

Surface-mediated Solid-phase Reaction. Part 2.¹ Highly Selective Mono- and Di-C-alkylation of 1,3-Dicarbonyl Compounds on the Surface of Alumina

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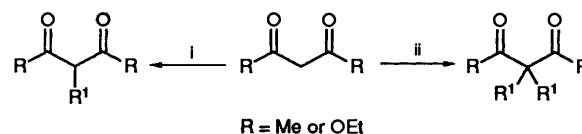
Highly selective mono- and di-C-alkylation of 1,3-dicarbonyl compounds with different, structurally varied alkyl halides has been achieved in high yields through a simple solvent-free reaction on the surface of alumina impregnated with sodium or potassium alkoxide.

Reactions using reagents or reactants on insoluble inorganic supports have stimulated considerable interest among synthetic chemists recently.² Advantages frequently claimed in favour of supported reagents compared with their homogeneous counterparts are ease of set-up and work-up, mild experimental conditions, rapid reactions, and gains in yield and/or selectivity. It has also been demonstrated that attempts to carry out the same reactions with unsupported reagents frequently either fail or result in the formation of a mixture of products. A recent modification in this technology is the technique of surface-mediated solid-phase reaction which has already gained much importance and popularity.³ In our previous paper,¹ we demonstrated a dramatic acceleration of Michael addition on the solid surface of alumina and herein wish to disclose a significant selectivity in C-alkylation of 1,3-dicarbonyl compounds.

Selective C-alkylation of 1,3-dicarbonyl compounds having two active hydrogen atoms through a simple and mild operation remains one of the more formidable problems in organic synthesis.⁴ The difficulties frequently encountered in the C-alkylation of 1,3-dicarbonyl compounds by traditional methods using bases are the presence of varying amounts of side products due to concomitant O-alkylation, di-C-alkylation, cleavage of 1,3-diketones and Claisen condensation.⁴ Although a number of

methods using thallium enolates,⁵ cobalt and other metal complexes,⁶ tetraalkylammonium fluorides⁷ and its other derivatives⁸ have been shown to be useful to overcome such difficulties, these methods have one or more limitations as regards the scope and generality of the reaction,⁹ the use of toxic materials, tedious and long reaction procedures, and/or relatively low yields of products.

We now report a solution to this problem which provides a simple and controlled procedure for the selective mono- as well as di-C-alkylation of 1,3-dicarbonyl compounds through a solvent-free reaction on the surface of alumina impregnated with sodium or potassium alkoxide (Scheme 1).



Scheme 1 Reagents and conditions: i, KOBu^t or NaOEt (1 equiv.) on Al₂O₃, R₁X (1 equiv.), room temp.; ii, NaOEt (2.5 equiv.) on Al₂O₃, R₁X (2 equiv.), room temp.

Results and Discussions

In a typical general procedure, the 1,3-dicarbonyl compound

Table 1 Mono- and di-C-alkylations of 1,3-dicarbonyl compounds on the surface of alumina

Entry	1,3-Dicarbonyl compounds	Alkyl halide	Mono-C-alkylation		Di-C-alkylation	
			t/h	Yield (%) ^a	t/h	Yield (%) ^a
1	MeCOCH ₂ CO ₂ Et	MeI	6	90	6	80
2	1	CH ₂ =CH-CH ₂ Br	0.5	88	1	85
3	1	BrCH ₂ CO ₂ Et	6	72	15	70
4	1	PhCH ₂ Br	5	85	24	80
5	CH ₂ (CO ₂ Et) ₂	MeI	5	80	5	78
6	2	CH ₂ =CH-CH ₂ Br	1	70	3	75
7	2	BrCH ₂ CO ₂ Et	6	75	20	82
8	2	PhCH ₂ Br	6	80	22	80
9	CH ₂ (COMe) ₂	MeI	22	86	24	75
10	3	CH ₂ =CH-CH ₂ Br	1	85	16	76
11	3	BrCH ₂ CO ₂ Et	16	75	22	72
12	3	PhCH ₂ Br	4	80	18	85
13		MeI	6	92	—	—
14	4	CH ₂ =CH-CH ₂ Br	0.5	92	—	—
15	4	PhCH ₂ Br	5	92	—	—
16	4	BrCH ₂ CO ₂ Et	6	86	—	—

^a The yield was calculated on the basis of isolated products after purification.

Table 2 IR and ¹H NMR data for alkylated products

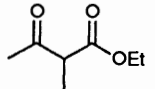
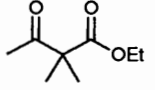
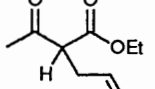
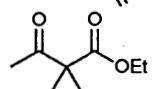
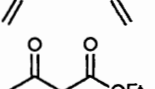
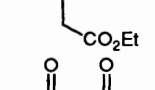
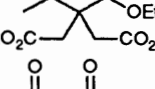
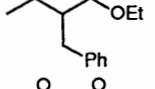
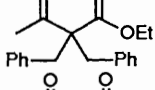
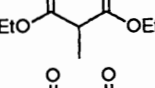
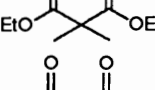
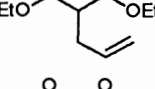
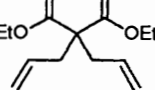
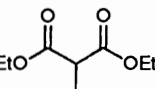
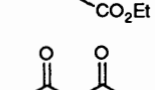
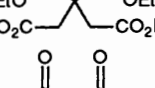
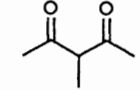
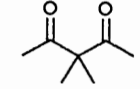
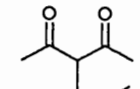
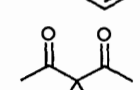
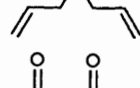
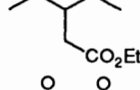
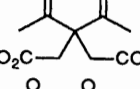
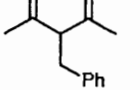
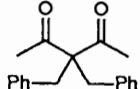
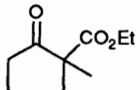
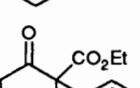
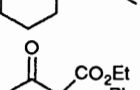
Alkylated product	$\nu_{\max}/\text{cm}^{-1}$	$\delta_{\text{H}}/\text{ppm}$
	1720, 1735	1.28 (3 H, t, <i>J</i> 7), 1.33 (3 H, d, <i>J</i> 7), 2.15 (3 H, s), 3.4 (1 H, q, <i>J</i> 7), 4.21 (2 H, q, <i>J</i> 7)
	1710, 1735	1.23 (3 H, t, <i>J</i> 7), 1.26 (6 H, s), 2.06 (3 H, s), 4.11 (2 H, q, <i>J</i> 7)
	1710, 1740	1.26 (3 H, t, <i>J</i> 8), 2.13 (3 H, s), 2.46 (2 H, m), 3.16–3.3 (1 H, m), 4.11 (2 H, q, <i>J</i> 8), 4.8–6.0 (3 H, m)
	1710, 1740	1.26 (3 H, t, <i>J</i> 7), 2.03 (3 H, s), 2.55 (4 H, d, <i>J</i> 6), 4.15 (2 H, q, <i>J</i> 7), 4.86–5.96 (6 H, m)
	1730	1.23 (3 H, t, <i>J</i> 6), 1.4 (3 H, t, <i>J</i> 7), 2.16 and 2.3 (3 H, 2 s), 2.76 (dd, <i>J</i> 3, 8), 4.0–4.3 (4 H, m)
	1715, 1735	1.26 (9 H, t, <i>J</i> 7), 2.2 (3 H, s), 3.0 (4 H, s), 3.9–4.3 (6 H, m)
	1710, 1735	1.16 (3 H, t, <i>J</i> 6), 1.77 and 2.06 (3 H, 2 s), 3.03 (2 H, m), 3.06 (1 H, m), 4.06 (2 H, q, <i>J</i> 6), 7.06 (5 H, s)
	1710, 1735	1.13 (3 H, t, <i>J</i> 7), 1.8 (3 H, s), 3.13 (4 H, s), 4.0 (2 H, q, <i>J</i> 7), 7.13 (10 H, s)
	1735, 1750	1.26 (6 H, t, <i>J</i> 7), 1.33 (3 H, d, <i>J</i> 7), 3.26 (1 H, q, <i>J</i> 7), 4.13 (4 H, q, <i>J</i> 7)
	1730	1.3 (6 H, t, <i>J</i> 7), 1.36 (6 H, s), 4.13 (4 H, q, <i>J</i> 7)
	1735, 1750	1.26 (6 H, t, <i>J</i> 8), 2.43–2.66 (2 H, m), 3.27 (1 H, m), 4.13 (4 H, q, <i>J</i> 7), 4.86–6.16 (3 H, m)
	1735	1.23 (6 H, t, <i>J</i> 6), 2.55 (4 H, d, <i>J</i> 6), 4.13 (4 H, q, <i>J</i> 7), 4.83–6.0 (6 H, m)
	1735, 1750	1.3 (3 H, t, <i>J</i> 7), 1.43 (6 H, t, <i>J</i> 7), 2.8 (2 H, d, <i>J</i> 7), 3.6 (1 H, t, <i>J</i> 7), 3.9–4.3 (6 H, m)
	1735	1.26 (12 H, t, <i>J</i> 7), 3.06 (4 H, s), 3.9–4.33 (8 H, m)
	1735	1.2 (6 H, t, <i>J</i> 7), 3.0–3.16 (2 H, dd, <i>J</i> 2.6), 3.4 (1 H, t, <i>J</i> 6), 4.10 (4 H, q, <i>J</i> 7), 7.13 (5 H, s)
	1725	1.13 (6 H, t, <i>J</i> 7), 3.16 (4 H, s), 4.03 (4 H, q, <i>J</i> 7), 7.16 (10 H, s)

Table 2 (continued)

	1700, 1720	1.26 (d, <i>J</i> 7) and 1.27 (s) (3 H), 1.96, 2.03, 2.06, 2.13 (6 H, 4 s), 3.56 (1 H, q, <i>J</i> 7) (enol present)
	1700, 1720	1.23 (6 H, s), 2.0 (6 H, s)
	1690, 1715	1.93, 2.0, 2.03, 2.06, 2.1 (6 H, 5 s), 2.53–3.1 (2 H, m), 3.56 (1 H, t, <i>J</i> 7), 4.86–6.13 (3 H, m) (enol present)
	1695, 1725	2.0 (6 H, s), 2.61 (4 H, d, <i>J</i> 6), 4.8–5.9 (6 H, m)
	1705, 1730	1.26 (3 H, t, <i>J</i> 7), 1.95, 2.06, 2.13, 2.2 (6 H, 4 s), 2.8 (d, <i>J</i> 7) and 3.23 (s) (2 H), 3.16 (<1 H, merged with 3.23 region), 4.13 (2 H, q, <i>J</i> 7) (enol present)
	1710, 1730	1.23 (6 H, t, <i>J</i> 7), 2.1 (6 H, s), 3.13 (4 H, s), 4.06 (4 H, q, <i>J</i> 7)
	1695, 1710	2.0 and 2.03 (6 H, 2 s), 3.16 (d, <i>J</i> 4) and 3.6 (s) (2 H), 3.7 (<1 H, merged with 3.6 region), 7.13 (5 H, s) (enol present)
	1690, 1705	2.0 (6 H, s), 3.2 (4 H, s), 6.8–7.23 (10 H, m)
	1710, 1735	1.2 (3 H, s), 1.26 (3 H, t, <i>J</i> 7), 1.46–2.53 (m, 8 H), 4.06 (2 H, q, <i>J</i> 7)
	1710, 1730	1.26 (3 H, t, <i>J</i> 7), 1.5–2.7 (10 H, m), 4.23 (2 H, q, <i>J</i> 7), 4.8–6.0 (3 H, m)
	1710br	1.3 (3 H, t, <i>J</i> 7), 1.46–2.66 (8 H, m), 2.9 (2 H, q, <i>J</i> 13), 4.0 (2 H, q, <i>J</i> 7), 7.06 (5 H, s)
	1710, 1730	1.22 (3 H, t, <i>J</i> 7), 1.26 (3 H, t, <i>J</i> 6), 1.63–2.5 (8 H, m), 2.56 (2 H, s), 4.1 (4 H, q, <i>J</i> 7)

was stirred on the surface of alumina impregnated with alkoxide base for 30 min, after which the alkyl halide was added and stirring was continued under nitrogen until completion of the reaction, as monitored by TLC or GC. The product was isolated in a pure state by simple filtration chromatography of the solid mass through a short plug of silica gel. The reaction conditions could be set to produce either mono- or di-*C*-alkylated product as desired in one step. For mono-*C*-alkylation, 1 equiv. of base (KO^tBu or NaOEt) and 1 equiv. of alkyl halide were used, whereas for dialkylation, 2.5 equiv. of NaOEt and 2 equiv. of alkyl halide produced best results. The results are reported in Table 1.

As shown in Table 1, a variety of 1,3-dicarbonyl compounds underwent selective mono- and di-*C*-alkylations with several structurally varied alkyl halides in high yields under this

procedure. Under the conditions of mono-*C*-alkylation, very little (not more than 6% by GC) *O*- and di-*C*-alkylations were observed and thus isolation of pure mono-*C*-alkylated products by chromatography through a short column of silica gel did not pose any problem. During di-*C*-alkylation no other side products have been isolated. The alkylations, in general, were complete within a reasonable time.

Alkylation of ethyl acetoacetate with ethyl halide on the surface of alumina impregnated with NaOMe was reported by Bram *et al.*¹⁰ but no attempt for generalisation as a synthetic method has been made. To the best of our knowledge, this is the first report providing control over mono- and di-*C*-alkylation of 1,3-dicarbonyl compounds through a surface-mediated reaction.

Presumably, the high efficiency of this procedure for regio-selective *C*-alkylation¹⁰ is primarily due to the absence of solvent which, often, has significant contribution towards *O*-alkylation of ambident anions¹¹ and association of enolate oxygen with the surface of alumina. Moreover, alumina is known to promote ionic addition and reduce entropy effects by bringing the two reactants together.^{2b}

In conclusion, this solid surface reaction provides a one-step controlled procedure for highly selective mono- as well as di-*C*-alkylation of 1,3-dicarbonyl compounds. The reagent employed is inexpensive, nontoxic and easily prepared. Moreover, convenience, simplicity of operation, general applicability with a broad spectrum of alkyl halides and high yield will make this procedure more useful and attractive in the field of organic synthesis. Nevertheless, this procedure clearly demonstrates the high potentiality of surface-mediated solid-phase technology.

Experimental

¹H NMR spectra were recorded at 60 MHz on EM 360 spectrometers of Varian Associates in CCl₄ solutions with Me₄Si as internal standard. IR spectra were recorded on a Perkin-Elmer 298 spectrometer as a thin film (neat). GLC was done on a Shimadzu GC-9A instrument using a SE-30 column (2 m) and nitrogen as carrier gas. Thin layer chromatography was done on precoated silica gel plates (E. Merck). Alumina, supplied by SRL, India (Aluminium oxide, neutral, Brockmann activity, grade 1 for column chromatography) was used in the reaction. Silica gel (60–120 mesh) used for filtration chromatography was also from SRL, India. All the chemicals and reagents are commercial products and distilled before use.

Preparation of Alumina Impregnated with Sodium or Potassium Alkoxide.—Alumina (10 times the weight of 1,3-dicarbonyl compounds, activated at 180 °C for 4 h under vacuum) was stirred with a freshly prepared solution of potassium *tert*-butoxide in *tert*-butyl alcohol, or sodium ethoxide in ethanol for 10 min at room temperature. The solvent was completely evaporated off under reduced pressure to leave an easy flowing white powder which was used for alkylation on the same day.*

General Procedure for Mono-*C*-alkylation.—The 1,3-dicarbonyl compound (5 mmol) was added on the surface of alumina impregnated with potassium *tert*-butoxide or sodium ethoxide (5 mmol) and stirred for 30 min under nitrogen. Alkyl halide (5 mmol) was then added and stirring was continued in the solid phase until completion of the reaction, as monitored by TLC or

GC. The solid mass was then taken in a column with a short plug of silica gel and eluted with methylene dichloride. Evaporation of solvent furnished practically pure product which was further purified by column chromatography over silica gel or short-path distillation (the lower yields in a few cases may be due to loss of materials during isolation and purification).

General Procedure for Di-*C*-alkylation.—The 1,3-dicarbonyl compound (5 mmol) was stirred with alumina impregnated with sodium ethoxide (12.5 mmol) for 30 min after which the alkyl halide (10 mmol) was added and stirring was continued under nitrogen until completion of the reaction (TLC or GC). The product was isolated in the same way as described in the procedure for mono-*C*-alkylation.

To check the preparative utility, both mono- and di-*C*-alkylations were also carried out in multigram scale (5–6 g) with a few substrates following same procedures.

The alkylated products are easily characterised by their spectral data (IR and ¹H NMR) which are presented in Table 2 for ready reference.

Acknowledgements

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* The supported reagent can be stored, if necessary, under nitrogen for subsequent uses. Recovered alumina can be recycled after washing and activation.

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