



Nucleophilic trifluoromethylation of arylidene Meldrum's acids

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ABSTRACT

A method for the trifluoromethylation of arylidene Meldrum's acids using Me_3SiCF_3 followed by transformation of the initial products to CF_3 -substituted esters and alcohols is described. The sequence of reactions is performed without isolation of intermediate compounds furnishing the final products in good overall yields.

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The Ruppert–Prakash reagent (Me_3SiCF_3) has found widespread application as a convenient source of trifluoromethyl carbanions allowing for the facile introduction of the CF_3 group into organic molecules.¹ While nucleophilic trifluoromethylations of $\text{C}=\text{O}$ and $\text{C}=\text{N}$ bonds have received considerable attention,^{2–4} addition of the CF_3 carbanion to electron-deficient alkenes (the Michael reaction) has remained virtually unexplored.⁵ Furthermore, conventional α,β -unsaturated aldehydes and ketones were reported to undergo trifluoromethylation with Me_3SiCF_3 preferentially at the carbonyl group.^{6,7}

Recently, we demonstrated that arylidenemalononitriles can be readily trifluoromethylated under mild conditions.⁸ At the same time, nucleophilic addition to arylidenemalonates was unsuccessful⁸ and likely to be associated with their low electrophilicity, as is supported by Mayr's reactivity scale (Fig. 1).⁹

We proposed that switching from malonates to the arylidene derivatives of Meldrum's acid (2,2-dimethyl[1,3]dioxane-4,6-dione) possessing a reactive $\text{C}=\text{C}$ bond, would allow easy nucleophilic trifluoromethylation. We also hoped that addition of the CF_3 carbanion would take place selectively at the alkene double bond leaving the carbonyl groups intact.

Compound **1a**, derived from anisaldehyde and Meldrum's acid, was selected as a model substrate, and its trifluoromethylation with Me_3SiCF_3 was studied (Scheme 1). The reaction was carried out in DMF using sodium acetate as the basic activator. To achieve complete conversion of **1a** the process had to be performed at elevated temperature (50 °C) and a stoichiometric amount of NaOAc (1.5 equiv) was required.¹⁰

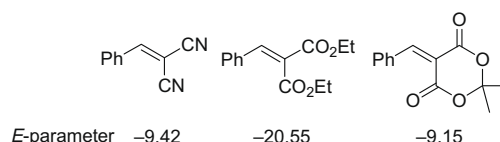
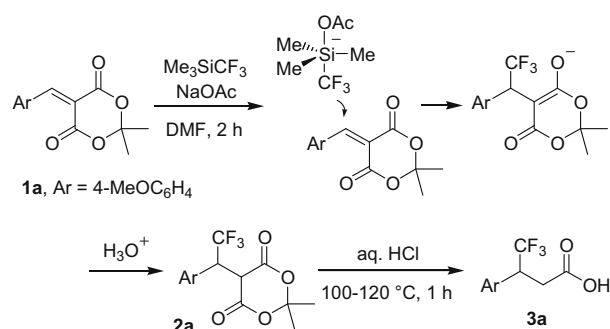


Figure 1. Electrophilicity E -parameters according to Mayr's scale.



Scheme 1.

Acidic aqueous work-up provided a crude sample of compound **2a**. However, decomposition of **2a** occurred upon chromatographic purification, which may be associated with the enhanced electrophilicity of the carbonyl groups. Therefore, the 1,3-dioxane **2a** was hydrolyzed with concomitant decarboxylation by heating the reaction mixture with aqueous hydrochloric acid. The carboxylic acid **3a** was isolated in 98% yield after purification by basic/acidic extractions.

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Conventional column chromatography of acid **3a** proved to be problematic due to significant tailing. In this regard, we decided to perform further transformation of the acids into esters and alcohols. It would also be desirable that the overall procedure starting from **1** would not require purification of the intermediate products. This seemed feasible since trifluoromethylation and decarboxylation proceed cleanly.

Thus, the crude acid **3a** was either converted to methyl ester **4a** by alkylation or reduced to alcohol **5a** in 88–90% overall yields based on starting material **1a** (Table 1, entries 1 and 2). Under the optimized conditions, a variety of arylidene derivatives were utilized for the trifluoromethylation reaction (Table 1). Substrates obtained from *para*- and *ortho*-substituted aldehydes, as well as from α,β -unsaturated and heteroaromatic aldehydes, gave good yields of products **4** and **5**.

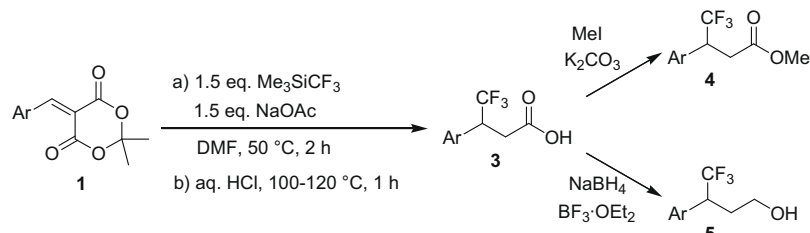
In the case of alkylidene substrates that contain acidic hydrogens adjacent to the double bond, reduced yields of products were observed. For example, compound **11** furnished ester **4i** in only 62% yield along with non-trifluoromethylated ester **6** (Scheme 2). The formation of ester **6** can be explained by deprotonation of **11** by the CF_3 carbanion at the trifluoromethylation stage. Similarly,

when an alkylidene substrate synthesized from cyclohexanone and Meldrum's acid was tested in this process, only traces of product were detected.

Trifluoromethylation of compound **1m** followed by standard decarboxylation and esterification gave hydroxy-substituted product **7** (Scheme 2). This product was formed even with 2.5 equiv of the silicon reagent thereby suggesting that elimination of the methoxy group does not occur during the trifluoromethylation step, but upon further acidic treatment.

In summary, a convenient protocol for the synthesis of CF_3 -substituted derivatives based on the Michael addition of a trifluoromethyl carbanion to arylidene Meldrum's acids has been developed. The trifluoromethylation reaction proceeds under mildly basic conditions and subsequent transformations of the 1,3-dioxane-4,6-diones provide esters or alcohols in good overall yields.¹¹ The reported method for the synthesis $\beta\text{-CF}_3$ -substituted esters is complementary to the approach based on conjugate addition of non-fluorinated nucleophiles to trifluorocrotonates,¹² with the present method enabling the direct introduction of fluorinated fragments.

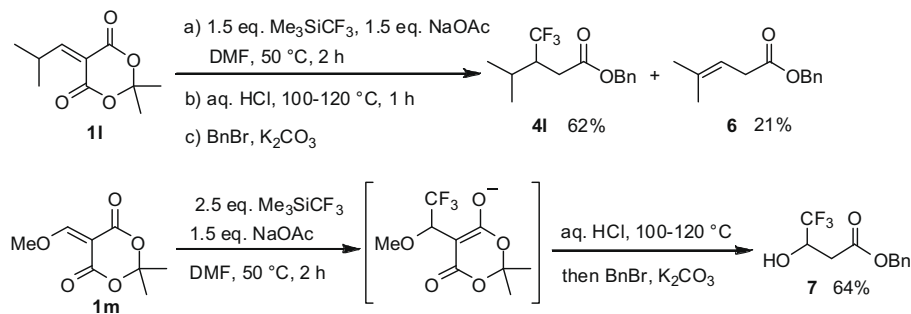
Table 1
Trifluoromethylation of arylidene Meldrum's acids



Entry	Ar	1	Product	Yield of 4 or 5 ^a (%)
1	4-MeOC ₆ H ₄	1a	4a	88
2	4-MeOC ₆ H ₄	1a	5a	90
3	Ph	1b	4b	76
4	4-O ₂ NC ₆ H ₄	1c	4c	83
5	4-ClC ₆ H ₄	1d	4d	88
6	2-MeOC ₆ H ₄	1e	4e	81
7	3,4,5-(MeO) ₃ C ₆ H ₂	1f	4f	85
8^b	4-Me ₂ NC ₆ H ₄	1g	5g	88
9	1-Naphthyl	1h	4h	75
10	(<i>E</i>)-Ph-CH=CH	1i	4i	74
11	2-Thienyl	1j	4j	75
12	2-Furyl	1k	4k	66

^a Overall yield of isolated product starting from **1**.

^b Reaction was performed with 2 equiv of Me_3SiCF_3 and 2 equiv of NaOAc at 70 °C for 5 h.



Scheme 2.

Acknowledgments

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Supplementary data

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.188.

References and notes

- For reviews on the chemistry of Me_3SiCF_3 , see: (a) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, 97, 757; (b) Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2001**, 112, 123; (c) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, 56, 7613.
- For addition to C=O bonds, see: (a) Prakash, G. K. S.; Panja, C.; Vaghoo, H.; Surampudi, V.; Kultyshev, R.; Mandal, M.; Rasul, G.; Mathew, T.; Olah, G. A. *J. Org. Chem.* **2006**, 71, 6806; (b) Kawano, Y.; Kaneko, N.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2006**, 79, 1133; (c) Mizuta, S.; Shibata, N.; Akiti, S.; Fujimoto, H.; Nakamura, S.; Toru, T. *Org. Lett.* **2007**, 9, 3707; (d) Fustero, S.; Albert, L.; Acena, J. L.; Sanz-Cervera, J. F.; Asensio, A. *Org. Lett.* **2008**, 10, 605.
- For addition to C=N bonds, see: (a) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Synlett* **2001**, 77; (b) Prakash, G. K. S.; Mogi, R.; Olah, G. A. *Org. Lett.* **2006**, 8, 3589; (c) Kirij, N. V.; Babadzhanova, L. A.; Movchun, V. N.; Yagupolskii, Y. L.; Tyrra, W.; Naumann, D.; Fischer, H. T. M.; Scherer, H. J. *Fluorine Chem.* **2008**, 129, 14; (d) Nelson, D. W.; Owens, J.; Hiraldo, D. J. *Org. Chem.* **2001**, 66, 2572.
- For results from our group, see: (a) Dilman, A. D.; Arkhipov, D. E.; Levin, V. V.; Belyakov, P. A.; Korlyukov, A. A.; Struchkova, M. I.; Tartakovsky, V. A. *J. Org. Chem.* **2007**, 72, 8604; (b) Dilman, A. D.; Arkhipov, D. E.; Levin, V. V.; Belyakov, P. A.; Korlyukov, A. A.; Struchkova, M. I.; Tartakovsky, V. A. *J. Org. Chem.* **2008**, 73, 5643; (c) Levin, V. V.; Kozlov, M. A.; Song, Y.-H.; Dilman, A. D.; Belyakov, P. A.; Struchkova, M. I.; Tartakovsky, V. A. *Tetrahedron Lett.* **2008**, 49, 3108; (d) Levin, V. V.; Dilman, A. D.; Belyakov, P. A.; Struchkova, M. I.; Tartakovsky, V. A. *Eur. J. Org. Chem.* **2008**, 5226.
- Only specific substrates, such as perfluoroalkyl-substituted chromones and quinolones, were trifluoromethylated, see: (a) Sosnovskikh, V. Ya.; Sevenard, D. V.; Usachev, B. I.; Rösenthaller, G.-V. *Tetrahedron Lett.* **2003**, 44, 2097; (b) Sosnovskikh, V. Ya.; Usachev, B. I.; Sevenard, D. V.; Rösenthaller, G.-V. *J. Org. Chem.* **2003**, 68, 7747; (c) Sosnovskikh, V. Ya.; Usachev, B. I.; Sevenard, D. V.; Rösenthaller, G.-V. *J. Fluorine Chem.* **2005**, 126, 779; (d) Sosnovskikh, V. Ya.; Usachev, B. I.; Permyakov, M. N.; Sevenard, D. V.; Rösenthaller, G.-V. *Russ. Chem. Bull.* **2006**, 55, 1687.
- Singh, R. P.; Kirchmeier, R. L.; Shreeve, J. M. *Org. Lett.* **1999**, 1, 1047.
- Trifluoromethylation of enones in combination with bulky aluminum reagents was studied, but the yields of the products of conjugate addition were moderate, see: Sevenard, D. V.; Sosnovskikh, V. Ya.; Kolomeitsev, A. A.; Königsmann, M. H.; Rösenthaller, G.-V. *Tetrahedron Lett.* **2003**, 44, 7623.
- Dilman, A. D.; Levin, V. V.; Belyakov, P. A.; Struchkova, M. I.; Tartakovsky, V. A. *Tetrahedron Lett.* **2008**, 49, 4352.
- (a) Kaumanns, O.; Lucius, R.; Mayr, H. *Chem. Eur. J.* **2008**, 14, 9675; (b) Kaumanns, O.; Mayr, H. *J. Org. Chem.* **2008**, 73, 2738; (c) Lemek, T.; Mayr, H. *J. Org. Chem.* **2003**, 68, 6880.
- When the reaction was performed with 0.2 equiv of NaOAc at 50 °C, only 17% conversion of starting substrate was observed. This suggests that the anion, which is formed after nucleophilic addition of the CF_3 group to **1a**, does not activate Me_3SiCF_3 .
- General procedures.** Trifluoromethylation: Silane Me_3SiCF_3 (222 μL , 1.5 mmol) and NaOAc (123 mg, 1.5 mmol) were added to a solution of **1** (1.0 mmol) in dry DMF (2 mL) at room temperature. The reaction mixture was stirred at 50 °C for 2 h, cooled to room temperature, and quenched with aq HCl (2 mmol, 280 μL of an aq 7 M solution). The resulting mixture was stirred at 100–120 °C for 1 h, cooled to room temperature, and diluted with water (10 mL). The aqueous phase was extracted with Et_2O (3×5 mL), the combined organic phase was filtered through Na_2SO_4 , and the solvents were removed under vacuum. The residue was dried in vacuum (ca. 1 mmHg) to remove AcOH to give a crude sample of acid **3**.
Esterification: The crude acid **3** was dissolved in dry DMF (2 mL) and was treated with MeI (125 μL , 2 mmol) and K_2CO_3 (276 mg, 2 mmol). The mixture was stirred for 1 h at room temperature, diluted with water (10 mL), and the aqueous phase was extracted with Et_2O /hexanes (1:1, 3×5 mL). The combined organic phase was filtered through Na_2SO_4 , the solvents were removed under vacuum, and the residue was purified by column chromatography.
Reduction: A solution of crude acid **3** in dioxane (2.0 mL) at 0 °C was treated with $\text{BF}_3\cdot\text{OEt}_2$ (317 μL , 2.5 mmol) and NaBH_4 (114 mg, 3.0 mmol). The mixture was stirred at 50 °C for 1.5 h and quenched by dropwise addition of water (10 mL). The aqueous phase was extracted with Et_2O (3×5 mL), the combined organic phase was filtered through Na_2SO_4 , the solvents were removed under vacuum, and the residue was purified by column chromatography.
- (a) Shinohara, N.; Haga, J.; Yamazaki, T.; Kitazume, T.; Nakamura, S. *J. Org. Chem.* **1995**, 60, 4363; (b) Konno, T.; Tanaka, T.; Miyabe, T.; Morigaki, A.; Ishihara, T. *Tetrahedron Lett.* **2008**, 49, 2106; (c) Gestmann, D.; Laurent, A. J.; Laurent, E. G. *J. Fluorine Chem.* **1996**, 80, 27; (d) Yamazaki, T.; Shinohara, N.; Kitazume, T.; Sato, S. *J. Fluorine Chem.* **1999**, 97, 91.