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

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1 Allenamides : Introduction

Allenamides are highly polarized allenes and stable surrogates of allenes. 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 allenes highly regioselective, which is generally difficult starting from simple allenes.

2 Trifluoromethylated Allenamides

The development of new methods for the synthesis of allamides and the use of these building blocks in organic synthesis has been extremely studied and are still active fields of research. However, little attention has been paid to the development of new classes of allamides, 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,
- 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 of 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 ones.

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 allynes followed by a sodium hydroxide-induced isomerization of the obtained trifluoromethylated propargylic amides.

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

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 fluoroketohydrazide-containing heterocycles.

Using results previously reported by Huang, we were able to perform the radical cyclization of a γ-trifluoromethylated allenamide to obtain the corresponding indole with 70% 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 successful approach for the synthesis of a tetrahydroquinazoline 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 fluoroketohydrazide-containing heterocycles.

4 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 allamides should be studied more deeply to gain knowledge about their behavior in a broader range of transformations or cycloaditions or addition reactions. In addition, the synthesis of other fluoroketohydrazide nitrogen heterocycles should be studied.

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References