Stereoselective Direct N-Trifluoropropenylation of Heterocycles with a Hypervalent Iodonium Reagent

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Abstract: The availability and synthesis of fluorinated enamine derivatives such as N-(3,3,3-trifluoropropenyl) heterocycles are challenging, especially through direct functionalization of the heterocyclic scaffold. Heterocycles, N-alkenylated molecules, are an important class from a synthetic aspect due to their transformability of the double bond. Among the subclasses of nitrogen heterocycles, the stereoselective N-trifluoropropenylation method based on the use of a bench-stable trifluoropropenyl iodonium salt is described. This reagent enables the straightforward trifluoropropenylation of various N-heterocycles under mild reaction conditions, providing trifluoromethyl enamine type moieties with high stereoselectivity and efficiency.

Nitrogen heterocycles are one of the most common and important molecular motifs in nature,[1] and a significant portion of biologically active molecules are based on this framework.[2] Among the subclasses of nitrogen heterocycles, N-alkenylated molecules are an important class from a synthetic aspect due to the transformability of the double bond[3] and several derivatives are used in the field of medicinal chemistry.[4] N-alkenylations can be achieved with hydroamination of alkynes[5] or the functionalization of vinyl species equipped with leaving groups via metal-catalyzed[6] or metal-free reactions.[7] The key aspect of these direct functionalizations is the stereoselectivity, thus the development of E- or Z-selective methods are desirable, however this is challenging.

Fluorine-containing molecules are more and more desired compounds in pharmaceutical, agrochemical and material sciences.[8] The strategic incorporation of fluorine atoms in organic compounds is a valuable tool for researchers to satisfy the developing needs and expectations for new API’s.[9] Therefore, versatile synthetic methodologies were developed for the installation of different fluorous functional groups into organic scaffolds.[10] Among these fluorous motifs, the 3,3,3-trifluoro-

propen-1-yl group is relatively rare and methods which enable its incorporation into heterocycles through the formation of new C–N bond are hardly available and mostly limited to some specific substrates, such as cyclic amides.[11] The N-trifluoropropenylation of enamides such as pyrrolidin-2-one can be achieved through the palladium[11a] or copper-catalyzed[11b] trifluoromethylation of N-vinylpyrrolidin-2-one with CF3I or under photocatalytic conditions (Figure 1a).[11c–e] While the product can be obtained with trifluoropropionaldehyde (Figure 1b),[11f] the use of 3,3,3-trifluoropropylmethyl gas as a C–CF3 surrogate requires the handling of gaseous reagent, but it was successfully applied as Michael acceptor in its reaction with 2'-deoxyiodouridine used for iodinated DNA bases (Figure 1c).[11g] The NH functionalities in uracil and thymine can be trifluoropropenylation with 2-bromo-3,3,3-trifluoropropene with moderate stereoselectivity (Figure 1c).[11h]

However, the applicability of the previous methods was demonstrated with only a few trifluoromethylated examples.

Recently, Meyer and Qacemi demonstrated the N-trifluoropropenylation of heterocycles such as pyrrole, pyrazole, triazole, and pyridine with the utilization of 2-chloro-3,3,3-trifluoroprop-1-ene (HCFO-1233xf) in a base-promoted transformation under mild reaction condition (Figure 1d).[12] The reaction favors the formation of the Z-isomer, but the Z/E isomeric ratio of trifluoropropenyl heterocycles was between 6:4–7:3.

Taking into consideration the importance of the compound class and the limitations of their versatile and selective synthesis, we aimed to develop a novel procedure which enables the direct introduction of trifluoropropenyl functional groups into heterocycles through the formation of new C–N bond in a selective and efficient manner under mild reaction conditions enabled by hypervalent iodonium species.[11i]

In our laboratory, we recently designed and synthesized a bench stable trifluoroisopropenyl iodonium salt (1) and studied its reactivity toward nitrogen nucleophiles. Primary amines provided trifluoromethylaziridines,[14] while the utilization of secondary amines ensured the synthesis of trifluoroalkyl amines and diamines through aziridinium intermediate.[15] To complete the spectrum of applicable nitrogen nucleophiles, we studied the reaction of nitrogen heterocycles with the trifluoropropenyl-iodonium salt to discover new synthetic possibilities and develop a stereoselective, versatile, and efficient methodology to the access of N-trifluoropropenyl heterocyclic species through a one-step direct functionalization (Figure 2).

We choose benzotriazole (2) as model substrate for the reactivity and optimization studies, focusing on the effect of base and solvent. To our delight, in dichloromethane with

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202102840

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Li$_2$CO$_3$ base the desired trifluoropropenylation of benzotriazole with 1.2 equivalent of iodonium reagent 1 the trifluoropropenylation took place on N-1 resulting 3 in 83% conversion in 2 h at 25 ºC (Table 1, Entry 1). However, formation of constitutional isomers was also observed as minor products$^{[16]}$ In further optimization, we aimed to improve both the selectivity and the efficiency of the trifluoropropenylation. In this regard, the use of other carbonates such as sodium and potassium resulted in lower conversions (80 % and 60 % respectively, Table 1, Entry 2 and 3). In the presence of NaH, product 3 formed in 75% conversion, while collidine could also be used effectively as simple organic base with complete reaction, providing the major product 3 in 85% conversion. Next, we studied some solvent-base pairs including EtOAc, THF, and MeCN as solvents and Li$_2$CO$_3$, Na$_2$CO$_3$, and collidine as bases to find the best
We found that the combination of MeCN and Li$_2$CO$_3$ provided the best conditions for the reaction, which took place in full regio- and stereoselectivity and the E-trifluoropropenylated benzotriazole 3 was isolated in 95% yield after workup.

After finding the optimal solvent-base pair for the transformation (we performed the same solvent-base optimization with indazole, and obtained the same result), we were also able to lower the iodonium salt loading to 1.1 equivalents without any diminution of isolated yield. Increasing the temperature had no effect on reaction time or yield.

With the optimized conditions in hand, we aimed to explore the scope of the reaction with the E-selective N-trifluoropropenylidation of various heterocycles bearing NH functionality. In this regard, reactions of pyrazoles provided the desired products under the optimized reaction conditions. Although the parent compound 1H-pyrazole could be trifluoropropenylated with full

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**Scheme 1.** Substrate scope. N–H heterocycles (0.30–1.00 mmol, 1.0 equiv), Li$_2$CO$_3$ (0.60–2.00 mmol, 2.0 equiv), trifluoroisopropenyl iodonium salt 1 (0.33–1.10 mmol, 1.1 equiv) and 3–10 mL of MeCN, room temperature, 2 h. [a] the major regioisomer is depicted on the scheme.
conversion (not shown), the isolation of this product was problematic due to its volatility. The presence of Br substituent on the pyrazole ring enabled the isolation of 4 in 80% yield after the trifluoropropenylation.

Next, we examined a series of 3,5-symmetrically disubstituted pyrazoles such as 3,5 dimethyl-pyrazole and its 4-iodinated derivative and we were able to isolate the corresponding products 5 and 6 in 63 and 80% yield, respectively. Symmetric 3,5-diaryl pyrazoles were trifluoropropenylated without difficulties and the products 7–13 were isolated in 53–90% yield range, similarly to the 4-iodo derivative 14 which was isolated in 50% yield.

In case of non-symmetrically substituted pyrazoles, the 3-phenyl and 3-trifluoromethyl-4-carboxetoxy substituted pyrazoles gave exclusively one constitutional isomer 15 and 16 in 86% and 63% yield, indicating the steric and electronic influence on the functionalization. Other non-symmetrically substituted 3,5-diaryl pyrazoles also reacted smoothly, however, only inseparable mixtures of constitutional isomers of 17, 18, and 19 could be isolated. In contrast, when 3-phenyl-5-trifluoromethylpyrazole was transformed, isomers 20 and 21 were isolated in 31 and 36% yield, respectively, similarly to products 22 and 23 which were separated and isolated with similar efficiency (48 and 39% yield, respectively).

In the 1H-imidazole series, 4-bromo, 2-ethyl, 4,5-diphenyl and 4-ethylcarboxylate derivatives underwent selective trifluoropropenylation and the corresponding enamines 24, 25, 26, and 27 were isolated in 61%, 50%, 89% and 95% yield, respectively.

Among the five membered nitrogen heterocycles having a ring NH functionality. Indazoles were also successfully trifluoropropenylated with iodonium reagent under the optimized conditions.

The reaction of unsubstituted indazole framework provided N-2-trifluoropropenylated product 29 selectively in 83% yield.

Presence of ethylcarboxylate group in the pyrazole ring caused the formation of two isomers 30 and 31 which were isolated after separation in 53% and 24%. Substituents such as Br, NO2, and TBDMSO on the benzene ring of indazole selectively form N-1-trifluoropropenylated products 32, 33, and 34 with similar high efficiency (83%, 87% and 88% respectively). Beside the indazole derivatives, benzimidazoles were also successfully transformed and the desired products (35, 36) were formed selectively and isolated in 74% and 40% yield.

In this series, we aimed for the transformation of indole, but we observed the formation of complex reaction mixture without the detection of the desired product. However, azaindoles were trifluoropropenylated successfully and enamine products 37 and 38 were isolated in 47% and 37% yields, respectively.

Although our model substrate benzoazaindole used for the optimization studies, gave exclusively one product (3) under the optimized conditions in 95% isolated yield, the reaction with its 4-nitro-substituted derivative gave three regioisomers 39, 40 and 41, which were isolated in 60%, 18%, and 15% respectively after chromatographic purification.

Using the iodonium based functionalization protocol N-trifluoropropenylated purine derivatives 42, 43, and 44 were also isolated in high yields, giving the products in 85%, 82%, and 83%, respectively.

To our delight, not just aromatic heterocycles, but also heterocyclic imides were transformed efficiently using the developed methodology. Phthalimide reacted smoothly and the corresponding trifluoropropenyl-phthalimide 45 was isolated in 80% yield. Phenytoin was also a suitable substrate for the transformation, and we were able to isolate the N-trifluoropropenylated product 46 in 60% yield.

On the basis of our previous studies, we propose a mechanism for the trifluoropropenylation (Figure 3).

After the deprotonation step, the heterocyclic anion attacks to the terminal sp2 carbon of the trifluoropropenyl moiety in a Michael addition type reaction, then the formed benzotriazolyl iodonium ylide (49) undergoes intramolecular proton transfer resulting anion 51. Alternatively, the stabilized carbanion (49) can be protonated by the HCO3- ion in an intramolecular fashion forming intermediate 50 which can be deprotonated by the base, with the resulting anion 51 undergoing E-selective elimination step to provide the final product 3.

To support the mechanistic hypothesis, especially the relevance of intramolecular and intermolecular proton transfers, we performed the reactions with both [1H] and [1D]-benzotriazole (2a and [D]2a) in MeCN and d9-MeCN, and measured the deuteration incorporation in the product (Scheme 2). The [1H] substrate 2a gave product 3 with 0% deuteration incorporation both in MeCN and d9-MeCN (isolated yields 95% and 87%). Trifluoropropenylation of [D]2a in MeCN resulted 19% deuteration incorporation, while in d9-MeCN the same reaction provided the product with 24% deuteration incorporation. In the presence of 1 equivalent of D2O, the deuteration incorporation increased about 15–20% independently from the substrate and the applied solvent, showing the possibility of intermolecular protonation. These results support that both H-atoms of trifluoropropenyl group of the product are dominantly derived from the reagent 1 through intramolecular proton transfer, but
intermolecular base assisted proton transfer could also operate, besides some minor solvent effect on the proton transfer.

In summary, we developed a novel methodology for the direct N-trifluoropropenylation of heterocyclic molecules with the use of a trifluoropropenyl iodonium salt. The reaction enables the stereoselective synthesis of trifluoromethyl enamines having the potential for further transformations and adds to the synthetic applicability of trifluoropropenyl iodonium species toward versatile nitrogen nucleophiles.

Acknowledgements

This research was funded by National Research, Development and Innovation Office (NKFIH, PD124592, KH130048); This work was completed in the ELTE Thematic Excellence Programme 2020 Supported by NKFIH – TKP2020-IKA-05. The authors thank the analytical measurements for László Bural and Tamás Gáti at Server Research Institute of Medicinal Chemistry. The authors thank for proofreading of this manuscript to Mr. Tyler J. Fulton at Caltech (Stoltz Lab).

Conflict of Interest

Keywords: enamines · iodonium salt · Michael addition · nitrogen heterocycles · trifluoromethyl

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The authors declare no conflict of interest.
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[16] For details see Supporting Information.

[17] The transformation of some additional heterocyclic systems was also unsuccessful. For details see Supporting Information.

Manuscript received: August 4, 2021
Accepted manuscript online: September 22, 2021
Version of record online: October 6, 2021