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Unexpected reactivity of trifluoromethylated olefins with indole: a mechanistic investigation

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ABSTRACT

Several trifluoromethylated compounds were reacted with indole sodium salt, leading to monofluorinated compounds. The unexpected products formation was rationalized by DFT calculations.

Organic fluorinated compounds have received great attention in all fields of science. Currently approximately 30% of all agrochemicals and 20% of pharmaceuticals contain fluorine. Incorporation of fluorine has also been applied in material sciences such as the useful polymer polytetrafluoroethylene (Teflon) that is perfluorinated and exemplifies the strength of the C–F bond.[1] Fluorine electronegativity, small size, and the significant electrostatic character of the C–F bond are responsible for the unique properties of fluorinated compounds.[2] The introduction of fluorine atoms into organic compounds imparts diverse properties, such as improved metabolic stability,[3] lipophilicity, or basicity,[4] enhancing, in some cases, the drug like properties of these molecules.[5] Thus, the drug candidates with one or more fluorine atoms have become a commonplace in medicinal chemistry. Indeed, the number of fluorinated drugs in the total number of drugs launched worldwide has been increasing during the last 5 years.[5]

In an attempt to explore the effect of fluorine in the anti-inflammatory activity of some indole derivatives, we focused on the synthesis of trifluoromethylated compounds.[6] In the course of our studies, we envisaged to introduce a 3,3,3-trifluorobut-2-en chain at position N-1 of the indole scaffold.

In the presence of nucleophiles (preferentially metallic), trifluoromethylated alkenes without other reactive functional groups are well known to easily react via S_N2' mechanisms (Scheme 1A).[2,6] However, we expected that compounds **1a**,[7] **1b**,[8] and **1c**[9] would react as electrophiles at the mesyl or tosyl group (Scheme 1B), based on the previous reports on the S_N2 reaction of these substrates.

To our surprise and in strong contrast with the literature, we have to conclude that under our experimental conditions fluorine is a better leaving group[10] than mesyl or tosyl, while in the literature it is shown that trifluoromethylated allyl bromide **1a** has been used in indium-mediated allylations to afford γ-coupling products when reacting with aldehydes[11] (*route c*, the S_N2 product was observed only in a small amount),[11a] and methanesulfonate **1b** and the toluene-4-sulfonic acid derivative **1c** have been reported to afford exclusively the S_N2 product (*route d*) when reacted with nucleophiles.[8,9]

Our first attempts to introduce the trifluoromethyl allylic chain at the indolic nitrogen atom consisted on the treatment of **1b** with **2**, in DMF at 0 °C (Scheme 2). Surprisingly, product **3** was isolated as a mixture of *Z*/*Z* and *Z*/*E* isomers in a 38% yield, instead of the expected S_N2 product, together with a little amount of isomerized **5a** (16%, exclusively the *Z* isomer). In order to understand the role of the solvent and base in the reaction outcome, several reaction conditions were tested (Table 1). First experiments were carried in DMF and the base loading was investigated (entries 1 and 3). The yield of **3** is dependent on the amount of NaH, with smaller amounts leading to lower product yields. In all experiments unreacted indole (starting material) was recovered. The dilution of the mixture had no influence on the reaction outcome (entry 2). However, the use of 2 equiv of the sodium salt of indole **2** (entry 4), significantly increased the yield of **3**. The nature of the metal revealed to be crucial for the fluorine elimination, since the formation of **3** was suppressed when BuLi was used (entry 9).

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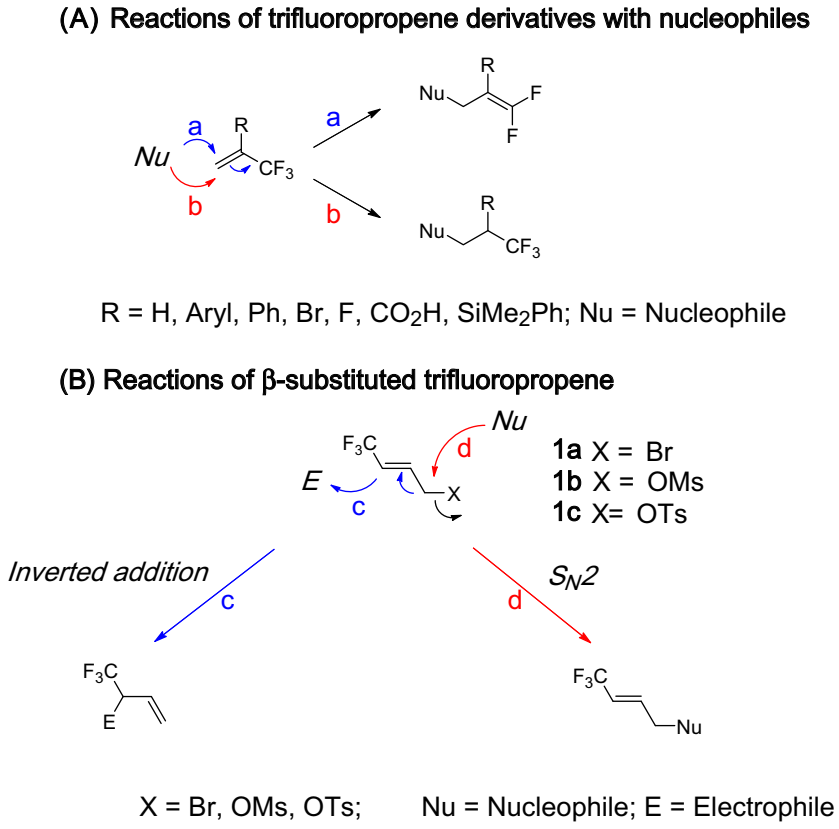
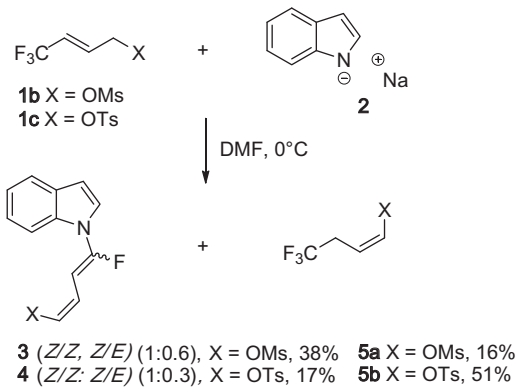


Scheme 1. Possible reactions of the trifluoromethylated alkenes.



Scheme 2. Reaction of **1b**/**1c** with the sodium salt of **2**.

The change in solvent influenced the products formation (entries 1and 6), and best results were obtained when DMF was used as solvent. Inverting the order of the reagents addition, addition of a suspension of sodium salt **2** to a solution of **1b**, enhanced the yield of the isomerized **5a** and almost suppressed the formation of **3** (entry 8), supporting that two competitive mechanisms take place. When **1c** was used the corresponding products **4** were isolated (entry 10). In any case was observed the S_N2 product. The importance of the electron-withdrawing effect of the CF_3 group on the reaction outcome was confirmed, as when the CF_3 group was replaced by a methyl group, compound **1d**,[11] the S_N2 product was obtained with both NaH and BuLi (entry 11). The corresponding S_N2 product was also isolated when **1b** reacted with cylohexylamine instead of **2**.

In all experiments the *Z*/*Z* isomer **3** was the major product. Structure **3** (*Z*/*Z* and *Z*/*E*) was assigned by ^1H, ^{13}C, ^{19}F NMR, and 2D experiments. The doublets found in the ^{13}C NMR strongly suggest that only one fluorine atom is present. The ^{19}F NMR (proton coupled) of **3** (*Z*/*Z*) shows a doublet signal at −93.0 ppm with 28.9 Hz, while for **3** (*Z*/*E*) a doublet of 5.9 Hz is observed at −81.8 ppm, thus confirming the proposed configurations.[12]

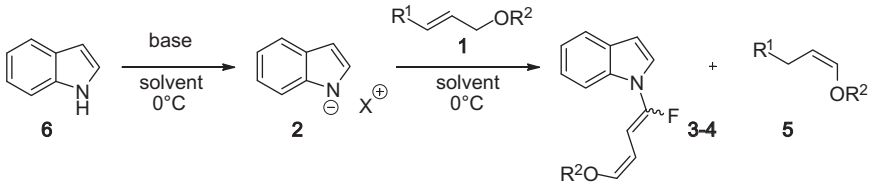
As stated in the introduction, fluoride elimination from trifluoro allylic chains is known, as a side product, under metal-mediated reactions.[13] Yamazaki group reported the formation of difluorinated products during the Michael addition of organocopper species to 3-[(*E*)-4,4,4-trifluorobut-2-enoyl]oxazolidin-2-ones.[13a] The same group observed the formation of a difluorinated diene as a product in S_N2 reactions of Grignard reagents toward CF_3-containing allylic acetates, in the presence of CuCN and TMSCl.[13]

Additionally, the reaction of α-substituted trifluoromethylated alkenes to give functionalized 1,1-difluoroalkenes, in the presence of a nucleophile in aprotic solvents has already been reported (Scheme 1, *route a*).[2,6]

In contrast with the literature known substrates, compound **1** has a good leaving group at β-position (mesyl or tosyl group), and as it is accepted that the C–F bond is strong and chemically stable, the formation of **3** from **1b** under our experimental conditions was an unexpected reaction outcome.

Thus, aiming at a proposal of a possible mechanism, we envisaged a full density functional theory (DFT) study,[14] by calculating all the intermediates (some of them observed by MS) and transition states (TSs) along the possible reaction pathways. In Scheme 3 is depicted a proposed mechanism on the basis of our calculated data, which indicates that the reaction occurs in three steps. Scheme 4 details the mechanism by presenting all the important TSs and intermediates as well as their relative energies. In all TSs it is very important to consider the explicit participation of a sodium ion. In the absence of this ion the TS energies become extre-

Table 1
Reaction conditions



Entry	**1** R^1; R^2	Solvent	Base (equiv)	Products	Yield[a] (%)
1	**1b** CF_3; Ms	DMF	NaH (1)	**3** (*Z*/*Z*)/(*Z*/*E*) (1:0.6)	38
				5a	16
2[b]	**1b** CF_3; Ms	DMF	NaH (1)	**3** (*Z*/*Z*)/(*Z*/*E*) (1:0.6)	47
				5a	1
3	**1b** CF_3; Ms	DMF	NaH (0.5)	**3** (*Z*/*Z*)/(*Z*/*E*) (1:0.6)	22
				5a	Trace
4[c]	**1b** CF_3; Ms	DMF	NaH (2)	**3** (*Z*/*Z*)/(*Z*/*E*) (1:0.5)	83
				5a	Trace
5[d]	**1b** CF_3; Ms	MeCN	NaH (1)	**3** (*Z*/*Z*)/(*Z*/*E*) (1:0.5)	40
				5a	7
6	**1b** CF_3; Ms	THF	NaH (1)	**3** (*Z*/*Z*)/(*Z*/*E*) (1:0.9)	3
				5a	9
7[d]	**1b** CF_3; Ms	THF	*t*-BuOK (1)	**3** (*Z*/*Z*)/(*Z*/*E*) (1:0.6)	29
				5a	6
8[e]	**1b** CF_3; Ms	THF	NaH (1)	**3** (*Z*/*Z*)/(*Z*/*E*) (1:0.5)	25
				5a	
9[f]	**1b** CF_3; Ms	THF	*n*-BuLi (1)	—	19
10	**1c** CF_3; Ts	DMF	NaH (1)	**4** (*Z*/*Z*)/(*Z*/*E*) (1:0.3)	17
				5b	51
11	**1d** CH_3; Ms	DMF	NaH (1)	S_N2 product	34
12[g]	**1b** CF_3; Ms	THF	—	S_N2 product	72

[a] The yields were calculated based on ^{1}H NMR of the isolated mixture of **3** and **5**, except entries 10, 11 and 12. 1 equiv of indole **6** has been used except in entry 5.
[b] The reaction was diluted 5 times.
[c] 2 equiv of **2** were used.
[d] Addition of crown-ether (1 mol %).
[e] Inverted order of reagents addition.
[f] No reaction.
[g] Cyclohexylamine was used as the nucleophile.

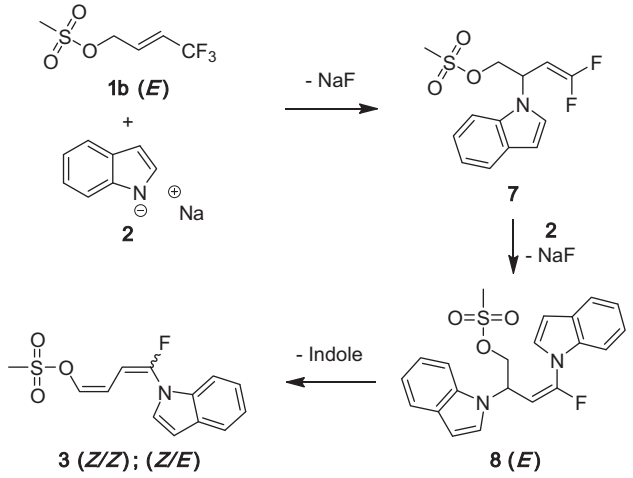
mely high or the TS structures cannot even be obtained, which is in agreement with the experimental data.

For the reaction of **1b** with **2**, we studied six different pathways (see SI). However, Scheme 4 shows only the two pathways (**TS-1** and **TS-2**) that lead to experimentally observed products (**5a** (*Z*) and **3**). All the other calculated TSs are more energetic than **TS-1** and **TS-2** in, at least, 20 kJ mol^{-1}, which means that they are irrelevant for the discussion.

The energy difference between the double-bond migration (**TS-1**) and the indole addition with concerted elimination of fluorine anion (**TS-2**) is minimal. Thus, these two pathways can co-exist and one or the other can be dominant depending on the reaction conditions (solvent, temperature, concentration), as was experimentally observed. The *Z* isomer of **5a** is preferentially formed due to strong restrictions on the TS conformation, as the sodium ion has to coordinate between the mesylic and the indolic groups. GC-MS experiments were carried (see SI, Table 4) and an intermediate with *m*/*z* (300) consistent with intermediate **7** was observed.

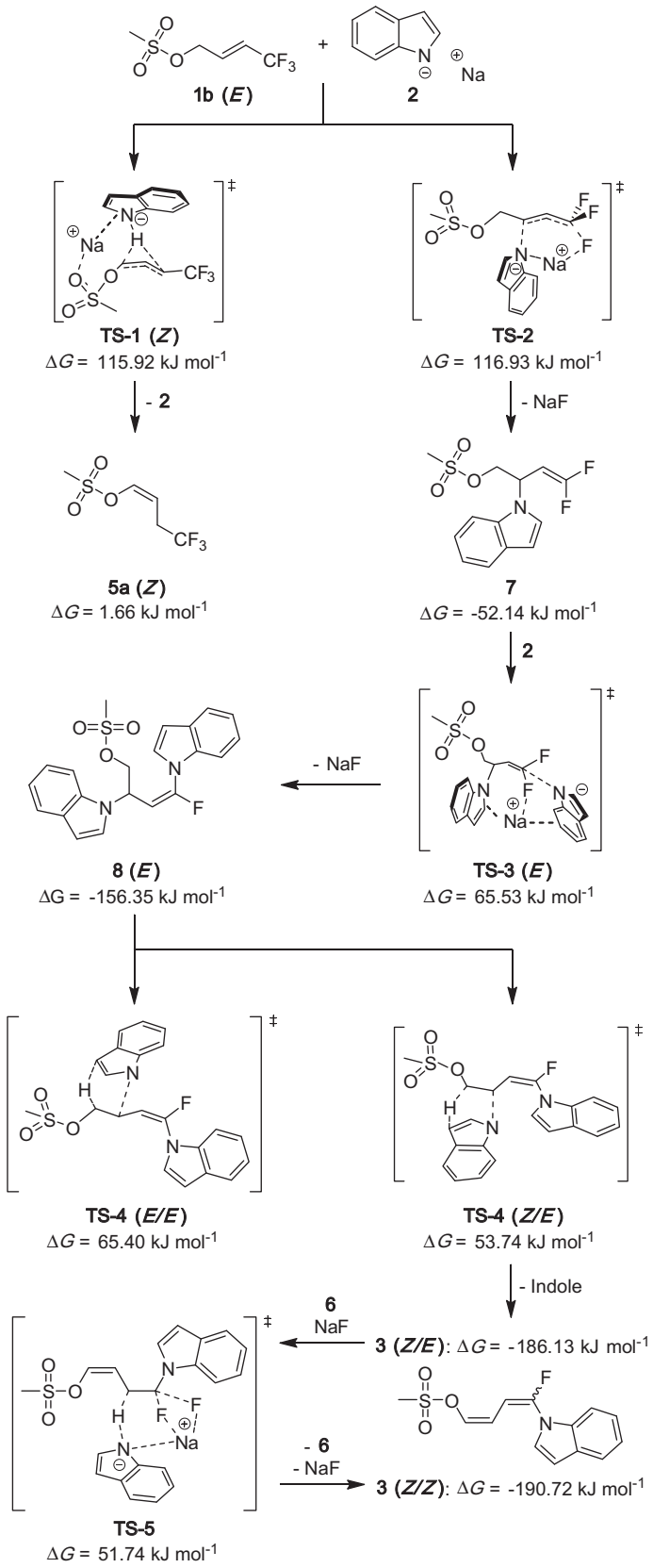
While compound **5a** (*Z*) is a dead-end, intermediate **7** can undergo fluorine substitution by indole anion to afford intermediate **8**. According to our calculations, only the *E* isomer of **8** can be formed, due to the lack of important electrostatic interactions in the TS with *Z* configuration. An alternative mechanism for the formation of **8** was tested, via an addition–elimination process, in which the indole anion adds to the intermediate **7** to form an anionic intermediate that undergoes fluorine elimination to originate **8**.

However, this possibility is not discussed in Scheme 4, as it originates considerably higher energetic TSs (see SI). Indole can be



Scheme 3. Proposed mechanism for the formation of **3**.

eliminated from intermediate **8** via two diastereomeric concerted TSs (**TS-4**), but high selectivity is expected, as **TS-4** (*Z*/*E*) is ca. 11.5 kJ mol^{-1} less energetic than **TS-4** (*E*/*E*). Thus, product **3a** (*Z*/*E*) is predicted to be preferentially formed, which does not fully agree with the experiment. Indeed, while the double-bond at the mesyl group side was experimentally obtained in *Z* configuration, the second double-bond was obtained as a *Z*/*E* mixture, with preference for the *Z* configuration. However, this result can be ex-



Scheme 4. Proposed mechanism for the formation of **3**. B3LYP/6-311++G(2df,2p)//B3LYP/6-31G(d,p), DMF, $T = 25$ °C (similar conclusions at 0 °C), radii = uaks.

plained, as the indole can catalyze the conversion of **3a** (*Z*/*E*) into **3a** (*Z*/*Z*), via **TS-5**, thus allowing for a mixture of configurations, as experimentally observed. The conclusion is that while structure **3a** (*Z*/*E*) is formed under kinetic control, isomer **3a** (*Z*/*Z*) is formed under thermodynamic control, which explains the relative variable amounts of both isomers, depending on the reaction conditions.

In summary, an unexpected reactivity was observed when compounds **1b** and **1c** were treated with indole sodium salt. A

mechanism was proposed, based on DFT studies, which fully rationalizes the experimental data. Six possible reaction pathways were considered, but only two lead to experimentally observable products (**3** and **5a**). The proposed mechanism identifies the importance of the metal ion and the reaction conditions on the final reaction outcome.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.055.

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