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Direct access to CF_3-propargyl amines and conversion to difluoromethyl imines

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Abstract—Trifluoromethyl aldimines reacted with acetylides in toluene at −78 °C to provide propargyl amines in good yields. From a chiral trifluoromethyl aldimine, the propargyl amines were obtained with excellent diastereoselectivities (de >98%). Trifluoromethyl propargyl amines could be further converted into difluoromethyl imines under basic conditions.

Propargyl alcohols and propargyl amines can serve as important building blocks for organic synthesis.[1] While propargyl alcohols can be prepared through a variety of transformations, reliable methods that provide direct access to propargyl amines are far fewer. Classical carbanion addition to *N*-alkyl aldimines prescribes the use of Lewis acidic additives for activating the aldimine substrate. By contrast, reactions of activated aldimines proceed without necessary additional activation.[1]

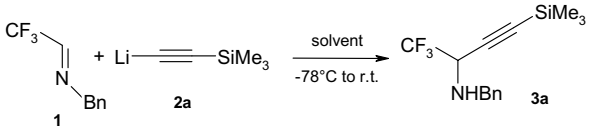
Despite the potential interest of fluorinated compounds,[2] the preparation of propargyl trifluoromethyl amines has not been intensively studied so far.

The addition of trimethylsilylacetylenes to trifluoromethyl iminium ions, generated from corresponding oxazolidines[3] or aminal[4] in the presence of Lewis acids, has been described. Another preparation has also been reported by addition of acetylides on more reactive CF_3-imines prepared from trifluoromethylated pyruvate.[5] However, to our knowledge the addition of acetylides on trifluoromethylated *N*-aryl and *N*-alkyl aldimines has not been reported so far. Herein, we describe the addition of acetylenic reagents on aldimines derived from fluoral.

First, the reaction has been explored with the *N*-benzyl-aldimine **1** and the lithium acetylide **2a** of trimethylsilylacetylene (1.2 equiv), generated in situ with *n*-BuLi (1.2 equiv), in usual various solvents. The reaction was carried out at −78 °C for 1 h, and then temperature was allowed to rise to room temperature. Results are summarized in Table 1.

In THF, the reaction led to a complex mixture with only traces of the propargyl amine **3a**. Maintaining the reaction medium at −50 °C or at 0 °C did not improve the addition reaction. When the reaction was conducted in ether, the propargyl trifluoromethyl amine **3a** was isolated in 64% yield, together with 25% of starting material and 11% of an unknown side product. The best selectivity was obtained in toluene, and the propargyl amine **3a** could be isolated in high yield (83%). The scope of this process towards starting aldimines **1**, **4** and acetylenic reagents, was then examined under improved reaction conditions (Table 2). In all cases, reactions were clean, and yields were good to excellent (71–95%).[6]

Table 1. Addition of trimethylsilyl acetylide on the *N*-benzyl-imine **1**[6]



Entry	Solvent	Yield (%)
1	THF	Traces
2	Ether	64
3	Toluene	83

Keywords: Trifluoromethyl aldimines; CF_3-propargyl amines; Difluoromethyl imines; Difluoromethyl propargyl amines.
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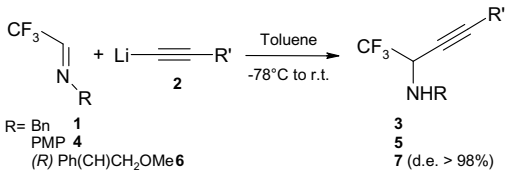
Table 2. Addition reaction of acetylides to aldimines[6]



Entry	Imine	2 R′	Products	Yields (%)
1	**1**	**2a** $SiMe_3$	**3a**	83
2	**1**	**2b** Bu	**3b**	94
3	**1**	**2c** Ph	**3c**	87
4	**4**	**2a**	**5a**	84
5	**4**	**2b**	**5b**	71
6	**4**	**2c**	**5c**	78
7	**6**	**2a**	**7a**	90
8	**6**	**2b**	**7b**	77
9	**6**	**2c**	**7c**	95

Recently, we have reported that using the imine **6** (prepared from the hemiacetal of fluoral and the methyl ether of the (*R*)-phenylglycinol as chiral *N*-substituent) in the vinylation reaction[7] and in the allylation reaction[8] yielded products with remarkable de. We then investigated the propargylation reaction from this chiral trifluoromethyl aldimine **6**. Under the optimized conditions, different trifluoromethyl homopropargyl amines **7** were obtained in good yield, and in excellent diastereoselectivities (de >98%). In all cases only one diastereoisomer was detected in ^{1}H and ^{19}F NMR of the crude.

Since the vinylation of the aldimine **6** provided the allyl amine with creation of an *R* centre confirmed by X-ray,[7] we assumed that propargyl amines had also the *R* configuration with the hypothesis of a chelation controlled mechanism with an attack opposite to the phenyl group (Fig. 1).

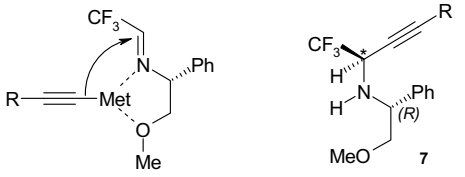
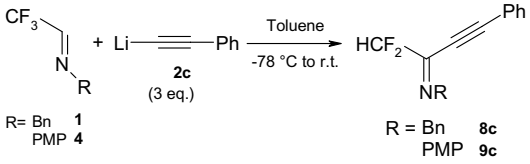


Figure 1.

An interesting result emerged during investigations on these propargylations. When the reaction was performed with the aldimine **1** and an excess of acetylide **2c** (3 equiv) in toluene under the above described conditions, the propargyl amine **3c** was accompanied with 60% of difluoromethyl imine **8c**. Similarly, the aldimine



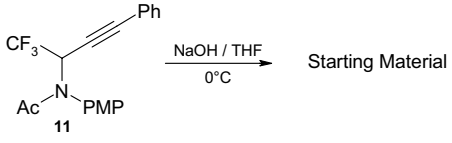
Scheme 1.

4 provided the difluoromethyl imine **9c** (60%). The amount of difluoromethyl imines could not be improved by changing conditions of the acetylide generation (Na, MgX salts) (Scheme 1).

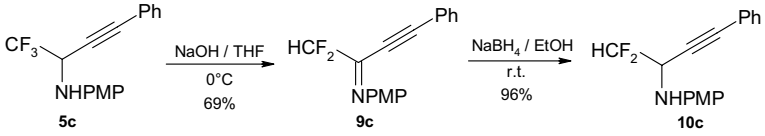
Like CF_3 substituted compounds, difluoromethyl containing compounds could exhibit interesting specific biological activities.[9] However, the difluoromethyl starting materials are less available than trifluoromethyl parent compounds.

Assuming that the imines **8**, **9** could result from a deprotonation of **3** or **5**, the access to CF_2H imines has then been attempted from CF_3-propargyl amines **3** and **5** under basic conditions (BuLi, LDA, LiHMDS, etc.). With amine **3**, no reaction occurred or decomposition was observed. With amine **5** the best result into difluoromethyl imine **9** could be obtained with 1.2 equiv of NaOH in THF (Scheme 2). With the amine **5c**, a total conversion was observed leading to the imine derivative **9c**, which was obtained in good yield. The preliminary studies to reduce the new difluoromethyl imine **9c** have been attempted with $NaBH_4$ in EtOH. Difluoropropargyl amine **10c** was obtained in good yield (Scheme 2).

Despite our efforts, the mechanism of the conversion of **5** or **4** to **9** could not be yet elucidated. Generation of a CF_2 moiety strongly suggests a deprotonation at the C_1 carbon, probably favoured by the presence of an alkynyl substituent,[10] followed by a loss of fluoride anion, then tautomerization. However, the reaction requires only 1.2 equiv of base, which normally should deprotonate the amine first. The fact that *N*-acyl amine **11** remained unchanged with NaOH, led us to believe that the NH function could be involved in the latter process (Scheme 3).



Scheme 3.



Scheme 2.

In summary, this letter describes a new use of aldimines derived from fluoral for an access to various fluorinated nitrogen containing compounds.[11] Trifluoromethyl propargyl amines were prepared from trifluoromethyl aldimines and various acetylides, and were obtained in good yield. Some of these trifluoromethyl amines are precursors of interesting difluoromethyl imines, which can further be easily reduced into difluoromethyl propargyl amines.

Acknowledgments

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6. Experimental procedure: to a solution of trimethylsilylacetylene (1.2 mmol, 170 μL) in toluene (10 mL) was dropped at −78 °C, *n*-BuLi (1.2 equiv, 1.6 N). After 1 h, the imine **1** (1.0 mmol, 187 mg) diluted in toluene (2 mL) was added slowly at this temperature and warmed at room temperature. Then, the mixture was hydrolyzed with a solution of saturated NH_4Cl (20 mL). The aqueous phase was extracted with ether (2×10 mL) and the combined organic layers dried on $MgSO_4$, were filtered and evaporated. The crude product was purified on silica gel to afford the propargyl amine **3a** (236 mg, 83%).
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10. Parallel studies have shown that such a deprotonation does not occur from corresponding allyl amine.
11. For a review on CF_3-aldimines and derivatives: Bégué, J.-P.; Bonnet-Delpon, D.; Crousse, B.; Legros, J. *Chem. Soc. Rev.*, submitted for publication.