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A new route to α-trifluoromethyl-α,β-unsaturated esters

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Abstract

The treatment of α-bromo-α,β-unsaturated esters with $FSO_2CF_2CO_2Me$ and CuI in DMF/HMPA constitutes a new synthetic scheme for the preparation of α-trifluoromethyl-α,β-unsaturated esters. © 2000 Elsevier Science Ltd. All rights reserved.

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Trifluoromethylated organic molecules often confer significant changes in chemical and physical properties. The importance of the effect of the trifluoromethyl group on biological activity is well known. Therefore, methods for the synthesis of tifluoromethylated compounds have received a growing interest in recent years.[1] Trifluoromethylation[2] and halogen-exchange reaction[3] are possible methods for constructing trifluoromethylated compounds, but these suffer from low reactivity and low selectivity. An alternative approach is the preparation and application of trifluoromethylated building blocks.[4] Among these, α-trifluoromethyl-α,β-unsaturated esters **1** have served as building blocks for the preparation of trifluoromethylated biologically active compounds.[5] Several years ago, Lang et al.[6] reported that the Reformatzky reaction of methyl 2,2-dichloro-3,3,3-trifluoropropionate with aldehydes followed by acylation and reductive elimination gave compound **1** formed as nearly a 1:1 mixture of *E*- and *Z*-isomers. We describe herein a new method for the predominant preparation of (*Z*)-α-trifluoromethyl-α,β-unsaturated esters **1**.

The new route to α-trifluoromethyl-α,β-unsaturated esters **1** was based on the trifluoromethylation of bromo-α,β-unsaturated esters **3** (Scheme 1). Ylide **2** was prepared from triphenylphosphine and ethyl bromoacetate in four steps in 50% overall yield.[7] The Wittig reaction of aldehydes with ylide **2** provided the *Z*-isomer of α-bromo-α,β-unsaturated esters **3** as the major product in high yield (Table 1). The *Z*- and *E*-isomer of compound **3c** and **3d** can be separated by column chromatography. However, other *Z*- and *E*-isomers of α-bromo-α,β-unsaturated esters could not be separated and the mixture was directly used in the next reaction. Although the reaction of the in situ generated trifluoromethylcopper reagent (CF_3Cu) with alkenyl and aryl halides is useful for direct introduction of the trifluoromethyl group into a molecule,[8] the coupling of in situ generated CF_3Cu with α-halo-α,β-unsaturated ester has

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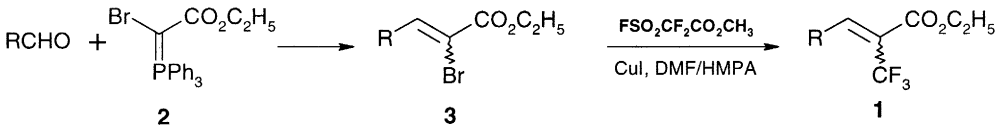
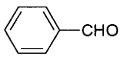
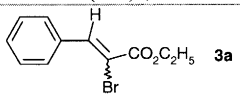
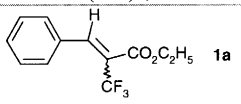
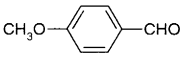
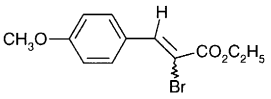
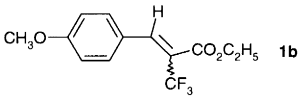
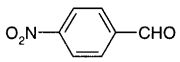
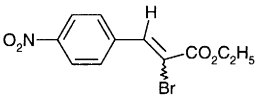
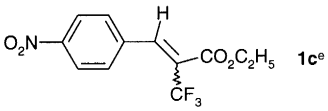
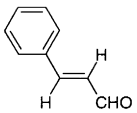
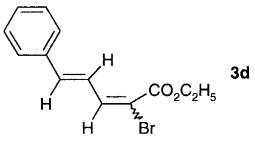
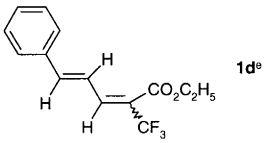
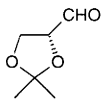
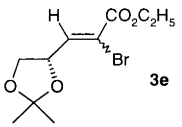
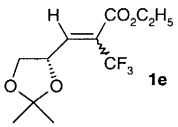
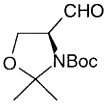
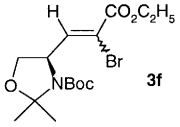
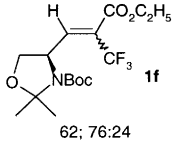


Scheme 1.

not been reported. We were delighted to observe that the treatment of an 83:17 mixture of *Z*- and *E*-**3a** with $FSO_2CF_2CO_2Me$ and CuI in DMF/HMPA[9] at 75°C gave a 61:39 mixture of *Z*- and *E*-**1a** in 90% isolated yield. Various kinds of bromo alkenes **3** were used for the preparation of α-trifluoromethyl-α,β-unsaturated esters **1** under the same reaction conditions (Table 1). The configuration of the double bond in **1** was determined by chemical shifts of the alkenyl proton: The alkenyl proton in the *Z*-isomer appeared at lower field than in the *E*-isomer.[6] The following points derived from the trifluoromethylation are noteworthy: (1) an excess of $FSO_2CF_2CO_2Me$ (3.0–4.5 equiv.) was necessary for the total conversion of bromo-α,β-unsaturated esters **3**, otherwise, the pure compound **1** was not obtained, because **1** and **3** could not be separated by column chromatography; (2) the *Z*-isomer of compound **1** was produced as the

Table 1
Synthesis of α-trifluoromethyl-α,β-unsaturated esters **1**

Entry	Aldehyde	Intermediate **3** Yield (%)[a]; Z:E[b]	Product **1** Yield (%)[c]; Z:E[d]
1		 **3a** 67; 83:17	 **1a** 90; 61:39
2		 **3b** 89; 92:8	 **1b** 93; 76:24
3		 **3c** 98; 86:14	 **1c**[e] 87; 89:11
4		 **3d** 87; 79:21	 **1d**[e] 42; 80:20
5		 **3e** 67; 92:8	 **1e** 68; 89:11
6		 **3f** 74; 95:5	 **1f** 62; 76:24

[a] Yields were based on aldehydes; [b] This ratio was determined by ^1H NMR; [c] Yields were based on **3**; [d] This ratio was determined by ^{19}F NMR; [e] These compounds were prepared from the Z-**3**

major product, but the double bond was isomerized in this reaction. A mixture of *Z*- and *E*-isomers of compound **1c** and **1d** was formed from the *Z*-isomer of compound **3c** and **3d**, respectively, (entries 3 and 4). When a mixture of *Z*- and *E*-isomers of compound **3** was used for the trifluoromethylation, the *Z*:*E* ratio of compound **1** decreased (entries 1, 2, 5 and 6); (3) in the case of compound **3d** (entry 4), the yield was low (42% isolated yield) because fluoro-containing by-products were produced and detected by ^{19}F NMR of the reaction mixture.

The preparation of α-trifluoromethyl-α,β-unsaturated esters is illustrated by the synthesis of **1c**: A solution of $FSO_2CF_2CO_2CH_3$ (1.80 ml, 14.15 mmol) in DMF (3.6 ml) was added dropwise over a period of 2 h to a mixture of *Z*-**3c** (1.00 g, 3.34 mmol), CuI (1.60 g, 8.39 mmol) and HMPA (1.5 ml) in DMF (9.0 ml) at 75°C. The reaction mixture was stirred at 75°C for 10 h before being cooled to room temperature. Saturated aq. NH_4Cl (10 ml) was added and the mixture was extracted with Et_2O (3×15 ml). The organic layer was washed with water, brine and dried over Na_2SO_4. The solvent was removed in vacuo. Purification of the residue by column chromatography on silica gel and elution with 15:1 hexanes:ethyl acetate to afford *Z*-**1c** (0.74 g, 77% isolated yield) as a white solid and *E*-**1c** (96 mg, 10% isolated yield) also as a white solid.[10]

In summary, a new method for the synthesis of α-trifluoromethyl-α,β-unsaturated esters was developed. We are currently trying to apply these developed procedures to the synthesis of nucleosides bearing trifluoromethyl groups.

Acknowledgements

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10. Compound *Z*-**1c**: ^{19}F NMR ($CDCl_3$, 376 MHz, CF_3CO_2H as an external standard, upfield positive) δ −19.0 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 (t, *J*=7.0 Hz, 3H), 4.26 (q, *J*=7.0 Hz, 2H), 7.54 (d, *J*=9.0 Hz, 2H), 8.11 (s, 1H), 8.27 (d, *J*=9.0 Hz, 2H); *m/z* (EI): 290 (M^++1, 12), 289 (M^+, 26), 244 (100); IR (KBr): γ_{max}: 1772, 1639, 1603, 1521 cm^{-1}. Anal. calcd for $C_{12}H_{10}F_3NO_4$: C, 49.83; H, 3.49; N, 4.84. Found: C, 49.80; H, 3.59; N, 4.84. Compound *E*-**1c**: ^{19}F NMR ($CDCl_3$, 376 Hz, CF_3CO_2H as an external standard, upfield positive) δ −12.6 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 (t, *J*=7.0 Hz, 3H), 4.39 (q, *J*=7.0 Hz, 2H), 7.51 (s, 1H), 7.53 (d, *J*=9.0 Hz, 2H), 8.27 (d, *J*=9.0 Hz, 2H); *m/z* (EI): 289 (M^+, 27), 244 (100); IR (KBr): γ_{max}: 1727, 1656, 1600, 1519 cm^{-1}. Anal. calcd for $C_{12}H_{10}F_3NO_4$: C, 49.83; H, 3.49; N, 4.84. Found: C, 49.86; H, 3.65; N, 4.78.