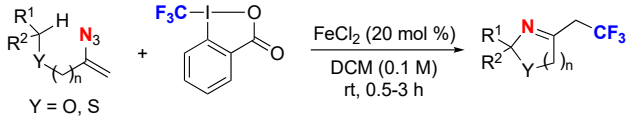
Syntheses of Trifluoroethylated *N*-Heterocycles from Vinyl Azides and Togni's Reagent Involving 1,n-Hydrogen-Atom Transfer Reactions

Steven Terhorst,[†] Deo Prakash Tiwari,[†] Daniela Meister,[†] Benedict Petran,[†] Kari Rissanen,[‡] and Carsten Bolm[†]*

[†] RWTH Aachen University, Institute of Organic Chemistry, Landoltweg 1, D-52074 Aachen, Germany

[‡] University of Jyvaskyla, Department of Chemistry, P.O. Box. 35, FI-40014 Jyväskylä, Finland

Supporting Information Placeholder



2,2,2-Trifluoroethyl-substituted 3-oxazolines, 3-thiazolines, and 5,6-dihydro-2*H*-1,3-oxazines have been obtained by reacting substituted vinyl azides with a combination of Togni's reagent and substoichiometric amounts of iron(II) chloride. Results of density functional theory (DFT) calculations support the proposed mechanism involving 1,n-Hydrogen-Atom Transfer (HAT) reactions.

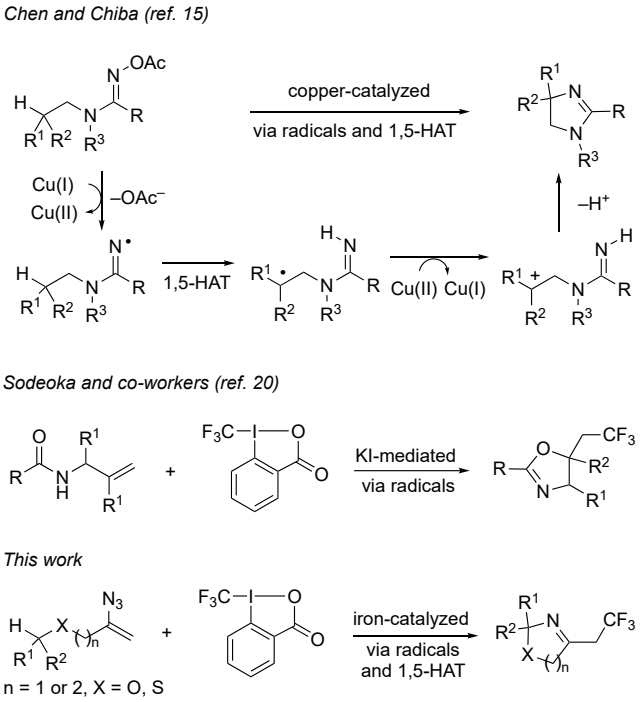
Nitrogen-containing heterocycles represent core structures of numerous materials, natural products, pharmaceuticals, and agrochemicals.[1–5] Among them, azolines are of particular importance.[6] Probably due to synthetic challenges 3-oxazolines are less explored compared to other compounds in this series.[7] A typical procedure for their preparation involves N-chlorination of the respective 1,3-oxazolidine followed by elimination of HCl upon treatment with base.[8]

Recent studies have shown that 1,n-Hydrogen-Atom Transfer (HAT) reactions can be very effective for synthesizing heterocycles.[9–14] This concept relies on the high reactivity of radicals which allows to selectively functionalize remote C–H bonds. For example, starting from amidoximes, Chen and Chiba generated amidinyl radicals by a redox-neutral copper catalysis, which provided dihydroimidazoles and quinazolines by 1,5-H shift (Scheme 1, top).[15] In 2017, Nevado and coworkers applied vinyl azides in such reactions leading to elaborated ketones when reacting with carboxylic acids as radical synthons.[16] Density functional theory (DFT) calculations suggested the formation of azide-derived imine radicals as key intermediates in the 1,5-H shift process.[17]

Fluorinated compounds are important as drugs and agrochemicals as fluoro substituents affect relevant properties such as lipophilicity, metabolic stability, and bioavailability.[4,18,19] Consequently, the introduction of trifluoromethyl groups has attracted much attention.[20] In the context of azoline chemistry, the trifluoromethylations of allylamides with Togni's reagent in the presence of alkali metal iodides leading to F_3C-containing 2-oxazolines described by Sodeoka and coworkers are noteworthy (Scheme 1, middle).[21]

In light of the aforementioned studies we wondered if such concepts could be combined allowing the preparation of 2,2,2-trifluoroethyl-substituted 3-oxazolines and related hetercycles.

Scheme 1. Previous Studies and Work Reported Here

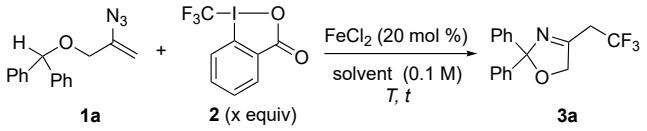


The success of this approach is documented here (Scheme 1, bottom).

For the initial proof-of-concept experiments and the subsequent optimization of the reaction conditions, 2-azidoallyl diphenylmethyl ether (**1a**) was selected as substrate, and Tog-

ni's trifluomethylating reagent **2** was activated by the addition of $FeCl_2$ (20 mol %). A short screening (Table 1) revealed that DCM, dichloroethane (DCE), 1,4-dioxane, and DMF were suitable solvents. The reaction temperature could be varied from 80 °C and ambient temperature with the latter being superior. Substituting $FeCl_2$ by the more commonly used CuI led to product formation as well (Table 1, entry 5). Finally, reacting **1a** with 2.5 equiv of **2** and 20 mol % of $FeCl_2$ in dry DCM at ambient temperature for 30 min provided 4-(2,2,2-trifluoroethyl)-substituted 3-oxazoline **3a** in 75% yield (Table 1, entry 8). Although an increase in yield of **3a** to 80% was observed when a combination of 3.5 equiv of **2** and 30 mol % of $FeCl_2$ was applied in DCM at 36 °C (Table 1, entry 6), the former conditions were considered satisfying for the subsequent substrate studies.

Table 1. Optimization Studies



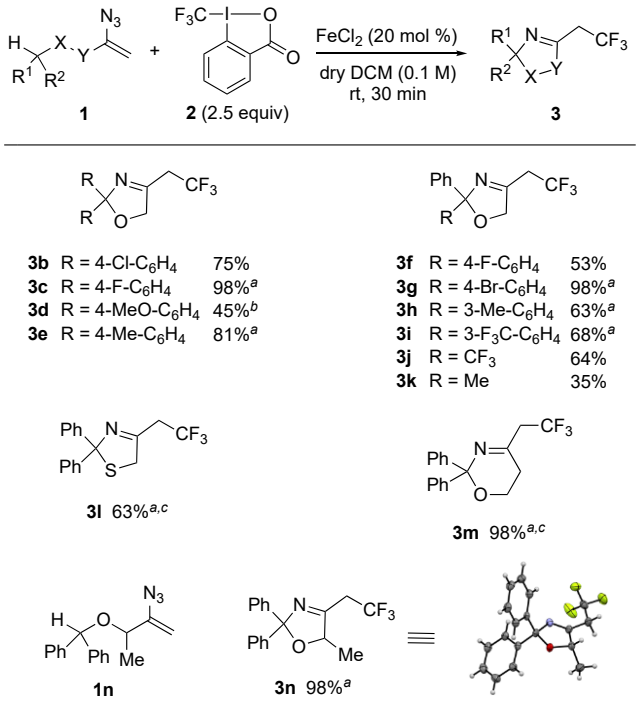
1a **2** (x equiv) **3a**

entry	solvent	**2** (equiv)	T (°C)	Time (h)	**3a** (%)
1	DCE	2.5	80	24	45
2	1,4-dioxane	2.5	80	24	55
3	1,4-dioxane	2.5	40	1	70
4	DCM	1.1	36	24	34
5[a]	DCM	1.5	36	24	33
6[b]	DCM	3.5	36	24	80
7	DMF	2.5	rt	0.5	73
8	DCM	2.5	rt	0.5	75

[a]Use of CuI (20 mol %) instead of $FeCl_2$. [b]Use of 30 mol % of $FeCl_2$.

Next, the substrate scope was evaluated (Scheme 2). In the first series, 2-azidoallyl diarylmethyl ethers (**1b-e**) with two identical 4-substituted aryl groups were applied. While the yields of the resulting 3-oxazolines with 4-chloro-, 4-fluoro-, and 4-methyl substituents (**3b**, **3c** and **3e**, respectively) were good (ranging from 75% to 98%), 4-methoxy-substituted product **3d** was isolated in only ca. 45% (containing significant amounts of unknown impurities). Hence, the electron-donating effect of the substituent appeared to hamper the formation of the heterocycle presumably by unduly radical or cation stabilization. The use of freshly prepared Togni's reagent proved beneficial. 2-Azidoallyl arylphenylmethyl ethers **1f-k** with different substituents on the aryl group showed analogous trends. The position of the aryl substituent was important as revealed by comparing the result of the cyclization of 3-substituted substrate **1h** with the one of its 4-substituted counterpart **1e**. Both starting materials led to the corresponding 3-oxazolines **3h** and **3e**, respectively, but for the latter product the yield was significanly higher (63% versus 81%). Also 2-azidoallyl 1-phenylalkyl ethers **1j** and **1k** cyclized illustrating that more alkyl substituents were tolerated. In this manner, 3-oxazolines **3j** and **3k** bearing trifluoromethyl and methyl groups, respectively, were obtained albeit in only moderate and low yield (64% and 35%). Probably, these substituents lowered the radical stability and reduced the rate of the 1,5-HAT.[22] Also thioether **1l** reacted affording 3-thiazoline **3l** in 63% yield. The moderate yield of **3l** could be due to a general sensitivity of such compounds matching earlier observations reported by Asinger and Offermanns.[23] Starting from 3-azido homoallyl ether **1m** and involving a 1,6-HAT, 5,6-dihydro-2*H*-1,3-oxazine **3m** was obtained in 98% yield (after 3 h of reaction time). Finally, ether **1n** with an additional methyl group at the oxygen-bearing carbon (as compared to **1a**) was applied which led to 3-oxazoline **3n** in 98% yield after only a few minutes. The molecular structure of this product was confirmed by single crystal X-ray structure analysis.[24,25]

Scheme 2. Substrate Scope



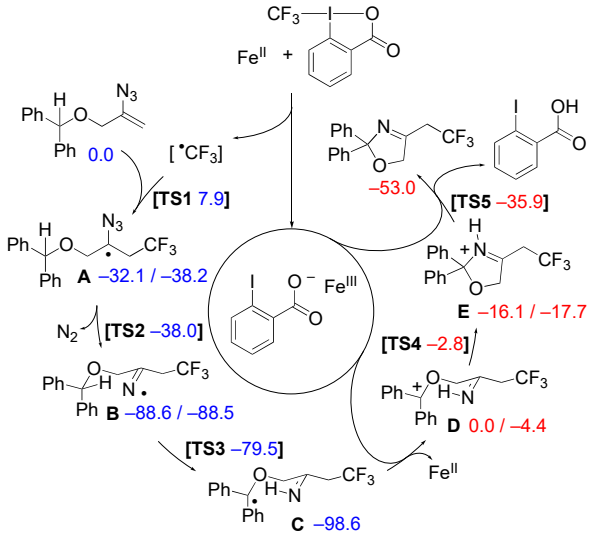
[a]Use of freshly prepared batch of Togni's reagent. [b]Containing unidentified impurities. [c]Reaction time of 3 h.

For evaluating the assumed intermediacy of radicals and a 1,5-HAT as well as the energy barriers of the underlying mechanism, the reaction path was investigated with density functional theory calculations using Gaussian09 version D.01.[26] All calculations were performed with the functional M06-2X and Grimme's D3 dispersion correction.[27,28] Optimizations were carried out with the def2-SVP basis set.[29] For final structures, a single point calculation with the def2-TZVP basis set and the IEFPCM solvent model for DCM was added.[29,30] A description of the computational details is provided in the Supporting Information. The energy values for barriers and intermediates are presented in Scheme 3.

Most intermediates contain two energetic values: the left one refers to the calculated minimum based on an IRC calculation after the previous transition state, the right value to the minimum calculated based on an IRC calculation of the following transition state. The difference in energy is caused by conformer changes. The transformation is initiated by the

reaction of Togni's reagent with the iron(II) salt generating a trifluoromethyl radical. This redox process also forms an iron(III) intermediate and 2-iodobenzoate.[31] The trifluoromethyl radical then attacks the 2-azido allyl fragment at the double bond with a barrier of 7.9 kcal/mol and an energy gain of 32.1 kcal/mol as represented in intermediate **A**. The radical is located next to the azidyl moiety leading to the release of nitrogen and formation of an iminyl radical, giving intermediate **B**.[32] This step is almost barrierless and leads to an energy gain of 50.4 kcal/mol. The following step is the 1,n-HAT via a 6-membered or 7-membered transition state, respectively, forming an imino group and a carbon-centered radical. For the 6-membered system studied here, the step requires 9.0 kcal/mol and leads to an energy gain of 10.1 kcal/mol. Next, intermediate **C** is oxidized by the iron(III)-complex. This pathway is described aside from the previously presented pathway because the lack of one electron renders both pathways incomparable. Therefore, compound **D** is set to 0.0 kcal/mol. A conformational change leads to an energy gain of –4.4 kcal/mol. The ring forming transition state requires only 1.6 kcal/mol. Compound **E** was difficult to optimize, and the energy values given here correspond to two different optimization strategies. Furthermore**,** **E** also corresponds to transition state **TS5** in which the deprotonation by iodobenzoate takes place. The final product corresponds to both minima of the TS, meaning compound **3a** and iodobenzcarboxylic acid (see Supporting Information, Fig. S8). In all cases the energy barriers are low leading to a gain of energy. Hence, both proposed mechanisms are regarded as plausible pathways.

Scheme 3. Plausible Mechanism with Calculated Energy Barriers. The Two Energy Values for a Structure Refer to Different Conformers of the Respective Compound, Related to the Respective Previous (Left Number) or Following (Right Number) Transition State



In summary, by using an iron(II) salt we generated trifluoromethyl radicals from Togni's reagent and allowed them to react with substituted vinyl azides. The newly generated iminyl radicals undergo 1,n-HAT reactions. Subsequent redox steps lead to heterocycles, which are difficult to prepare by other means. The proposed reaction pathway was supported by results from DFT calculations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General experimental procedure, list of unsuitable substrates, computational details, analytical data including NMR spectra (PDF)

Accession Codes

CCDC 1983428 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

*E-mail: Carsten.Bolm@oc.rwth-aachen.de

ORCID

Steven Terhorst: 0000-0002-2103-8716

Kari Rissanen: 0000-0002-7282-8419

Carsten Bolm: 0000-0001-9415-9917

Notes

The authors declare no competing financial interest.

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