A Straightforward Entry to γ-Trifluoromethylated Allenamides and Their Synthetic Applications

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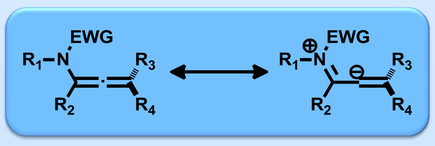
1 Allenamides : Introduction

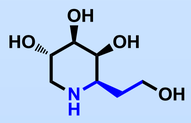
Allenamides : highly polarized allenes and stable surrogates of allenamines

Allenamides are stable surrogates of the more labile and highly sensitive allenamines. They display a unique balance between stability and reactivity, mostly due to the delocalization of the nitrogen lone pair into both the allene and the electron-withdrawing group. The strong polarization of the allene renders transformation involving addition of electrophiles or nucleophiles to allenamides highly regioselectives, which is generally difficult starting from simple allenes.

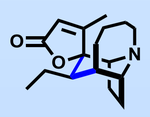


Use in organic synthesis [1]

Allenamides have proven themselves to be very useflul building blocks in organic synthesis,They have been shown to perform well in a broad range of transformations including addition reactions, cycloadditions and metal-catalyzed cyclizations and they also have been used in natural product synthesis as demonstrated with the two examples below.



1-deoxy-D-galactohomonojirimycine



parvineostemonine

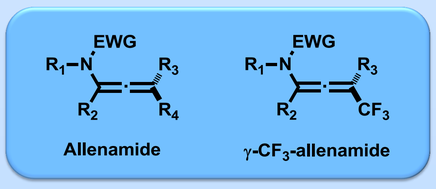
2 Tfrifluoromethylated Allenamides

The development of new methods for the synthesis of allenamides and the use of these building blocks in organic synthesis have been extremely studied and are still active fields of research. However, little attention has been paid to the development of new classes of allenamides, despite their important synthetic potential.

In this context, we were interested in the development of a new class of allenamides, γ-trifluoromethylated allenamides.

Indeed, the introduction of a trifluoromethyl group into allenamides should:
- deeply modify the properties of these molecules : lipophilicity, bioavailability, metabolic stability or even recognition towards receptors, [2]
- allow to modulate their reactivity,
- extend the range of their synthetic applications.

Moreover, this additional trifluoromethyl group could be incorporated in products resulting from the transformations ef these push-pull allenes.

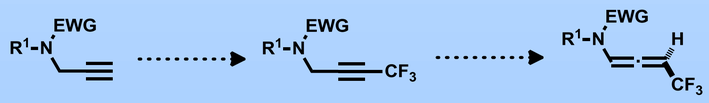


3 Synthesis of Trifluoromethylated Allenamides

Our Strategy: base-induced isomerization of trifluoromethylated alkynes

Among the numerous methods developed for the synthesis of allenamides, the isomerization of propargylic amides under basic conditions is still one of the most efficient one.

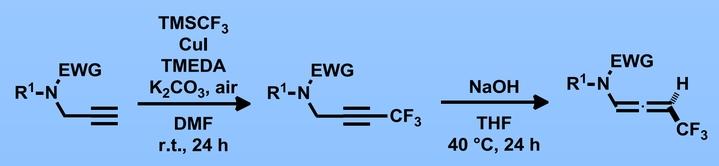
Capitalizing on our experience for the synthesis of trifluoromethylated alkynes, [3] we envisioned the two-step sequence shown below for the synthesis of γ-trifluoromethylated allenamides.



We present here a two-step procedure based on the use of simple and readily available propargylic amides as starting materials to perform the trifluoromethylation of the alkyne followed by a sodium hydroxyde-induced isomerization of the obtained trifluoromethylated propargylic amides. [4]

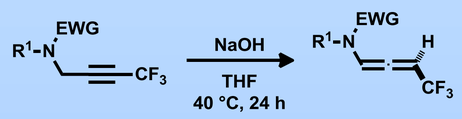
Optimized conditions

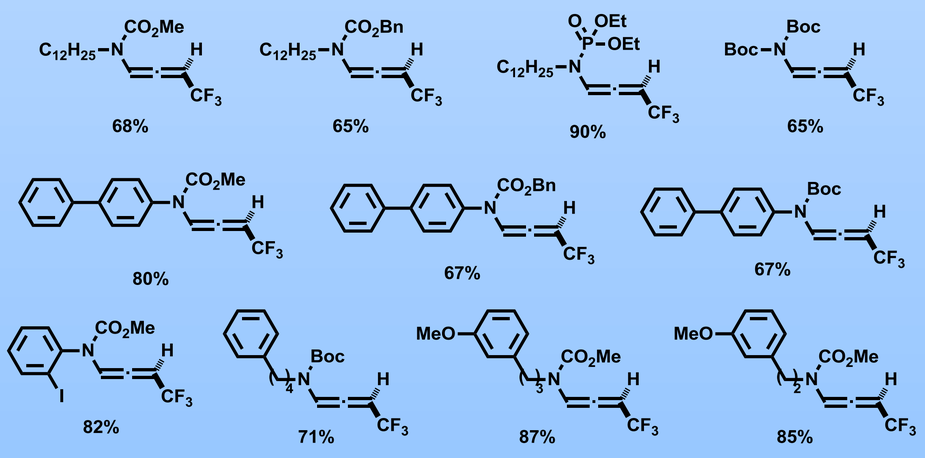
After optimization of the reaction conditions for the base-induced isomerization, we found that sodium hydroxyde in THF at 40°C is able to promote a clean and selective isomerization without competitive formation of the corresponding ynamide. The conditions used for the first trifluoromethylation step are those previously reported for the synthesis of trifluoromethylated alkynes. [3]



4 Scope of the Reaction

The scope of the reaction was evaluated using various propargylic carbamates and phosphoramidates bearing aromatic and aliphatic chains using our optimized conditions.



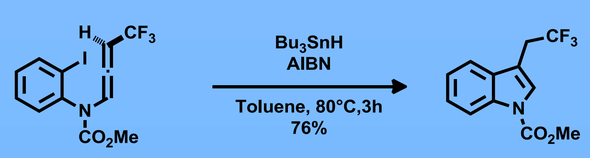


The reaction performs in good to excellent yields and tolerates the presence of various carbamates as well as diethylphosphoramidate as protecting groups for the nitrogen atom. The trifluoromethylation/isomerization sequence is compatible with electron-rich aromatics as well as iodoaromatics. The isomerization step is however limited to the preparation of disubstituted allenamides.

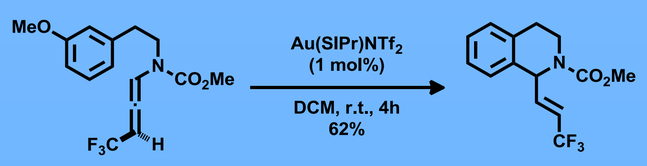
5 Synthesis of Heterocycles

After developing an efficient process for the synthesis of γ-trifluoromethylated allenamides, we next turned our attention on the reactivity of these building blocks, and in particular on their use for the synthesis of fluoroalkylated nitrogen-containing heterocycles.

Using results previously reported by Hsung, [5] we were able to perform the radical cyclization of a γ-trifluoromethylated allenamide to obtain the corresponding indole with 76% yield.



Next, we envisioned the use of gold catalysis for the cyclization of γ-trifluoromethylated allenamides. We were not able to obtain 5- or 7-membered ring using this strategy. However, it was a successfull appraoch for the synthesis of a tetrahydroisoquinoleine derivative as shown below.



This brief study of the reactivity of γ-trifluoromethylated allenamides clearly demonstrates their potential as building blocks for organic synthesis and notably for the synthesis of fluoroalkylated nitrogen heterocycles.

6 Conclusion and Perspectives

In conclusion, we have developed an efficient entry to γ-trifluoromethylated allenamides, a new class of push-pull allenes.

This two-step sequence performs under relatively mild conditions and presents various advantages :

- ✓ Operational simplicity
- ✓ Fairly general and broad scope
- ✓ Readily available starting materials

Perspectives : the reactivity of this new class of allenamides should be studied more deeply to gain knowledge about their behavior in a broader range of transformations such as cycloadditions or addition reactions. In addition, the synthesis of other fluoroalkylated nitrogen heterocycles should be studied.

1. (a) L.-L. Wei, H. Xiong, R. P. Hsung, *Acc. Chem. Res.* **2003**, *36*, 773. (b) T. Lu, Z. Lu, Z. X. Ma, Y. Zhang, R. P. Hsung, *Chem. Rev.* **2013**, *113*, 4862. (c) X. Yang, F. D. Toste, *Chem. Sci.* **2016**, *7*, 2653. (d) Y. Wang, P. Zhang, Y. Liu, F. Xia, J. Zhang, *Chem. Sci.* **2015**, *6*, 5564. (e) H. Faustino, I. Varela, J. L. Mascarenas, F. Lopez, *Chem. Sci.* **2015**, *6*, 2903. (f) C. Hernández-Díaz, E. Rubio, J. M. González, *Eur. J. Org. Chem.* **2016**, 265. (g) Y. Wang, P. Zhang, D. Qian, J. Zhang, *Angew. Chem. Int. Ed.* **2015**, *54*, 14849. (h) Achmatowicz, M.; Hegedus, L. S. *J. Org. Chem*. **2004**, *69*, 2229. (i) Antoline, J.E.; Hsung, R. P.; Huang, J.; Song, Z.; Li, G. *Org. Lett*. **2007**, *9*, 1275.
2 Purser, S.; Moore, P. R.; Swallow, S.; *Gouverneur*, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
3 C. Tresse, C. Guissart, S. Schweizer, Y. Bouhoute, A.-C. Chany, M.-L. Goddard, N. Blanchard, G. Evano, *Adv. Synth. Catal.* **2014**, *356*, 2051.
4 C. Guissart, A. Dolbois, C. Tresse, S. Saint-Auret, G. Evano, N. Blanchard, *Synlett* **2016**, *27*, 2575.
5 Shen, L.; Hsung, R. P. *Org. Lett.* **2005**, *7*, 775.