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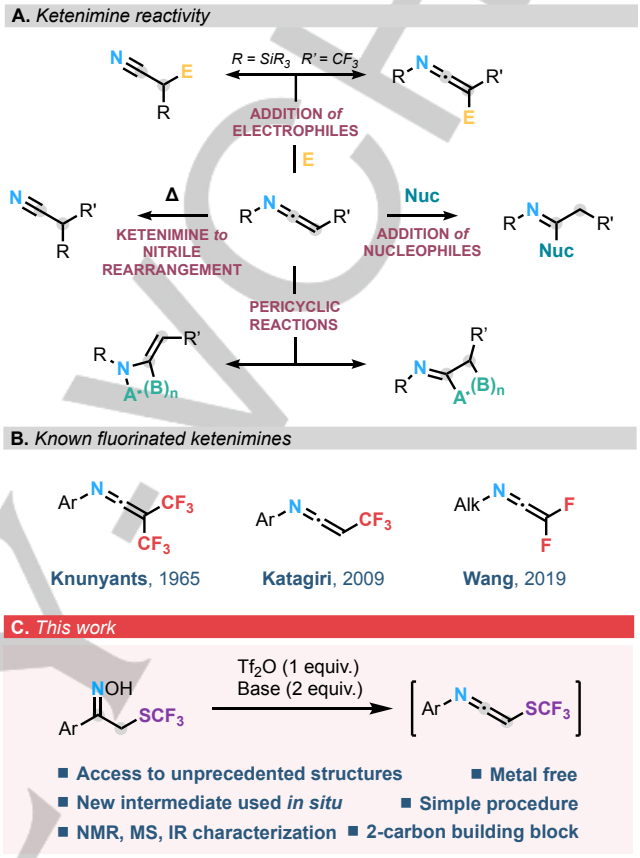
# Synthesis and use of trifluoromethylthiolated ketenimines

Thomas Guérin,[a] Nadiia V. Pikun,[b] Ryutaro Morioka,[c] Armen Panossian,[a] Gilles Hanquet*[a] and Frédéric R. Leroux*[a]

**Abstract:** The synthesis of trifluoromethylthiolated ketenimines is herein described. They are easily synthesized from the corresponding α-trifluoromethylthiolated oximes upon activation with triflic anhydride and a base. The presumed nitrilium ion resulting from the Beckmann rearrangement is deprotonated to lead to the key intermediate, whose stability brought by the fluorinated substituent was unforeseeable. The reaction of these new building blocks with a variety of nucleophiles affords a vast array of cyclic and acyclic products bearing the valuable $SCF_3$ moiety.

Decades of chemical research have shown that the fluorine atom and the fluorine-containing motifs profoundly impact the structure, reactivity and function of organic and inorganic molecules.[1] Fluorine-containing compounds are nowadays synthesized in pharmaceuticals, agrochemicals, polymers and electronic research on a routine basis. As an example, it is well established that fluorine atom(s) and/or fluoroalkyl group(s) can lead to many beneficial effects in a biologically active molecule.[2, 3] In the past decade, fluorine chemistry greatly expanded with insightful contributions from research groups aiming at developing novel synthetic methods and reagents for the regio- and stereoselective introduction of fluorine or fluorine-containing groups into molecular scaffolds. Indeed, the fluorine chemistry field is still developing at a rapid pace and one of the current challenges is the search for Emergent Fluorinated Substituents (EFS) that would not only give new reactivity and functions to man-made molecules but also eventually lead to improved biological activity or even a novel mode of action. Such EFS are based on carbon (e.g. $CHF_2$), on carbon linked to a heteroatom e.g. ($O\text{-}CF_3$, $S\text{-}CF_3$), or based on sulfur (e.g. $SF_5$). From an industrial perspective, it should be noted that $CHF_2$, $OCF_3$, $SF_5$ and $SCF_3$ groups are quite rarely encountered and there is an urgent need to develop academic as well as industrial viable approaches towards scaffolds substituted by these EFS.[4]

The ways of introducing the EFSs are important as they are clearly cost-determining in a chosen synthetic route. In the early stage of drug development, the late-stage introduction of fluorinated moieties in advanced synthetic intermediates is highly desirable and various methods are now available; however, this late-stage introduction is tedious and relies on expensive




**Scheme 1.** Context of the present work.

reagents.[5] On the other hand, most fluorinated compounds are often produced on an industrial scale from simple starting building blocks.[2a-d] Ketenimines are very versatile intermediates, capable of undergoing a variety of reactions such as nucleophilic additions and pericyclic reactions (**Scheme 1**, A).[6] Among them fluorinated ketenimines are understudied, most likely as only few synthetic methods are available to prepare them. As a matter of fact since the seminal work of Knunyants in 1965 on bis(trifluoromethyl)arylketenimines, [7] only the trifluoromethyl and bis(difluoro) derivatives by, respectively, Katagiri in 2009[8] and Wang in 2019[9] were reported (**Scheme 1**, B). The $SCF_3$ substituent has witnessed in recent years a huge interest and different methods for its direct introduction by means of electrophilic, nucleophilic as well as radical sources have been assessed.[10] Therefore, we decided to try to access a ketenimine bearing the $SCF_3$ moiety to further complete the range of fluorinated ketenimines available (**Scheme 1**, C). Access to ketenimine **1a** was envisioned to be possible through the Beckmann rearrangement of ketoxime **2a**. Treatment of **2a** with one equivalent of triflic anhydride in toluene, in the presence of two equivalents of Hünig's base led to a stable intermediate whose mass in GC-MS matched **1a**'s. The reaction was highly

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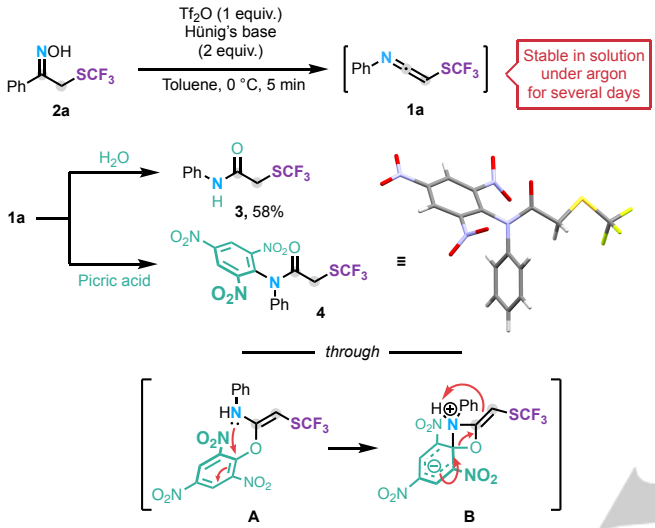
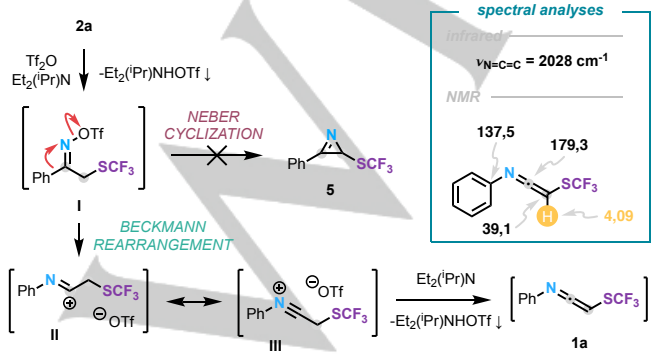
exothermic and, if carried out under air, the major product was amide **3** (**Scheme 2**) resulting from water addition onto the electrophilic sp carbon of **1a**. All signs seemed to be strongly indicating of the effective formation of the desired ketenimine **1a**. Furthermore, the reaction of **1a** with picric acid led to amide **4**, presumably through Meisenheimer complex **B** produced after intramolecular cyclization of imidate **A** (**Scheme 2**). A solution of **1a** under argon turned out to be stable for several days as indicated by GC-MS monitoring, yet any attempt to isolate it failed, leading to amide **3**.



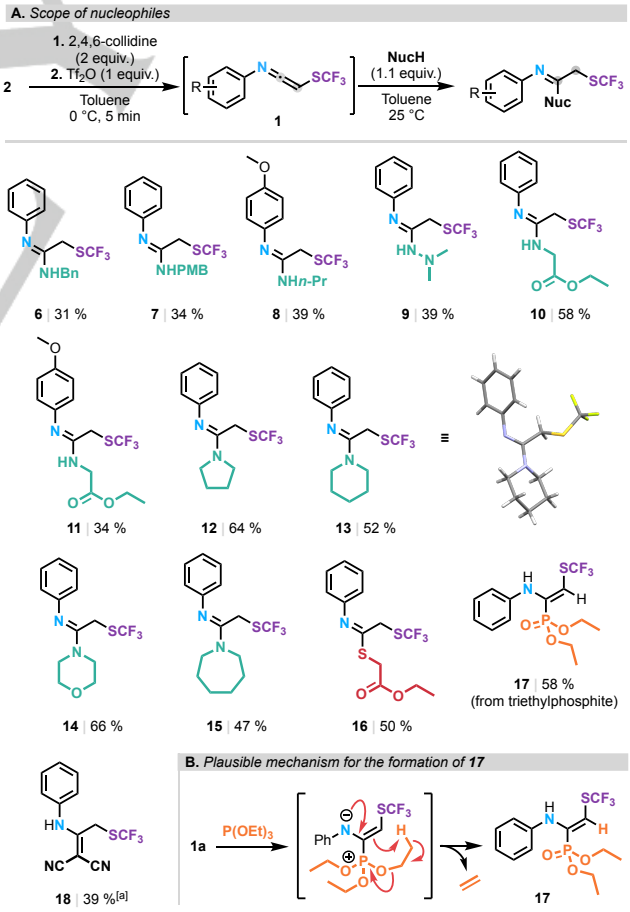

**Scheme 2.** Synthesis of **1a** and its reaction with oxygen-centered nucleophiles.

Though rather inclined to believe in the ketenimine nature of **1a**, we had to further characterize it. Although less coherent with the formation of **3** and **4**, we could not totally exclude **1a** to be actually azirine **5** produced by a Neber rearrangement, and isomassic to **1a**. NMR leaned on the ketenimine side as the upfield proton was likely vinylic, despite its adjacent carbon being very shielded. Nevertheless, infrared analysis cleared all remaining doubt by showing a clear band at 2028 $cm^{-1}$, characteristic of the stretching band $\nu_{N=C=C}$.[6a] Thus we are proposing the mechanism to be as follows (**Scheme 3**): first the oxime is converted into its triflic ether derivative **I**. **I** then undergoes a Beckmann rearrangement, the phenyl group migrates onto the nitrogen as the triflate anion departs, to form **II**, a mesomeric form of nitrilium **III**. **II**, or **III** is then deprotonated by the remaining equivalent of base to form ketenimine **1a**.




**Scheme 3.** Spectral data of **1a** ($^{13}C$ NMR shifts in blue and $^{1}H$ in yellow, in ppm, in $C_6D_6$) and a plausible mechanism for its formation.

Next, we submitted various amines to the reaction with intermediate **1a**. We were delighted to observe a very clean GC chromatogram in each occurrence with only the expected product obtained in the reaction. After a rapid screening of bases and oxime activators (see supporting information) we studied the scope of the reaction (**Scheme 4**). Primary amines gave modest yields (products **6**-**8**, **10**, **11**), comparable to the one obtained with *N*,*N*-dimethylhydrazine (product **9**). Secondary amines gave the corresponding amidines with better yields (**12**-**15**), that we attributed to their increased nucleophilicity. Modifying the aryl moiety for a *p*-anisyl group did not really affect the outcome of the reaction (**8**, **11**) and we thus preferred to focus on the scope of nucleophiles. To our great pleasure thiols and phosphites react with **1a** to give respectively thioimidate **16** and α-aminophosphonate **17** (**Scheme 4**, A). In this last example, we believe the product forms *via* elimination of ethylene (**Scheme 4**, B).[11] We were also pleased to see that malonitrile could add to **1a** to form acrylonitrile **18**. Several substrates, however, did not lead to the expected products. Indole left the ketenimine **1a** unreacted while diethylphosphite led to a complex mixture. Unlike picric acid (see **Scheme 2**), aliphatic alcohols did not afford the corresponding imidates.




**Scheme 4.** Scope of the nucleophiles affording acyclic products. [a] 3 equiv. of base were used.

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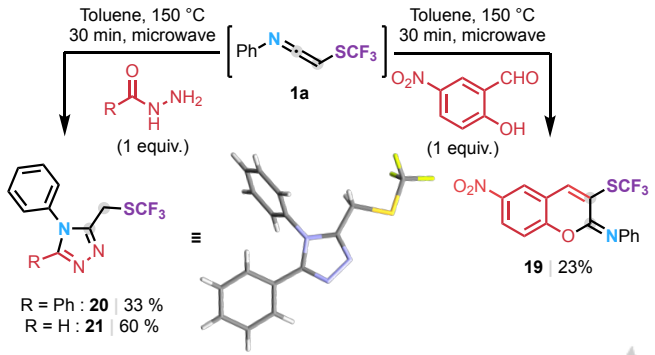
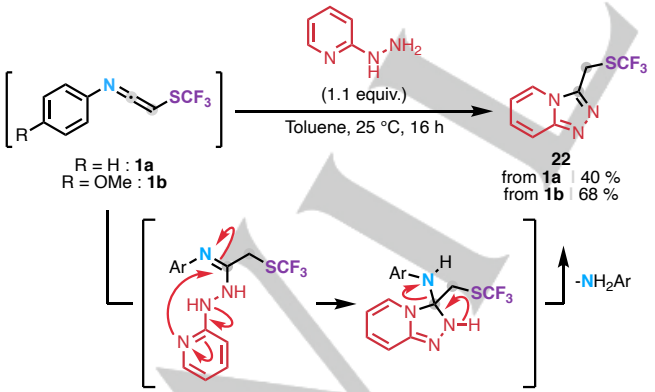
We then envisioned using ambiphilic reagents, bearing both nucleophilic and electrophilic moieties in order to access the corresponding heterocyclic compounds after *N*- or *C*-cyclization.[6c] Our first attempts implied diverse salicylaldehydes derivatives. Although the reaction at room temperature was irreproducible, microwave conditions gave consistent results. Yet the isolated yield turned out to be quite poor, indeed product **19** was obtained in only 23 % yield (**Scheme 5**). However, this methodology would provide the only alternative to access 3-trifluoromethylthio coumarins (after hydrolysis) to the one described in the literature, using expensive $AgSCF_3$.[12] **1a** could react similarly with benzoic or formic hydrazides to form the corresponding 1,2,4-triazoles **20** and **21** resulting from *N*-cyclization.



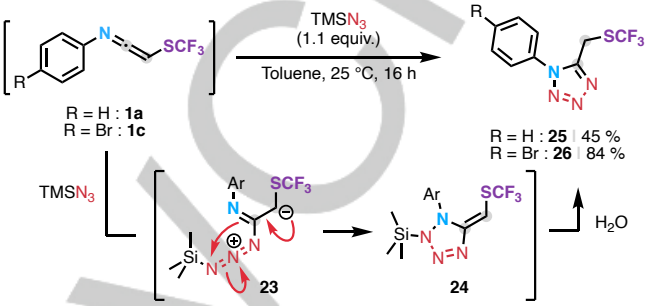

**Scheme 5.** Reaction with ambiphilic reagents.

Having established the feasibility to access heterocyclic compounds through *N*- or *C*-cyclization, we wondered whether the aniline group resulting from the 1,2-phenyl shift could be eliminated by the condensation of a second nucleophilic position on the coupling partner. Thus, we used 2-hydrazinopyridine and could indeed isolate [1,2,4]triazolo[4,3-*a*]pyridine **22** in 68 % yield (**Scheme 6**) from ketenimine **1b**.




**Scheme 6.** Reaction with a bisnucleophilic reagent.

All of the aforementioned nucleophiles being well-defined electron-rich centers, we wondered if the reaction occurs with a masked nucleophile. For this we used trimethylsilyl azide in the hope to perform an azidotrimethylsilylation across one double bond of the ketenimine. Interestingly, the resulting product did not display the characteristic azide stretching band at ca. 2100 $cm^{-1}$ in infrared spectroscopy. Our product bearing a $CH_2SCF_3$ moiety according to $^1H$ and $^{13}C$ NMR, we believe that the distal nitrogen of $TMSN_3$ acts as any other nucleophile and attacks the sp carbon of **1** to form **23** and, after *N*-cyclization, intermediate **24** that rearomatizes through protodesilylation in the presence of water to give the corresponding 4*H*-tetrazoles **25** and **26** (**Scheme 7**).




**Scheme 7.** Reaction with $TMSN_3$ and cyclization of the presumed imidoyl azide intermediate.

In conclusion, we have developed a simple method to access trifluoromethylthiolated ketenimines. We could show that these unprecedented structures react under metal-free conditions with a variety of nucleophiles to form acyclic trifluoromethylthiolated products. When an electrophilic moiety is present on the nucleophilic reagent, trifluoromethylthiolated heterocycles can be synthesized, allowing for rapid structure diversification through the addition of a C-C-$SCF_3$ unit. The reactivity of the ketenimines in other types of reactions is currently being explored in our laboratory. These original intermediates should likely prove to be useful in the synthesis of bioactive compounds.

## Acknowledgements

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**Keywords:** ketenimines • heterocycles • rearrangement • organofluorine compounds • trifluoromethylthioethers

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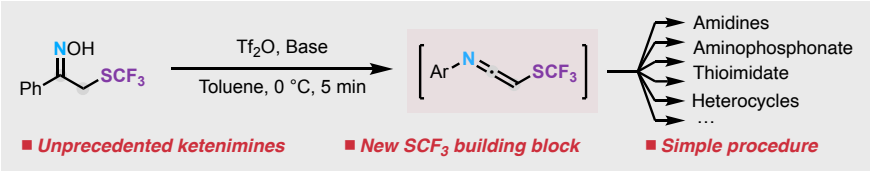


*Thomas Guérin, Nadiia V. Pikun, Ryutaro Morioka, Armen Panossian, Gilles Hanquet* and Frédéric R. Leroux**
***Page No. – Page No.***

**Synthesis and use of trifluoromethylthiolated ketenimines**

We herein disclose the first synthesis of trifluoromethylthiolated ketenimines. They are quickly and easily formed from α-trifluoromethylthiolated oximes through a Beckmann rearrangement and deprotonation of the nitrilium intermediate. Their interest is exemplified by many reactions, such as the direct addition of several *C*-, *O*-, *N*-, *S*- and *P*-centered nucleophiles as well as their incorporation into valuable heterocycles through cascade reactions.