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

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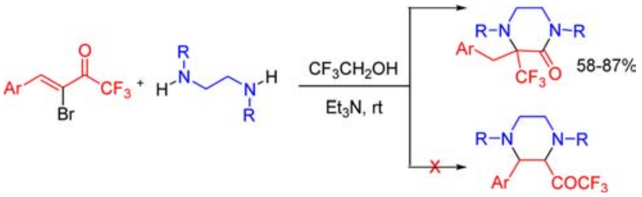
ABSTRACT



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,

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

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incorporation of fluorine (usually CF_3 group or fluorine atom(s)) is a powerful tool of modern drug design and drug discovery.[3]

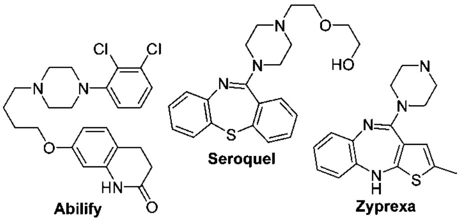


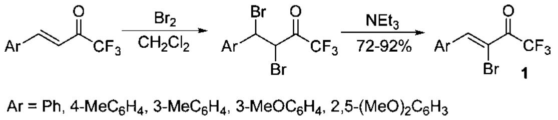
Figure 1. Some piperazine-derived drugs.

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] CF_3 enones are of special interest because they are very valuable building blocks for the preparation of various trifluoromethylated heterocycles.[5] The reactivity of CF_3 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 derivatives[6] 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.

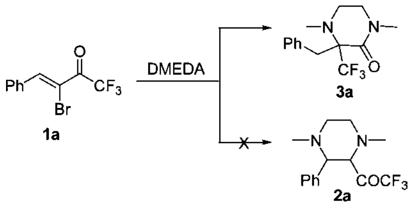
Starting bromo enones **1a**–**e** were prepared in high yields from α,β-unsaturated CF_3 ketones by the classical bromination–dehydrobromination sequence without isolation of the intermediate dibromo derivatives (Scheme 1).[6]

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_2O	DMEDA	42
2	Et_2O	Et_3N	51
3	EtOH	Et_3N	25
4	$(CF_3)_2CH(OH)$	Et_3N	19
5	CF_3CH_2OH	Et_3N	**84**
6	Pyridine	Et_3N	8
7	DMSO	Et_3N	18
8	DMF	Et_3N	18
9	acetone	Et_3N	30
10	CH_2Cl_2	Et_3N	20
11	THF (−20 °C)	Et_3N	36
12	THF	Et_3N	59
13	MeCN	Et_3N	50
14	Et_3N	Et_3N	6
15	PhH	Et_3N	24
16	H_2O	Et_3N	0

[a] ^{19}F 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 CF_3 substituted piperazines (based on the trifluoropyruvic acid derivatives[9] or

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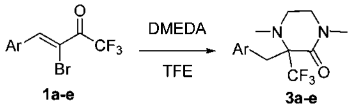
corresponding aldehydes[10]) have been described so far in the literature.

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

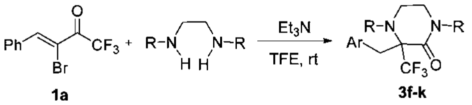


entry	Ar	product **3** (yield, %)[a]
1	Ph	**3a** (80)
2	4-MeC_6H_4	**3b** (78)
3	2,5-$(MeO)_2C_6H_3$	**3c** (58)
4	3-MeC_6H_4	**3d** (75)
5	3-$MeOC_6H_4$	**3e** (73)

[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*-Pr	**3g**, 87 (90)
3	Bn	**3h**, 79 (87)
4	cyclohexyl	**3i**, 85 (92)
5	allyl	**3j**, 83 (93)
6	$MeOCH_2CH_2$	**3k**, 79 (85)

[a] Isolated yield (yield determined by ^{19}F 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 amines[11] 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, ^{13}C, ^{15}N, ^{19}F) and 2D NMR and IR spectroscopy, mass spectrometry, and elemental analysis. Thus, both ^1H and ^{13}C 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 $ArCH_2$ 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).

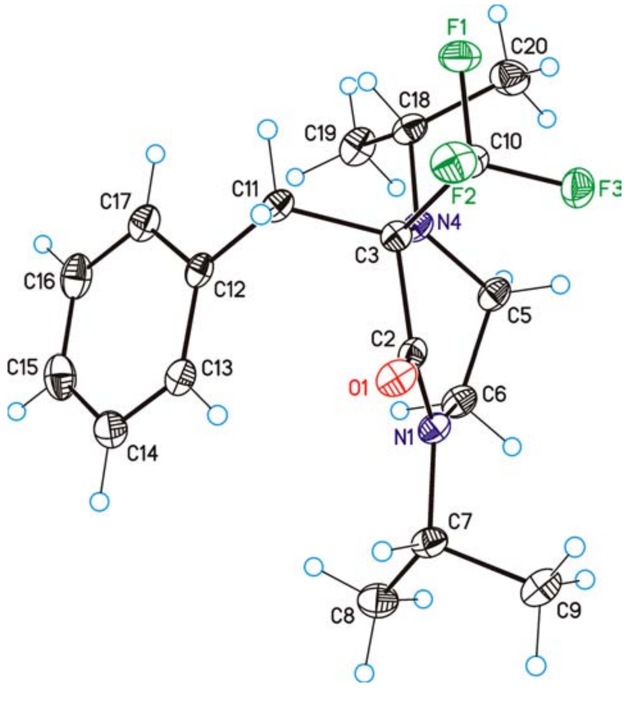


Figure 2. X-ray crystal structure of **3g**.

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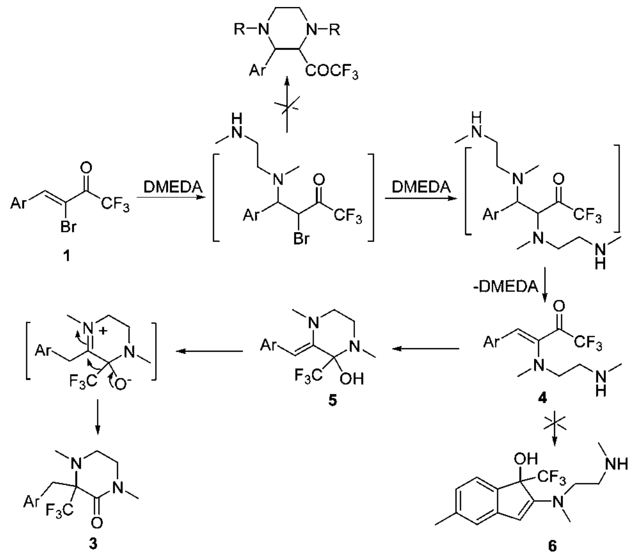
In order to understand the mechanism of these unusual transformations, we have monitored the reaction of α-bromoenone **1b** with DMEDA by NMR. Thus, the ^{19}F NMR spectrum of the reaction mixture registered after stirring of enone **1b** and DMEDA for 1.5 h at room temperature showed the presence of one principal intermediate ($\delta = -80.3$ ppm) and the final heterocycle **3b** ($\delta = -66.4$ ppm). The ^{1}H 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 C(OH)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 pK_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 (pK_a 9.3) resulting in very low yield of the product (19%).

Thus, the reactions of fluorinated bromo enones **1** with the secondary amines[6] 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 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]

Scheme 2. Plausible Mechanism of the Reaction



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 ^{1}H, ^{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.

The authors declare no competing financial interest.

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