



# Methyl fluoroalkanoate as methyl-transferring reagent. Unexpected participation of $B_{Al}2$ ( $S_N2$ ) mechanism in the reaction of methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate with amines



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## ABSTRACT

In the reaction of methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate with arylamines or arylmethylamines, an unexpected methyl transfer from the ester to the amine by the  $B_{Al}2$  ( $S_N2$ ) mechanism was observed leading to the corresponding *N*-methylamines under specific conditions. The reaction was accompanied by the formation of amides via  $B_{Ac}2$  mechanism. The unexpected methyl transfer is highly dependent on the structure of the starting amine and is supported by the absence of solvent and high temperature.

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## 1. Introduction

The transfer of methyl group from ester to amine is a well established reaction. It proceeds as the  $S_N2$  reaction at the methyl group and is characteristic for methyl alkyl- or aryl-sulfonates, the presence of excellent sulfonate or sulfate leaving group being the key factor [1]. In contrast, this type of mechanism is quite rare for methyl alkanooates, where nucleophiles usually react at the carbonyl carbon to substitute the methoxy group by tetrahedral  $B_{Ac}2$  mechanism [2]. The reaction analogous to sulfonate chemistry (assigned as  $B_{Al}2$ ) is limited to derivatives of highly acidic acids: the methyl transfer from ester to amine was observed for methyl salicylate [3], *o*-nitrobenzoate [4] and dimethyl oxalate or fumarate [4]. The methyl transfer was also accomplished with dimethyl carbonate [5]. Heating of 2-amino-2'-hydroxy-3'-(methoxycarbonyl)binaphthol gave intermolecular methyl transfer in solid state [6]. As other examples of a  $B_{Al}$  mechanism, ring-opening of lactones [7], *N*-allylation under nickel catalysis [8], formation of *N*-methyl-pyridiniumcarboxylic acid from methyl

pyridinecarboxylates [9], or ring-closure during gas-phase pyrolysis [10] can be considered.

In this article, we report unexpected methyl transfer from methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate (TFMP, **1**) to amines by the  $B_{Al}2$  mechanism, depending both on the nature of the amine and the reaction conditions. In general, the alternative  $B_{Al}1$  mechanism is not accounted as it requires an unlikely formation of methyl cation in solution.

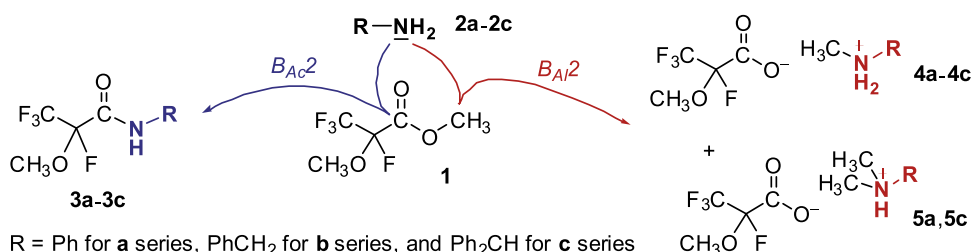
## 2. Results and discussion

During our study of chemistry of TFMP, we found that the reaction of the TFMP with amines **2a–2c** leads to the corresponding amides **3** (Scheme 1), however, under specific conditions the TFMP can act as a methylation agent. The transferring of one or two methyl groups to the nitrogen atom thus yielded unexpected products, namely *N*-methyl- and *N,N*-dimethylalkylammonium fluoroalkanoates **4** and **5** (Scheme 1).

In the first set of qualitative experiments, we studied the role of substrate, solvent and reaction temperature. The ratio of products in the crude reaction mixtures was determined by <sup>19</sup>F NMR spectroscopy (the signal of CF group of amides **3** can be observed at –136 ppm, for the salts **4** and **5** it can be found at –132 ppm), while

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**Scheme 1.** Reaction of TFMP (**1**) with amines **2a-2c**.

**Table 1**  
Screening of amidation/methyl transfer in the reaction of TFMP (**1**) with amines **2**.

Entry	Amine	Temp. (°C)	Time (h)	Solvent	Conversion of <b>1</b> (%)	<b>3</b> :( <b>4</b> + <b>5</b> ) ratio	<b>2</b> : <b>6</b> : <b>7</b> <sup>a</sup> ratio
1	<b>2a</b>	Reflux	24	THF	0	No reaction	No reaction
2	<b>2a</b>	100	72	None	100	15:85	59:31:10
3	<b>2b</b>	rt	48	Heptane	95	98:2	n.d.
4	<b>2b</b>	rt	16	Methanol	100	>99:1	n.d.
5	<b>2b</b>	rt	336	THF	100	89:11	n.d.
6	<b>2b</b>	Reflux	26	THF	100	69:31	n.d.
7	<b>2b</b>	Reflux	72	1,4-Dioxane	73	56:44	n.d.
8	<b>2c</b>	Reflux	10	THF	<1	No reaction	No reaction
9	<b>2c</b>	115	24	None	81	36:64	85:7:8

<sup>a</sup> **6** and **7** are the corresponding *N*-methyl and *N,N*-dimethyl derivatives of amine **2**, resp.

the degree of methylation of the amines **2** was obtained by GC–MS analysis of the amine mixture formed after alkalization of the crude reaction mixture with sodium hydroxide. The results are listed in Table 1.

Thus, aniline (**2a**) as the least nucleophilic amine did not react with TFMP in refluxing THF (Table 1, entry 1). Similarly, the reactivity of benzhydramine (**2c**) was negligible under these conditions probably due to steric hindrance of the amino group (Table 1, entry 8). The reactivity dramatically changed when the solvent was omitted and the reaction temperature was raised. Thus, the reaction of aniline (**2a**) with 8-fold excess of TFMP at 100 °C for 9 h gave after alkalization a mixture of starting aniline (**2a**), *N*-methylaniline (**6a**) and *N,N*-dimethylaniline (**7a**) in a 59:31:10 ratio. Small amount of amide **3a** in the crude reaction product was also detected (Table 1, entry 2). Analogous reaction of TFMP with equivalent of benzhydramine (**2c**) at 115 °C gave after alkalization a mixture of starting amine **2c**, *N*-methylbenzhydramine (**6c**) and *N,N*-dimethylbenzhydramine (**7c**) in a 85:7:8 ratio (Table 1, entry 9). About one third of starting TFMP was converted to the corresponding amide **3c**.

Benzylamine (**2b**) as a highly nucleophilic amine proved to be most sensitive to the reaction conditions and hence its reactivity was studied in detail. The amide **3b** was formed almost exclusively at room temperature, even when non-polar heptane or polar methanol as the solvent was used (Table 1, entries 3 and 4). However, the same reaction in THF afforded a mixture of amide **3b**

and *N*-benzylammonium salt **4b** in a 89:11 ratio (Table 1, entry 5). Raising the temperature to reflux increased the content of salt **4b** to a 69:31 ratio (Table 1, entry 6) and further enhancement of the temperature to 100 °C (refluxing 1,4-dioxane as the solvent) led to the ratio of 45:55 (Table 1, entry 7). This identifies the reaction temperature as the key factor in the competition between amidation by the B<sub>Ac</sub>2 mechanism (the alternative B<sub>Al</sub>1 mechanism is unlikely) and the methyl transfer by the B<sub>Al</sub>2 mechanism.

In the preparative experiments (Table 2), conditions of entry 2 (110 °C, no solvent) using the excess of aniline to minimize double methylation were employed for the synthesis of *N*-methylanilinium salt **4a**, which was isolated in a 55% yield, along with 5% of amide **3a**. Analogously, conditions of entry 9 (115 °C, no solvent) allowed the isolation of the corresponding salt **4c** in a 64% yield and of the corresponding benzhydramide **3c** in a 23% yield. Unfortunately, neither crystallization nor column chromatography gave the salt **4c** of good purity. Similarly, the conditions of entry 4 (MeOH as solvent, r.t.) were employed for the synthesis of *N*-benzylamide **3b**, which was isolated in an excellent 92% yield, while the conditions of entry 7 (refluxing 1,4-dioxane) allowed the isolation of the corresponding salt **4b** in a 29% yield and *N*-benzylamide **3b** in 37% yield.

Finally, the diamine containing both arylamino and arylmethylamino group, 2-(aminomethyl) aniline (**2d**), was employed in the reaction with TFMP. In analogy to the reaction of benzylamine

**Table 2**  
Preparation of amides **3** and salts **4** by the reaction of TFMP (**1**) with amines **2**.

Entry	Amine	Temp. (°C)	Time (h)	Solvent	yield of <b>3</b> (%)	yield of <b>4</b> (%)
1	<b>2a</b>	110	24	None	5	55
2	<b>2b</b>	rt	16	Methanol	92	Traces
3	<b>2b</b>	Reflux	72	1,4-Dioxane	37	29
4	<b>2c</b>	115	24	None	23	64

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