Mendeleev Communications

Mendeleev Commun., 2026, **36**, 53–54

Photochemical synthesis of 3-trifluoromethyl-2,3-dihydrobenzofuran-3-ols

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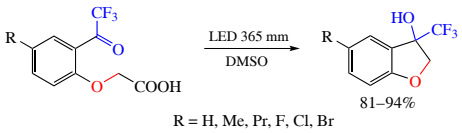
DOI: 10.71267/mencom.7842

A catalyst-free photochemical synthesis of 3-trifluoromethyl-2,3-dihydrobenzofuran-3-ols *via* heterocyclization of 2-[2-(trifluoroacetyl)phenoxy]acetic acids by irradiation with 365 nm light is proposed.



Keywords: photochemistry, organofluorine compounds, 2,3-dihydrobenzofuran-3-ol, 2-(trifluoroacetyl)phenols, cyclization.

Oxygen-containing heterocycles are widely represented among natural and bioactive substances.[1,2] A special place among them is occupied by 2,3-benzofurans which also exhibit various biological activities,[3,4] for example, anti-inflammatory,[5,6] anti-cancer,[7] antifungal,[8] antibacterial,[9] and others[10–12] (see examples in Figure 1). On the other hand, the introduction of fluorine atoms into a molecule often helps to increase its activity by improving bioavailability.[13,14] In this regard, up to 20% of modern medicines contain fluorine atoms, and therefore the creation of new methods for synthesizing fluorinated compounds is of considerable interest.

In our previous work we discovered interesting photo-transformations of 2-(2-formylphenoxy)acetic acid into hydroxychromanones and benzofuranones.[15] In this work (Scheme 1), we decided to study the phototransformations of analogous trifluoroacetyl derivatives **2** of phenoxyacetic acid available from 2-(trifluoroacetyl)phenols **1**. For this purpose, we subjected the initial compound **2a** to 365 nm irradiation. As a solvent, similarly to previous works,[15,16] we used DMSO since it provided the greatest effectiveness for the phototransformations. We found herein that the photoconversion resulted in the formation of a single pure product lacking carboxy-group. Mass spectrometry data also indicated the elimination of CO_2 during the reaction. A more detailed analysis showed that the photoconversion resulted in the formation of compound **3a** having a benzofuranol ring with a 3-positioned trifluoromethyl group. A similar photoconversion was previously observed for aldehyde derivatives, but the yields of the products were low.[15,17] Since the reaction yield was close to quantitative, no further optimization of the conditions was performed.

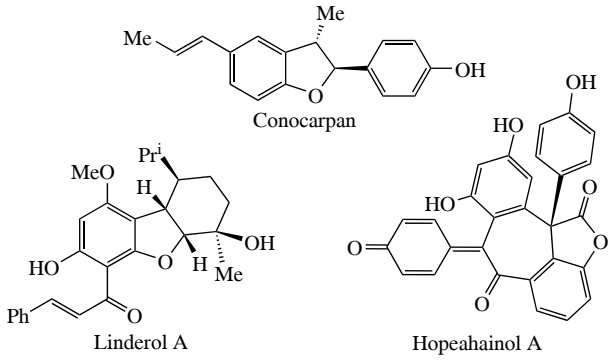
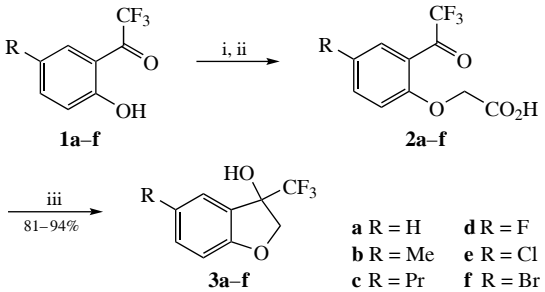


Figure 1 Biologically active 2,3-dihydrobenzofurans.

Next, we synthesized a series of starting compounds **2a–f** and briefly studied the reaction scope (see Scheme 1). Using the proposed approach, six new compounds **3a–f** were synthesized. In all cases, the reaction provided a very high yield, close to quantitative, and no column chromatography was needed for the purification of the products. The structure of the obtained compounds was additionally confirmed by heteronuclear 2D NMR spectroscopy of derivative **3a** (Figure 2).

Finally, we performed a brief investigation of the reaction mechanism. We showed that the addition of radical quencher (TEMPO or BHT, see Online Supplementary Materials for details) had negligible effect on the reaction rate, suggesting the absence of long-lived radical intermediates and supporting an intramolecular pathway. Based on our previous observations,[15,16] the phototransformation could occur *via* hydrogen atom transfer (HAT) to the excited carbonyl group (bi-radical species **i1**



Scheme 1 *Reagents and conditions*: i, $BrCH_2CO_2Et$, K_2CO_3, DMF, 80 °C; ii, H_2O, AcOH, H_2SO_4, Δ; iii, LED 365 nm, DMSO, 6 h.

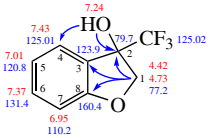


Figure 2 Study of compound **3a** by heteronuclear NMR spectroscopy. Chemical shifts of ^1H (red), ^{13}C (blue) are given, the most important spin–spin interactions are marked with arrows.

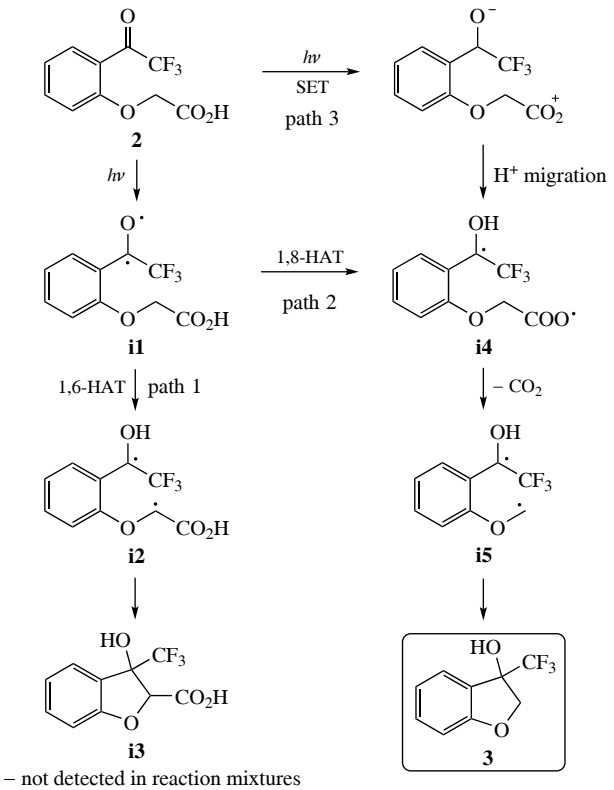


Figure 3 Proposed reaction mechanisms.

formed after photoexcitation, Figure 3). The more preferable 1,6-HAT (path 1) involving the methylene fragment should lead to 2,3-dihydrobenzofuran-2-carboxylic acids **i3** *via* bi-radical **i2**. However, the decarboxylation of these products remains unclear, as they may exhibit significant stability. Moreover, such intermediates were never detected, and the D_2O addition did not lead to the formation of a product **3** with deuterium incorporated into the methylene fragment (see Online Supplementary Materials for details). An alternative route *via* 1,8-HAT (path 2) from the carboxylic group, followed by excited state decarboxylation of **i4**, could form the products *via* bi-radical **i5**. Nevertheless, this pathway is likely hindered by the increased C(O)O–H bond dissociation energy[18] despite literature precedents for 1,8-HAT.[19] A more plausible mechanism (path 3) involves photoinduced single-electron transfer (SET)[20] followed by proton migration. Trifluoroacetyl derivatives are well-established as efficient electron acceptors in SET processes,[21] while carboxy groups can act as electron donors.[22] This sequential transformation generates the same radical intermediate **i4** as in the 1,8-HAT pathway, which subsequently undergoes CO_2 elimination and cyclization to yield the final product **3**.

To summarize, we have developed a simple and effective synthesis of 3-trifluoromethyl-2,3-dihydrobenzofuran-3-ols from the corresponding 2-[2-(trifluoroacetyl)phenoxy]acetic acids by the action of 365 nm irradiation. The reaction proceeds with a virtually quantitative yield and does not require the utilization of additional reagents and catalysts.

This work was supported by The Russian Science Foundation (grant no. 25-13-00043).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7842.

References

1 J. Cossy and A. Guérinot, in *Advances in Heterocyclic Chemistry*, eds. E. F. V. Scriven and C. A. Ramsden, Academic Press, 2016, vol. 119, pp. 107–142; https://doi.org/10.1016/bs.aihch.2016.03.002.
2 M. D. Delost, D. T. Smith, B. J. Anderson and J. T. Njardarson, *J. Med. Chem*., 2018, **61**, 10996; https://doi.org/10.1021/acs.jmedchem.8b00876.
3 S. Antus, T. Kurtán, L. Juhász, L. Kiss, M. Hollósi and Z. S. Májer, *Chirality*, 2001, **13**, 493; https://doi.org/10.1002/chir.1067.
4 Z. Chen, M. Pitchakuntla and Y. Jia, *Nat. Prod. Rep*., 2019, **36**, 666; https://doi.org/10.1039/C8NP00072G.
5 G.-J. Huang and J.-S. Yang, *Chem. – Asian J*., 2010, **5**, 2075; https://doi.org/10.1002/ASIA.201000209.
6 L. Baumgartner, S. Sosa, A. G. Atanasov, A. Bodensieck, N. Fakhrudin, J. Bauer, G. Del Favero, C. Ponti, E. H. Heiss, S. Schwaiger, A. Ladurner, U. Widowitz, R. Della Loggia, J. M. Rollinger, O. Werz, R. Bauer, V. M. Dirsch, A. Tubaro and H. Stuppner, *J. Nat. Prod*., 2011, **74**, 1779; https://doi.org/10.1021/np200343t.
7 Y. Mimaki, A. Kameyama, Y. Sashida, Y. Miyata and A. Fujii, *Chem. Pharm. Bull*., 1995, **43**, 893; https://doi.org/10.1248/cpb.43.893.
8 K. Minagawa, S. Kouzuki, K. Nomura, T. Yamaguchi, Y. Kawamura, K. Matsushima, H. Tani, K. Ishii, T. Tanimoto and T. Kamigauchi, *J. Antibiot*., 2001, **54**, 890; https://doi.org/10.7164/antibiotics.54.890.
9 T. Rukachaisirikul, P. Innok, N. Aroonrerk, W. Boonamnuaylap, S. Limrangsun, C. Boonyon, U. Woonjina and A. Suksamrarn, *J. Ethnopharmacol*., 2007, **110**, 171; https://doi.org/10.1016/j.jep.2006.09.022.
10 K. C. Nicolaou, Q. Kang, T. R. Wu, C. S. Lim and D. Y.-K. Chen, *J. Am. Chem. Soc*., 2010, **132**, 7540; https://doi.org/10.1021/ja102623j.
11 H. M. Ge, C. H. Zhu, D. H. Shi, L. D. Zhang, D. Q. Xie, J. Yang, S. W. Ng and R. X. Tan, *Chem. – Eur. J*., 2008, **14**, 376; https://doi.org/10.1002/chem.200700960.
12 S. Apers, A. Vlietinck and L. Pieters, *Phytochem. Rev*., 2003, **2**, 201; https://doi.org/10.1023/B:PHYT.0000045497.90158.d2.
13 M. Inoue, Y. Sumii and N. Shibata, *ACS Omega*, 2020, **5**, 10633; https://doi.org/10.1021/acsomega.0c00830.
14 G. Shabir, A. Saeed, W. Zahid, F. Naseer, Z. Riaz, N. Khalil, Muneeba and F. Albericio, *Pharmaceuticals*, 2023, **16**, 1162; https://doi.org/10.3390/ph16081162.
15 E. A. Zhigileva, V. E. Opryshko, A. V. Eshtukov-Scheglov, D. S. Ivanov, D. I. Rudik, A. A. Mikhaylov, I. A. Ivanov, A. Yu. Smirnov and M. S. Baranov, *Org. Biomol. Chem*., 2024, **22**, 7848; https://doi.org/10.1039/D4OB01194E.
16 E. R. Zaitseva, V. E. Opryshko, D. S. Ivanov, A. A. Mikhaylov, A. Yu. Smirnov and M. S. Baranov, *Org. Biomol. Chem*., 2023, **21**, 9082; https://doi.org/10.1039/D3OB01520C.
17 T. Horaguchi, C. Tsukada, E. Hasegawa, T. Shimizu, T. Suzuki and K. Tanemura, *J. Heterocycl. Chem*., 1991, **28**, 1261; https://doi.org/10.1002/jhet.5570280518.
18 A. Banerjee, Z. Lei and M.-Y. Ngai, *Synthesis*, 2019, **51**, 303; https://doi.org/10.1055/s-0037-1610329.
19 M. Nechab, S. Mondal and M. P. Bertrand, *Chem. – Eur. J*., 2014, **20**, 16034; https://doi.org/10.1002/chem.201403951.
20 H. Cao, X. Tang, H. Tang, Y. Yuan and J. Wu, *Chem. Catal*., 2021, **1**, 523; https://doi.org/10.1016/j.checat.2021.04.008.
21 F.-F. Tan and Z.-C. Li, *Front. Chem*., 2025, **13**, 1602003; https://doi.org/10.3389/fchem.2025.1602003.
22 Y. Yoshimi, M. Masuda, T. Mizunashi, K. Nishikawa, K. Maeda, N. Koshida, T. Itou, T. Morita and M. Hatanaka, *Org. Lett*., 2009, **11**, 4652; https://doi.org/10.1021/ol9019277.

Received: 6th May 2025; Com. 25/7842