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Nucleophilic trifluoromethylation of acyl chlorides using the trifluoromethyl iodide/TDAE reagent

Naoto Takechi,[a] Samia Aït-Mohand,[a] Maurice Médebielle[b] and William R. Dolbier, Jr.[a,*]

[a] *Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA*
[b] *Université Claude Bernard-Lyon 1, Laboratoire SERCOF (UMR CNRS 5622), Batiment E. Chevreul, 43, Bd du 11 novembre 1918, F-69622 Villeurbanne, France*

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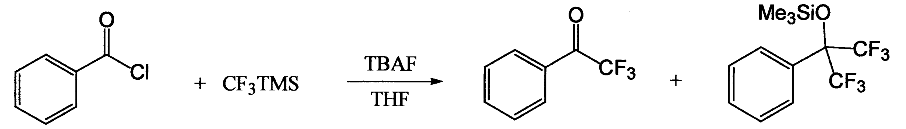
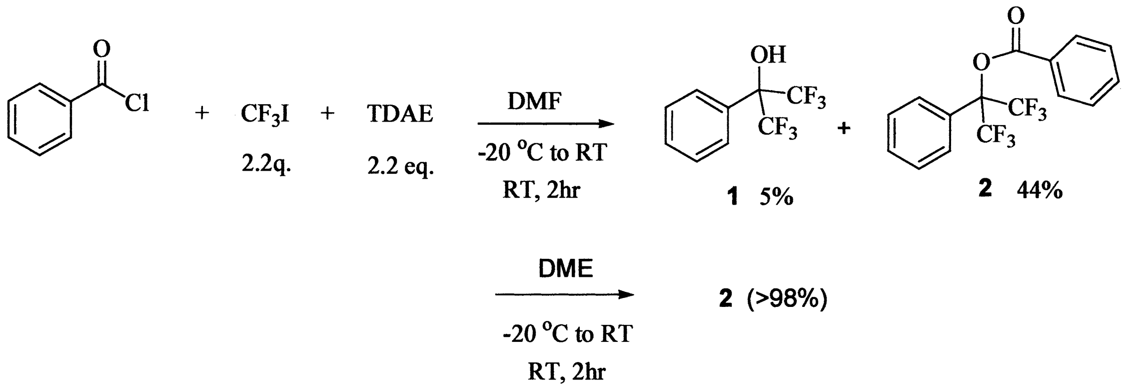
Abstract—Chemoselective bis-trifluoromethylation of acyl chlorides using the CF_3I/TDAE-derived nucleophilic trifluoromethyl anion reagent is reported. Very high yields are obtained of an ester product formed by sequential nucleophilic bis-trifluoromethylation, followed by acylation of the resultant alcoholate. © 2002 Elsevier Science Ltd. All rights reserved.

In spite of the widespread application of (trifluoromethyl)trimethylsilane (Me_3SiCF_3) as a nucleophilic trifluoromethylating agent and the numerous papers on the subject,[1–3] there has been only one, brief mention of its reactions with acyl chlorides, that by Krishnamurti, Bellew, and Prakash in 1991.[4] In this paper, it was claimed that the reaction of Me_3SiCF_3 with benzoyl chloride led to competitive single and double addition, to form ketone and alcohol products, respectively. However, neither yields nor experimental details were provided.

Curious about the lack of literature on the reaction,[5,6] and recognizing that a chemoselective reaction with acyl chlorides could be quite useful, we decided to take a close look at the reaction of our recently developed CF_3I/TDAE-derived trifluoromethyl anion reagent with acyl chlorides. Using our usual conditions of 2.2 equiv. of CF_3I and TDAE in DMF at −20°C (but no light), warming to room temperature and then stirring at room temperature for 2 h, led to rather disappointing results, with only 5% of alcohol **1** being formed, along with a second product in 44% yield.[7] Isolation and





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* Corresponding author. Fax: 352-846-1962; e-mail: wrd@chem.ufl.edu

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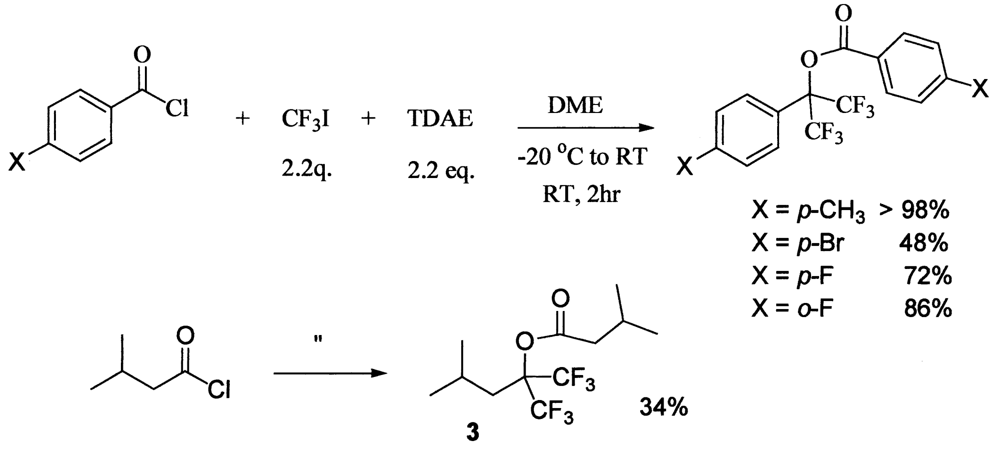
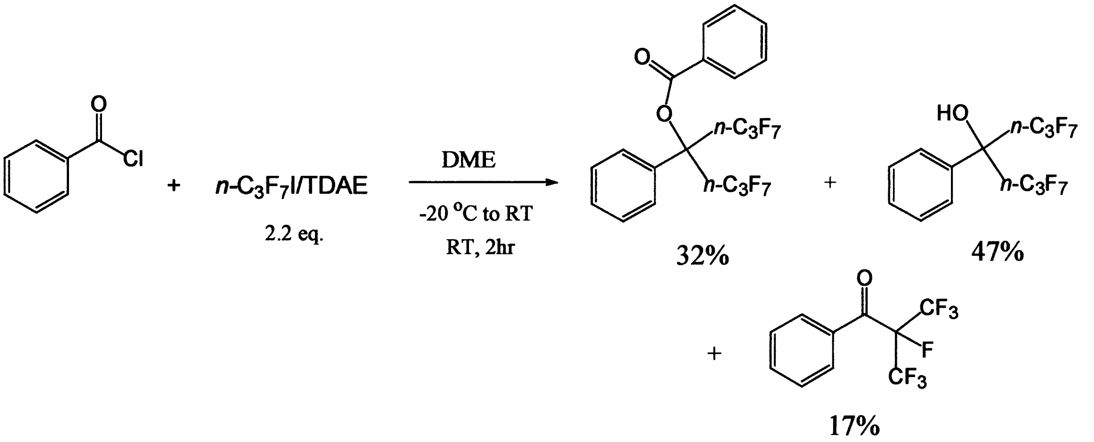




characterization of the major product demonstrated that it was not the expected ketone, but instead the benzoate ester (**2**) of alcohol **1**.[8]

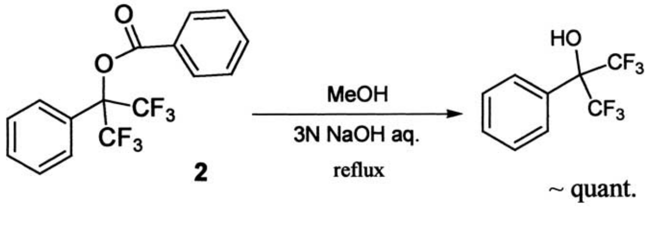
Trying other solvents and conditions, it was quickly determined that 1,2-dimethoxyethane (DME) was the preferred solvent for this reaction, with a quantitative yield of benzoate ester **2** being obtained in an overnight reaction at room temperature. Further optimization indicated that stirring at room temperature for 2 h was sufficient, and that, unlike in the earlier reported reaction with aldehydes and ketones, the reaction with benzoyl chloride was not enhanced by light.[9]

It should be noted that, with only 2.2 equiv. of CF_3I being used and 2 equiv. of CF_3^- anion reagent being *required* stoichiometrically, this reaction must be very efficient with respect to the utilization of the trifluoromethyl anion. When the reaction was carried out using an insufficient amount of trifluoromethyl anion reagent (i.e. 1.1 equiv. of both CF_3I and TDAE), **2** was still the major product (22%), with but 3% of the ketone being formed.

The high chemoselectivity exhibited in this reaction clearly indicates that the mechanistic sequence of steps in the reaction, involving initial CF_3^- addition, loss of Cl^-, second addition of CF_3^-, and finally acylation, must become progressively faster along the sequence, so that ester **2** is essentially the only observed product of the reaction in DME when the stoichiometry is fulfilled.

The reaction appears to be general for aroyl chlorides, as indicated by the examples given below, and preliminary results indicate that aliphatic acyl chlorides can also be acceptable substrates. Thus, use of isobutyryl chloride in the reaction produced ester **3** as the only observable product in 34% yield.

Lastly, when n-C_3F_7I was used in place of CF_3I in this reaction, a good yield of a mixture of ester and alcohol, plus rearranged ketone[10,11] were obtained, as shown below. Apparently, steric influences serve to minimize the final acylation step, and the product of rearranged i-$C_3F_7^-$ anion addition must be sterically inhibited from further alkylation. Recently Petrov reported related results for the addition of $C_2F_5^-$ and i-$C_3F_7^-$ anions to benzoyl chloride.[6]



Although this clean reaction of trifluoromethyl anion with acyl chlorides may find little synthetic use, considering the fact that half of the acyl chloride is consumed in acylating the alcoholate to form the ester product, the obtained esters can nevertheless be readily converted to the respective bis-trifluoromethyl-substituted alcohols by transesterification using methanolic KOH.

Acknowledgements

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2. Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613–7632.
3. Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2001**, *112*, 123–131.
4. Krishnamurthy, R.; Bellew, D. R.; Prakash, G. K. S. *J. Org. Chem.* **1991**, *56*, 984–989.
5. To our knowledge, the only other related work is that of Petrov, who obtained a 56% yield of ketone from the reaction of benzoyl chloride with 1 equiv. of *i*-C_3F_7I/TDAE, whereas its reaction with 2 equiv. of C_2F_5I/TDAE led to a mixture of ketone and alcohol products (33 and 17% yield, respectively).[6]
6. Petrov, V. A. *Tetrahedron Lett.* **2001**, *42*, 3267–3289.
7. All yields reported in this paper were determined by ^{19}F NMR using trifluoromethylbenzene as internal standard.
8. Ester **2** was characterized by NMR and mass spectrometry: white solid, mp 46–47°C; ^1H NMR, δ 8.14 (m, 2H), 7.69 (m, 1H), 7.54 (m, 2H), 7.39–7.50 ppm (m, 5H); ^{19}F NMR, δ −70.7 ppm (s); ^{13}C NMR, δ 162.1, 134.6, 130.5, 130.4, 129.1, 128.8, 128.3, 127.3, 126.9, 122.1 (q, $J=288$ Hz), 83.8 (m, $J=30$ Hz); HRMS (EI), calcd for $C_{16}H_{10}O_2F_6$: 348.0585; found: 348.0585.
9. Typical reaction procedure: Into a 3-necked flask equipped with a dry ice reflux condenser and nitrogen inlet were added, at −35°C, 8 mL of anhydrous DME, benzoyl chloride (0.50 mL, 4.3 mmol), and CF_3I (1.86 g, 9.5 mmol). The solution was stirred and warmed to −20°C, and then to it was added TDAE (2.20 mL, 9.5 mmol) at −20°C. The reaction mixture was vigorously stirred and warmed to rt. It was then stirred at rt for 2 h and the resulting orange-red solution was filtered, and the solid was washed with ether. The ether solution was washed with water, and the resulting aq. solution was extracted with ether. The combined ether solutions were washed with brine (three times) and dried over Na_2SO_4. The solvent was removed, and the crude product analyzed by ^{19}F NMR to determine the yield (using trifluoromethylbenzene as internal standard).
10. The rearranged ketone undoubtedly derived from isomerization of the *n*-C_3F_7 anion to the *i*-C_3F_7 anion by the well-precedented anionic mechanism involving elimination/addition of fluoride ion.[11]
11. Chambers, R. D.; Vaughan, J. F. S. In *Organofluorine Chemistry. Fluorinated Alkenes and Reactive Intermediates*; Chambers, R. D., Ed.; Springer: Berlin, 1997; Vol. 192, pp. 1–88.