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Synthesis of α-Trifluoromethylated Nitrogen Heterocycles

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The syntheses of various α-trifluoromethylated nitrogen heterocycles have been achieved from readily available α-(trifluoromethyl)homoallylamine through a ring-closing metathesis.

Introduction

Nitrogen heterocyclic moieties are structural elements of many alkaloidic natural products and drug candidates,[1] as, for example, solenopsine, balanol, motuporamine, or pinidine.[2] Among them, the piperidine ring continues to be extensively used in pharmaceutical research. Indeed, recently it has been reported that there were over 12 000 compounds affording piperidine entities mentioned in clinical or preclinal studies during a recent 10-year period.[3]

On the other hand, the last years have shown a tremendous increase of new organofluorine compounds[4] due to the unique properties exhibited by such substrates.[5] Among them, trifluoromethyl-substituted molecules constitute a particular class because of the specific properties, such as the high lipophilicity, brought by the CF_3 moiety. Recently, such molecules found outstanding applications in the pharmaceutical field,[6] as illustrated by Efavirenz[7] (anti-HIV) and Celecoxib[8] (antiarthritic), two recent drugs used in the treatment of human diseases.

In our program on the synthesis of potential new drugs bearing a fluoroalkyl group, we focused our interest on an easy access to α-trifluoromethylated nitrogen heterocyclic compounds not only for their potential intrinsic bioactivity but also as potential fluorinated synthons for further functionalization.

Results and Discussion

The synthesis of substituted piperidines has been largely described in the literature through many different strategies.[9] For our part, we have recently described an easy access to α-(trifluoromethyl) homoallylamine from fluoral hemiketal[10] and it appears to us that this product should be an interesting starting material to achieve the synthesis of α-trifluoromethylated nitrogen heterocyclic compounds. Furthermore, recent works from Brigaud et al.[11] and Enders et al.[12] demonstrated the possibility to obtain this trifluoromethylated precursor in a pure enantiomeric form, allowing the extrapolation of the strategy presented below to a stereoselective one.

In this preliminary work, we want to validate the racemic route to α-trifluoromethylated nitrogen heterocylic compounds, according to the retrosynthetic analysis given in Sheme 1, in which we have chosen, as a key step, a ring closure metathesis (RCM), a well-known strategy for the synthesis of piperidine rings.[13] The starting point of this convergent synthesis was the preparation of the

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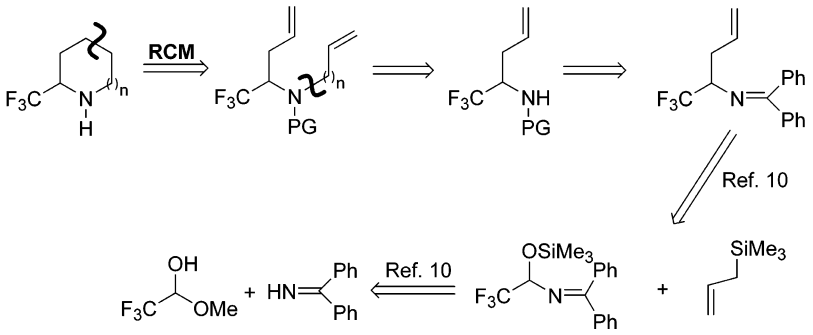
SCHEME 1. Retrosynthesis of α-Trifluoromethylated Nitrogen Heterocyles



SCHEME 2. Synthesis of α-Trifluoromethylated Homoallylamine

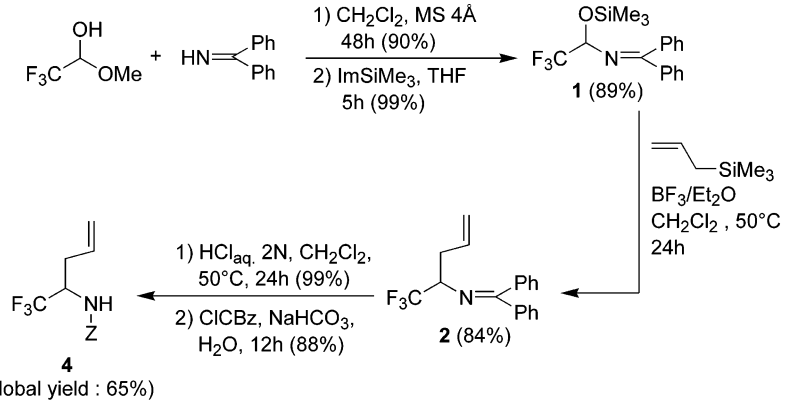
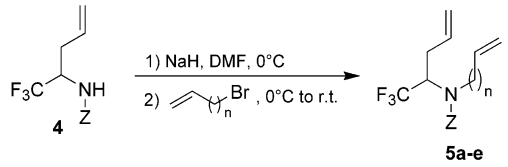


TABLE 1. Alkylation of 4



entry	*n*	**5**[a] (%)
1	1	**5a** (80)
2	2	**5b** (0)
3	3	**5c** (56)
4	4	**5d** (70)
5	6	**5e** (71)

[a] Isolated yield.

trifluoromethylated homoallylamine **4**. Following our previous results,[10] the preparation was optimized as summarized in Scheme 2.

This sequence can be easily scaled up to produce starting material in large quantities. For instance, 20 g of **4** have been produced in one batch.

The protected homoallylamine **4** was then alkylated with various *ω*-alkenyl bromides (Table 1).

Because of the low nucleophilicity of **4**, prior deprotonation in DMF was needed to achieve alkylation. Good yields were generally obtained except with 4-bromo-but-1-ene, for which *β*-elimination matched substitution.

These precursors were then engaged in a RCM in the presence of one of the two commercially available Grubbs catalysts (Scheme 3, Table 2).

RCM was efficient to obtain medium-sized heterocycles (six- and eight-membered), even with 1% of catalyst **6**

SCHEME 3. Grubbs Catalysts

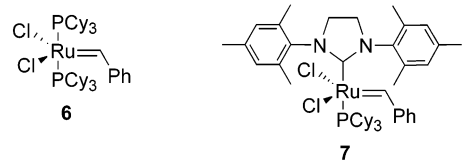
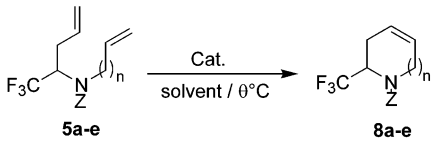


TABLE 2. RCM from 4



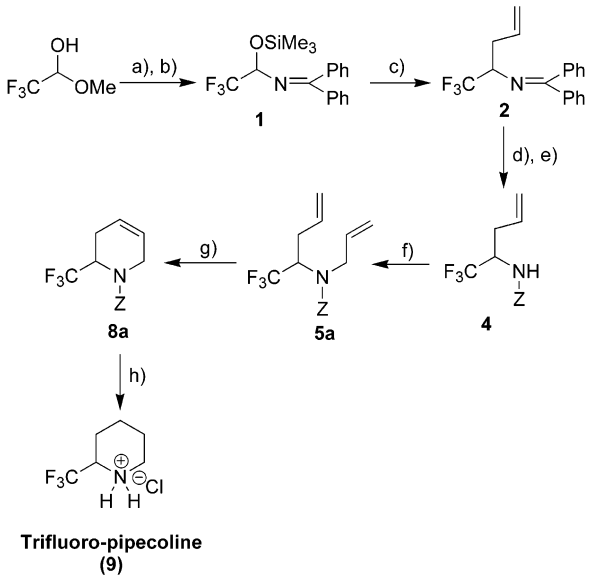
entry	**5** (mol L^{-1})	n	catalyst	solvent/*T* (°C)	time	**8**[a] (%)
1	**5a** (0.1)	1	**6** (5%)	CH_2Cl_2/50	5 h	**8a** (66)
2	**5a** (0.1)	1	**6** (5%)	CH_2Cl_2/RT	5 h	**8a** (98)
3	**5a** (0.1)	1	**6** (1%)	CH_2Cl_2/RT	5 h	**8a** (91)
4	**5c** (0.1)	3	**6** (1%)	CH_2Cl_2/RT	5 h	**8c** (80)
5	**5d** (0.1)	4	**6** (1%)	CH_2Cl_2/RT	1 d	**8d** (0)
6	**5d** (0.1)	4	**6** (1%)	Toluene/110	1 d	**8d** (0)
7	**5d** (0.001)	4	**6** (10%)	CH_2Cl_2/RT	5 d	**8d** (0)
8	**5d** (0.001)	4	**7** (10%)	CH_2Cl_2/RT	2 d	**8d** (40)[b]
9	**5e** (0.001)	6	**6** (10%)	CH_2Cl_2/RT	5 d	**8e** (0)
10	**5e** (0.001)	6	**7** (10%)	CH_2Cl_2/RT	7 d	**8e** (5)[b]

[a] Isolated yield. [b] Crude yield determined by ^{19}F NMR with internal standard ($PhOCF_3$).

(entries 1−4). Nevertheless, the access to higher homologues was relatively disappointing (entries 5−10), even under usual high-dilution conditions.

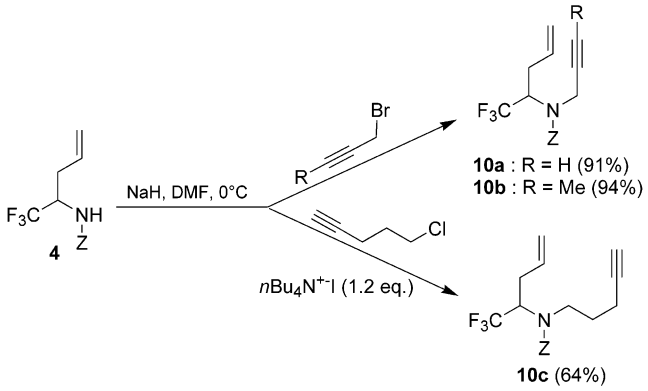
However, this strategy provided an efficient synthesis of dehydropiperidines, which was our first objective on our route toward bioactive compounds. As an illustration of this method, the synthesis of trifluoropipecoline,[14] the

SCHEME 4. Synthesis of Trifluoropipecoline[a]



[a] Reagents and conditions: (a) benzophenone imine, MS 4 Å, CH_2Cl_2, rt, 48 h (90%); (b) $ImSiMe_3$, THF, rt, 5 h (99%); (c) allylTMS, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 50 °C, 24 h (84%); (d) 2 N HCl_{aq}, CH_2Cl_2, 50 °C, 24 h (99%); (e) ClCbz, $NaHCO_3$, H_2O, rt, 12 h (88%); (f) NaH, allylBr, DMF, 3 h (80%); (g) **6** (1% mol), CH_2Cl_2, rt, 5 h (91%); (h) (i) Pd/C, H_2, EtOH, rt, 24 h, (ii) HCl (99% from **8a**).

SCHEME 5. Synthesis of Enynes 10

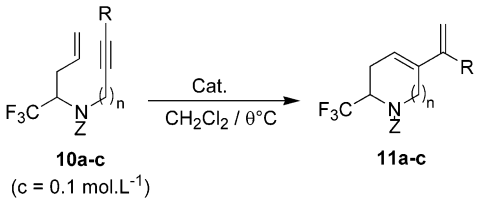


fluorinated analogue of a well-known bioactive substance,[15] has been achieved with a global yield of 47% from fluoral hemiketal. (Scheme 4).

To explore the scope of this strategy toward nitrogen heterocyclic cores as synthons for further syntheses, the formation of dienes was examined through enyne metathesis. For this purpose, various enynes were synthesized from **4**. (Scheme 5).

These enynes in hand, the optimal conditions were determined to achieve RCM with satisfactory yields (Table 3).

TABLE 3. RCM of Enynes



entry	**10**	catalyst	*T* (°C)	time (days)	**11** (%)
1	**10a**	**6** (1%)	rt	1	**11a** (8)
2	**10a**	**6** (5%)	50	1	**11a** (40)
3	**10a**	**7** (5%)	50	1	**11a** (44)
4	**10b**	**6** (1%)	rt	1	**11b** (6)
5	**10b**	**7** (1%)	rt	3	**11b** (60)
6	**10b**	**6** (5%)	50	1	**11b** (70)
7	**10b**	**7** (5%)	50	1	**11b** (75)
8	**10c**	**7** (5%)	50	1	**11c** (0)

Because of a lower reactivity of **10**, compared to **5**, heating at 50 °C was required to obtain good results. The use of catalyst **7**, known to be more efficient than **6**, did not significantly increase the yields. It can be also noticed that, according to the literature,[16] terminal enynes gave lower yields than internal enynes (entries 2, 3 and 6, 7). As mentioned previously, larger cycles could not be obtained (entry 8).

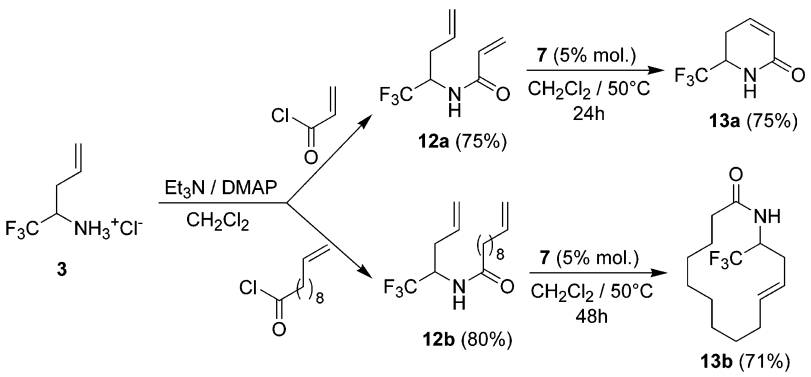
Finally, the extension of this strategy to the synthesis of α-trifluoromethylated lactam was then envisaged (Scheme 6).

In this case, only catalyst **7** gave rise to cyclization. It can be also noticed that macrolactam was also obtained with good yields.

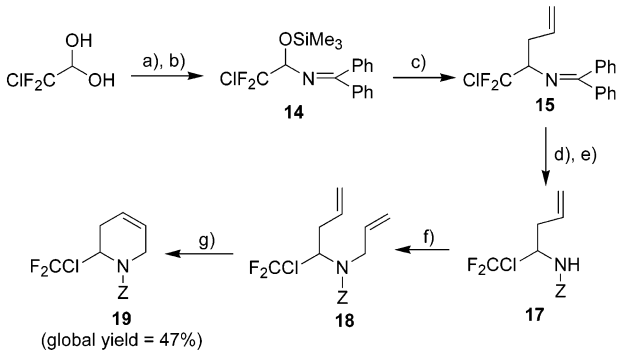
Thus, such routes to various trifluoromethylated nitrogen heterocycles seem to be valuable on a synthetic point of view, since they start from the same α-(trifluoromethyl)homoallylamine **3**.

This method also allowed access to other fluorinated compounds starting from other fluorinated aldehydes, as illustrated in Scheme 7 by the synthesis of α-(chlorodifluoromethyl)-dehydropiperidine. In conclusion, we have described a direct and efficient synthesis of α-fluoroalky-

SCHEME 6 α-Trifluoromethylated Lactam Synthesis



SCHEME 7. Synthesis of 19[a]



[a] Reagents and conditions: (a) benzophenone imine, MS 4 Å, CH_2Cl_2, rt, 48 h (84%); (b) $ImSiMe_3$, THF, rt, 5h (94%); (c) allylTMS, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 50 °C, 24 h (94%); (d) 2 N HCl_{aq}, CH_2Cl_2, 50 °C, 24 h (99%); (e) ClCbz, $NaHCO_3$, H_2O, rt, 12 h (88%); (f) NaH, allylBr, DMF, 3 h (80%); (g) **6** (1% mol), CH_2Cl_2, rt, 5h (91%).

lated nitrogen heterocycles from commercial or readily available fluoroaldehydes. The obtained compounds present valuable synthetic potentials for further syntheses. The use of such synthons in multistep preparations of fluorinated bioactive compounds is under progress in our laboratory and will be published in due course.

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Supporting Information Available: Typical procedures and physical data of compounds **1**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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