A Convenient Method for Selective *C*-Alkylation of 2-Methyl-1,3-diketones

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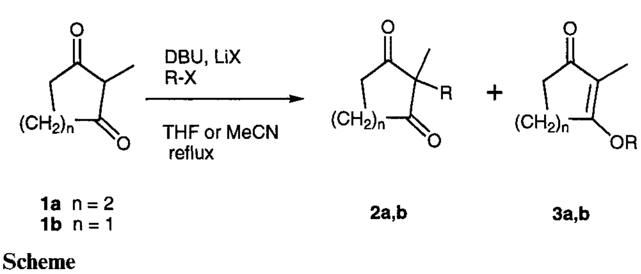
A simple and efficient *C*-alkylation of 2-methyl-1,3-diketones using a combination of lithium iodide and DBU has been developed.

It is well documented that *O*-alkylation often competes with *C*-alkylation in the alkylation of stabilized metal enolates such as those of β-dicarbonyl systems. Especially, the alkylation of highly enolic cyclic β-diketones results in the formation of significant amounts of *O*-alkylated products. Though factors which tend to favor *C*-alkylation have been unveiled[1-3] and the literature offers a few methods[4-9] for effecting the *C*-alkylation, they sometimes utilize complex, toxic and expensive reagents, need longer reaction time, and are often less selective. Some of them have been questioned with respect to reproducibility and generality.[3,10]

As a part of our ongoing research project, we were in need of various 2,2-disubstituted 1,3-dicarbonyl compounds. In search of a simple and practical method for selective *C*-alkylation, we found that 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) catalyzed the alkylation of 2-methyl-1,3-diketones in the presence of lithium halides to furnish the desired *C*-alkylated products in high yield as well as with high selectivity.



Scheme

We extensively investigated the alkylation of enolates from 2-methyl-1,3-cyclohexane- (**1a**) and -pentanedione (**1b**), since cyclic 1,3-diketones are especially prone to *O*-alkylation due to their "W" geometry and steric hindrance at the carbon.[1] The type and degree of reactivity of an enolate ion is often influenced by the nature of the cation present, the lithium cation forms a tightly associated ion pair which favors *C*-alkylation, compared with sodium or potassium.[1-3] The enolates of 2-methyl-1,3-diketones were prepared by the action of DBU in the presence of anhydrous LiI in dry THF or acetonitrile. The enolate was then heated with the alkylating agent until the reaction was complete.

The results of some representative examples are presented in Table 1. For comparison, some reported chemical yields of precedents are also included in this table. Softer and polarizable alkylating agents such as benzyl bromide and allyl bromide gave excellent results to yield **2a** almost exclusively (entry 1, 2). The alkylation with comparatively less reactive and base-sensitive methyl bromoacetate required a longer reaction time and a significant amount of *O*-alkylated product **3a** was isolated (entry 3). The reaction of 2-methyl-1,3-cyclopentanedione (**1b**) was very sluggish in THF, probably due to its lower solubility, but proceeded smoothly in acetonitrile with good selectivity and satisfactory yield (entry 4).

The fact that the choice of alkylating agent may exert a significant influence on the proportion of *C*- and *O*-alkylated products has been correlated by the HSAB appraisal.[11-14] It is known that the percentage of *O*-alkylated product decreases considerably as the alkylating halide changes from Cl to Br to I.[1-3,14-16] With the aim of studying the possibility of in situ formation of alkyl iodide in the presence of LiI, the alkylation of 2-methyl-1,3-cyclohexanedione with benzyl bromide and chloride was carried out. In the absence of both additive and DBU, the alkylation could not proceed. The conversion and selectivity were poor with only DBU. LiCl and LiBr were equally selective but the latter had a better catalytic effect. Among lithium halides employed, LiI was superior in both selectivity and chemical yield (Table 2). It is interesting to note that NaI has a similar catalytic effect (entry 5), while the selectivity was inferior because

Table 1. LiI–DBU Catalyzed Alkylation of 2-Methyl-1,3-diketones[a]

Entry	Diketone **1**	R-X	Time (h)	Yield[b] **2** (%)	Yield[b] **3** (%)	*O*/*C*-Alkyl. Ratio	Reported Yield **2** (%)
1	**1a**	$PhCH_2Br$	11	91	4	0.04	40,[6] 70[5]
2	**1a**	$CH_2{=}CHCH_2Br$	13	81	2	0.03	40,[6] 70[5]
3	**1a**	MeO_2CCH_2Br	23	77	13	0.17	
4	**1b**	$PhCH_2Br$[c]	20	70	3	0.04	72,[d,4] 65[5]
5	3-methyl-2,4-pentanedione	$PhCH_2Br$	10	85	3	0.04	

[a] Reactions were carried out in refluxing THF with each 1.1 equiv of LiI and DBU and 2.0 equiv of RX.
[b] Isolated yield.
[c] Reaction was run in refluxing MeCN.
[d] Benzyl chloride was used in place of benzyl bromide.

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Table 2. Alkylation of 2-Methyl-1,3-cyclohexanedione (**1a**) with Benzyl Bromide, Chloride and Iodide[a,b]

Entry	Additive	Yield (%)[c]			*O*/*C*-Alkylation Ratio
		Combined	**2a** (R = Bn)	**3a** (R = Bn)	
With Benzyl Bromide[d]					
1	none	60	47	13	0.27
2	LiCl	66	57	9	0.17
3	LiBr	94	80	14	0.18
4	LiI	95	91	4	0.04
5	NaI	92	77	15	0.20
With Benzyl Chloride[e]					
6	LiBr	41	31	10	0.32
7	LiI	83	76	7	0.09
With Benzyl Iodide[d]					
8	none	66	62	4	0.06
9	LiBr	91	82	9	0.11

[a] The reactions were carried out with benzyl halide (2.0 equiv) and DBU (1.1 equiv) in the presence of the additive (1.1 equiv) in THF under reflux.

[b] In the absence of DBU the alkylation did not proceed.

[c] Isolated yield.

[d] Refluxed for 11 h.

[e] Refluxed for 18 h.

of the larger size of the counter cation.[1-3] Table 2 also presents the comparison of alkylation of the same substrate with benzyl chloride and iodide. Even though the rate of reaction with benzyl iodide is much slower due to the lower reactivity of the electrophile, LiI is again found to be an excellent additive in this system (entry 7). The possibility of in situ conversion of the chloride to the softer electrophile, benzyl iodide, is supported by the experiments with benzyl iodide.

The present *C*-alkylation method based on a combination of DBU and lithium iodide appears to have broad generality, and offers an easy access to synthetically important and useful intermediates.[7,17-20]

All reactions were carried out under a positive pressure of argon. The reaction progress was monitored by TLC on silica gel 60 F_{245} by using a solvent system of EtOAc/hexane. Reaction products isolated were characterized by ^{1}H NMR (200 MHz in $CDCl_3$) and IR spectra, and identified by a comparison with those of reported values. THF was refluxed and freshly distilled from sodium–benzophenone ketyl under nitrogen, and MeCN was distilled from CaH_2. Additives were all commercial products and were dried at 120 °C under reduced pressure for several hours prior to use.

Alkylation Using LiI–DBU; Typical Procedure:

To a stirred suspension of 2-methyl-1,3-cyclohexanedione (75 mg, 0.6 mmol) and anhydr. LiI (90 mg, 0.66 mmol) in dry THF (1.25 mL) was added DBU (100 mg, 0.66 mmol). The mixture was stirred for 30 min at r. t. After addition of benzyl bromide (200 mg, 1.2 mmol), the resulting mixture was refluxed for 11 h with stirring, and then poured into ice–water. The mixture was extracted with EtOAc and the organic extract was successively washed with water, 5 % aq sodium thiosulfate and brine. The residue, after drying and concentration, was purified by preparative TLC (silica gel; 50 % EtOAc in hexane) to afford the *C*-alkylated product **2a** (R_f = 0.74, 116 mg, 91 % yield) together with the *O*-alkylated product **3a** (R_f = 0.33, 5 mg, 4 % yield).

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