Selective α-Mono- and α,α-Dialkylations of 1,3-Diketones Using Solid Base Prepared from Sodium Ethoxide and Alumina

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Synopsis. The alkylation of 1,3-diketones with alkyl halides using a solid base prepared from sodium ethoxide and alumina was carried out. The amount of 0.4 mol of sodium ethoxide on 50 g of alumina showed the best reactivity for alkylation. Selective mono- and dialkylation could be achieved by controlling the reaction temperature.

Recently, considerable attention has been focused on the application of solid bases to organic synthesis via carbanion intermediates.[1-3] Solid bases comprising RONa/alumina have been applied to reactions of β-dicarbonyl compounds.[4-6] However, the preparation of solid bases requires some specific pre- and aftertreatments, such as calcination at a high temperature (400—500 °C).[2-6] This is one of the reasons why solid bases have not been used very widely in organic synthesis. We report here on a convenient method for the preparation of a solid base using commercially available alumina without any specific pre- or aftertreatment on the application of a solid base to α-alkylation of β-diketones.

Sodium-mounted alumina was prepared as described in the experimental section. Although the FT-IR spectrum of sodium ethoxide, itself, and a mixture of the sodium ethoxide and alumina showed a strong absorption peak at 1590 cm^{-1}, that of the sodium-mounted alumina showed no absorption peak at this wavenumber, indicating the absence of sodium ethoxide on the alumina surface. Sodium might exist as a metastable sodium aluminate on the alumina surface.[2] The solid base was less hygroscopic than either sodium hydroxide or sodium hydride, and the basicity of the solid base did not decrease after lefting it stand in a glass bottle. The base could be handled without much care regarding humidity.

The methylation of 1-phenyl-1,3-butanedione (**1a**), whose pK_a is 8.23,[7] with methyl iodide (**2a**) and alumina having various amounts of sodium (containing 0.1—0.9 mol on 50 g of alumina) in acetonitrile was carried out. In each run, the amount of the solid base used was not constant, but the total amount of sodium contained in the solid base was constant, two equivalent molar amounts toward **1a**. Despite the constant total sodium amount, the production of 2-methyl-1-phenyl-1,3-butanedione[8] (**3a**) was remarkably affected by the proportion of sodium to alumina (Fig. 1). A solid base mounted with about 0.4 mol of sodium on 50 g of alumina showed the best reactivity. The reactivity decreased in regions with less or more than 0.4 mol of sodium on 50 g of alumina. These results presumably indicate that the surface structure changes with the amount of mounting sodium, and that alumina mounted with around 0.4 mol of sodium per 50 g has a good structure for carbanion formation from **1a**.

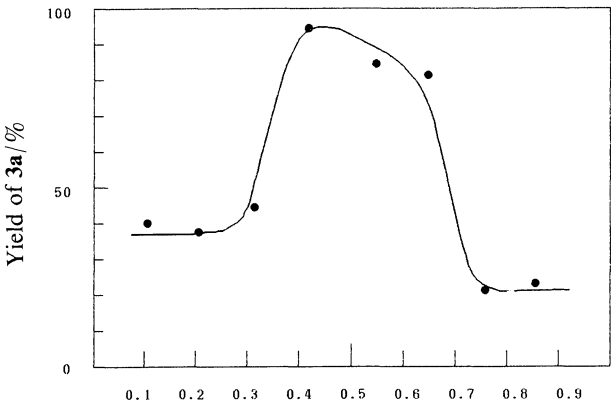

Fig. 1. Methylation of 1-phenyl-1,3-butanedione (**1a**) with methyl iodide (**2a**) in the presence of various amount of sodium-mounted alumina.

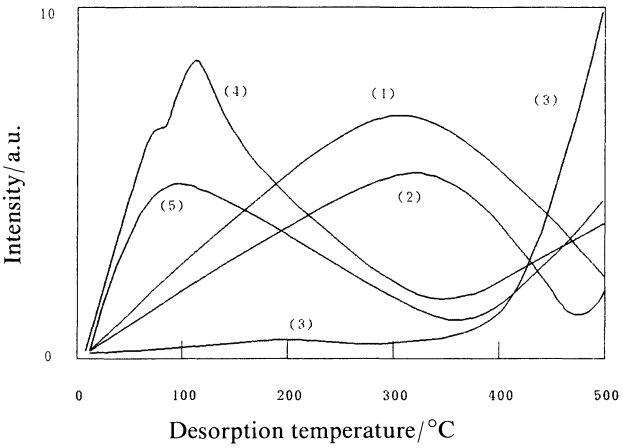

Fig. 2. TPD spectra of various amount of sodium-mounted alumina. Concentration of mounted sodium on 50 g of alumina; (1): 0.2 mol, (2): 0.3 mol, (3): 0.4 mol, (4): 0.5 mol, (5): 0.7 mol.

This was supported by the results involving the CO_2 temperature-programmed desorption (TPD).[9] The TPD spectra of various amounts of sodium on alumina are shown in Fig. 2. The TPD spectrum of 0.4 mol of sodium per 50 g of alumina showed no maximum points below at 500 °C, and the intensity of the spectrum showed a rapid increase at around 500 °C, predicting the presence of a maximum point at over 500 °C. On the other hand, the TPD spectrum of other samples showed maximum points below 500 °C. These results indicate that there are, at least, three different types of basic sites on sodium-mounted alumina. The TPD maximum

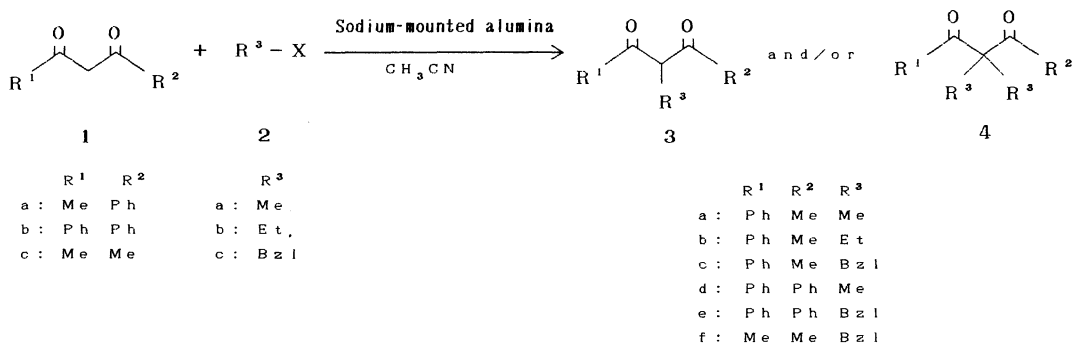

Table 1. Reaction Conditions and Yields of **3**, **4**, and **5**

Entry	1	2		Molar ratio 2/1	T °C	Yield/%[a]		
		R^3	X			3	4	5
1	**a**	Me	I	1	90	73	—	—
2	**a**	Et	I	1	90	70	—	—
3	**a**	Bzl	I	1	90	73	—	—
4	**a**	Bzl	Br	1	90	60	—	—
5	**a**	Bzl	Cl	1	90	38	—	—
6	**b**	Me	I	1	90	79	—	—
7	**b**	Bzl	I	1	90	81	—	—
8	**c**	Bzl	I	1	40	86	—	—
9	**a**	Me	I	2	140	—	66	—
10	**a**	Bzl	I	2	140	—	47	—
11	**b**	Bzl	I	2	140	—	10	40
12	**c**	Bzl	I	2	90	—	76	—

a) Isolated yields.

point at a lower temperature can be explained in terms of the presence of a weaker basic site. The results of TPD suggest that a solid base mounted with 0.4 mol of sodium on 50 g of alumina has larger amounts of strong basic sites than do other conditioned bases. The strength of the solid bases seems to be explained in terms of the appropriate dispersion of sodium on the alumina surface. The carbanion might be efficiently formed from **1a** on a strong basic site. A solid base should have a similar basicity to sodium ethoxide, which has been used for α-methylation of **1a**.

In methylation using a solid base, a solvent is still required for dissolving **1a** and methyl iodide (**2a**), and for suspending the solid base to produce the carbanion from **1a** efficiently. However, no reaction occured when a protic solvent, such as ethanol, was used. Protic solvents may damage the basic sites of sodium-mounted alumina. This, as well as the FT-IR analysis described above, indicates that an effective base for the reaction is not ethoxide on the surface.

The reaction of **1a** with ethyl iodide (**2b**) in acetonitrile, with sodium-mounted alumina (0.4 mol/50 g) at 90 °C also gave monoethylated diketone **3b** in 70% yield (Entry 2). The efficiency of the alkylation seems to be affected by the hardness of the carbon–halogen bond. The reaction of **1a** with benzyl iodide, bromide, and chloride under the same conditions gave **3c** in 73, 60, and 38% yield, respectively (Entries 3—5). Since iodide is the best leaving group, the reaction seems to be an S_N2 reaction between an alkyl halide and a carbanion of **1a**. Similarly, a reaction of 1,3-diphenyl-1,3-propanedione (**1b**) with methyl and benzyl iodide under the same conditions gave monoalkylated compounds **3d** and **3e** in 79 and 81%, respectively. No *O*-alkylated nor 2,2-dialkylated compounds could be obtained under these reaction conditions.[10] However, the reaction of 2,4-pentanedione (**1c**) with benzyl iodide did not give the monobenzylated compound **3f**, but the dibenzylated compound **4f** in 76% yield under the same conditions. When the reaction was performed at 40 °C, on the other hand, exclusive monoalkylation occurred to give **3f** in 86% yield. These results indicate that the number of alkyl groups introduced to the α-position of the 1,3-diketones **1** can be controlled by the reaction temperature; dialkylation can be expected to be achieved at a higher temperature than 90 °C in **1a** and **1b**. Indeed, 2,2-dimethyl-1-phenyl-1,3-butanedione (**4a**) was obtained in 66% yield when **1a** was reacted with methyl iodide at 140 °C in a sealed tube. Similarly, the reaction of **1a** with benzyl iodide at 140 °C gave **4c** in 47% yield. The reaction of **1b** with benzyl iodide under the same conditions, also gave **4e**, though the yield was only 10%. In this case, the second *C*-alkylation competed with *O*-alkylation; the compound **5e** was obtained in 40% yield as a main product. Steric repulsion seems to be an important factor for the second *C*-alkylation.

Experimental

Mps were determined on a Yanagimoto Melting Point Apparatus and were uncorrected. Bp for micro-scale distillation indicate the bath temperature. IR spectra were recorded on a JASCO A-3 spectrometer, NMR spectra on JEOL FX-90Q spectrometer in $CDCl_3$ solution using tetramethylsilane as an internal standard.

Preparation of Sodium-Mounted Alumina. Alumina (50 g) was added to an ethanol solution of sodium ethoxide, prepared by dissolving an appropriate amount of sodium in absolute ethanol, and then kept stand for 2 h. After removing the solvent in vacuo, a residual white solid was dried at 130 °C in an electronic oven for 24 h.

General Procedure for Alkylation of 1,3-Diketones 1. A 1,3-diketone **1** (0.2 mmol) and an alkylhalide **2** (0.2 mmol) were dissolved in 30 cm^3 of CH_3CN or some other appropriate solvent. The solution and sodium-mounted alumina (0.4 mol/50 g, 0.46 g, corresponding to 0.4 mmol of sodium) were placed in a sealed glass tube and heated at a set temperature (see Table 1) for 10—12 h. The solid base was filtered off and the filtrate was concentrated in vacuo. The residue was chromatographed on a silica-gel column (Merck Kieselgel 60). Elution with a mixture of hexane-ethyl acetate gave **3** and/or **4**. For dialkylation, 0.2 mmol of a 1,3-diketone **1**, 0.4 mmol of an alkyl halide **2** and 0.92 g of sodium-mounted alumina

were used. The structures of products **3a-f**, **4a**, and **4f** were determined by direct comparisons with authentic samples,[8,11-14]

2,2-Dibenzyl-1-phenyl-1,3-butanedione (4c): Bp 195 °C/4 mmHg (1 mmHg=133.222 Pa); IR (neat) 1710 and 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.92 (3H, s, CH_3), 3.47 (4H, ABq, J=13.9 Hz, CH_2), 7.0—7.3 (10H, m, aromatic), 7.4—7.6 (3H, m, aromatic), and 7.8—7.9 (2H, m, aromatic). Found: C, 84.0; H, 6.2%. Calcd for $C_{24}H_{22}O_2$: C, 84.1; H, 6.4%.

2,2-Dibenzyl-1,3-diphenyl-1,3-propanedione (4e): Mp 140.5—141 °C (from hexane-ethyl acetate); IR (KBr) 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.67 (4H, s, CH_2), 6.9—7.4 (16H, m, aromatic), and 7.8—7.9 (4H, m, aromatic). Found: C, 86.1; H, 5.9%. Calcd for $C_{29}H_{24}O_2$: C, 86.1; H, 6.0%.

2-Benzyl-3-benzyloxy-1,3-diphenyl-2-propen-1-one (5e): Mp 154—154.5 °C (from hexane-ethyl acetate); IR (KBr) 1630, 1330 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.69 (2H, s, CH_2), 4.30 (2H, s, CH_2), 6.6—6.7 (2H, m, aromatic), 7.1—7.3 (3H, m, aromatic), 7.21 (5H, s, aromatic), 7.4—7.6 (3H, m, aromatic), 7.54 (5H, s, aromatic), and 7.8—7.9 (2H, m, aromatic). Found: C, 85.9; H, 5.7%. Calcd for $C_{29}H_{24}O_2$: C, 86.1; H, 5.9%.

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