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Tetrahedron Letters 45 (2004) 6749–6751
Tetrahedron Letters

Access to diversely α-substituted cyclopentenones from α-chlorocyclopentenones

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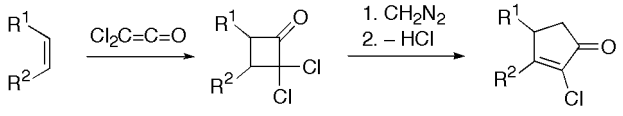
Received 28 June 2004; accepted 12 July 2004
Available online 30 July 2004

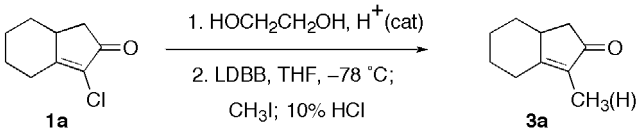
Abstract—α-Chlorocyclopentenones can readily be transformed into a variety of α-substituted cyclopentenones via their dimethyltrimethylene acetals.

The development of effective new approaches to substituted cyclopentenones constitutes a worthwhile synthetic pursuit because of their ubiquitousness in nature and their usefulness as synthetic building blocks. The sequence developed several years ago in our laboratory, consisting of regio- and stereoselective [2 + 2] cycloaddition of dichloroketene with olefins, followed by diazomethane ring expansion and dehydrochlorination, leads efficiently to α-chlorocyclopentenones (Scheme 1);[1] however, a proven procedure for replacing the α-chloro group in cyclopentenones by other α-substituents has not been available.

Recently, in the context of the total synthesis of several guaiane sesquiterpenes,[1d] it became necessary to effect the transformation of an α-chlorocyclopentenone into an α-methylcyclopentenone. Since no effective method could be found for the conversion of an α-chloro enone into an α-alkyl enone, a procedure was developed for the



Scheme 1.



Scheme 2.

required methylation.[2] The extension of this procedure for the preparation of a variety of α-substituted conjugated cyclopentenones is now described.

In early optimization studies it was found that when the ethylene acetal of α-chlorocyclopentenone **1a**[1b,c] (Scheme 2) was allowed to react for 1 h at −78 °C with a preformed solution of LDBB[3] (Yus and co-workers' standard metallation conditions[2b]) and then treated with excess iodomethane for 20 min, followed by dilute HCl, the desired α-methylcyclopentenone (**3a**, CH_3)[1b,4] could be obtained in 59% yield, together with 5% of the α-unsubstituted cyclopentenone (**3a**, H). Some improvement was realized by using LDMAN[5] instead of LDBB; optimal results were ultimately achieved with in situ generated LDMAN as the electron transfer reagent at −65 °C in combination with the dimethyltrimethylene acetal, which is known to be more stable to[6a] (and in[6b]) organometallics than the ethylene acetal. With these modifications, the above methylation could be reproducibly achieved in 90% isolated yield.

Various electrophiles can be used in the sequence to give the corresponding α-substituted cyclopentenones (Table 1). For example, the vinyllithium intermediate derived from dimethyltrimethylene acetal **2a**[7] on treatment with three primary alkyl iodides produces the corresponding

Keywords: Lithiation; Acetals; Electron transfer; Cyclopentenones; Carbanions.
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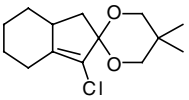
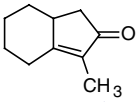
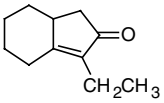
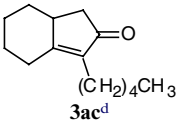
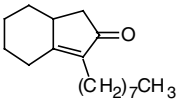
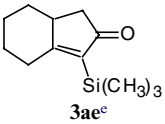
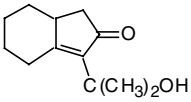
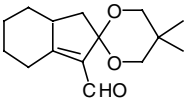
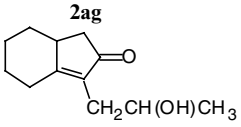
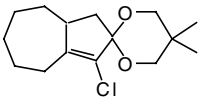
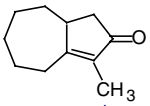
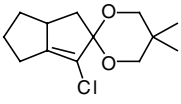
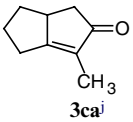
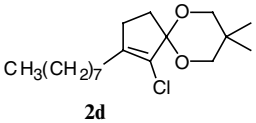
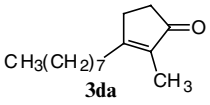
doi:10.1016/j.tetlet.2004.07.049

Table 1. Synthesis of diversely α-substituted cyclopentenones

Entry	Substrate	Electrophile	Product	Yield[a] (%)
1	 **2a**	CH_3I	 **3aa**[b]	90 (6)
2	**2a**	CH_3CH_2I	 **3ab**[c]	77 (17)
3	**2a**	$CH_3CH_2OSO_2CF_3$	**3ab**	51 (14)
4	**2a**	$CH_3(CH_2)_4I$	 **3ac**[d]	66 (28)
5	**2a**	$CH_3(CH_2)_7I$	 **3ad**	75 (15)
6	**2a**	$(CH_3)_3SiCl$	 **3ae**[e]	67 (12)
7	**2a**	$(CH_3)_2CO$	 **3af**	51 (35)[f]
8	**2a**	$(CH_3)_2NCHO$	 **2ag**	63[g] (4)
9	**2a**		 **3ah**	51[h]
10	 **2b**	CH_3I	 **3ba**[i]	88 (5)
11	 **2c**	CH_3I	 **3ca**[j]	66 (8)
12	 **2d**	CH_3I	 **3da**	77 (4)

[a] Yields are for isolated, homogeneous products. Except for entry 1, yield optimization was not attempted. Yields in parentheses are for α-unsubstituted enone side products.
[b] Refs. 1b and 4.
[c] Ref. 8.
[d] Ref. 9.
[e] Ref. 10.
[f] 4-Hydroxy-4-methylpentan-2-one was also isolated.
[g] Acetal **2ag** was not hydrolyzed.
[h] Hydroxy enone **3ah** (dr=1:1) suffered partial decomposition on silica gel chromatography.
[i] Ref. 4.
[j] Ref. 11.

α-alkyl cyclopentenones **3ab**,[8] **3ac**,[9] and **3ad** (entries 2,4,5) in good overall yields, despite some protonation of the vinyllithium through elimination in the halides (and, perhaps, adventitious introduction of moisture). Triflates appear to be inferior to iodides (entries 2 and 3). Chlorotrimethylsilane, acetone, and dimethylformamide have also been used to produce, respectively, α-trimethylsilyl cyclopentenone **3ae**[10] (entry 6), tertiary alcohol **3af** (entry 7), and aldehyde **2ag** (entry 8); the reaction with propylene oxide yields selectively the expected secondary alcohol **3ah** (entry 9). In addition, two other bicyclic α-chloro enone acetals, bicyclo-[5.3.0]decenone derivative **2b** and bicyclo[3.3.0]octenone derivative **2c**, as well as a monocyclic α-chloro enone acetal, cyclopentenone derivative **2d**, have also been found to undergo facile lithiation–alkylation–hydrolysis to give in good yields enones **3ba**,[4] **3ca**,[11] and **3da** (entries 10–12), respectively.[12]

In summary, it has been shown that α-chlorocyclopentenones can readily be transformed, via their dimethyltrimethylene acetals, into a variety of α-substituted cyclopentenones. The LDMAN-mediated metal–chlorine exchange, the key step, is effected through in situ generation of the reagent, which is both convenient and efficient. Since α-chlorocyclopentenones themselves are easily prepared, this methodology provides a simple route to α-substituted cyclopentenones and nicely complements other procedures for accessing these useful compounds.

Acknowledgements

We thank Prof. P. Dumy for his interest in our work, The Research Ministry for fellowship awards to A.G. and Y.C., and the Université Joseph Fourier and the CNRS (UMR 5616, FR 2607) for financial support.

References and notes

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12. General procedure for preparation of chloro acetals: A mixture of the α-chloro enone (11.7 mmol), 2,2-dimethyl-1,3-propanediol (175.0 mmol), trimethyl orthoformate (31.6 mmol), *p*-toluenesulfonic acid hydrate (4.7 mmol), and molecular sieves was vigorously stirred in dichloromethane (50 mL) at 20 °C for 15 h, whereupon solid K_2CO_3 was added. The crude reaction product was isolated in the usual way and purified by flash chromatography on silica gel (treated with 2.5% v/v of triethylamine) with ethyl acetate in pentane to give unreacted α-chloroenone and the desired acetal (50–70% yield, 100% brsm). Selected physical data for acetal **2a**: mp 58 °C. IR 1720, 1303, 1109 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.75$ (s, 3H), 0.94–1.09 (m, 1H), 1.15–1.41 (m, 2H), 1.28 (s, 3H), 1.61 (dd, $J = 13.0$, 4.9 Hz, 1H), 1.73–1.89 (m, 3H), 1.90–2.03 (m, 1H), 2.41–2.74 (m, 3H), 3.49–3.64 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 22.3$, 22.7, 25.8, 25.9, 26.2, 30.4, 35.3, 36.5, 41.4, 72.5, 72.7, 108.0, 124.1, 145.4. MS (DCI) *m/z* 257 (MH^+, 100%). Anal. Calcd for $C_{14}H_{21}ClO_2$: C, 65.49; H, 8.24. Found: C, 65.33; H, 8.47. General procedure for preparation of α-substituted cyclopentenones: To a suspension of Li powder in mineral oil (6.0 mmol) was added a solution of the chloro acetal (1.0 mmol) in THF (4.0 mL), followed by *N*,*N*-dimethyl-1-naphthylamine (1.0 mmol). The mixture was cooled to −65 °C, stirred for 2 h (complete metallation, by TLC), and then treated with the electrophile (5 mmol; 20 mmol for CH_3I). After being stirred for an additional 30 min at −65 °C, the mixture was allowed to warm slowly to 20 °C and then treated with 1 N HCl (2 mL). The resulting mixture was extracted twice with ether/pentane (3:2) and the combined organic layers were washed successively with 2% $Na_2S_2O_3$, satd $NaHCO_3$, water, and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography on silica gel with ether in pentane. Selected physical data for 3-methyl-1,4,5,6,7,7a-hexahydro-inden-2-one (**3aa**):[1b,4] IR 1700, 1653 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.97$–1.11 (m, 1H), 1.24–1.39 (m, 1H), 1.42–1.58 (m, 1H), 1.67 (s, 3H), 1.80–2.18 (m, 5H), 2.49–2.58 (m, 2H), 2.80–2.88 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 7.8$, 25.8, 26.8, 28.9, 35.3, 40.5, 41.6, 133.0, 176.1, 209.3. MS (DCI) *m/z* 151 (MH^+, 100%).