A Convenient Synthesis of α-Alkoxycarbonyl-α, β-unsaturated Trifluoromethyl Ketones

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α-Alkoxycarbonyl-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.

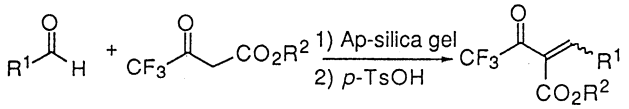
The method gives the products in moderate to good yields.

α-Alkoxycarbonyl-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-alkoxycarbonyl-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-alkoxycarbonyl-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-alkoxycarbonyl-α,β-unsaturated trifluoromethyl ketones **3** as shown below.



1 2 3

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 groups[6] (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 CH_2Cl_2 as an eluent.

Table 1. Synthesis of α–alkoxycarbonyl-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-$CH_3C_6H_4$	Et	86	61	1 : 1.4
3	4-ClC_6H_4	Et	83	55	1 : 1.4
4	2,4-$Cl_2C_6H_3$	Et	75	43	1 : 1.8
5	Cyclohexyl	Et	99	70[e]	1 : 1.8
6	4-$CH_3C_6H_4$	*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-alkoxycarbonyl-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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3 D. Mead, R. Loh, A. E. Asato, and R. S. H. Liu, *Tetrahedron Lett.*, **26**, 2873 (1985); W. S. Huang and C. Y. Yuan, *J. Chem. Soc., Perkin Trans. 1*, **1995**, 741.

4 A. Gazit and Z. Rappoport, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 2863.

5 Typical spectral data for ethyl benzaltrifluoroacetoacetate (**3a**) : ^1H NMR ($CDCl_3$) *E*- isomer : δ 1.33 (t, *J* = 7.1Hz, 3H), 4.35 (q, *J* = 7.1Hz, 2H), 7.36-7.45 (m, 5H), 8.00 (s, 1H). *Z*- isomer : δ 1.30 (t, *J* = 7.1Hz, 3H), 4.37 (q, *J* = 7.1Hz, 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 $CDCl_3$ 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.

6 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.