One-Pot *C*-Arylmethylation of Active Methylene Compounds with Aromatic Aldehydes Induced by a Me_3SiCl-NaI-MeCN Reagent

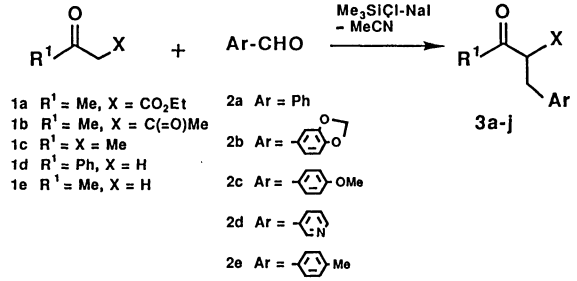
Takashi SAKAI,* Kazuyoshi MIYATA, Sadao TSUBOI, and Masanori UTAKA*
Department of Applied Chemistry, Faculty of Engineering, Okayama University, Tsushima, Okayama 700
(Received August 4, 1989)

Synopsis. Reaction of active methylene compounds with aromatic aldehydes in the presence of chlorotrimethylsilane-sodium iodide-acetonitrile reagent gave *C*-arylmethylated products, the reduced condensation products, although the reaction either with aliphatic primary aldehydes or with isobutyraldehyde afforded alkylidenation products or dihydrofurans.

C-Arylmethylation at α-position of ketonic active methylene compounds is a fundamental and important process in organic synthesis. However the conventional method with arylmethyl halides under basic conditions often suffered from dialkylation and/or self-condensation of the ketonic substrates especially in the case of 1,3-diketones.[1] For example, acetylacetone is required to be converted to a cobalt complex for *C*-benzylation with benzyl bromide. Moreover, the yield remained moderate due to the formation of by-products.[2] In order to avoid the problems, sequential reactions of the Knoevenagel condensation with aromatic aldehyde followed by reduction of the resulting carbon-carbon double bond is sometimes forced to take.[3] In this paper, we describe a development of one pot method for the *C*-arylmethylation by use of aromatic aldehydes and a chlorotrimethylsilane-sodium iodide-acetonitrile reagent.[4] Meanwhile, we recently reported that the reagent can be used for reduction of carbon-carbon double bond of conjugated enones[5a] and for deoxygenation of benzylic alcohols.[5b] On the other hand, chlorotrimethylsilane has been known to catalyze the Knoevenagel condensation.[6] The present reaction is of a successful combination of these reactions and simplified the classical stepwise procedure, although it is not suitable for aliphatic aldehydes. Primary aliphatic aldehydes gave merely Knoevenagel condensation products and isobutyraldehyde yielded dihydrofurans and/or γ-lactones.

In a typical reaction, ethyl acetoacetate (**1a**) (1 mol) was allowed to react with benzaldehyde (**2a**) (1 mol) in the presence of the Me_3SiCl-NaI-CH_3CN reagent (5 mol) in acetonitrile at room temperature to 60 °C for 16 h to give benzylated product **3a** in an 82% yield (Scheme 1, Table 1). The reaction with acetylacetone (**1b**) gave product **3e** quantitatively, much increasing the yield as compared with that in the cobalt complex method (53% yield).[2] Interestingly, methyl ethyl ketone (**1c**), acetophenone (**1d**) and acetone (**1e**) also gave the corresponding benzylated compounds **3h** (67%), **3i** (76%), and **3j** (17%), respectively. The results using various aldehydes are summarized in Table 1.

A possible mechanism is depicted in Scheme 2. Condensation of enol or enol silyl ether **4** with iodinated silyl ether **5**[7] gives β-iodo ketone intermediate **6**,[8,9] which would be readily reduced to ketone **3** by in situ generated HI in a similar manner to that discussed previously.[5] The reaction, thus, requires two moles of the reagents, which are consumed to give hexamethyldisiloxane and iodine. The mechanism is supported by the fact that the reaction of **1a** with **2a** carried out at lowered temperature (0 °C—room temperature) gave ethyl 2-benzylidene-3-oxobutanoate (**7**) (45% yield), exclusively, by elimination of HI from **6**. In addition, ethyl 2-(α-iodobenzyl)-3-

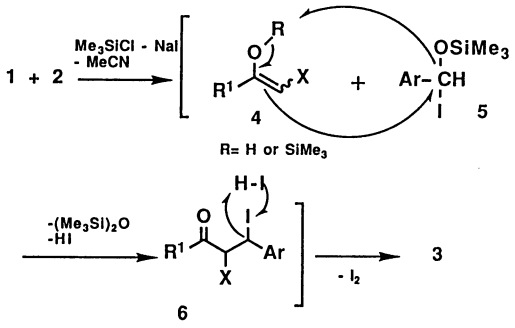


Scheme 1.

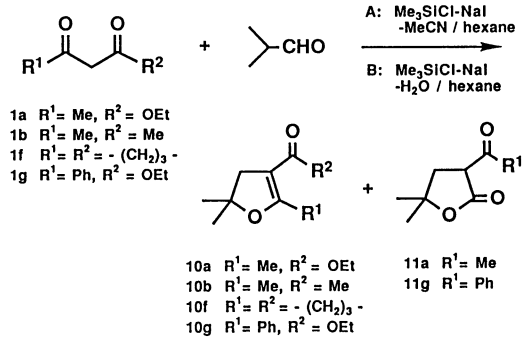
Table 1. *C*-Arylmethylation of Active Methylene Compounds **1** with Aromatic Aldehydes **2**

Substrate	Aldehyde	Product[a]				
1	**2**	**3**	R^1	X	Ar	Yield/%
1a	**2a**	**3a**	Me	CO_2Et	Ph	82
1a	**2b**	**3b**	Me	CO_2Et	3,4-(Methylenedioxy)phenyl	73
1a	**2c**	**3c**	Me	CO_2Et	*p*-Methoxyphenyl	60
1a	**2d**	**3d**	Me	CO_2Et	3-Pyridyl	29
1b	**2a**	**3e**	Me	C(=O)Me	Ph	100
1b	**2c**	**3f**	Me	C(=O)Me	*P*-Methoxyphenyl	80
1b	**2e**	**3g**	Me	C(=O)Me	*P*-Tolyl	100
1c	**2a**	**3h**	Me	Me	Ph	67
1d	**2a**	**3i**	Ph	H	Ph	76
1e	**2a**	**3j**	Me	H	Ph	17

a) Known compounds.



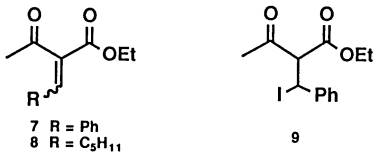
Scheme 2.



Scheme 3.

oxobutanoate (**9**) could be isolated (68% yield) by changing the solvent to ether.

Application of the present reaction to hexanal gave a mixture of unidentified products, while the reaction using ether as a solvent in place of acetonitrile at 0 °C—room temperature yielded merely a condensation product **8**.



In contrast, the reaction of **1b** with isobutyraldehyde in hexane at reflux temperature provided 4-acetyl-2,2,5-trimethyl-2,3-dihydrofuran (**10b**) in a 33% yield (Scheme 3, Table 2). The yield was markedly improved up to a quantitative one by replacing acetonitrile with the same mole of water. Favorably, the reaction can be done at room temperature. Herein, the water would be consumed to generate anhydrous HI, which may be a promoter of the reaction. The reaction is applicable to 1,3-cyclohexanedione (**1f**), giving **10f**, although the yield was moderate. The present dihydrofuran synthesis also simplified the conventional stepwise method, which involves the Knoevenagel condensation and an acidic (HCl or H_2SO_4) cyclization.[10a] Moreover, the reaction applied to β-keto esters **1a** and **1g** afforded dihydrofurans **10a, g** together with γ-lactone derivatives **11a, g** in moderate to low yields.

Table 2. Reaction of Active Methylene Compounds with Isobutyraldehyde in the Presence of Me_3SiCl-NaI

Substrate	Reactn. Condn.[a]	Product(s) (Yield/%)[b]	
		Dihydrofuran **10**	Lactone **11**
1a	A	**10a**[c] (23)	**11a**[c] (21)
1b	A	**10b**[c] (33)[d]	
	B	**10b** (100)[d]	
1f	A	**10f**[e] (17)	
	B	**10f** (45)	
1g	A	**10g**[c] (13)	**11g**[f] (41)

a) A: Reaction with Me_3SiCl-NaI-MeCN (5 mol equivalents) in hexane under reflux for 24 h; B: Reaction with Me_3SiCl-NaI-H_2O (5 mol equivalents) in hexane at room temperature for 24 h. b) Isolated by preparative TLC (hexane-acetone, 3:1). c) Spectral data were consistent with those reported. See Ref. 10a. d) Purified by distillation (bp 115—120 °C (28 mmHg, 1 mmHg=133.322 Pa.)). e) See Ref. 10b. f) New compound.

Experimental

General. IR spectra were taken on a JASCO A 102 spectrometer. ^1H NMR spectra (60 MHz) were measured with a JEOL JNM-PMX60 SI spectrometer. Chemical shifts are reported in value (ppm) down field from tetramethylsilane. Preparative TLC was done on silica gel (E. Merck, Kiesel gel 60 PF_{254}). Elemental analyses were performed by Mr. Eiichiro Amano of our laboratory using a Yanagimoto MT-3 CHN recorder. All active methylene compounds **1a—e** and aldehydes **2a—e** are commercially available.

General Procedure for the Reaction of Active Methylene Compounds 1 with Aromatic Aldehydes 2. To a stirred mixture of Me_3SiCl (1.28 ml, 10 mmol), NaI (1.50 g, 10 mmol), **1** (2 mmol), and MeCN (10 ml) was added **2** (2 mmol) at 0 °C. The mixture was stirred for 6 h at room temperature and then for additional 10 h at 60 °C. After addition of water, the organic layer was extracted with ether, washed with aqueous $Na_2S_2O_3$ to remove liberated iodine and then with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil was purified by preparative TLC on silica gel (hexane-ether, 3:1) or by vacuum distillation to give product **3**. Compounds **3a**[11a] and **3j** were identified by comparison of the spectral data with that reported in the literature[11a] and with that of authentic sample, respectively. IR and ^1H NMR spectral data, which are not given in the literatures, are shown below.

Ethyl 4-Piperonyl-3-oxobutanoate (3b):[11b] IR (neat) 1745, 1720, 1645, 1613 cm^{-1}; ^1H NMR (CCl_4) δ=1.20 (3H, t, J=7 Hz, CH_3), 2.04, 2.10 (3H, two s with a similar intensity), 2.97 (2H, d, J=7 Hz), 2.60 (1H, dd, J=6 and 7 Hz), 4.08 (2H, q, J=7 Hz), 5.83 (2H, s), 6.57 (3H, s).

Ethyl 2-(*p*-Methoxyphenyl)methyl]-3-oxobutanoate (3c):[11c] IR (neat) 1735, 1712, 1620, 1610, 1600, 1580 cm^{-1}; ^1H NMR (CCl_4) δ=1.13 (3H, t, J=7 Hz), 2.15 (3H, s), 2.95 (2H, d, J=7 Hz), 3.60 (1H, dd, J=6 and 7 Hz), 3.76 (3H, s), 4.12 (2H, q with shoulder, J=7 Hz), 6.50—7.10 (4H, m), 12.80 (s, trace, enol OH).

Ethyl 3-Oxo-2-(3-pyridylmethyl)butanoate (3d):[11d] IR (neat) 1740, 1715, 1595, 1575 cm^{-1}, ^1H NMR (CCl_4) δ=1.23 (3H, t, J=7 Hz), 2.19 (3H, s), 3.10 (2H, d, J=7 Hz), 2.70 (1H, dd, J=6 and 8 Hz), 4.13 (2H, q, J=7 Hz), 6.95—8.65 (4H, m).

3-Benzyl-2,4-pentanedione (3e):[11e] IR (neat) 1730, 1705, 1605 cm^{-1}; ^1H NMR (CCl_4) δ=1.96 (3H, s), 1.99 (3H, s), 3.02 (1.2H, d, J=7 Hz), 3.57 (0.8H, s, $PhC\underline{H}_2$- of enol form), 3.58 (0.6H, t, J=7 Hz), 7.07 (5H, s), 16.69 (0.4H, s, enol OH).

3-[(*p*-Methoxyphenyl)methyl]-2,4-pentanedione (3f):[11f] IR (neat) 1728, 1700, 1612, 1591 cm^{-1}; ^1H NMR (CCl_4) δ=2.00 (6H, s), 2.97 (1.3H, d, J=7 Hz), 3.72 (0.7H, s, $PhC\underline{H}_2$ of enol form), 3.69 (3H, s), 3.78 (0.65H, t, J=7 Hz), 6.50—7.20 (4H, m), 16.64 (0.35H, s, enol OH).

3-(*p*-Tolylmethyl)-2,4-pentanedione (3g):[11g] IR (neat) 1735, 1705, 1605 cm^{-1}; ^1H NMR (CCl_4) δ=2.00 (6H, s), 2.27 (3H, s), 3.00 (1.4H, d, J=7 Hz), 3.55 (0.6H, s, $PhCHPhC\underline{H}_2$ of enol form), 3.81 (0.7H, t, J=7 Hz), 6.94 (5H, s), 16.66 (0.3H, s, enol OH).

3-Methyl-4-phenyl-2-butanone (3h):[11h] IR (neat) 1715 cm^{-1}; ^1H NMR (CCl_4) δ=1.02 (3H, d, J=7 Hz), 1.93 (3H, s), 2.17—3.33 (3H, m), 7.09 (5H, m).

1,3-Diphenyl-1-propanone (3i):[11i] IR (neat) 1680, 1596, 1575 cm^{-1}; ^1H NMR (CCl_4) δ=3.62—2.70 (4H, m), 6.90—8.10 (10H, m).

Ethyl 2-Benzylidene-3-oxobutanoate (7):[12] The reaction was carried out in the presence of Me_3SiCl-NaI-MeCN (5 mol equivalents) in ether at 0 °C—room temperature for 7 h and worked up in a usual manner to give **7** in a 45% yield. The IR and ^1H NMR were consistent with those reported.[12]

Ethyl 2-Acetyl-2-octenoate (8).[13] The reaction was carried out in a manner described above to give **8** (48% yield): IR (neat) 1735, 1680, 1640, 1620 cm^{-1}; ^1H NMR (CCl_4) δ=0.8—1.6 (9H, m), 2.20, 2.24 (3H, s), 2.0—2.5 (2H, m), 4.16, 4.22 (2H, q, J=7 Hz), 6.67, 6.75 (1H, t, J=8 Hz).

Ethyl 2-(α-Iodobenzyl)-3-oxobutanoate (9). The reaction was done at 0—5 °C in a similar manner to that of foregoing experiment. Recrystallization from hexane-ether (10:1) gave crystalline product **9** (67% yield): mp 68.2—70.0 °C; IR (KBr) 1735, 1710, 1275 cm^{-1}; ^1H NMR (CCl_4) δ=0.89, 1.34 (3H t, J=7 Hz), 1.90, 2.35 (3H, s), 3.84, 4.22 (2H, q, J=7 Hz), 4.22, 4.49 (1H, d, J=12 Hz), 5.45, 5.54 (1H, d, J=12 Hz), 7.23 (5H, m). Found: C, 45.37; H, 4.14%. Calcd for $C_{13}H_{15}O_3I$: C, 45.11; H, 4.37%.

3,5,6,7-Tetrahydro-2,2-dimethyl-4(2*H*)-benzofuranone (10f):[10b] IR (neat) 1725, 1625 cm^{-1}; ^1H NMR (CCl_4) δ=1.41 (6H, s), 2.15 (6H, m), 2.52 (2H, m).

3-Benzoyl-5,5-dimethyl-4,5-dihydro-2(3*H*)-furanone (11g): IR (neat) 1765, 1685 cm^{-1}; ^1H NMR (CCl_4) δ=1.36 (3H, s), 1.42 (3H, s), 1.92—2.80 (2H, m), 4.06 (1H, m), 7.36 (3H, m), 7.89 (2H, m). Found: C, 71.35; H, 6.45%. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47%.

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