Base-Promoted Michael Reaction Concomitant with Alkylation of Cyclic-1,3-diones, an Efficient Approach to 2-Substituted Vinylogous Esters

Subhadip De, Lakshmana K. Kinthada, Alakesh Bisai*

Department of Chemistry, Indian Institute of Science Education and Research (IISER) Bhopal, ITI (Gas Rahat) Building, Govindpura, Bhopal, MP 462 023, India
Fax +91(755)4092392; E-mail: alakesh@iiserb.ac.in

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Abstract: Vinylogous esters can be synthesized by a base-promoted Michael reaction concomitant with alkylation of the cyclic 1,3-dione substrate. The methodology provides a wide range of 2-substituted vinylogous esters in good to excellent yields.

Key words: vinylogous esters, cyclohexenones, Michael reaction, alkylation, diones

Functionalized vinylogous esters such as **1a** and **1b** (Figure 1) play an important role in the synthesis of several natural products and drug molecules. Functionalized cyclohexenones provide an attractive synthetic platform to access various architecturally interesting natural products and drug molecules.[1,2] Prevalent structures are 2-alkylated-2-cyclohexenones such as (*R*)-5-methyl-2-alkylcyclohexen-2-ones **2b**–**f**, which serve as precursors for a wide range of naturally occurring terpenoids and alkaloids.[3–9] Naturally occurring (*R*)-pulegone (**4a**) has been exhaustively used for the synthesis of (*R*)-5-methyl-2-alkylcyclohexen-2-ones.[4a,6,9] Recently, enantioenriched enones have been synthesized through organocatalytic direct Michael reactions followed by aldol condensation.[4a,10] However, one of the classical ways to synthesize these compounds is through the Stork–Danheiser sequence with 2-substituted vinylogous esters such as **1a** and **1b** using a hydride nucleophile.[11]

The use of vinylogous esters has already been recognized in various areas of organic synthesis.[12,13] Prompted by this synthetic potential, we decided to develop a base-promoted methodology for the synthesis of a variety of 2-substituted vinylogous esters **5** from cycloalkane 1,3-diones **6**, ethyl acrylate, and alkyl halides. We proposed that treatment of 1,3-cyclohexanedione **6** with acrylates in the presence of a catalytic amount of base could afford a Michael adduct **7a**, which, upon subsequent treatment with alkyl halides, could lead to the formation of a variety of vinylogous esters **5** (Scheme 1).

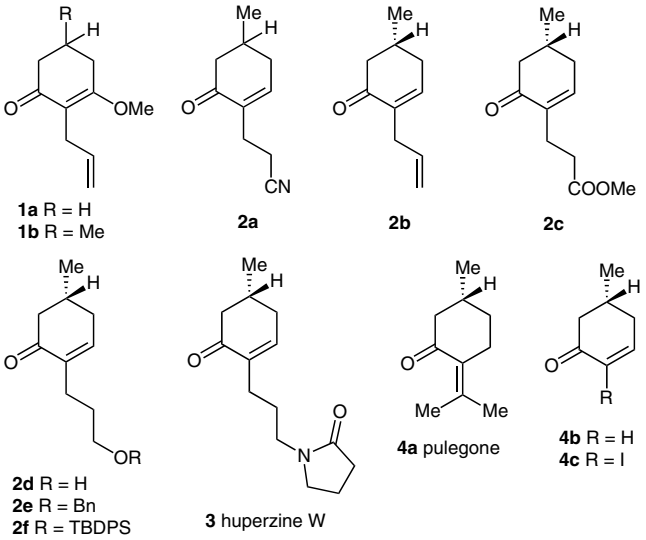
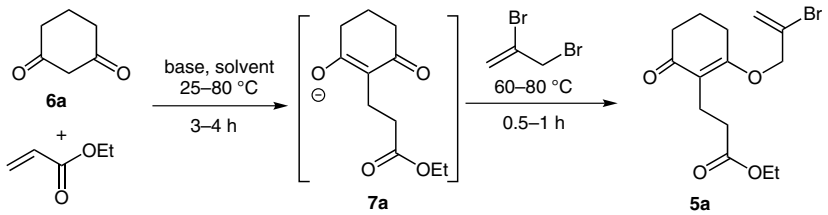


Figure 1 Important 2-alkyl-2-cyclohexenone intermediates

Initially, 1,3-cyclohexanedione **6a** was treated with ethyl acrylate in the presence of bases such as NaH, K_2CO_3, Na_2CO_3, Cs_2CO_3, *t*-BuOK in different solvents and at a range of temperatures (first step) and then treated with 2-bromoallyl bromide (second step); the results are summarized in Table 1. It was found that the Michael reaction required elevated temperature (80 °C) to form adducts **7** selectively, without any double alkylation.[14] Upon complete conversion of starting material **6** into Michael adducts **7**, the reaction mixture was treated with 2-bromo-



Scheme 1 One-pot Michael reaction followed by alkylation

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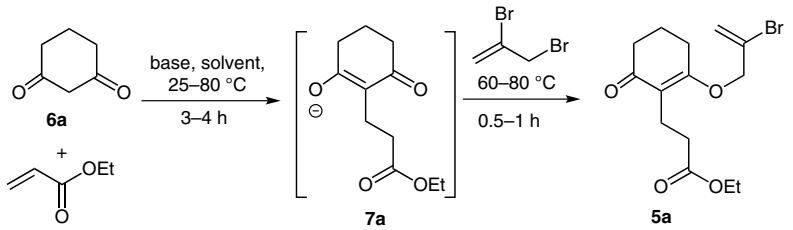
allyl bromide (1.2 equiv) and heating was continued for the time specified (Table 1). A survey of solvents led to the observation that reactions performed in *N*,*N*-dimethylformamide (DMF; entries 4, 8, and 15) and dimethyl sulfoxide (DMSO; entries 6, 10, 12, and 16), worked efficiently, whereas those conducted in tetrahydrofuran (THF) or acetonitrile (MeCN) were ineffective (Table 1). Among various conditions screened, it was found that NaH in DMSO (entry 6) and Cs_2CO_3 in DMSO (entry 16) were optimum for the Michael reactions (requiring nearly 3 h for the first step) and alkylations (requiring typically 0.5–1 h, second step).

With the optimized conditions in hand, we then turned our attention to the substrate scope for the synthesis of 2-substituted vinylogous esters. A variety of primary halides such as methyl iodide, benzyl bromide, propargyl bromide, allyl bromide, and 2-bromoallyl bromide were found to be suitable alkylating agents under the optimized conditions (Figure 2). In most cases, 1,3-cyclohexanedione (**6a**) afforded vinylogous esters **5a**–**e** in good to very high yields compared to those obtained with 1,3-cyclopentadione (**6b**; see **5f**–**j** in Figure 2). In the latter case the reactions were always associated with the formation of unidentified materials.

Table 1 Optimization of Vinylogous Ester Synthesis



Entry	Base[a]	Solvent	Temp (°C)	Time (h)[b]	Yield (%)[c,d]
1	NaH	THF	25	12/4	traces
2	NaH	DMF	25	12/4	52
3	NaH	THF	60	4/1	9
4	NaH	DMF	80	4/1	90
5	NaH	MeCN	50	3/1.5	79
6	NaH	DMSO	80	3/1	93
7	K_2CO_3	THF	60	5/5	75
8	K_2CO_3	DMF	80	4/1	82
9	K_2CO_3	MeCN	50	6/3	57
10	K_2CO_3	DMSO	80	3/1	84
11	Na_2CO_3	DMF	80	4/1	40[e]
12	Na_2CO_3	DMSO	80	4/1	63
13	Cs_2CO_3	THF	60	4/1	dec.
14	Cs_2CO_3	MeCN	50	4/1	74
15	Cs_2CO_3	DMF	80	3/1	83
16	Cs_2CO_3	DMSO	80	3/1	92
17	*t*-BuOK	THF	60	4/1	dec.
18	*t*-BuOK	MeCN	50	4/2	30
19	*t*-BuOK	DMSO	80	4/1	dec.
20	*t*-BuOK	DMF	80	4/1	21

[a] Base (1.5 equiv) was used under an inert atmosphere.
[b] Times refer to the first Michael step followed by alkylation.
[c] Reaction conditions: **6a** (0.5 mmol), ethyl acrylate (0.75 mmol), solvent (2 mL).
[d] Isolated yield.
[e] Decomposition accounts for the rest of the mass balance.

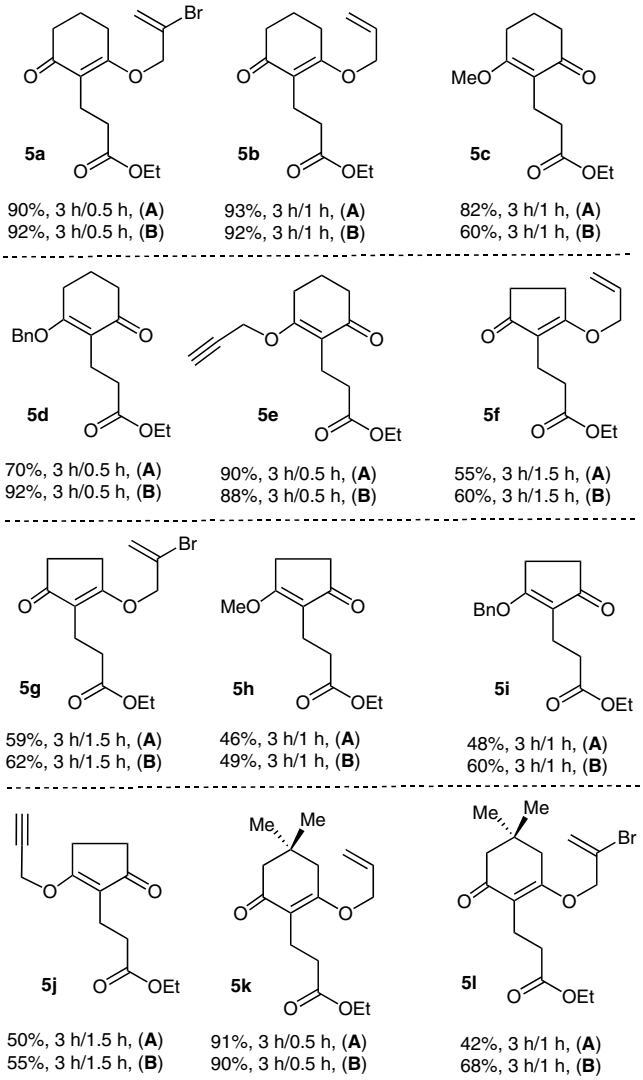


Figure 2 Substrate scope for vinylogous ester synthesis

5,5-Dimethyl-1,3-cyclohexanedione (**6c**) has been widely used in the synthesis of terpenoids and their analogues.[15,16] Thus, extending our methodology, we were able to synthesize vinylogous esters **5k**–**o** from **6c** as well as substrates **5p**–**t** from 5-dimethyl-1,3-cyclohexanedione (**6d**) under optimized conditions A and B, as shown in Figure 3. Gratifyingly, in most cases, the reaction proceeded cleanly to afford vinylogous esters **5k**–**t** in good to high yields under both sets of conditions.

To conclude, we report a convenient procedure for the preparation of cyclohexane/pentane based 2-substituted vinylogous esters **5a**–**t** through base-promoted Michael reaction concomitant with alkylation of 1,3-cyclohexane/pentane diones under mild conditions.[17] Applying this strategy, a wide variety of substrates has been synthesized in good to high yields. Further efforts in this direction are in progress and will be reported in due course.

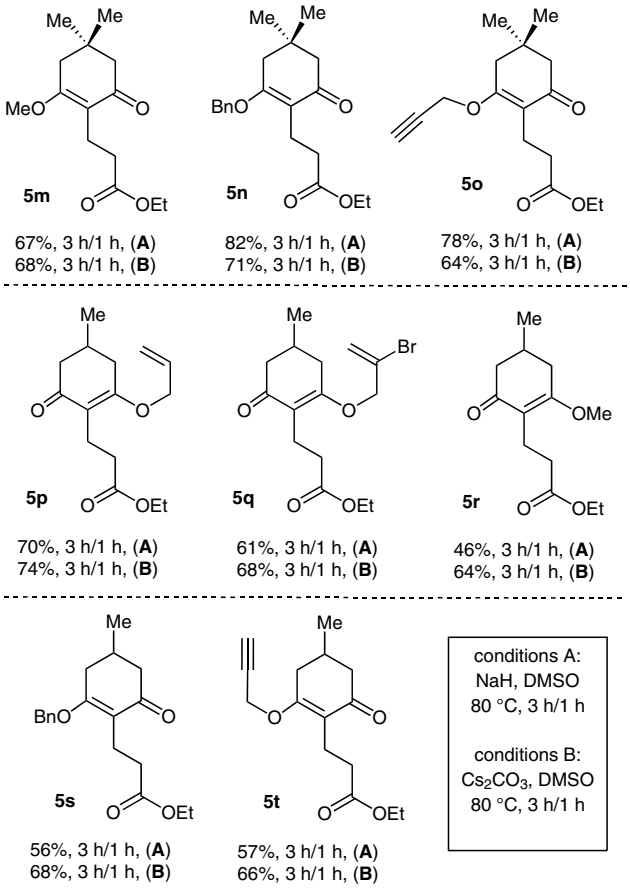


Figure 3 Substrate scope for vinylogous ester synthesis

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(17) **Synthesis of Vinylogous Esters; General Procedure:** A flame-dried, round-bottomed flask was charged with cyclic 1,3-dione (1 mmol) and ethyl acrylate (1.3 mmol) in DMSO (5 mL). To this solution was added NaH or Cs_2CO_3 (1.2 mmol) and the reaction mixture was stirred at 80 °C for the indicated time. Upon completion of the Michael reaction (typically, TLC showed complete conversion of starting materials after 3 h of reaction), alkyl halide (1.2 mmol) was added and the reaction mixture was heated at 80 °C for the indicated time (typically 1 h). Upon completion of the alkylation (TLC), the reaction mixture was acidified with 2 M HCl. The resulting mixture was extracted with EtOAc (4 × 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (petroleum ether–EtOAc) to give the pure product.

Ethyl 3-{2-[(2-Bromoallyl)oxy]-6-oxocyclohex-1-en-1-yl}propanoate (5a): R_f = 0.54 (EtOAc–hexane, 50%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.95 (m, 1 H), 5.69 (m, 1 H), 4.63 (t, *J* = 1.44 Hz, 2 H), 4.10 (q, *J* = 7.12 Hz, 2 H), 2.65 (m, 2 H), 2.55 (t, *J* = 6.2 Hz, 2 H), 2.34–2.38 (m, 4 H), 1.99 (m, 2 H), 1.24 (t, *J* = 7.16 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.9, 173.4, 170.2, 126.5, 119.0, 117.9, 70.4, 60.1, 36.3, 33.0, 25.1, 20.9, 18.0, 14.2; IR (film): 2939, 1728, 1628, 1589, 1446, 1385, 1354, 1277, 1169, 1072, 1041, 856 cm^{-1}; HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for [$C_{14}H_{19}BrO_4$+Na]$^+$: 353.0359; found: 353.0342.

Ethyl 3-[2-(Allyloxy)-6-oxocyclohex-1-en-1-yl]propanoate (5b): R_f = 0.59 (EtOAc–hexane, 50%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.88–5.98 (m, 1 H), 5.31–5.36 (m, 1 H), 5.24–5.28 (m, 1 H), 4.55 (m, 2 H), 4.08 (q, *J* = 7.12 Hz, 2 H), 2.59–2.64 (m, 2 H), 2.55 (t, *J* = 6.24 Hz, 2 H), 2.33 (m, 4 H), 1.95 (m, 2 H), 1.22 (t, *J* = 7.16 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.0, 173.6, 171.8, 132.8, 118.2, 117.5, 68.1, 60.1, 36.3, 33.1, 25.3, 20.9, 17.9, 14.2 cm^{-1}; IR (film): 2931, 1724, 1597, 1438, 1385, 1265, 1184, 1076, 1030, 930, 860 cm^{-1}; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for [$C_{19}H_{21}O_4$+Na]$^+$: 313.1434; found: 313.1273.

