Pergamon

Tetrahedron Letters 41 (2000) 763–766

TETRAHEDRON
LETTERS

Alkylation of carbonyl compounds in the $TiCl_4$-promoted reaction of trimethylsilyl enol ethers with ethylene oxide[†]

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Received 13 October 1999; accepted 17 November 1999

Abstract

Titanium tetrachloride promoted reaction of trimethylsilyl enol ethers with ethylene oxide affords homoaldol type products in moderate/good yields. The reaction is believed to proceed via the titanium enolates. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: alkylation; titanium tetrachloride; epoxide; enolates.

Epoxide ring opening with organometallic nucleophiles is a well-known reaction and a synthetically useful method of C–C bond formation.[1] However, the analogous reaction of oxiranes with enolates is less well investigated. The few successful examples include structurally simple carboxylic acid dianions or amide anions as reaction intermediates, often under forcing conditions, or reactions of aluminium ester-enolates, where the desired products were obtained in moderate to good yields.[2] To the best of our knowledge, the reaction of cyclononanone Li-enolate with propene oxide catalyzed by Me_3Al is the sole example of a successful direct alkylation of a ketone with an epoxide, which seemingly lacks generality.[3] Therefore, indirect routes to the products of ketone/epoxide coupling were devised, relying on the enhanced nucleophilicity of the corresponding imine or hydrazone carbanions.[4] While these methods work well with structurally simple ketones, we experienced difficulties during attempted alkylation of sterically hindered ketones and enones; as an example, the formation of the *N*,*N*-dimethylhydrazone from 4,4-dimethylcyclopentenone required 14 days, and it proved unreactive towards ethylene oxide under the reported conditions.[4b]

We set out to develop a new method for the alkylation of carbonyl compounds with ethylene oxide, based on the anticipated reactivity of enoxysilanes towards oxiranes under the conditions of the Mukaiyama reaction.[5] In the first experiment, a CH_2Cl_2 solution of cyclopentanone TMS–ether (1 equiv.) and ethylene oxide (1 equiv.) was treated with $TiCl_4$ (1 equiv.) at −78°C. To our pleasure, the desired

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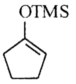
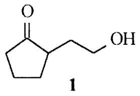
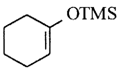
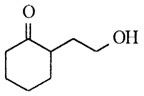
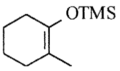
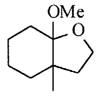
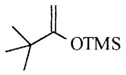
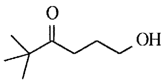
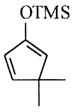
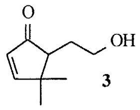
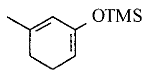
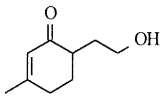
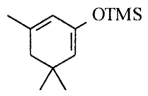
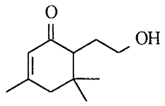
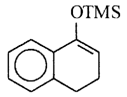
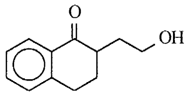
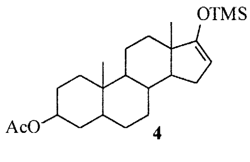
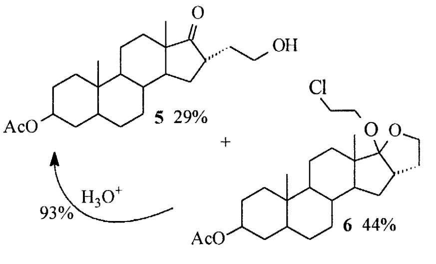
[†] Dedicated to Professor Živorad Čeković, on the occasion of his 65th birthday.

PII: S0040-4039(99)02149-8

Table 1

Entry	Silyl enol ether	Product	Yield[a, b]
1		 **1**	46%
2			55%[c]
3			41%[d] (78%)
4			61%
5	 **2**	 **3**	60%
6			60%
7			49% (75%)
8			38% (79%)
9	 **4**	 **5** 29% + **6** 44%	70%[e] (73%)[f]

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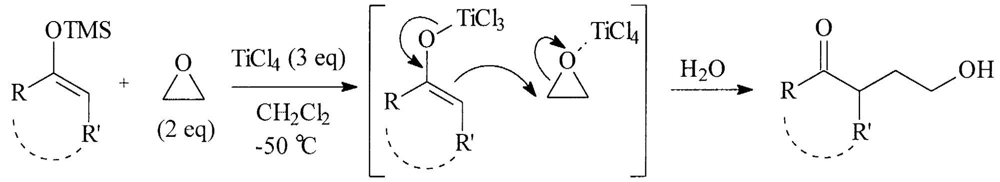
a) yields of isolated, pure compounds; b) Yield calculated on the basis on the recovered starting compound; c) determined by GC; d) after treatment of the crude reaction mixture with H_2O/MeOH/HF; e) total yield of the isolated hydroxy compound **5** after the hydrolysis of chloro derivative **6**; f) combined yield of both products **5** and **6** alkylation product **1** was obtained, albeit in low yield, along with a large amount of cyclopentanone. An important observation was made in this reaction: immediately after the addition of $TiCl_4$ the reaction mixture turned dark-red — the characteristic colour of Ti-enolates.[6] This was surprising, as the formation of Ti-enolates from silyl enol ethers and $TiCl_4$ was reported to take place only at rt, where so-formed intermediates undergo rapid decomposition.[7] Attempts to pre-form the Ti-enolate by allowing the TMS-enol ether to react with $TiCl_4$ prior to the addition of oxirane resulted in exclusive formation of a cyclopentanone self-condensation product. However, in situ formation of cyclopentanone Ti-enolate by the addition of excess $TiCl_4$ (3 equiv.) to a solution of the silyl enol ether (1 equiv.) and ethylene oxide (2 equiv.), allowing the reaction mixture to reach −50°C, and quenching the reaction after the red coloration fades, afforded 2-(2-hydroxyethyl)-cyclopentanone **1** in 46% isolated yield. Encouraged by this result, and in order to test the generality of this new reaction, we prepared a number of structurally different TMS-enol ethers and submitted them to the above reaction conditions. In all cases the desired products were obtained in moderate to good yields; the results of these experiments are summarized in Table 1. Acyclic, cyclic, aromatic ketones and enones all reacted cleanly giving the alkylated products and varying amounts of the starting ketone as the only constituents of the reaction mixtures after work-up.[8] In the case of the steroid **4** two products were isolated, namely **5** and its acetal derivative **6**. The latter was subsequently hydrolyzed into **5** (H_2O, HCl, THF, 93%), to afford the desired compound **5** in 70% total yield. Remarkably, this reaction proceeded with complete stereoselectivity, a single isomer was obtained, and was tentatively assigned as **5α**.



Scheme 1.

We believe that the reaction proceeds through the intermediacy of a titanium enolate, as outlined in Scheme 1. This hypothesis is supported by several observations: (a) the reaction mixture is intensively red coloured, and the coloration vanishes immediately upon aqueous quenching; (b) yields are substantially reduced, and the amount of unreacted parent ketone increased, when quenching is performed before the colour fades out; (c) under the same, or even more forcing conditions, the reaction of TMS-enol ethers with oxirane fails to produce detectable amounts of products when $TiCl_4$ is substituted by other Mukaiyama-type activators, such as TMSI, TMSOTf, $BF_3 \cdot Et_2O$ or $SnCl_4$, indicating that formation of the Ti-enolate is essential for the success of the reaction.

To summarize, $TiCl_4$-promoted reactions of enoxysilanes with ethylene oxide offer a new method of alkylation of carbonyl compounds. Work is in progress in our laboratory in order to establish the scope and limitations of this reaction, and to provide further mechanistic clarification.

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8. Typical procedure: To a cold (−78°C) solution of **2** (860 mg; 3.97 mmol) and ethylene oxide (278 μl; 5.58 mmol) in CH_2Cl_2 (58 ml), $TiCl_4$ (1.04 ml; 9.53 mmol) was added dropwise, and the reaction mixture was allowed to reach −60°C. After 2 h the initially dark-red coloured reaction mixture turned faint-pink, when the reaction was quenched with H_2O (20 ml). After a usual work-up the crude reaction product was dissolved in CH_3CN (30 ml), and stirred for 2 h at rt with few drops of dilute aqueous HF (in order to hydrolyze the silylated products). Standard work-up, followed by purification by column chromatography (eluent: petroleum–ether/acetone=9/1) afforded 370 mg (60%) of **3**, as a colourless oil (isolated yields of products, especially of those containing cyclohexanone structural subunit were somewhat reduced during purification, due to proclivity of these compounds to isomerise on standing into cyclic hemiacetal forms). Spectral data for **3**: ^{1}H NMR: 7.52 (d, J=5.6 Hz, 1H); 6.05 (d, J=5.6, 1H); 3.92–3.76 (m, 3H); 2.26–2.19 (m, 1H); 1.81–1.74 (m, 2H); 1.26 (s, 3H); 1.07 (s, 3H); ^{13}C NMR: 212.82 (C); 173.53 (CH); 129.93 (CH); 62.42 (CH_2); 56.83 (CH); 44.77 (C); 28.62 (CH_2); 26.90 (CH_3); 24.71 (CH_3); Ir_{film}: 3403, 2960, 2871, 1697, 1590, 1046; $MS/CI_{isobutane}$: 155 (M+1; 100%); 137 (M+1−18; 21%).