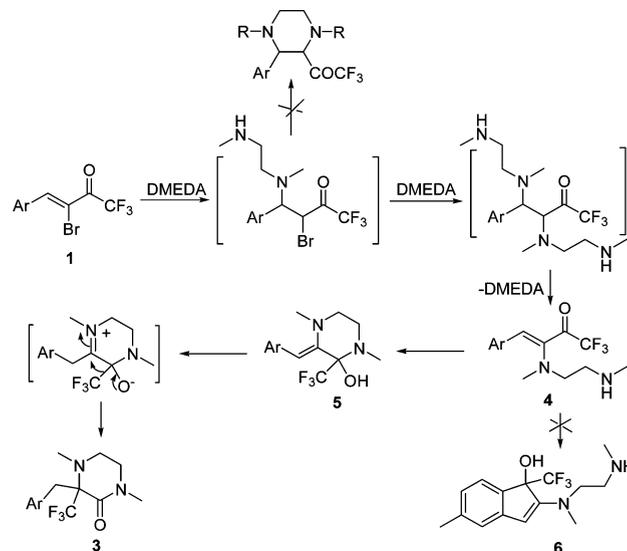
On the bases of NMR monitoring and literature data concerning captodative alkenes reactivity, we suggest the following reaction mechanism (Scheme 2). The first step of all cascade of transformations is the formation of aminoenone **4** which proceeds according to the usual scheme of nucleophilic vinylic substitution in *gem*-activated haloalkenes and includes the aza-Michael addition–nucleophilic substitution–elimination sequence. The second reaction step is an intramolecular cyclization of captodative aminoenone **4** to form piperazinol **5**.

Because of the presence of the CF_3 group this intermediate has rather acidic hydroxyl group. In presence of quite basic piperazine nitrogen the intramolecular proton transfer takes place to generate the corresponding iminium salt. Finally, 1,2-shift of the trifluoromethyl group as internal nucleophile to iminium electrophilic center occurs to give the target heterocycle **3** (Scheme 2). According to this scheme, polar protic solvents should facilitate the process. Probably trifluoroethanol has a well tuned balance of acidity and polarity providing higher yields of target products **3**.¹³ This solvent has $\text{p}K_{\text{a}}$ 12.4 in water, which is at least 1000 times higher in comparison to other alcohols. It should be noted that hexafluoro-2-propanol is most probably too acidic ($\text{p}K_{\text{a}}$ 9.3) resulting in very low yield of the product (19%).

Thus, the reactions of fluorinated bromo enones **1** with the secondary amines⁶ and diamines bearing two secondary amino groups proceed in a similar mechanism including the formation of captodative aminoenone **4** as the key intermediate. However, because of the presence of an additional nucleophilic N-center, chemoselective

(13) Zhdanko, A. G.; Gulevich, A. V.; Nenajdenko, V. G. *Tetrahedron* **2009**, *65*, 4692.

Scheme 2. Plausible Mechanism of the Reaction



cyclization with the formation of intermediate **5** takes place. As a result, a new type of cascade transformations is initialized leading finally to rearranged product **3** instead of formation of the indenol **6**.⁶ The demands for the presence of the strong electron withdrawing group at carbonyl fragment, accounts for the unique role of trifluoromethyl group in this transformation. It should be also noted that the observed reactivity of fluorinated bromoenones **1** differs significantly from the behavior of nonfluorinated acetylenic ketones (having the same oxidation level) in the reaction with diamines.¹⁴

In conclusion, an efficient method for building up the trifluoromethylated piperazine core from corresponding CF_3 bromo enones **1** and N,N' -disubstituted ethylenediamines was developed. To the best of our knowledge, this is the first example of the migration of the CF_3 group to an adjacent carbon atom of the heterocycle. Further application of this method for the synthesis of fluorinated heterocyclic compounds is now in progress.

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Supporting Information Available. Experimental procedures, characterization data, and ^1H , ^{13}C , and ^{19}F NMR spectra for all synthesized compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.