Alkylation and Acylation of Active Methylene Compounds Using 1,8-Diazabicyclo[5.4.0]undec-7-ene as a Base[1)]

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Active methylene compounds are selectively monoalkylated with alkyl halides in benzene using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base. Selectivity of monoalkylation decreases when the reaction is carried out in a polar solvent. Ethyl acetoacetate is O-acylated with acyl halides in the presence of DBU in acetonitrile to give the (*E*)-enol esters stereoselectively.

Alkylation and acylation of active methylene compounds are important reactions in organic chemistry and have been studied extensively.[2)] Most reactions have been carried out in hydroxylic or dipolar aprotic solvents, for the anion species of active methylene compounds are not soluble in less polar solvents. Recent development of phase transfer method[3)] or the method of ion pair extraction[4)] has enabled this reaction to be carried out in a nonpolar solvent. The merits of the reaction in a nonpolar solvent are found in the simple work-up better yields and better selectivity.[3-4)] In a previous paper it has been shown that carboxylic acids are esterified with alkyl halides in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene.[5)] In this paper we wish to report that active methylene compounds are alkylated or acylated with alkyl halides or acyl halides, respectively, in the presence of DBU. The new procedure is noteworthy for affording the selectively monoalkylated products in alkylation of active methylene compounds and the (*E*)-enol esters stereoselectively in acylation of ethyl acetoacetate.

Results and Discussion

Alkylation of active methylene compounds (Ia—f) was carried out as follows. A mixture of Ia—f, DBU, and alkyl halides (RX) in benzene was stirred at room temperature for an appropriate period, after which the DBU-hydrogen halide (DBU·HX) was either filtered off or washed out with water from the reaction mixture. The products were purified by distillation, recrystallization or column chromatography. The products of the reaction of Ia—c were also analyzed by GLPC to

$$\underset{\text{Ia—f}}{CH_2(Y)(Z)} + RX \xrightarrow[\text{benzene}]{\text{DBU}} \underset{\text{IIa—f}}{RCH(Y)(Z)} + \underset{\text{IIIa—f}}{RRC(Y)(Z)} + DBU\cdot HX \quad (1)$$

Ia: Y=CN, Z=$COOC_2H_5$
Ib: Y=CCH_3 (=O), Z=CCH_3 (=O)
Ic: Y=CCH_3 (=O), Z=$COOCH_3$
Id: Y=$COOCH_3$, Z=$SO_2C_6H_4$-CH_3-(*p*)
Ie: Y=CC_6H_5 (=O), Z=SO_2CH_3
If: Y=CCH_3 (=O), Z=$SO_2C_6H_5$

determine the exact ratio of monoalkylation to dialkylation (II/III). Results are summarized in Table 1. The O-alkylated products are also formed in alkylation of Ib or Ic, but the yields of them are poor, so discussion of O-alkylation is omitted in this paper.

The monoalkylated products (IIa—f) are important intermediates in organic synthesis, for example, they are readily coverted to the corresponding nitriles, ketones or esters by dealkoxycarbonylation or desulfonylation, and IIa, IIc, or IId can be the starting materials for the preparation of α,β-unsaturated nitriles,[6)] α,β-unsaturated ketones,[7)] or α,β-unsaturated esters,[8)] respectively.

Alkylation of Ia—f has been done by various method, but the present procedure has some advantages over the conventional methods. First, the reaction proceeds in benzene, making the work-up very simple. Secondly, as seen in Table 1, the new procedure gives the monoalkylated products exclusively. In general, the selective monoalkylation of relative stable carbanions involves difficulties such as concurrent dialkylation.[9)] This problem becomes paticularly serious in alkylation of ethyl cyanoacetate (Ia). Alkylation of Ia with ethyl iodide was carried out under various conditions to search for the best monoalkylation method. Results are summarized in Table 2. As can be seen from Table 2, the method using DBU in benzene gives monoalkylated products more selectively than the other methods and is far more superior to the ion pair extractive method of Bröndstrom[4)] which has been the best monoalkylation method known to date.[10)] The use of a nonpolar solvent such as benzene is important for this selective monoalkylation, since the ratio of mono to dialkylation decreases when the reaction is carried out in a polar solvent. The ratio of monoalkylation increases when alkylation of Ia is carried out in a nonpolar solvent, but such a tendency is not observed in alkylation of the sodium salt of Ia(Table 2). Bröndstrom and Junggern also point out that polarity of the solvent causes no appreciable effect on the ratio of mono to dialkylation in alkylation of the tetrabutylammonium salt of Ia.

The concurrent occurrence of mono and dialkylation can occur if the proton transfer equilibrium between the unreacted anion (I^-) and the monoalkylated product (II) is established at a rate comparable with that of the alkylation process.[11)] The small ratio of dialkylation in the reaction using DBU in benzene can be explained by assuming that this conditions suppress proton transfer relative to alkylation. However, it is difficult to discuss

Table 1. Alkylation of active methylene compounds (Ia—f) with alkyl halides (RX) in benzene in the presence of DBU

Substrate	RX	Time (h)	Composition of products (%)				Isolated yield of II (%)
			I[a]	II[b]	III[c]	IV[d]	
Ia	C_2H_5I	3.0	9	83	8		80
Ia	n-C_3H_7I	3.0	17	76	7		
Ia	i-C_3H_7I	4.0	38	61	1		
Ia	n-C_4H_9Br	15.0	8	88	4		65
Ia	n-C_4H_9I	5.0	6	90	4		77
Ib	C_2H_5I	2.0	11	81	5	3	
Ib	n-C_3H_7I	4.5	8	82	4	6	
Ib	n-C_4H_9Br	6.5	9	80	1	10	
Ic	C_2H_5I	1.0	7	85	3	5	
Ic	n-C_4H_9I	3.0	6	87	0	7	
Id	n-C_4H_9Br	15.0					93
Id	n-$C_8H_{17}Br$	15.0					81
Id	CH_2=CH-CH_2Br	15.0					96
Ie	CH_3I	1.0					80
Ie	C_2H_5I	5.0					76
If	CH_2=CH-CH_2Br	5.0					80
If	n-C_3H_7I	15.0					72

a) Starting materials. b) Monoalkylated products. c) Dialkylated products. d) O-alkylated products.

Table 2. Effects of base and solvent on alkylation of ethyl cyanoacetate with ethyl iodide

Base	Solvent	Composition of products (%)		
		I[a]	II[b]	III[c]
DBU	benzene	9	83	8
DBU	THF	18	72	10
DBU	CH_3CN	17	66	17
DBU	DMF	8	64	28
NaH	THF	26	29	45
NaH	CH_3CN	23	55	22
NaH	DMF	9	58	33
C_2H_5ONa	C_2H_5OH	21	42	37
$(n\text{-}C_4H_9)_4N^+OH^-$	$CHCl_3$	14	72	14[d]

a) Starting materials. b) Monoalkylated products. c) Dialkylated products. d) Data from Ref. 4a.

this matter further at the present stage, for we do not have the precise information about the structures of the reactive species in such solvents.[12]

Recently, it has been reported that DBU is effective as a base for dialkylation of active methylene compounds in *N,N*-dimethylformamide (DMF).[13] This and the results in Table 2 tell us that the use of DBU in a polar solvent is preferable when dialkylation or second alkylation in stepwise alkylation of I is the desired reaction. In fact, alkylation of Ia successively with butyl iodide in benzene and with ethyl iodide in DMF gave ethyl 2-cyano-2-ethylhexanoate in a good overall yield (60 %). The second step could also be carried out in benzene, but the reaction proceeded more slowly in benzene than in DMF.

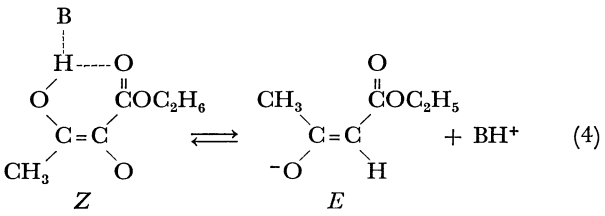
$$\text{Ia} + n\text{-}C_4H_9I \xrightarrow[\text{benzene}]{\text{DBU}} n\text{-}C_4H_9\text{-}\underset{\displaystyle CN}{\overset{\displaystyle COOC_2H_5}{\underset{|}{\overset{|}{CH}}}} \quad (2)$$

(77%)

$$n\text{-}C_4H_9\text{-}\underset{\displaystyle CN}{\overset{\displaystyle COOC_2H_5}{\underset{|}{\overset{|}{CH}}}} + C_2H_5I \xrightarrow[\text{DMF}]{\text{DBU}} n\text{-}C_4H_9\text{-}\underset{\displaystyle CN}{\overset{\displaystyle COOC_2H_5}{\underset{|}{\overset{|}{C}}}}\text{-}C_2H_5 \quad (3)$$

(78%)

Acylation of ethyl acetoacetate with acyl chlorides was carried out in the presence of DBU. Various bases such as sodium hydride, triethylamine, or pyridine have so far been used for this reaction. In general, the reaction using sodium hydride gives the C-acylated products and the reaction using triethylamine or pyridine gives the O-acylated products consisted of the mixture of the *E* and *Z* enol esters.[14] The composition of these mixtures depends on the initial concentration of the enolate, for acyl chlorides are much more reactive than most alkylating reagents. The DBU salt of ethyl acetoacetate upon treatment with acyl chlorides gave the *E* enol esters stereoselectively, the selectivity became poor when acylation was carried out in benzene. The results of acylation are summarized in Table 3. Selectivity of the formation of the *E* isomers is poor in acylation induced by triethylamine. These results suggest that the reactive forms of the enolate consist of the mixture of the *E* and *Z* form and the ratio of them depends on the nature of solvent and bases. The ^1H NMR and carbon spectra indicate that the triethylamine salt of β-dicarbonyl compounds in a nonpolar solvent is best described as one in which the chelated enol form of β-dicarbonyl compounds is hydrogen bonded to triethylamine.[15] From the analogy of the triethylamine salt, the DBU salt is also considered as the similar hydrogen bonded complex in a nonpolar solvent. In a polar solvent, these complexes become the solvent separated ions, where the *E* conformation would be preferred since the oxygen atoms bearing negative charge are maximally separated. The DBU salt is more easily solvated than the triethylamine salt, for the DBU salt has a larger and more delocalized cation than the triethylamine salt.



Consequently, acylation of ethyl acetoacetate with acyl chlorides using DBU in acetonitrile gives the *E* enol esters stereoselectively. For synthetic purposes, the *E* enol esters are very important, for the reaction of them with dialkyl cuprates gives the *E* isomers of β-dialkyl-α, β-unsaturated esters in good yields with high stereospecificity, which are important intermediates in the synthesis of natural products.[14]

Table 3. The reaction of ethyl acetoacetate with acyl chloride in the presence of DBU

RCCl (O)	Solvent	Yield (%)[a]	Isomer distribution of product	
			E(%)	*Z*(%)
CH_3CCl (O)	CH_3CN	53	97	3
C_6H_5CCl (O)	CH_3CN	79	97	3
$(CH_3)_3CCCl$ (O)	CH_3CN	95	100	0
C_6H_5CCl (O)	benzene	55	67	33
C_6H_5CCl (O)	CH_3CN[b]	75	84	16

a) Yield of isolated products. b) Triethylamine was used as a base.

In summary, DBU can be used as a base for alkylation of various active methylene compounds and acylation of ethyl acetoacetate, and the reaction proceeds both in a polar and in a nonpolar solvent. The merit of the use of DBU can be found in that the reaction course is easily controlled by polarity of the solvent.

Experimental

Solvents, DBU, and other commercially obtained materials were purified by distillation. The IR spectra were recorded with a Hitachi 215 spectrophotometer. The ^1H NMR spectra were recorded using a JEOL PS-100 spectrometer with TMS as an internal standard. GLPC analyses were performed with a Varian Aerograph 920 using a column containing Silicone-DC-550 (20%). Most of the starting materials and products were prepared by the literature methods. Sulfonyl ester (Id) was prepared by the reaction of methyl chloroacetate with sodium *p*-toluenesulfinate in DMF.[16] Keto sulfone (Ie) was prepared by the reaction of ethyl benzoate with the anion of dimethyl sulfone.[17] Keto sulfone (If) was prepared by the reaction of chloroacetone with sodium benzenesulfinate in DMF.[16]

Alkylation of Ia—c. A solution of alkyl halides (0.01 mol) in benzene (10 ml) was added to a stirred solution containing Ia—c (0.01 mol) and DBU (0.01 mol) in 50 ml of benzene. The reaction mixture was stirred at room temperature for the period indicated in Table 1, then washed with water, and the organic layer was dried over anhydrous magnesium sulfate. After removal of the solvent the residue was analyzed by GLPC. The results are given in Table 1. Some typical procedure to isolate the pure products is given below. Physical and spectral properties of the products are in good agreement with the literature value.

Ethyl 2-Cyanohexanoate (IIa, R=n-C_4H_9) from Butyl Bromide. A solution of butyl bromide (13.7 g, 0.1 mol) in 50 ml of benzene was added to a solution of ethyl cyanoacetate (11.3 g, 0.1 mol) and DBU (15.2 g, 0.1 mol) in 100 ml of benzene and the mixture was stirred at room temperature for 15 h. The reaction mixture was then washed with water, the organic layer was dried over anhydrous magnesium sulfate, and distilled. Ethyl 2-cyanohexanoate; bp 130°C/22 mmHg (lit,[18] 108 °C/8 mmHg), 11.0 g (65% yield). NMR (CCl_4) δ=0.95 (3H, t, J=4.8 Hz), 1.2—1.4 (7H, m), 1.9 (2H, m), 3.5 (1H, t, J=5.6 Hz), 4.25 (2H, q, J=7.2 Hz); IR (neat) 2250 cm^{-1} (CN), 1740 cm^{-1} (C=O).

Ethyl 2-Cyanohexanoate from Butyl Iodide. A mixture of ethyl cyanoacetate (6.7 g, 0.05 mol), DBU (7.6 g, 0.05 mol), and butyl iodide (9.2 g, 0.05 mol) in 150 ml of benzene was stirred at room temperature for 5 h, and was worked up as above to give ethyl 2-cyanohexanoate (6.5 g, 77% yield). The purity of the product was more than 95 %.

Ethyl 2-Cyano-2-ethylhexanoate. A mixture of ethyl 2-cyanohexanoate (3.4 g, 0.02 mol), DBU (3.1 g, 0.02 mol), and ethyl iodide (3.2 g, 0.02 mol) in 50 ml of DMF was stirred at room temperature for 5 h. The reaction mixture was worked up as above. Ethyl 2-cyano-2-ethylhexanoate; bp 141 °C/22 mmHg, 3.1 g (78% yield). NMR (CCl_4) δ=0.9 (6H, t, J=4.8 Hz), 1.25 (3H, t, J=7.2 Hz), 1.3 (4H, m), 1.8 (4H, m), 4.2 (2H, q, J=7.2 Hz); IR (neat) 2250 cm^{-1} (CN), 1740 cm^{-1} (C=O).

Ethyl 2-Cyanobutanoate (IIa, R=C_2H_5). A mixture of ethyl cyanoacetate (10.4 g, 0.1 mol), DBU (15.2 g, 0.1 mol), and ethy iodide (15.6 g, 0.1 mol) in 200 ml of benzene was stirred at room temperature for 3 h. The reaction mixture was then worked up as above to give 2-cyanobutanoate (11 g, 80% yield, bp 109 °C/29 mmHg) which contains ethyl cyanoacetate (about 5%) and dialkylated product (about 5%). They could not be separated by simple distillation.

Alkylation of Id. Methyl 2-(p-Tolylsulfonyl)hexanoate (IId, R=n-C_4H_9). A mixture of Id(11.0 g, 0.05 mol), DBU (7.6 g, 0.05 mol), and butyl bromide (6.9 g, 0.05 mol) in benzene (150 ml) and DMF (5 ml) was stirred at room temperature for 15 h. The reaction mixture was then washed with water and the organic layer was dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was chromatographed on silica gel with benzene as an eluent to give methyl 2-(*p*-tolylsulfonyl) hexanoate (13.6 g, 93% yield). Mp 54—55 °C; NMR ($CDCl_3$) δ=0.9 (3H, t, J=4.8 Hz), 1.28 (4H, m), 1.90 (2H, m), 2.48 (3H, s), 3.60 (3H, s), 3.70 (1H, t, J=5.6 Hz), 7.3 (2H, d, J=8.0 Hz), 7.6 (2H, d, J=8.0 Hz); IR (Nujol) 1740 cm^{-1} (C=O), 1320, 1140 cm^{-1} (SO_2).

Methyl 2-(p-Tolylsulfonyl)decanoate (IId, R=n-C_8H_{17}). A mixture of Id (2.3 g, 0.01 mol), DBU (1.52 g, 0.01 mol), and octyl bromide (1.94 g, 0.01 mol) in benzene (20 ml) and DMF (5 ml) was stirred at room temperature for 15 h. The reaction mixture was worked up as above, and the crude product was chromatographed on silica gel with benzene as an eluent to give methyl 2-(*p*-tolylsulfonyl)decanoate as a colorless oil in 81 % yield (2.7 g). NMR ($CDCl_3$) δ=0.88 (3H, t, J=4.8 Hz), 1.22 (12H, m), 1.82 (2H, m), 2.42 (3H, s), 3.60 (3H, s), 3.70 (1H, s, J=5.6 Hz), 7.30 (2H, d, J=8.0 Hz), 7.60 (2H, d, J=8.0 Hz); IR (neat) 1740 cm^{-1} (C=O), 1320, 1140 cm^{-1} (SO_2).

Methyl 2-(p-Tolylsulfonyl)-4-pentenoate (IId, R=CH_2-CH=CH_2). A mixture of Id (4.56 g, 0.02 mol), DBU (3.04 g, 0.02 mol),

and allyl bromide (2.44 g, 0.02 mol) in benzene (100 ml) and DMF (5 ml) was stirred at room temperature for 5 h. The reaction mixture was worked up as above to give methyl 2-(*p*-tolylsulfonyl)-4-pentenoate (5.1 g, 96% yield) as a colorless oil. NMR ($CDCl_3$) δ=2.40 (3H, s), 2.60 (2H, m), 3.60 (3H, s), 3.80 (3H, s), 5.00 (2H, m), 5.58 (1H, m), 7.25 (2H, d, J=8.0 Hz), 7.60 (2H, d, J=8.0 Hz); IR (neat) 1740 cm^{-1} (C=O), 1600 cm^{-1} (C=C), 1320, 1140 cm^{-1} (SO_2).

Alkylation of Ie. α-Methylsulfonylpropiophenone (IIe, R=CH_3). A mixture of Ie (1.0 g, 0.005 mol), DBU (0.76 g, 0.005 mol), and methyl iodide (0.71 g, 0.005 mol) in benzene (10 ml) and DMF (2 ml) was stirred at room temperature for 1 h. The reaction mixture was then washed with water and the organic layer was dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was recrystallized from ethanol to give colorless needles (0.85 g, 80% yield), mp 55 °C (lit,[16] 56—57 °C). NMR ($CDCl_3$) δ=1.80 (3H, d, J=7.8 Hz), 2.98(3H, s), 4.98 (1H, q, J=7.8 Hz), 7.7—8.2 (5H, m).

α-Methylsulfonylbutyrophenone (IIe, R=C_2H_5). A mixture of Ie (1.0 g, 0.005 mol), DBU (0.76 g, 0.005 mol), and ethyl iodide (0.8 g, 0.005 mol) in benzene (10 ml) and DMF (2 ml) was stirred at room temperature for 5 h. The reaction mixture was worked up as above, and the crude product was recrystallized from ethanol to give the product (0.86 g, 76 % yield) as colorless needles, mp 110 °C (lit,[19] 113 °C). NMR ($CDCl_3$) δ=1.0 (3H, t, J=7.8 Hz), 2.3 (2H, q, J=7.8 Hz), 1.98 (3H, s), 4.80 (1H, t, J=7.8 Hz), 7.5—7.8 (5H, m).

Alkylation of If. 3-Phenylsulfonylhex-5-en-2-one (IIf, R=CH_2–CH=CH_2). A mixture of If (1.93 g, 0.01 mol), DBU (1.52 g, 0.01 mol), and allyl bromide (1.27 g, 0.01 mol) in 50 ml of benzene was stirred at room temperature for 5 h. The reaction mixture was worked up as above, and the crude product was chromatographed on silica gel with benzene as an eluent to give the product (1.8 g, 80% yield) as a colorless oil. NMR (CCl_4) δ=2.30 (3H, s), 2.50 (2H, m), 4.15 (1H, t, J=7.2 Hz), 5.00 (2H, m), 5.51 (1H, m), 7.6 (5H, m); IR (neat) 1725 cm^{-1} (C=O), 1310, 1140 cm^{-1} (SO_2).

3-Phenylsulfonyl-3-hexanone (IIf, R=n-C_3H_7). A mixture of IIf (1.93 g, 0.01 mol), DBU (1.52 g, 0.01 mol), and propyl iodide (1.7 g, 0.01 mol) in 50 ml of benzene was stirred at room temperature for 15 h. The reaction mixture was worked up as above and the crude product was chromatographed on silica gel with benzene as an eluent give the product (1.7g, 72 % yield as a colorless oil. NMR (CCl_4) δ=0.85 (3H, t, J=4.8 Hz), 1.20 (2H, m), 1.78 (2H, m), 2.38 (3H, s), 4.16 (1H, t, J=5.6 Hz), 7.6—7.9 (5H, m); IR (neat) 1725 cm^{-1} (C=O), 1310, 1140 cm^{-1} (SO_2).

General Procedure of Acylation of Ethyl Acetoacetate. A solution of an acyl chloride (0.012 mol) in 10 ml of acetonitrile was added dropwise over 30 minutes to a stirred solution of ethyl acetoacetate (1.3 g, 0.01 mol) and DBU (1.8 g, 0.012 mol) in 10 ml of acetonitrile maintained below 5 °C by an ice bath. The reaction mixture was then stirred at room temperature for 3 h and was worked up by addition of water and ether, separation, and extaction of water layer with ether. The combined ethereal layers were washed with water, dried over anhydrous magnesium sulfate, and distilled to give the O-acylated product (enol ester), and the *E*/*Z* ratio of the product was determined by GLPC. The yield and the *E*/*Z* ratio of the product are given in Table 3. The following enol esters were prepared by this procedure.

Ethyl (E)-3-Benzoyloxy-2-butenoate: Bp 112 °C/0.4 mmHg (lit,[14a] 111 °C/0.4 mmHg); NMR (CCl_4) δ=1.30 (3H, t, J=7.2 Hz), 2.45 (3H, s), 4.20 (2H, q, J=7.2 Hz), 5.82 (1H, s), 7.2—8.2 (5H, m); IR (neat) 1750, 1725 cm^{-1} (C=O).

Ethyl (E)-3-Acetoxy-2-butenoate: Bp 110 °C/19 mmHg (lit,[14c] 78 °C/5 mmHg); NMR (CCl_4) δ=1.25 (3H, t, J=7.2 Hz), 2.10 (3H, s), 2.30 (3H, s), 4.05 (2H, q, J=7.2 Hz), 5.50 (1H, s); IR (neat) 1755, 1730 cm^{-1} (C=O).

Ethyl (E)-3-Pivaloyloxy-2-butenoate: Bp 103 °C/3 mmHg (lit,[20] 100 °C/2.5 mmHg); NMR (CCl_4) δ=1.26 (9H, s), 1.35 (3H, t, J=7.2 Hz), 2.32 (3H, s), 4.12 (2H, q, J=7.2 Hz), 5.55 (1H, s); IR (neat) 1755, 1730 cm^{-1} (C=O).

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