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Selective Michael additions of primary and secondary amines to perfluoroalkylated sulfoxides and sulfones as a tool for fluorous tagging

Caroline Magnier-Bouvier,[a] Jean-Claude Blazejewski,[b] Chantal Larpent[b] and Emmanuel Magnier[b,*]

[a]*LADIR, UMR-CNRS 7075, Bâtiment C, 2 rue Henry Dunant, 94320 Thiais, France*
[b]*Institut Lavoisier, UMR-CNRS 8180, Université de Versailles-St-Quentin-en-Yvelines, 45 avenue des Etats-Unis, 78035 Versailles Cedex, France*

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Abstract—Vinyl tridecafluorohexyl sulfoxide **1** and sulfone **2** are shown to be highly reactive towards Michael addition with a broad range of secondary and primary amines. Full selectivity for monofunctionalization of primary amines can be achieved by a proper choice of reagent **1** or **2** depending on amine basicity.

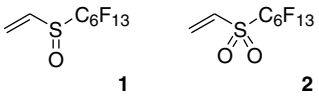
The quest for new nitrogen based ligands, especially in the field of catalysis,[1] still remains a stimulating incentive for synthetic studies devoted to the functionalization of primary and secondary amines. Hetero-Michael addition to α,β-unsaturated sulfoxides and sulfones, thanks to the greatly enhanced reactivity of the double bond, has proven to be a useful tool for this purpose.[2–4] The asymmetric versions of this reaction have also been published.[5]

In order to enhance the reactivity of such kind of Michael acceptors, a promising approach may rely on the synergistic effect induced by the linkage of strongly electron withdrawing fluorinated substituents[6,7] to the already activating sulfone (or sulfoxide) groups.

Recent physico-chemical studies have clearly highlighted the importance of the trifluoromethylsulfonyl group in organic chemistry,[8] and have also brought some fundamental results concerning both trifluoromethylsulfoxide[9] and sulfone.[10] To the best of our knowledge, this area has been scarcely studied and only a short list of conjugate additions to aromatic fluorinated sulfones have been reported,[11,12] while the same reactions with trifluoromethyl vinyl-sulfoxide and sulfone are still less numerous.[13–15]

We recently disclosed an efficient multigram scale synthesis of vinyl tridecafluorohexyl sulfoxide **1** and vinyl tridecafluorohexyl sulfone **2** (Fig. 1).[16] Our preparation avoided the use of toxic reagents and was sufficiently convergent to be extended to various perfluorinated chains. The higher reactivity of compounds **1** and **2** compared to non-fluorinated phenyl vinyl substituted analogues has already been demonstrated through Diels–Alder cycloadditions studies.[17]

In this letter, we present some recent results illustrating the great potential of compounds **1** and **2** for the introduction of fluorinated tags via Michael additions.



1 **2**

Figure 1.

Keywords: Aza-Michael; Perfluoroalkyl chains; Sulfone; Sulfoxide; Fluorous tags.
* Corresponding author. Tel./fax: +33 0 1 39 25 44 66; e-mail: magnier@chimie.uvsq.fr

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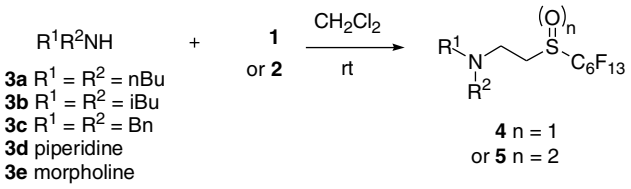
We first focused on the reaction between Michael acceptors **1** and **2** and secondary amines as depicted in Scheme 1.

These results illustrate the extraordinary efficiency of both sulfone **2** and sulfoxide **1** to act as Michael acceptors (Table 1). Dibutylamine **3a**, diisobutylamine **3b** and dibenzylamine **3c** reacted with sulfone **2** within 15–30 min at room temperature, giving rise to the corresponding light fluorinated amines **5a–c** in good to quantitative yields without the need for further purification (entries 1, 3 and 4). Moreover, no special care had to be taken for these reactions, successfully performed by simply mixing all reagents in dichloromethane. Similarly, Michael adducts **4a**, **4c** were obtained with the less reactive sulfoxide **1** provided that the reaction time is increased to 16 h (entries 2 and 5). Cyclic amines like piperidine **3d** and morpholine **3e** (entries 6–8) exhibited a high reactivity and the corresponding Michael adducts **5d–e** and **4d** could be isolated in a pure form after the removal of the solvent.

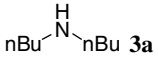
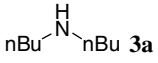
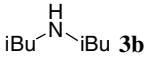
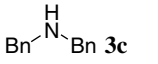
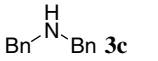
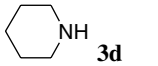
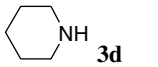
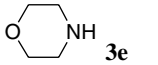


Scheme 1.

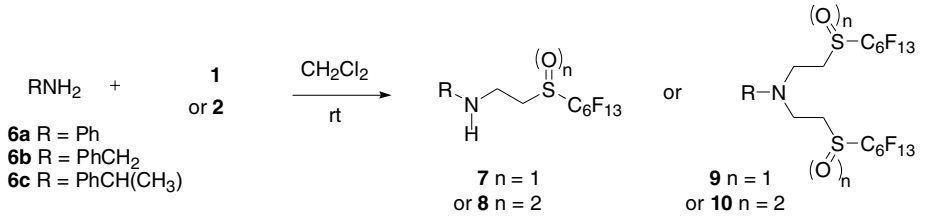
We next studied the reactivity of the perfluorinated Michael acceptors **1** and **2** towards primary amines with the goal of achieving a monoalkylation, thus enabling further functionalization (Scheme 2 and Table 2).

Aniline **6a** has proven to be a poor nucleophile in Michael additions.[18] Despite its low reactivity, this amine readily reacted with sulfone **2** at room temperature with a remarkable selectivity. The product of monoaddition **8a** was formed exclusively whatsoever the number of equivalents of sulfone **2** or the reaction time (entries 1 and 2). On the other hand, the reaction with the more reactive benzylamine **6b** is not so specific and gave rise to a mixture of monoadduct **8b** and diadduct **10b** even in the presence of only 1 equiv of sulfone **2** (entry 3). However, and contrary to the case of aniline **6a**, if the proportion of sulfone **2** is twice that of benzylamine **6b**, bis alkylated amine **10b** is isolated in a quantitative yield (entry 4). In order to obtain selectively a monoadduct with this amine we examined the behaviour of the less reactive[3a] sulfoxide **1** in this reaction. We were pleased to find that the use of a stoichiometric amount of sulfoxide **1** gave rise exclusively to the monoalkylated adduct **7b** in a quantitative yield, resurrecting thus a high degree of selectivity (entry 5). Also to be noted, the introduction of 3 equiv of **1**, despite its tamed reactivity, enabled the full dialkylation of benzylamine **6b** to give the bis-adduct **9b** in a good yield (entry 6). The efficiency of this strategy was proved once more by the selective Michael additions of a chiral amine **6c** with the total control of selectivity by the proper use of sulfoxide **1** or sulfone **2** and total integrity of the asymmetric centre (entries 7 and 8).

Table 1. Michael addition with secondary amines and sulfoxide **1** or sulfone **2**

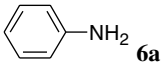
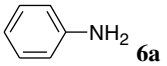
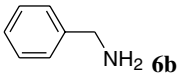
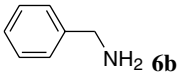
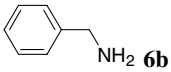
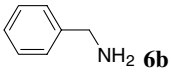
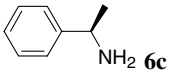
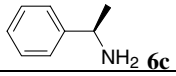
Entry	Amine[a]	Michael acceptor	Time (h)	Product	Yield (%)[b]	Melting point °C
1	 **3a**	**2**	0.25	**5a**	100[c]	Liq.
2	 **3a**	**1**	16	**4a**	100[c]	50.5
3	 **3b**	**2**	0.5	**5b**	100[c]	Liq.
4	 **3c**	**2**	0.5	**5c**	88	Oil
5	 **3c**	**1**	16	**4c**	70	Liq.
6	 **3d**	**2**	1	**5d**	86	65.8
7	 **3d**	**1**	1	**4d**	85	83.1
8	 **3e**	**2**	1	**5e**	90	76.3

[a] Both amine and Michael acceptor are introduced in stoichiometric amounts.
[b] Isolated yields, the spectroscopic data (^{1}H, ^{19}F, ^{13}C NMR, MS) are in full accordance with the expected structures.
[c] Without purification.



Scheme 2.

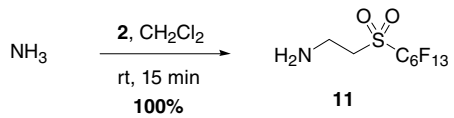
Table 2. Michael addition with primary amines and sulfoxide **1** or sulfone **2**

Entry	Amine	Michael acceptor	Equiv	Time (h)	Product	Yield (%)[a]	Melting point °C
1	 **6a**	**2**	1	1	**8a**	81	99.3
2	 **6a**	**2**	2	24	**8a**	80	99.3
3	 **6b**	**2**	1	1	**8b/10b**[b]	—	—
4	 **6b**	**2**	2	1	**10b**	100[c]	83.6
5	 **6b**	**1**	1	48	**7b**	100[c]	65.7
6	 **6b**	**1**	3	16	**9b**	90	68.4
7	 **6c**	**2**	2	1	**10c**	86[d]	86.0
8	 **6c**	**1**	2	48	**7c**	84[d]	45.1

[a] Isolated yields, the spectroscopic data (^{1}H, ^{19}F, ^{13}C NMR, MS) are in full accordance with the expected structures.
[b] Ratio of **8b/10b** 46:54.
[c] Without purification.
[d] Purified by precipitation with pentane; compound **7c** was isolated as a 1/1 mixture of diastereoisomers.

Interestingly, ammonia also reacted quite easily with sulfone **2** giving rise, quantitatively in a few minutes to the potentially attractive fluorous primary amine **11** (Scheme 3).[19]

The reported results clearly demonstrated the great reactivity of vinyl tridecafluorohexyl sulfoxide **1** and vinyl tridecafluorohexyl sulfone **2** and the easy control of the selectivity. The simplicity of the experimental protocol and product isolation, as well as the high yields are also appealing.



Scheme 3.

Besides the obvious advantages induced by an efficient and rapid way to introduce a fluorinated tag in amino ligands for use in fluorous organocatalysis or biphasic catalysis,[20,21] the synthetic potential of the adducts obtained is full of promise. The presence of a polar function (sulfone or sulfoxide) will permit further functionalization by simple deprotonation of one of the vicinal protons to the sulfur atom. Moreover, our strategy insures the introduction of an ethylene spacer between the fluorinated part and the amine function, preserving sufficient basicity or nucleophilicity properties.[22] Furthermore, depending on the molecular weight of the amine, some of the reported Michael adducts (for instance **4a** and **5a**) may be considered as light fluorous molecules. In this context, sulfoxide **1**, sulfone **2**, as well as primary amine **11** may find applications as scavengers for fluorous solid phase extraction (F-SPE) purposes.[23]

Some applications in fluorous biphasic catalysis with perfluorinated amino ligands are under current study in our laboratory and will be reported in due course. In the case of incomplete reaction, the resultant amine adduct can be isolated either by precipitation in pentane or by quick column chromatography on silica gel.

Dibutylamine **3a** (62 mg, 0.49 mmol) was added to a stirred solution of sulfone **2** (0.2 g, 0.49 mmol) in dichloromethane (9 ml). After 15 min of stirring, the reaction media was concentrated under vacuum giving 0.26 g (100%) of the pure corresponding amine **4a**. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.42$ (t, 2H, CH_2–SO_2, $^3J = 6.6$ Hz), 3.19 (t, 2H, N-CH_2–CH_2–SO_2, $^3J = 6.6$ Hz), 2.49 (t, 2H, Pr–CH_2–N, $^3J = 7.2$ Hz), 1.38 (m, 4H, CH_2), 0.96 (t, 3H, CH_3, $^3J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 53.4, 48.4, 45.3, 29.3, 20.4, 13.8. ^{19}C NMR (188 MHz, $CDCl_3$): $\delta = -81.5$ (m, 3F), −114.0 (m, 2F), −121.0 (m, 2F), −122.4 (m, 2F), −123.4 (m, 2F), −126.8 (m, 2F). MS (CI NH_3): $m/z = 540$ (MH^+, 100).

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