

An Efficient and Simple β -Acylvinyl Anion Equivalent for Cyclohexenones

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Summary: Dilithio species available from treatment of $\Delta^{3,4}$ -3-bromocyclohexenone ketals with two equivalents of *n*-butyllithium serve as one-pot equivalents of β -vinyl-carbanions of cyclohexenones. These former ketals are available in good yield from the corresponding β -bromocyclohexenone by direct ketalization under controlled conditions.

In recent years two basic strategies have been employed to generate β -acylvinyl anion equivalents, i.e., 1. In one, the beta position of a latent carbonyl system is activated toward proton abstraction by an electron-withdrawing group (cyano,¹ nitro,² phenylthio,³ sulfonyl⁴), the resulting carbanion reacted with an electrophile, and the activating group eliminated to introduce the required unsaturation. The second method has involved lithiation of a vinyl substituent (bromo,⁵ trialkylstannyl⁶) beta to a latent carbonyl group followed by reaction of the resulting organometallic compound with electrophiles. While these studies have employed some novel methods, utilization of these reagents on a moderate-scale reaction is often inconvenient and/or expensive. Our need



1



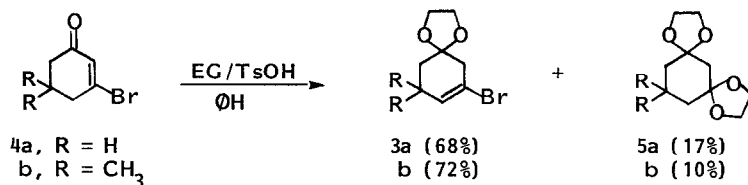
2



3

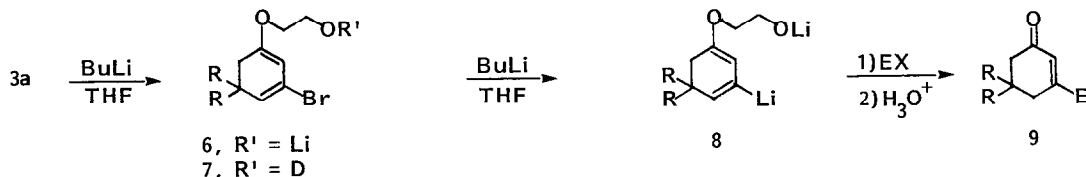
for a convenient β -acylvinyl anion reagent and our experience with lithiated ketals as metallated quinone⁷ and α -acylvinyl^{8,9} anion equivalents suggested examination of the chemistry of compounds related to 2. In spite of its simplicity and its obvious potential as a β -acylvinyl anion equivalent, neither compound 2 nor 3 could be found in the literature. We note here that ketalization of β -bromocyclohexenones¹⁰ affords ketals of type 3, and these compounds serve as a versatile one-pot equivalent of the β -acylvinyl anion of cyclohexenones.

The ketalization of 4a under standard conditions affords a time-dependent mixture of 3a and the diketal 5a; 3a can be isolated in 68% yield by control of the reaction conditions.¹¹ The structure of 3a was assigned primarily on the basis of its NMR spectrum and decoupling studies [NMR



($CCl_4/200$ MHz) δ 6.05 (seven-line m, 1 H), 3.98 (s, 4 H), 2.64 (d, $J \approx 1.8$ Hz, 2 H), 2.24 (m, 2 H), and 1.74 (t $J = 6.5$ Hz, 2 H)]. Irradiation of the vinyl hydrogen changed the doublet at 2.64 δ to a barely discernible triplet ($J \approx 1.0$ Hz) and markedly simplified the multiplet at 2.24 δ . Irradiation of the 2.24 δ signal collapsed the triplet at 1.74 δ to a singlet and the vinyl multiplet to a triplet ($J = 1.8$ Hz) while irradiation at 2.64 δ simplified the multiplet at 2.24 δ and changed the vinyl multiplet to a triplet ($J = 4.0$ Hz). These decoupling data and the chemistry described herein are only consistent with structure **3a**. The structure of **3b** has been assigned by analogy with that of **3a**: NMR ($CCl_4/90$ MHz) δ 5.73 (poorly resolved t, $J \approx 1.0$ Hz, 1 H), 3.92 (s, 4 H), 2.54 (br, s, 2 H), 2.59 (s, 2 H), and 1.12 (s, 6 H).

The reaction of **3a** with one equivalent of *n*-butyllithium gave after quenching with deuterium oxide a conjugated diene which has been assigned as **7** on the basis of its IR and NMR spectra.



Mild acidic hydrolysis of **7** afforded **4a**. However, if **3a** was treated with two equivalents of *n*-butyllithium, an electrophilic agent added, and the reaction mixture worked-up with dilute acid, functionalized cyclohexenones **9** are obtained in excellent overall yields (Table 1).¹² While the reactions reported in Table 1 were performed with pure **3a** and **3b**, the presence of the bisketal **5** does not appear to interfere with the organolithium chemistry. In the hydrolytic workup, it is converted to the 1,3-diketone which can be extracted from functionalized cyclohexenone with saturated sodium carbonate solution. In this manner a 90:10 mixture of **3a** and **5a** was reacted with cyclohexen-2-one to afford after workup as above 75% of functionalized cyclohexenone. The dilithio species **8** shows quite general reactivity yielding functionalized cyclohexenones with aldehydes and ketones as well as reactive halides. Furthermore, the chemistry works equally well to furnish 3-substituted 5,5-dimethylcyclohexenones, suggesting that its utility may only be limited by the availability of the requisite β -bromenone.

Table 1. Functionalizations of Cyclohexenones

entry	starting material	electrophile	yield ^a of 9 (%)
1	3a	iodomethane	82 ^b
2	3a	iodoethane	71 ^b
3	3a	chlorotrimethylsilane	79 ^b
4	3a	cyclohexanone	80 ^c
5	3a	cyclopentanone	76 ^c
6	3a	benzaldehyde	75 ^b
7	3a	CO ₂	66 ^d
8	3a	cyclohexenone	77 ^{b,f}
9	3b	iodomethane	86 ^b
10	3b	cyclohexanone	82 ^e

^aAll yields are for products isolated by silica gel chromatography or crystallization. ^bProducts were liquids. ^cmp 50-51 °C. ^dmp 89-91 °C. ^emp 94-95 °C. ^fOnly 1,2-addition product noted.

This work demonstrates that one of the simplest synthons for a β -acylvinyl anion may be one of the most convenient and useful, especially for cyclohexenones. Extrapolation of this chemistry to acyclic systems and methods to circumvent regiochemical problems attendant unsymmetrical systems are planned and will be detailed in our full manuscript.

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(11) A solution of 10 g (0.06 mol) of **4a**, 7.08 g (0.11 mol) of ethylene glycol, and 200 mg of *p*-toluenesulfonic acid monohydrate in 800 ml of benzene was refluxed for 4 h with azeotropic removal of water. The reaction was conveniently monitored by VPC (6' × 1/8" column of 5% SE-30 on 60/80 Chromosorb G at 120 °C) with the retention times in the following order: **4a**, **3a**, and then **5a**. The solution was washed with 5% sodium bicarbonate (100 ml), brine (50 ml), and dried over calcium sulfate. Concentration gave 14 g of colorless liquid which was chromatographed on Activity II neutral alumina (5 × 20 cm column, 8-10% ether/petroleum ether as eluant). Elution proceeded as follows: 0-125 ml, nil; 125-450 ml, 8.5 g (68%) of **3a** as a colorless liquid [IR (neat) 2955 (m), 2930 (m), 2882 (m), 1362 (m), 1337 (m), 1145 (m), 1118 (s), 1060 (s), 1023 (s), 950 (m), 852 cm⁻¹ (m)].

Elution was continued as follows: 450-750 ml, nil; 750-1000 ml, 2.1 g (17%) of **5a** as long needles [mp 62-63 °C; IR (KBr) 2955 (s), 2879 (s), 1232 (s), 1187 (s), 1108 (s), 1082 (vs), 1035 (s), 950 (s), 852 cm⁻¹ (s); NMR (CCl₄) δ 3.82 (s, 8 H), 1.72 (s, 2 H), 1.55 (s, br, 6 H)].

Alternatively, the product can be distilled through a 5" Vigreux column (bp 80-83 °C, 2.5 mm) to give a 51% yield of a 95:5 mixture of **3a** and **5a** on a 20-g-scale ketalization.

(12) The following procedure is representative. To a -78 °C solution of 1.44 g (6.6 mmol) of **3a** in 75 ml of dry tetrahydrofuran was added dropwise 9.1 ml of 1.59 *M* *n*-butyllithium (2.2 equiv). The resulting solution was stirred at -78 °C for 0.5 h (the color changed from a clear pink to brown and finally to a cloudy pale yellow suspension). The cyclohexanone (0.96 g, 9.8 mmol) was added and the reaction mixture stirred at -78 °C for 1 h and at room temperature for 1 h. After pouring the reaction mixture into 30 ml of 5% hydrochloric acid and standard workup, the crude product was filtered through a short silica gel column (30% ether/petroleum ether as eluant) to give after concentration 1.02 g (80%) of product alcohol, mp 50-51 °C.

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