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Synthesis of new difluoroalkyl propargylic ketones and their use for the preparation of fluorinated heterocycles

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ABSTRACT

Synthetic methodology studies are reported towards the preparation of new propargylic ketones with CF_2R side chains. These molecules are used for the synthesis of various types of five- or six-membered heterocycles with difluoroalkyl side chains.

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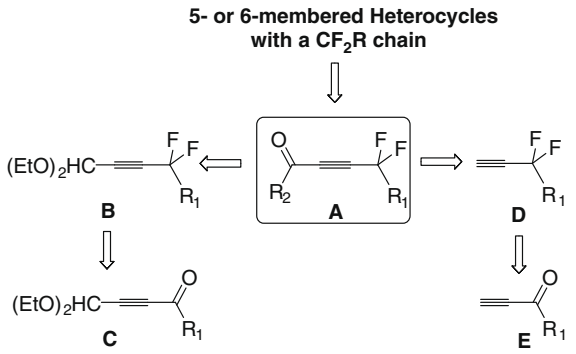
It is well established that the introduction of fluorine in organic molecules strongly modifies their physical, chemical, and biological activities and this has been already of much use in fluorobiorganic chemistry.[1] Moreover, heterocycles are widely employed in bioorganic and medicinal chemistry.[2] Therefore, it is of much interest to develop flexible routes to new fluorinated heterocycles. It is well known that propargylic ketones can be used as a versatile starting material in the preparation of various types of heterocycles.[3] In this context, it appears important to develop easy and efficient access to propargylic ketones which are fluorinated on the side chains.

As part of our research program in fluorine chemistry, we recently published the synthesis of new pyrimidines containing a difluoromethyl group in benzylic position, starting from propargylic ketones with a CHF_2 side chain.[4] In order to extend our research to the preparation of pyrimidines with new difluorinated alkyl side chains (CF_2R), we became interested in the synthesis and uses of the corresponding fluorinated propargylic intermediates. Therefore, the purpose of this publication is to report the synthesis of new difluoroalkyl propargylic ketones (type **A**) and their use as precursors, not only of pyrimidines but also for other six- and five-membered heterocycles.

Based on our retrosynthetic analysis for type **A** difluorinated propargylic ketones, two different routes can be easily envisaged (Scheme 1).

The first one has strong analogies with the strategy developed earlier for the preparation of molecules with the difluoromethyl side chain.[4] It involves gemdifluorination of a type **C** monoprotected dicarbonyl compound,[5] followed by introduction of the required R_2 group in a few steps, starting from the masked aldehyde. The second pathway, using a different disconnection, involves the gemdifluorinated intermediates **D**, easily accessible from propargylic



Scheme 1. Two different routes to the difluorinated propargylic ketones **A**.

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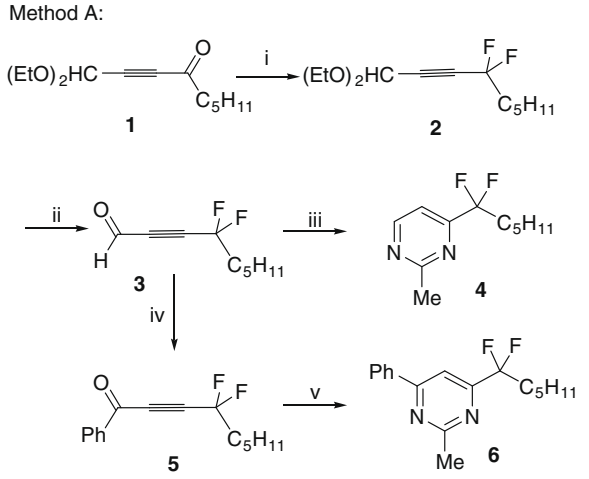
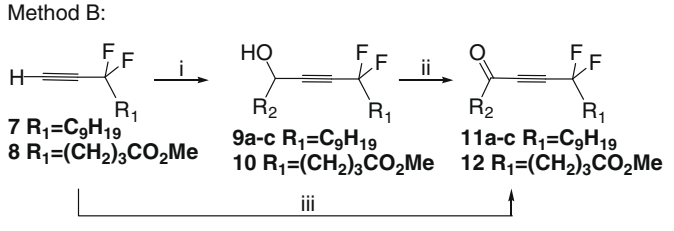
ketones **E**.[6] Then a direct, or stepwise, introduction of the COR_2 groups should afford the desired intermediates **A**. Following these strategies, the molecular diversity can be introduced at both the beginning (for R_1 group) and a later stage (in the case of R_2 group).

We will describe our results for the preparation of the desired fluorinated intermediates by using each of these two methods.

- Our first attempts (by using method A) were about starting from the known[5] gemdifluorinated propargylic acetal **2** (Scheme 2). After deacetalization with formic acid,[7] the crude aldehyde **3** was reacted with acetamidine hydrochloride in the presence of Na_2CO_3, thus leading to the pyrimidine **4** in a modest 35% overall yield from **2**. In order to introduce a phenyl group as a model for the R_2 substituent, a phenyllithium addition was performed on **3**, affording alcohol in low yield (23%). This was followed by an IBX oxidation to give fluoride **5** in 15% overall yield from **3**. This propargylic ketone afforded, after reaction with acetamidine, the expected pyrimidine **6** in 61% yield. Even if these reactions were not fully optimized, the overall yields were not satisfactory and the diversification, obtained through the **3** to **6** sequence, might become an issue when considering various types of functionalized R_2 substituents.
- We then checked the second strategy (method B). In that case, the difluorinated propargylic ketones **11a–c** and **12** should be obtained from the known propargylic intermediates **7**,[5] and **8**,[6] which are already gemdifluorinated. By using various coupling methods, it should be possible to obtain the required propargylic ketones **11a–c** and **12** in one, or two, step(s) from simple reagents such as aldehydes, ketones, and acylchlorides.



Scheme 2. Reagents and conditions: (i) DAST (2.2 equiv) neat under Ar, 55 °C, 5 h (90%); (ii) HCO_2H/CH_2Cl_2, reflux 5.5 h (70%); (iii) MeC(NH)NH_2·HCl (1.2 equiv), Na_2CO_3 (2.4 equiv), CH_3CN, reflux overnight (51%); (iv) (1) PhLi (1.5 equiv), THF, −70 °C to −40 °C; 1 h (23%) then IBX (1.2 equiv), DMSO/THF, 35 °C, 5 h (67%) (v) MeC(NH)NH_2·HCl (1.2 equiv), Na_2CO_3 (2.4 equiv), CH_3CN, reflux overnight (61%).



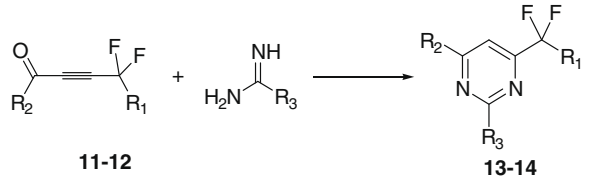
Scheme 3. Reagents and conditions: (i) (1) *n*-BuLi (1.1 equiv), under Ar, THF, −78 °C, 1 h then (2) R_2CHO (1.2 equiv), −78 °C to rt; (ii) IBX (1.2 equiv), DMSO/THF, 35 °C, 5 h. The yields are given in Table 1.

The two-step sequence was checked first and the reaction of the lithium derivatives from **7** and **8** with aldehydes gave the corresponding alcohols **9a–c** and **10**. After oxidation with IBX, these intermediates afforded the desired difluorinated propargylic ketones **11a–c** and **12**. This sequence gave fair (for **12**) to good overall yields in the case of ynones **11** (Table 1). On the contrary, the one-step sequence to prepare ketones from **7** proved to be less satisfactory. The palladium-mediated coupling (ex. Sonogashira) with acyl chlorides was ineffective. On the other hand, the use of Weinreb amine derivatives was possible but the best we could achieve was a 50% conversion rate and a 31% yield. Furthermore, the reaction conditions must be carefully controlled in order to avoid in situ addition of the *N*-methyl-methoxyamine on the ynone formed during the synthesis.[8] Therefore, the two-step path from **7** and **8** is more efficient and it has been used with different alkyl and aryl substituents R_2.

The first application of these new intermediates was to prepare six-membered difluorinated heterocycles, and more specifically pyrimidines in order to complete our previous work.[4] The reaction of the fluorinated propargylic ketones **11a–c** and **12** with various amidine/guanidine derivatives afforded the desired pyrimidines in very good yields as indicated in Scheme 4 and Table 2.

Table 1
Propargylic ketones **11** and **12** produced via Scheme 3

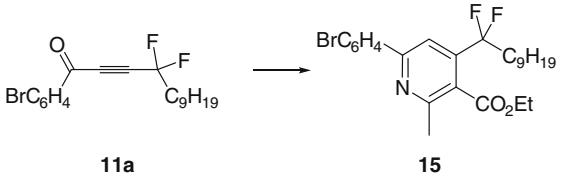
Entry	Compound	R_1	R_2	Yield step 1 (%)	Yield step 2 (%)
1	**11a**	n-C_9H_{19}	p-BrC_6H_4	88	93
2	**11b**	n-C_9H_{19}	Me	80	79
3	**11c**	n-C_9H_{19}	t-$BuPh_2SiO(CH_2)_4$	70	82
4	**12**	$(CH_2)_3CO_2Me$	p-BrC_6H_4	54	73



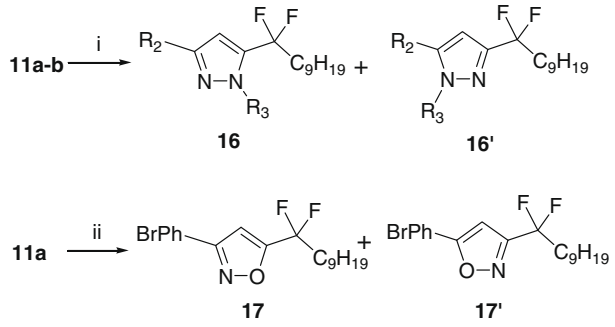
Scheme 4. Reagents and conditions: Na_2CO_3, CH_3CN, reflux. The yields are given in Table 2.

Table 2
Pyrimidines **13** and **14** produced via Scheme 4

Entry	Compound	R_1	R_2	R_3	Yield (%)
1	**13aw**	n-C_9H_{19}	p-BrC_6H_4	Me	75
2	**13ax**	n-C_9H_{19}	p-BrC_6H_4	Ph	95
3	**13ay**	n-C_9H_{19}	p-BrC_6H_4	NH_2	82
4	**13az**	n-C_9H_{19}	p-BrC_6H_4	NHAc	67
5	**13bw**	n-C_9H_{19}	Me	Me	84
6	**13cw**	n-C_9H_{19}	$(CH_2)_4OSiPh_2tBu$	Me	82
7	**14**	$(CH_2)_3CO_2Me$	p-BrC_6H_4	Me	81



Scheme 5. Reagents and conditions: ethyl acetoacetate (1.7 equiv), NH_4OAc (17 equiv), EtOH, rt overnight then I_2.



Scheme 6. Reagents and conditions: (i) R_3NHNH_2 (1.4 equiv), EtOH, 1 h, rt or reflux; (ii) NH_2OH (1 equiv), EtOH, reflux, 24 h (47%).

Table 3
Pyrazoles **16**, **16′**, and **17** produced via Scheme 6

Entry	Compound	R_2	R_3	Ratio **16**:**16′**	Yield (%)
1	**16aw**	*p*-BrC_6H_4	Me	100:0	73
2	**16ax** + **16′ax**	*p*-BrC_6H_4	Ph	6:94	64
3	**16bx** + **16′bx**	Me	Ph	8:92	83

Moreover, starting from **11a**, the Bohlmann–Rahtz reaction[9,10] afforded the pyridine **(15)** with a 70% yield (Scheme 5).

Another complementary aspect was to study the reactivity of our new fluorinated propargylic ketones as intermediates for the synthesis of five-membered heterocycles, such as pyrazoles[11] and isoxazoles[12] with a difluoroalkyl side chain. In both cases, we used literature methodologies and an interesting aspect of these reactions was to determine if the fluorine atoms have any effect on the regioselectivity of the cyclocondensation processes. The results are given in Scheme 6 and Table 3.

The reaction of methylhydrazine with gemdifluoro-ynone **11a** afforded exclusively the desired pyrazole **16aw** while on reaction with phenyl hydrazine, a 6/94 ratio of **16ax** and **16′ax** was obtained. The same reaction was observed in the case of ynone **11b**. These results are fully consistent with the regioselectivities observed in the literature for nonfluorinated ynones. Therefore for the synthesis of pyrazoles, the fluorine atoms on the side chain have no significant effect on the regioselectivity of the cyclocondensation.

When it comes to the formation of isoxazoles, a slightly different result is obtained. Indeed, according to the literature,[12] the reaction with nonfluorinated ynones (in ethanol at reflux) should lead to the regioisomers corresponding to **17** only, whereas adding pyridine should afford a (1:3) mixture of isomers **17** and **17′**. However, experiments showed that starting from gemdifluoro-ynone **11a**, the same (1:3) mixture of **17** and **17′** is obtained in both cases, with a 47% yield. Therefore, starting from these fluorinated intermediates, the formation of isoxazole is proved to be possible but the presence of pyridine has no influence on the regioselectivity of the cyclocondensation.

In conclusion, we have established simple and efficient routes to the new gemdifluoro-ynones **11a–c** and **12**. Starting from these versatile intermediates, it was possible to prepare efficiently several types of six- and five-membered heteroaromatic systems with difluoroalkyl side chains. These methodologies should be of much use for the preparation of new chemical libraries of bioactive fluorinated heterocyclic compounds.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, spectral and analytical data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.116.

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