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Environmentally Compatible Access to α -Trifluoromethylseleno-enones.

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Dedicated to Antonio Togni on the occasion of his 65th birthday and retirement.

α -trifluoromethylselenolated enones constitute valuable building-blocks for further synthesis of innovative fluorinated compounds. Herein, we described an easy access to such compounds in "green conditions" through a Morita-Baylis-Hillman like reaction. These conditions have also been extended to higher fluorinated homologs.

Keywords: Fluorine • Trifluoromethylselenyl • Morita-Baylis-Hillman • Enones • Selenium

Introduction

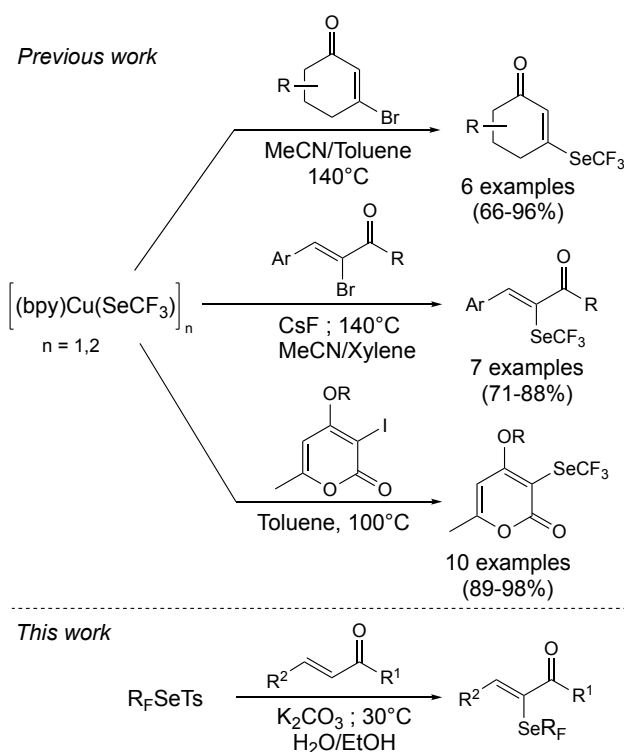
Nowadays, fluorinated molecules find more and more uses in a wide panel of applications, mainly due to their peculiar properties.^[1-13] In the race of the development of molecules dedicated to targeted applications, fine tuning of physico-chemical properties is highly investigated. In this objective, new fluorinated moieties have been developed these last years.^[14] In particular merging of chalcogens and trifluoromethyl group has recently known a growing interest,^[15-21] particularly because of the increased lipophilicity brought by such substituents to the molecules.^[22, 23]

Despite its negative reputation, selenium is an important element either for human physiology^[24] or in the design of new compounds for various applications from materials^[25, 26] to life sciences^[27-36] and drug design.^[37-43] Consequently, the design of CF_3Se -molecules constitutes an interesting strategy for the development of new innovative substrates.

On the other hand, carbonyl compounds are an important family of molecules found either in natural and bioactive compounds^[44-48] or in the toolbox of building-blocks for further syntheses.^[49-52] Therefore, trifluoromethylselenolated carbonyl compounds could constitute pertinent substrates for various purposes.

Results and Discussion

If a few syntheses of trifluoromethylselenolated carbonyl compounds have been already described,^[53-62] only two methods described the access to CF_3Se -enones whereas such substrates are very interesting as building-blocks because of their higher reactivity.^[60-62] These methods are based on the use of a $[\text{CF}_3\text{SeCu}]$ complex, implying stoichiometric amount of copper, and the preliminary preparation of corresponding vinyl bromides (or iodides). Furthermore, only acyclic α - CF_3Se - α,β -unsaturated carbonyl compounds β -substituted with an aryl moiety or pyrones were described (scheme 1).^[61, 62]



Scheme 1. State of the art about synthesis of trifluoromethylselenolated α,β -carbonyl compounds.

Morita-Baylis-Hillman reaction is a well-known approach to easily obtain α,β -unsaturated carbonyl compounds.^[63-65] Recently, we have developed a new family of reagent, namely the trifluoromethylselenosulfonates (**1**), as donor of CF_3Se^+ species.^[20, 21, 59, 66] Consequently, an adaptation of Morita-Baylis-Hillman reaction by using our reagents as electrophilic partners has been considered.

The reaction was studied with trifluoromethylselenotoluenesulfonate (CF_3SeTs , **1a**) as reagent and cyclohexone as model substrate (Table 1).

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Table 1. Morita-Baylis-Hillman like reaction between **1a** and **2a**.

N°	1a (eq.)	catalyst (eq.)	solvent ^c	T (°C)	t (h)	3a (%) ^b
1	1	DMAP (1)	THF	30	15	< 5
2	1	DMAP (1)	CH ₂ Cl ₂	30	15	16
3	1	DMAP (1)	CH ₃ CN	30	15	45
4	1	DMAP (1)	DMF	30	15	7
5	1	DMAP (1)	DMSO	30	15	< 5
6	1	DMAP (1)	MeOH	30	15	56
7	1	DMAP (1)	H ₂ O	30	15	58
8	1	DMAP (1)	H ₂ O / MeOH ^a	30	15	70
9	1	DMAP (1)	H ₂ O / MeOH ^a	30	1	66
10	1	DABCO (1)	H ₂ O / MeOH ^a	30	1	39
11	1	Et ₃ N (1)	H ₂ O / MeOH ^a	30	1	50
12	1	DBU (1)	H ₂ O / MeOH ^a	30	1	42
13	1	PPh ₃ (1)	H ₂ O / MeOH ^a	30	1	< 5
14	1	DMAP (1)	EtOH	30	1	61
15	1	DMAP (1)	H ₂ O / EtOH ^a	30	1	63
16	1.2	DMAP (1)	H ₂ O / MeOH ^a	30	1	67
17	1.5	DMAP (1)	H ₂ O / MeOH ^a	30	1	78
18	1.5	DMAP (0.2)	H ₂ O / MeOH ^a	30	1	25
19	1.5	DMAP (1)	H ₂ O / MeOH ^a	45	1	78
20	1.5	K ₂ CO ₃ (1)	H ₂ O / MeOH ^a	30	15	82
21	1.5	K ₂ CO ₃ (1)	H ₂ O / EtOH ^a	30	15	91
22	1.5	K ₂ CO ₃ (1)	H ₂ O / EtOH ^a	30	1	51
23	1.5	K ₂ CO ₃ (0.5)	H ₂ O / EtOH ^a	30	15	46
24	1.5	K ₂ CO ₃ (1.5)	H ₂ O / EtOH ^a	30	15	62

^[a] ratio 1:1. ^[b] Determined by ¹⁹F NMR with PhOCF₃ as an internal standard.

DMAP was first used as catalyst. In aprotic solvents, the observed yield increased with solvent polarity (entries 1-3).^[67] However, polar solvents with a higher Gutmann's donor number^[67] appeared to be deleterious to the reaction (entries 4-5). Protic solvents seem to favor the reaction with similar results obtained in methanol or water (entries 6-7). A 1:1 ratio of both solvents considerably increased the yield (entry 8). Similar results were observed in 1h instead of 15h. (entry 9). Others common catalysts were also attempted but with disappointing results (entries 10-13). Because of methanol toxicity, ethanol was also considered, as substitute. The obtained results remained interesting but slightly lower than in MeOH (entries 14-15). An excess of reagent **1a** favors the reaction and good results were obtained with 1.5 equivalents (entries 16-17). Stoichiometric amount of catalyst is required, lower yield being observed

with only 20 mol% (entry 18). An increase of temperature had no influence on the reaction (entry 19).

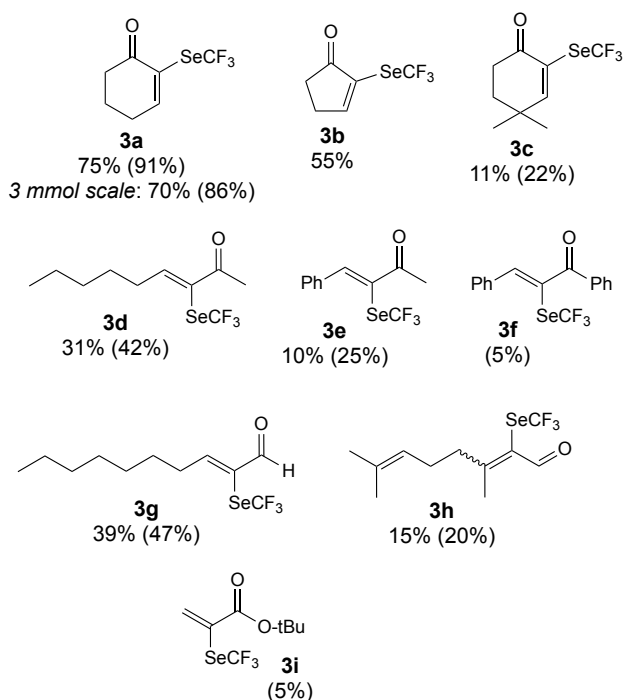
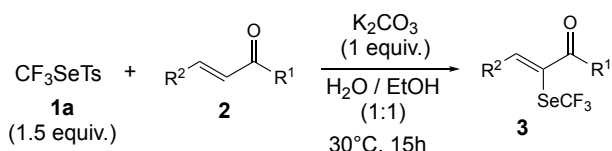
In the idea to perform this reaction in green conditions, eco-compatible surrogate of DMAP was searched. Because Morita-Baylis-Hillman reactions were described by using K₂CO₃ in methanol,^[68] such a catalyst was also envisaged. Delightfully, a good yield, better than with DMAP, was observed (entry 20) in 15h. Under these conditions, this time the use of ethanol instead of methanol was a better choice (entry 21).

Nevertheless, in these conditions, the reaction kinetic appeared slower (entry 22). Noteworthy that excess or default of K₂CO₃ have been deleterious for the reaction (entries 23-24). Finally, the optimal "green" conditions have proven to be 1.5 equivalent of **1a** in EtOH/H₂O (1:1) in presence of K₂CO₃ for 15h (entry 21).

With these conditions in hand, several enones were tested (scheme 2). If satisfactory yields were obtained with cyclic enones (**2a-b**), the reaction is very sensitive to steric hindrance with an important yields decrease with crowding augmentation (**3c-f**). In case of compounds **3e-f**, an electronic effect could be also considered, the reactivity of double bond being decreased due to resonance with aromatic ring. It should be noticed that isolated yields are often lower due to high volatility of formed compounds.

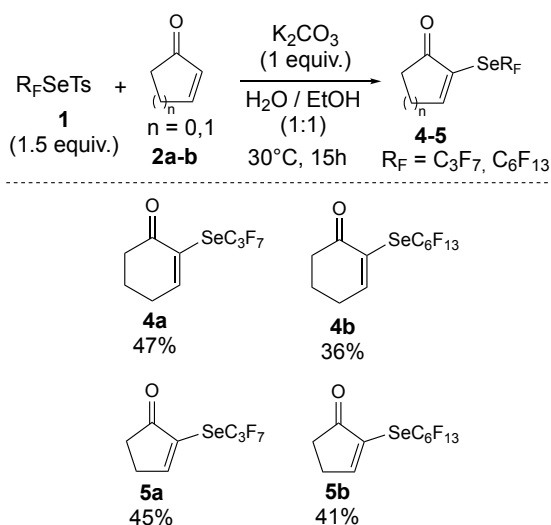
Enals react also in the same conditions to furnish corresponding CF₃Se-compounds (**3g-h**). Similar negative steric hindrance influence was also observed. In contrast, α,β -unsaturated esters provided the expected products only with very low yield (**3i**), maybe due to a competitive saponification reaction or steric hindrance of tertio-butyl group. Interestingly, the reaction was scaled-up to 3 mmol scale with similar results (**3a**).

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Scheme 2. Synthesis of α -trifluoromethylselenolated enones. Isolated yields, in parentheses, yields determined by ^{19}F NMR with PhOCl_3 as an internal standard.

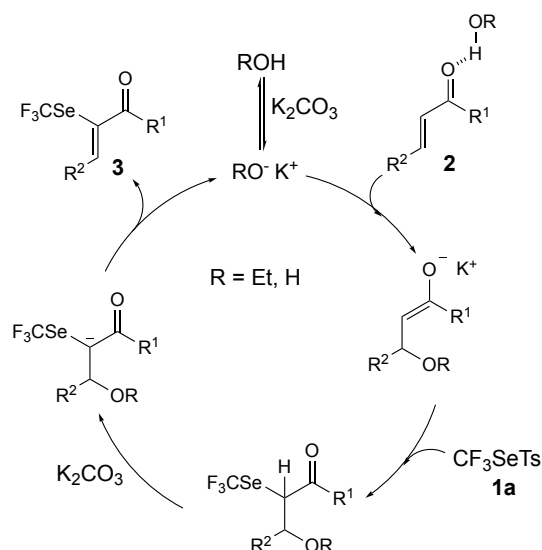
Since reagents with other fluoroalkyl moieties were also synthesized, reaction was also performed with higher homologs (scheme 3). The expected products were obtained with satisfactory results. These molecules constitute the first examples of α -perfluoroalkylselenolated enones. As previously observed, the yield decreases with the length of the perfluoroalkyl chain.^[69]



Scheme 3. Synthesis of α -perfluoroalkylselenolated enones. Isolated yields.

In a mechanistic point of view, potassium ethanolate, in situ generated by deprotonation of ethanol by K_2CO_3 , could reasonably be envisaged as

“nucleophilic catalyst” to initiate the reaction (scheme 4). Such an activation was previously shown in literature with methanolate.^[68] Alternatively, potassium hydroxide, arising from water, could, potentially, play also this role. Proticity of solvent could also favor the 1,4-addition onto enones thanks a hydrogen-bond activation of carbonyl function. Generation of expected product **3**, by released of catalyst mediated by deprotonation with K_2CO_3 , may be highly facilitated by the increased acidity of proton in α position of carbonyl group, due to the presence of the electron withdrawing CF_3Se group.



Scheme 1. Mechanism proposal.

Conclusions

To conclude a simple method was described to easily obtain α -perfluoroalkylseleno- α,β -unsaturated carbonyl compounds. This strategy is based on a green approach from starting material easily available. Furthermore, for the first time α -perfluoroalkylselenolated enones were synthesized, in particular with the unusual $\text{C}_6\text{F}_{13}\text{Se}$ group. The observed yields remain globally medium, but this method stays, however, competitive for the synthesis of such specific compounds with a high synthetic value.

Experimental Section

Synthesis of 2-[(trifluoromethyl)selenanyl]cyclohex-2-en-1-one (3a)

To a flask equipped with a magnetic stirrer are added **1a** (0.45 mmol, 1.5 equiv.), **2a** (0.3 mmol, 1.0 equiv.), K_2CO_3 (0.3 mmol, 1.0 equiv.) in EtOH (1 mL) and H_2O (1 mL). The reaction mixture is stirred 15h at 30°C. The reaction mixture is, then, partitioned between Et_2O and water. The aqueous layer is extracted with Et_2O and the combined organic layers are washed with brine, dried over MgSO_4 , filtered and concentrated to dryness (under moderate vacuum). The crude residue is then purified by flash chromatography (Pentane/ Et_2O , 8:2) to afford the desired product **3a** (75%).

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Supplementary Material

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/MS-number>.

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Author Contribution Statement

K. G., A. T., C. G., E. M., T. B. conceived and designed the experiments. K. G., A. T., C. G., carried out the experiments. K. G., A. T., C. G., E. M., T. B. interpreted the results. and wrote the manuscript.

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