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

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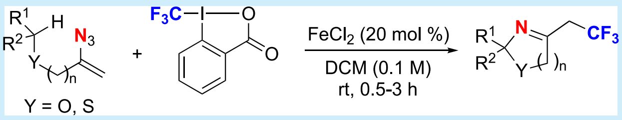
**ABSTRACT:** 2,2,2-Trifluoroethyl-substituted 3-oxazolines, 3-thiazolines, and 5,6-dihydro-2*H*-1,3-oxazines have been obtained by reacting substituted vinyl azides with a combination of Togni's reagent and substoichiometric amounts of iron(II) chloride. The results of density functional theory calculations support the proposed mechanism involving 1,*n*-hydrogen-atom transfer 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 have been 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]

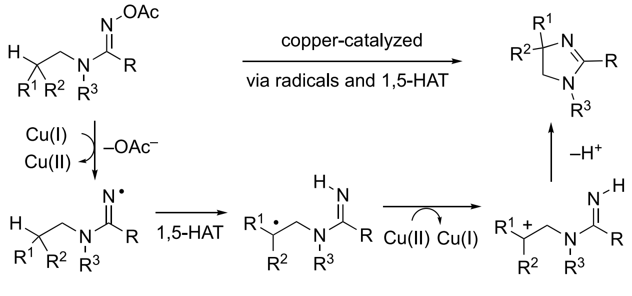
Recent studies have shown that 1,*n*-hydrogen-atom transfer (HAT) reactions can be very effective for synthesizing heterocycles.[9−14] This concept relies on the high reactivity of radicals that allows the selective functionalization of remote C−H bonds. For example, starting from amidoximes, Chen and 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 co-workers applied vinyl azides in such reactions leading to elaborated ketones upon reaction g 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 a great deal of 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 co-workers are noteworthy (Scheme 1, middle).[21]

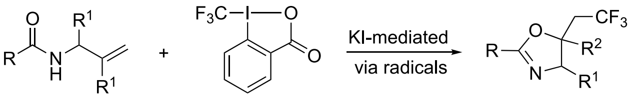
In light of the aforementioned studies, we wondered if such concepts could be combined allowing the preparation of 2,2,2-trifluoroethyl-substituted 3-oxazolines and related heterocycles.

**Scheme 1. Previous Studies and Work Reported Here**

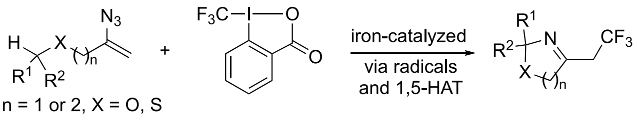
*Chen and Chiba (ref. 15)*



*Sodeoka and co-workers (ref. 20)*



*This work*



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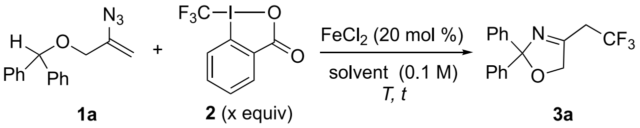
The success of this approach is documented here (Scheme 1, bottom).

For the initial proof-of-concept experiments and the subsequent optimization of the reaction conditions, 2-azidoallyl diphenylmethyl ether (**1a**) was selected as the substrate, and Togni'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 to ambient temperature, with the latter being superior. Substituting $FeCl_2$ by the more commonly used CuI also led to product formation (Table 1, entry 5). Finally, reacting **1a** with 2.5 equiv of **2** and 20 mol % $FeCl_2$ 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 the yield of **3a** to 80% was observed when a combination of 3.5 equiv of **2** and 30 mol % $FeCl_2$ was applied in DCM at 36 °C (Table 1, entry 6), the former conditions were considered satisfying for the subsequent substrate studies.

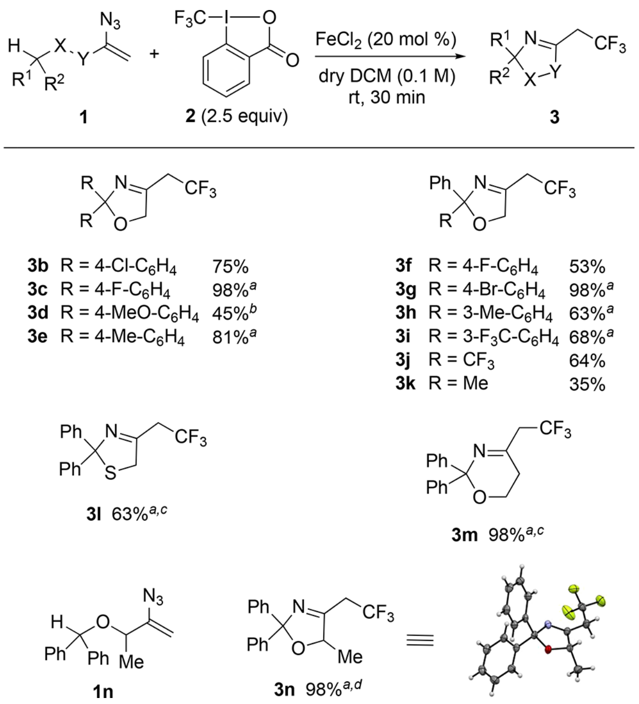
**Table 1. Optimization Studies**



| 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] With CuI (20 mol %) instead of $FeCl_2$. [b] With 30 mol % of $FeCl_2$.

**Scheme 2. Substrate Scope**



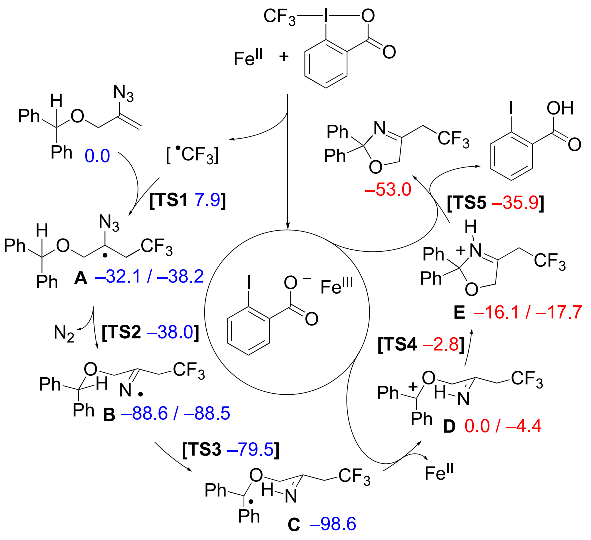
[a] With a freshly prepared batch of Togni's reagent. [b] Containing unidentified impurities. [c] Reaction time of 3 h. [d] For the X-ray crystal structure of **3n** shown at the right: The thermal displacement parameters are shown at the 50% probability level.

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 ∼45% yield (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 to be 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 that 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% vs 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 yields (64% and 35%, respectively). Probably, these substituents decreased the radical stability and the rate of 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 reaction for 3 h). 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]

To evaluate 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 DFT 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, and 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,

**Scheme 3. Plausible Mechanism with Calculated Energy Barriers**[a]



[a]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.

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 six- or seven-membered transition state, forming an imino group and a carbon-centered radical. For the six-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 Figure S8). In all cases, the energy barriers are low leading to a gain of energy. Hence, both proposed mechanisms are regarded as plausible pathways.

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 at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01566.

> General experimental procedure, list of unsuitable substrates, computational details, analytical data, including NMR spectra, and X-ray crystal data (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.

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### Notes

The authors declare no competing financial interest.

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