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Simple Method for α-Alkylation of α,β-Unsaturated Enones Through the Michael Addition

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Abstract: *Treatment of enones and Michael acceptors with a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene in 1,3-dimethyl-2-imidazolidinone at 185 °C afforded the corresponding α-substituted enones in good yields.*

Methods allowing direct introduction of a substituent onto an enone at the α-position are of importance to organic synthesis. The resultant enones can be functionalized further at the β-position by the Michael addition. Such a strategy provides a complement to the commonly used technique that involves the reverse addition procedure, namely conjugate addition to enones followed by trapping of the resultant enolates with a carbon electrophile.[1]

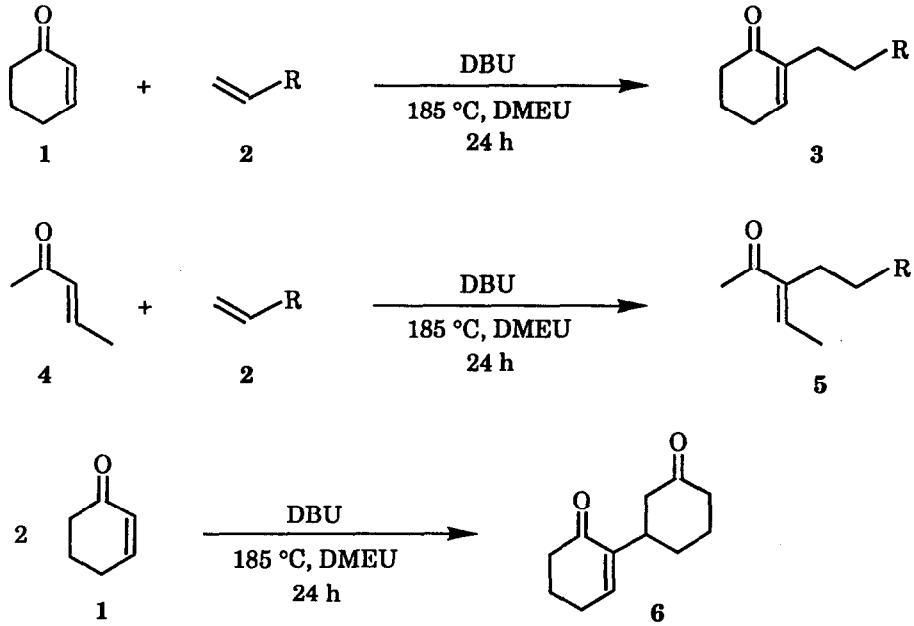
α-Functionalization of α,β-unsaturated enones can be accomplished by several methods.[2] Recent developments include the Pd-catalyzed coupling of α-iodoenones with alkenyl- or aryltributylstannanes,[3] the hydroxymethylation of α-bromo-α,β-enones,[4] the α-alkylation of α,β-enones with dimethyl acetal and trimethylsilyl triflate in pyridine,[5] and the coupling of triflyloxy-α,β-enones with vinyl or aryl tin reagents.[6,7]

We now report here a direct method for facile introduction of an alkyl group at the α-position of enones. This method involved the addition of an enone to a Michael acceptor in 1,3-dimethyl-2-imidazolidinone (DMEU) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the catalyst at elevated temperature (Scheme 1). The enones employed included 2-cyclohexen-1-one (**1**) and 3-penten-2-one (**4**); the Michael acceptors included ethyl acrylate (**2a**), phenyl vinyl sulfone (**2b**), acrylonitrile (**2c**), and 2-cyclohexen-1-one (**1**). The yields of the desired adducts (**3a–c**, **5a–c**, and **6**) ranged from 55–85% (see Table).

The general experimental procedure can be illustrated by the α-substitution of 2-cyclohexen-1-one (**1**) with ethyl acrylate (**2a**). To a DMEU solution of **1** (0.5 M) was added **2a**

(1.30 equiv) and DBU (0.20 equiv). The reaction tube was sealed and heated at 185° C for 24 h. Then the mixture was cooled, poured into ether, and washed with water. After the organic layer was dried ($MgSO_4$) and concentrated, the residue was purified by radial thin-layer chromatography with a silica gel plate. The desired α-substituted enone **3a** was isolated in 80% yield.

Scheme 1



For **2**, **3**, and **5**: (**a**) R = CO_2Et, (**b**) R = SO_2Ph, (**c**) R = CN.

In optimizing the reaction conditions, we tested many combinations of base and solvent. Our results in the Table indicate that DBU and DMEU were the most appropriate base and solvent, respectively, for this type of reaction. In the reactions of **4** with **2**, we obtained acyclic enones **5** with the vinyl methyl group trans to the acetyl group. Our stereochemical assignment was supported by the ^1H NMR nuclear Overhauser effect experiments. While irradiating **5a–c** at the frequency of the =CHMe quartet (δ 6.75–7.00 ppm), we observed significant enhancement (19.2% for **5a**, 7.8% for **5b**, and 9.7% for **5c**) of the singlet for the CH_3CO (δ 2.16–2.34 ppm). Enone **1** can be "dimerized" to give an 85% yield of **6**, which however was not genereted in the reactions of **1** with various Michael acceptors **2a–c**.

α-Functionalization of α,β-unsaturated enones, esters, and nitriles with aldehydes can be accomplished by use of diazabicyclo[2.2.2]octane (DABCO) as the catalyst.[8–12] It has been proposed that the first step in these reactions involves a Michael addition of DABCO to the α,β-unsaturated species. We found that the reaction involving DBU as the catalyst

Table. Introduction of a Substituent at the α-Position of α,β-Unsaturated Enones by Use of Michael Acceptors and 0.2 equiv of Bases in Solvent at 185 °C.

α,β-enone	Michael acceptror	base	solvent	product[§]	yield (%)
1	2a	DBU	DMEU	3a	80
1	2a	DBU[†]	DMEU	3a	82
1	2a	$N(n\text{-}Pr)_3$	DMEU	3a	55
1	2a	DABCO	DMEU	3a	30
1	2a	DMAP[‡]	DMEU	3a	5
1	2a	DBU	DMF[‡]	3a	70
1	2a	DBU	MeCN	3a	55
1	2a	DBU	THF	3a	0
1	2a	DBU	*p*-dioxane	3a	4
1	2a	DBU	MeOH	3a	0
1	2a	DBU	toluene	3a	2
1	2b	DBU	DMEU	3b	60
1	2c	DBU	DMEU	3c	55
4	2a	DBU	DMEU	5a	76
4	2b	DBU	DMEU	5b	70
4	2c	DBU	DMEU	5c	60
1	1	DBU	DMEU	6	85

[†] 1.0 equiv was employed.

[‡] DMAP = 4-(dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide.

[§] IR, ^1H NMR, ^{13}C NMR, and mass spectra of all products are consistent with the proposed structures. The ^1H NMR spectra (δ ppm, $CDCl_3$) for **3a**: 1.26 (t, J = 7.1 Hz, 3 H, CH_3), 1.95–2.04 (m, 2 H), 2.34–2.55 (m, 8 H), 4.13 (q, J = 7.1 Hz, 2 H, OCH_2), 6.81 (t, J = 4.2 Hz, 1 H, C=CH); for **3b**: 1.89–1.97 (m, 2 H), 2.31–2.37 (m, 4 H), 2.62 (t, J = 7.7 Hz, 2 H, $SCCH_2$), 3.31 (t, J = 7.7 Hz, 2 H, SCH_2), 6.85 (t, J = 3.9 Hz, 1 H, C=CH), 7.57–7.71 (m, 3 H), 7.93 (d, 2 H); for **3c**: 2.01–2.09 (m, 2 H), 2.42–2.60 (m, 8 H), 6.98 (t, J = 4.1 Hz, 1 H, C=CH); for **5a**: 1.21 (t, J = 7.1 Hz, 3 H, OCH_3), 1.88 (d, J = 7.0 Hz, 3 H, $C{=}CCH_3$), 2.26 (s, 3 H, $COCH_3$), 2.32 (t, J = 7.6 Hz, 2 H, CH_2CO_2), 2.58 (t, J = 7.6 Hz, 2 H, $C{=}CCH_2$), 4.07 (q, J = 7.1 Hz, 2 H, OCH_2), 6.75 (q, J = 7.0 Hz, 1 H, C=CH); for **5b**: 1.85 (d, J = 7.1 Hz, 3 H, $C{=}CCH_3$), 2.16 (s, 3 H, $COCH_3$), 2.62 (t, J = 7.8 Hz, 2 H, $C{=}CCH_2$), 3.12 (t, J = 7.8 Hz, 2 H, SCH_2), 6.76 (q, J = 7.1 Hz, 1 H, C=CH), 7.51–7.65 (m, 3 H), 7.87 (d, 2 H); for **5c**: 2.02 (d, J = 7.1 Hz, 3 H, $C{=}CCH_3$), 2.34 (s, 3 H, $COCH_3$), 2.50 (t, J = 6.9 Hz, 2 H, CH_2CN), 2.65 (t, J = 6.9 Hz, 2 H, $C{=}CCH_2$), 7.00 (q, J = 7.1 Hz, 1 H, C=CH); for **6**: 1.44–1.75 (m, 2 H), 1.80–2.07 (m, 4 H), 2.16–2.41 (m, 8 H), 2.91–2.98 (m, 1 H), 6.66 (t, J = 4.2 Hz, 1 H, C=CH).

underwent by a different pathway, as indicated by the results of the following reactions. Reacting **1** with isobutyraldehyde in acetonitrile, we were able to generate the aldol adduct 2-(1-hydroxy-2-methylpropyl)-2-cyclohexen-1-one (~50% yield) in the presence of the catalyst DBU, but not DABCO. Amri and Villieras[10] reported that, in the presence of DABCO, methyl vinyl ketone (no γ protons) reacts with acetaldehyde in THF to give the aldol adduct 3-(1-hydroxyethyl)-3-buten-2-one in 81% yield. We found that use of DBU, instead of DABCO, for the same reaction lead to the recovery of the starting materials only. Consequently we conclude that, for the reactions shown in Scheme 1, an acidic γ proton of **1** and **4** was removed by DBU. The resultant dienolate then reacted with a Michael acceptor (i.e., **1** and **2**) to form an adduct, in which the C–C double bond at the β,γ-position migrated to the thermodynamically more stable position to give the α,β-unsaturated enones **3**, **5**, and **6**.[13]

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