

A Convenient Synthesis of α -Alkoxy carbonyl- α, β -unsaturated Trifluoromethyl Ketones

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α -Alkoxy carbonyl- α, β -unsaturated trifluoromethyl ketones are easily prepared by Knoevenagel condensation of aldehydes with trifluoroacetoacetates in the presence of silica gel functionalized with amino groups and *p*-toluenesulfonic acid.

The method gives the products in moderate to good yields.

α -Alkoxy carbonyl- α, β -unsaturated methyl ketones are effective fungicides against *Cochliobolus miyabeanus*, *Piricularia oryzae*, *Colletotrichum lagenarium*.¹

In attempts to improve the biological activity of organic compounds, the replacement of hydrogen by fluorine has become a common practice for medicinal chemists.² This led us to prepare α -alkoxy carbonyl- α, β -unsaturated trifluoromethyl ketones and study their properties. Although many methods of synthesizing α, β -unsaturated trifluoromethyl ketones have been reported,³ those of α -alkoxy carbonyl-substituted compounds have not been known.

Knoevenagel condensation is one of the useful reactions in the formation of α, β -unsaturated compounds. However, the condensation of active methylene compounds having trifluoroacetyl group with carbonyl compounds appears to be difficult because the addition of a catalyst amine to the former compounds occurs preferentially.⁴

This report describes Knoevenagel condensation of aldehydes **1** with trifluoroacetoacetates **2** in the presence of silica gel functionalized with amino groups and *p*-toluenesulfonic acid, to give α -alkoxy carbonyl- α, β -unsaturated trifluoromethyl ketones **3** as shown below.

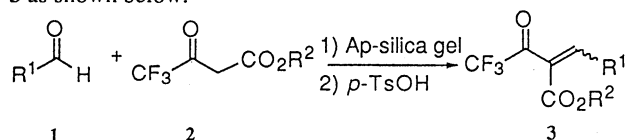


Table 1 shows the results of this reaction. In the presence of usual catalyst such as piperidine/AcOH, the condensation gives the corresponding product in low yield (see footnote d in Table 1), whereas the use of silica gel functionalized with amino groups and *p*-toluenesulfonic acid affords the products in moderate to good yields. All the compounds are obtained as a mixture of *Z*- and *E*-isomers.⁵

A typical procedure is as follows: To a solution of 2 mmol of benzaldehyde and 2 mmol of ethyl trifluoroacetoacetate in dry benzene (4 ml) was added silica gel functionalized with amino groups⁶ (0.3 g). The mixture was refluxed with stirring for 2 h. *p*-Toluenesulfonic acid (1 mmol) was then added and the mixture was further refluxed for 1 h. After removal of the solvent, the residue was chromatographed on silica gel using CH₂Cl₂ as an eluent.

Table 1. Synthesis of α -alkoxy carbonyl- α, β -unsaturated trifluoromethyl ketones

Entry	R ¹	R ²	Conv. / % ^a	Yield / % ^b	Z : E ^c
1	Ph	Et	90	58 ^d	1 : 2.1
2	4-CH ₃ C ₆ H ₄	Et	86	61	1 : 1.4
3	4-ClC ₆ H ₄	Et	83	55	1 : 1.4
4	2,4-Cl ₂ C ₆ H ₃	Et	75	43	1 : 1.8
5	Cyclohexyl	Et	99	70 ^e	1 : 1.8
6	4-CH ₃ C ₆ H ₄	<i>i</i> -Pr	89	58	1 : 1.4

^a Referred to the consumed **1** by GLC analysis. ^b Determined by GLC analysis. ^c Determined by ¹H NMR. ^d In the presence of piperidine/AcOH, the product was obtained in 23% yield. ^e Isolated yield.

In conclusion, the present investigation offers a method for the preparation of α -alkoxy carbonyl- α, β -unsaturated trifluoromethyl ketones with the advantages of easy work-up, simple reaction conditions, and affording the products in satisfactory yields.

The biological activity of **3** is under study.

References and Notes

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- Typical spectral data for ethyl benzaltrifluoroacetoacetate (**3a**): ¹H NMR (CDCl₃) *E*-isomer: δ 1.33 (t, *J* = 7.1 Hz, 3H), 4.35 (q, *J* = 7.1 Hz, 2H), 7.36-7.45 (m, 5H), 8.00 (s, 1H). *Z*-isomer: δ 1.30 (t, *J* = 7.1 Hz, 3H), 4.37 (q, *J* = 7.1 Hz, 2H), 7.42-7.55 (m, 5H), 7.82 (s, 1H). *Z*-isomers of ethyl benzalacetoacetates are unstable in solution and isomerize to their *E*-isomers. See W. M. Phillips and D. J. Currie, *Can. J. Chem.*, 47, 3137 (1969). After **3a** was allowed to stand in CDCl₃ for 2 days, the ratio of integral peak at 7.82 ppm to 8.00 ppm changed from 1 : 2.1 to 1 : 6.7.
- Silica gel functionalized with amino groups was prepared by reaction of silica gel with 3-aminopropyltriethoxysilane. See E. Angeletti, C. Canepa, G. Marinetti, and P. Venturello, *J. Chem. Soc., Perkin Trans. 1*, 1989, 105.