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Mendeleev Commun., 2022, **32**, 629–631

Mendeleev Communications

Highly diastereoselective multicomponent synthesis of polysubstituted 2-hydroxy-2-trifluoromethylpiperidines with four and five stereogenic centers

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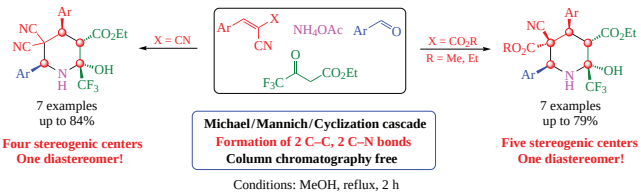
DOI: 10.1016/j.mencom.2022.09.020

The Michael–Mannich cascade cyclization of cyano olefins, ethyl 4,4,4-trifluoro-3-oxobutanoate, aromatic aldehydes and ammonium acetate provides convenient stereoselective formation of ethyl 5,5-dicyano-4,6-diaryl-2-hydroxy-2-(trifluoromethyl)piperidine-3-carboxylates with four stereogenic centers and dialkyl 4,6-diaryl-5-cyano-2-hydroxy-2-(trifluoromethyl)piperidine-3,5-dicarboxylates with five stereogenic centers. Ammonium acetate plays dual role, acting as a base and as a nitrogen source.



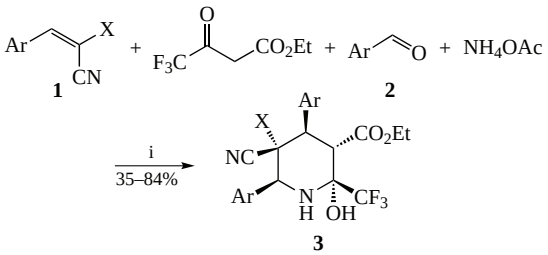
Keywords: multicomponent reactions, trifluoromethylpiperidines, ammonium acetate, C–H acids, stereoselectivity.

Piperidine and its derivatives play an important role in the discovery of drugs exhibiting various biological activities.[1–3] 2-Hydroxypiperidines are hepatic metabolites with biological activity and functional properties.[4] It is well known that the introduction of fluorine into organic molecules often leads to a sharp change in their physical, chemical, and biological properties.[5–7] In particular, the trifluoromethyl group is the key structural unit in many fluorinated compounds of biological and pharmaceutical importance. As a result, fluorine-containing heterocycles are now widely recognized as important organic molecules showing interesting biological activity with potential for medical and agricultural applications.[8–11]

In recent decades, the growing number of studies in the field of multicomponent processes is connected with the fact that methodology of multicomponent 'one-pot' reactions has serious advantages compared to an ordinary multi-step synthesis.[12–14] Recently, we carried out a multicomponent synthesis of substituted piperidines using NH_4OAc or aqueous ammonia as a source of nitrogen for the piperidine cycle.[15–17]

In continuation of our research on the application of electron-deficient olefins as synthons in the synthesis of various cyclic[18,19] and heterocyclic[20,21] compounds, in this work we present four-component synthesis of new trifluoromethyl-substituted piperidines with several stereogenic centers (Scheme 1). Refluxing of cyano-substituted olefins **1**, ethyl 4,4,4-trifluoro-3-oxobutanoate, aromatic aldehydes **2** (both with electron-withdrawing and electron-donating substituents) and ammonium acetate leads to products, among which ethyl 5,5-dicyano-4,6-diaryl-2-hydroxy-2-(trifluoromethyl)piperidine-3-carboxylates **3a–g** have four stereogenic centers while dialkyl 4,6-diaryl-5-cyano-2-hydroxy-2-(trifluoromethyl)piperidine-3,5-dicarboxylates **3h–n** have five such centers. This technique was developed in the study of substituted 1,4,5,6-tetrahydropyridines.[22] Several papers describing multicomponent synthesis of piperidines containing a trifluoromethyl group at C^2 are known.[23–25]

The NMR spectra of products **3** displayed only one set of signals suggesting stereoselective formation of individual diastereomers. The assignment for compounds **3d** and **3j** was performed by means of 2D ^1H–^{13}C HSQC and ^1H–^{13}C HMBC spectra. At low field, the proton spectrum of **3d** contained three groups of signals with strong coupling and overlapping referred to aromatic hydrogens and singlet at δ 7.10 ppm from hydroxy function. At medium field (3–5 ppm), four signals from piperidine were located where singlet at δ 3.87 ppm belonged to NH, multiplet at δ 3.85 ppm corresponded to CH_2, and two methoxy-groups appeared at δ 3.76 and 3.78 ppm. The only signal at high field was triplet at δ 0.84 ppm from CH_2CH_3. Two



a	Ar = Ph, X = CN, 64%	**h**	Ar = Ph, X = CO_2Me, 79%
b	Ar = 4-MeC_6H_4, X = CN, 57%	**i**	Ar = 4-MeC_6H_4, X = CO_2Me, 69%
c	Ar = 2-$MeOC_6H_4$, X = CN, 65%	**j**	Ar = 4-ClC_6H_4, X = CO_2Me, 72%
d	Ar = 3-$MeOC_6H_4$, X = CN, 71%	**k**	Ar = 4-BrC_6H_4, X = CO_2Me, 55%
e	Ar = 4-$MeOC_6H_4$, X = CN, 55%	**l**	Ar = 4-$O_2NC_6H_4$, X = CO_2Me, 43%
f	Ar = 4-FC_6H_4, X = CN, 84%	**m**	Ar = 2-ClC_6H_4, X = CO_2Et, 35%
g	Ar = 4-$O_2NC_6H_4$, X = CN, 47%	**n**	Ar = 4-ClC_6H_4, X = CO_2Et, 55%

Scheme 1 *Reagents and conditions*: i, olefin **1** (3 mmol), ethyl 4,4,4-trifluoro-3-oxobutanoate (3 mmol), aldehyde **2** (3 mmol), NH_4OAc (6 mmol), MeOH (7 ml), reflux, 2 h.

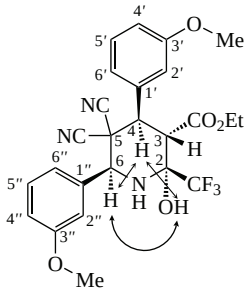


Figure 1 ^{1}H–^{1}H correlation in NOESY spectrum of compound **3d**.

aromatic signals in carbon spectrum were missed due to large broadening because of restricted rotation of aryl moiety, so another ^{13}C NMR spectrum was recorded at 333 K to detect them. Two aryl carbons and two methoxy groups gave overlapped signals what was determined by heteronuclear correlations. Relative arrangement of other piperidine substitutes was established using ^{1}H–^{1}H NOESY. The key spatial interactions are shown in Figure 1. Therefore, piperidine derivative **3d** with four streogenic centers has (2*R**,3*S**,4*R**,6*S**) configuration.

The proton spectrum of compound **3j** consisted of four doublets from *para*-substituted phenyls and singlet from OH at the low field. Four signals from piperidine protons, *viz*. those of NH (singlet at δ 3.75 ppm), methoxy-group (singlet at 3.48 ppm), and CH_2 (quartet at δ 3.82 ppm) were found at the medium field (3–5 ppm). Signal for CH_2CH_3 protons appeared as triplet at δ 0.84 ppm. The carbon spectrum showed all necessary peaks with one broadened singlet at 130.15 ppm from C^{o}. Relative configuration of CN and CO_2Me groups at C^5 was determined by analysis of proton–carbon spin coupling. The value for SSCC between H^6 and nitrile carbon is about 8 Hz, which indicates the axial position of the interacting nuclei. Relative arrangement of other piperidine substituents was established using ^{1}H–^{1}H NOESY. The key spatial interactions (Figure 2) reveal that piperidine derivative **3j** with five streogenic centers has (2*R**,3*S**,4*R**,5*R**,6*S**) configuration.

Configuration of compounds **3d** and **3j** are the most thermodynamically stable because the bulky substituents are positioned to minimize sterical crowding. We suppose that the formation of isomers with the *cis*-configuration of 2-hydroxy and 3-ethoxycarbonyl groups is also associated with the presence of a hydrogen bond between them.

A possible reaction pathway is shown in Scheme 2. The Michael addition of ethyl 4,4,4-trifluoro-3-oxobutanoate to cyano olefin **1** generates ethyl 2-(2-dicyano-1-arylethyl)-4,4,4-trifluoro-3-oxobutanoate **A**, which is followed by the Mannich addition of *in situ* generated arylimine to form ethyl 5-amino-4-cyano-3,5-diaryl-2-(trifluoroacetyl)pentanoate **B**. The sequence concludes with the intramolecular cyclization of **B** to give corresponding substituted 2-hydroxy-2-trifluoromethyl-piperidines **3**.

In conclusion, we have developed a four-component stereoselective single-step synthesis of substituted

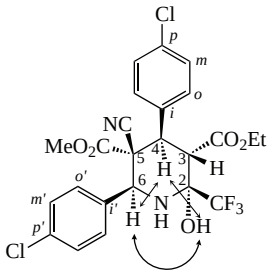
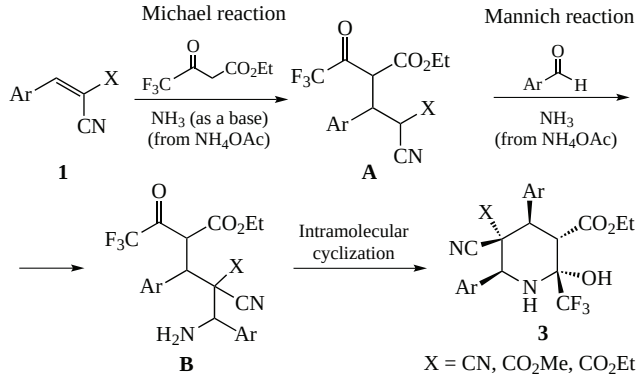


Figure 2 ^{1}H–^{1}H correlation in NOESY spectrum of compound **3j**.



Scheme 2

2-hydroxy-2-(trifluoromethyl)piperidines, utilizing cyano olefins (benzylidenemalononitriles or benzylidenecyano-acetates), ethyl 4,4,4-trifluoro-3-oxobutanoate, aromatic aldehydes and ammonium acetate as a nitrogen source for the piperidine cycle. Our method allows one to obtain ethyl (2*R**,3*S**,4*R**,6*S**)-4,6-diaryl-5,5-dicyano-2-hydroxy-2-(trifluoromethyl)piperidine-3-carboxylates with four stereogenic centers and dialkyl (2*R**,3*S**,4*R**,5*R**,6*S**)-4,6-diaryl-5-cyano-2-hydroxy-2-(trifluoromethyl)piperidine-3,5-dicarboxylates with five stereogenic centers. The products were purified by simple filtration, and column chromatography was avoided entirely.

This work was supported by the Russian Science Foundation (grant no. 17-73-20260).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.09.020.

References

1 M. von Itzstein, W.-Y. Wu, G. B. Kok, M. S. Pegg, J. C. Dyason, B. Jin, T. van Phan, M. L. Smythe, H. F. White, S. W. Oliver, P. M. Colman, J. N. Varghese, D. M. Ryan, J. M. Woods, R. C. Bethell, V. J. Hotham, J. M. Cameron and C. R. Penn, *Nature*, 1993, **363**, 418.
2 C. U. Kim, W. Lew, M. A. Williams, H. Liu, L. Zhang, S. Swaminathan, N. Bischofberger, M. S. Chen, D. B. Mendel, C. Y. Tai, W. G. Laver and R. C. Stevens, *J. Am. Chem. Soc*., 1997, **119**, 681.
3 I. Borza and G. Domany, *Curr. Top. Med. Chem.*, 2006, **6**, 687.
4 H. den Ouden, L. Pellis, G. E. H. M. Rutten, I. K. Geerars-van Vonderen, C. M. Rubingh, B. van Ommen, M. J. van Erk and J. W. J. Beulens, *Metabolomics*, 2016, **12**, 27.
5 *Organofluorine Chemistry: Principles and Commercial Application*, eds. R. E. Banks, B. E. Smart and J. C. Tatlow, Plenum Press, New York, 1994.
6 *Organic Chemistry in Medicinal Chemistry and Biochemical Applications*, eds. R. Filler, Y. Kobayashi and L. M. Yagupolskii, Elsevier, Amsterdam, 1993.
7 N. Iwai, R. Sakai, S. Tsuchida, M. Kitazume and T. Kitazume, *J. Fluorine Chem.*, 2009, **130**, 434.
8 S. Buscemi, A. Pace, A. P. Piccionello, G. Macaluso, N. Vivona, D. Spinelli and G. Giorgi, *J. Org. Chem.*, 2005, **70**, 3288.
9 F. He, S. Guo, A. Dai, R. Zhang and J. Wu, *Chin. J. Org. Chem.*, 2021, **41**, 3303.
10 S. Guo, W. Zhao, Y. Wang, W. Zhang, S. Chen, P. Wei and J. Wu, *J. Agric. Food Chem.*, 2021, **69**, 12891.
11 L.-X. Zhao, J.-J. Hu, Z.-X. Wang, M.-L. Yin, Y.-L. Zou, S. Gao, Y. Fu and F. Ye, *Pestic. Biochem. Physiol.*, 2020, **170**, 104684.
12 *Multicomponent Reactions in Organic Synthesis*, eds. J. Zhu, Q. Wang and M. Wang, Wiley, Weinheim, 2015.
13 A. N. Vereshchagin, *Russ. Chem. Bull.*, 2017, **66**, 1765.
14 A. Dömling, *Chem. Rev.*, 2006, **106**, 17.
15 A. N. Vereshchagin, K. A. Karpenko, M. N. Elinson, E. O. Dorofeeva, A. S. Goloveshkin and M. P. Egorov, *Mendeleev Commun.*, 2018, **28**, 384.
16 A. N. Vereshchagin, K. A. Karpenko, M. N. Elinson, A. S. Goloveshkin, I. E. Ushakov and M. P. Egorov, *Res. Chem. Intermed.*, 2018, **44**, 5623.

17 A. N. Vereshchagin, K. A. Karpenko, M. N. Elinson, A. S. Goloveshkin, E. O. Dorofeeva and M. P. Egorov, *Res. Chem. Intermed.*, 2020, **46**, 1183.
18 M. N. Elinson, S. K. Feducovich, T. A. Zaimovskaya, A. N. Vereshchagin, S. V. Gorbunov and G. I. Nikishin, *Russ. Chem. Bull*., 2005, **54**, 1593 (*Izv. Akad. Nauk, Ser. Khim.*, 2005, 1547).
19 A. N. Vereshchagin, M. N. Elinson, N. O. Stepanov and G. I. Nikishin, *Mendeleev Commun.*, 2009, **19**, 324.
20 M. N. Elinson, S. K. Fedukovich, T. A. Zaimovskaya, A. N. Vereshchagin and G. I. Nikishin, *Russ. Chem. Bull.*, 2003, **52**, 2241 (*Izv. Akad. Nauk, Ser. Khim*., 2003, 2122).
21 M. N. Elinson, A. N. Vereshchagin and F. V. Ryzhkov, *Curr. Org. Chem.*, 2017, **21**, 1427.
22 A. N. Vereshchagin, T. M. Iliyasov, K. A. Karpenko, V. A. Smirnov, I. E. Ushakov and M. N. Elinson, *Chem. Heterocycl. Compd.*, 2021, **57**, 929.
23 L. Zhou, F. Yuan, Y. Zhou, W. Duan, M. Zhang, H. Deng and L. Song, *Tetrahedron*, 2018, **74**, 3761.
24 W. Shi, Y. Wang, Y. Zhu, M. Zhang, L. Song and H. Deng, *Synthesis*, 2016, **48**, 3527.
25 B. Dai, Y. Duan, X. Liu, L. Song, M. Zhang, W. Cao, S. Zhu, H. Deng and M. Shao, *J. Fluorine Chem.*, 2021, **133**, 127.

Received: 29th March 2022; Com. 22/6846