Pergamon

Tetrahedron Letters 40 (1999) 3279–3282

TETRAHEDRON
LETTERS

Tandem Michael/intramolecular aldol reactions mediated by secondary amines, thiols and phosphines

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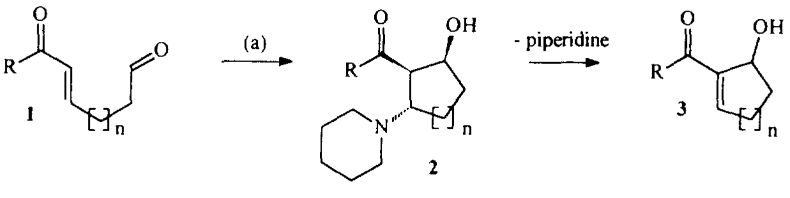
Received 4 November 1998; revised 15 February 1999; accepted 23 February 1999

Abstract: The secondary amine mediated Baylis-Hillman reaction has been found to proceed *via* a tandem Michael addition/intramolecular aldol followed by a slow elimination step; it was also observed that similar processes can be effected using phosphines and thiols as mediators. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Cyclisation, Michael reactions, aldols.

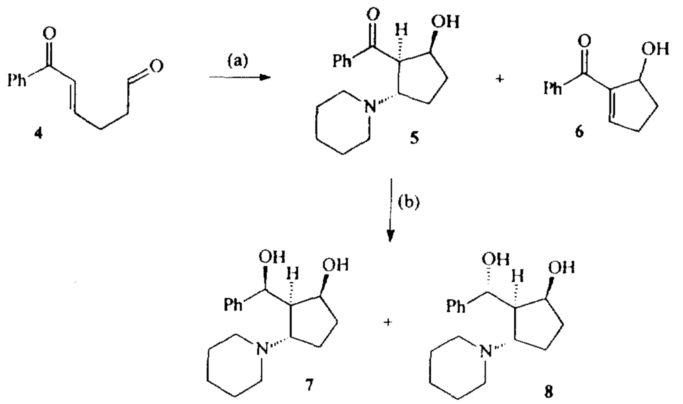
We have previously reported the preparation of substituted cyclopentenols and cyclohexenols **3** from the enone-aldehydes **1** catalysed by secondary amines in a process reminiscent of the Baylis-Hillman reaction.[1] Preliminary evidence suggested that the reaction was proceeding *via* a tandem Michael addition/intramolecular aldol process giving intermediates such as **2**, which was followed by a slow elimination step. We were thus eager to investigate the mechanism of this process further and to ascertain the generality of this reaction by employing other nucleophiles.



(a) Piperidine, $CDCl_3$, rt., 20-50% 3-5 days, R = Ph, alkyl; n = 1, 2.

To this end, we treated aldehyde **4** with an excess of piperidine in chloroform and found that the reaction proceeded to completion rapidly (ca 10 min) to give a product with ^1H nmr signals indicative of **5**, together with a small amount of the cyclopentenol **6** (ca 5%). We found that the intermediate **5** was stable for long periods of time (>7 days) in chloroform solution and very little further conversion to **6** was observed.

PII: S0040-4039(99)00419-0



(a) 1.3 eqv. piperidine, $CHCl_3$, 10 min, rt., (b) $NaBH_4$, MeOH, 0°C.

In addition, evaporation of the chloroform, followed by treatment of a methanolic solution of **5** with sodium borohydride gave a separable 1:1.3 mixture of the diols **7** and **8** in 67% overall yield, the former providing crystals suitable for X-ray analysis[2] which confirmed the relative stereochemistry of the intermediate **5**, as that illustrated (Fig 1).

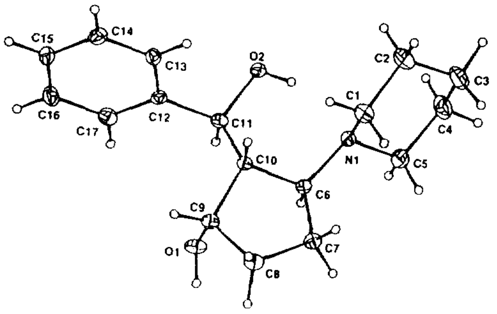


Figure 1.

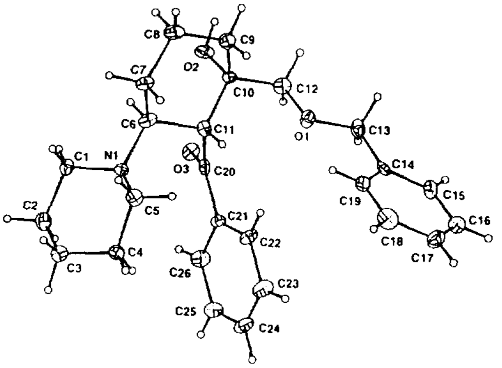
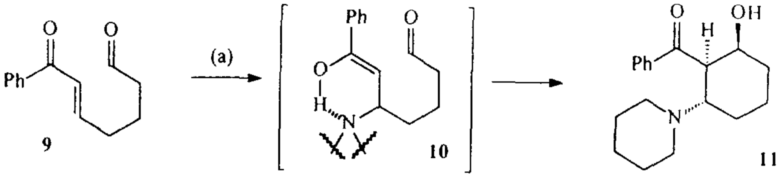


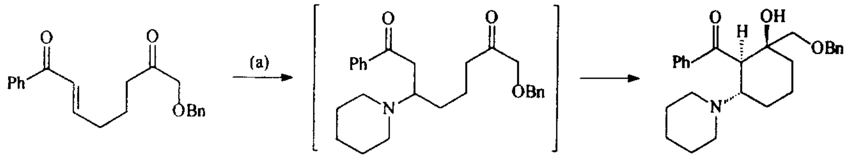
Figure 2.

We repeated this reaction with the enone **9** and were pleased to find conversion of this material into a compound with similar ^{1}H nmr data to **5**; the presence of signals at δ = 3.2 (1H, ddd, J = 3, 12, 12 Hz), 3.6 (1H, dd, 1.8, 12 Hz) and 4.2 (1H, br m) ppm, indicating the stereochemisty illustrated in structure **11**. In addition, it was apparent that the reaction leading to **11** was proceeding *via* an intermediate enol, possibly of structure **10**, as indicated by signals at δ = 4.3 (1H, dt, J = 14, 7.5 Hz), 5.8 (1H, d, 14 Hz) ppm. Again **11** was found to be stable in solution for prolonged periods with only ca ~ 10% conversion to the cyclohexenol **3** (R = Ph, n = 2) being observed over 28 days. An analogous sequence of reactions also occurred with N-methylpiperazine.



(a) 1.3 eqv. piperidine, $CHCl_3$, >90%.

More direct evidence for the stereochemical outcome of this reaction comes from the piperidine mediated cyclisation of **12**[6] leading to the cyclohexane **14** *via* the observed (nmr) intermediate **13**. Interestingly this cyclisation took considerably longer to effect, requiring six days for complete reaction, possibly reflecting the lower reactivity of ketones as electrophiles. In addition we were able to isolate (60% yield) and obtain crystals of **14** suitable for X-ray analysis[2] which again confirmed the stereochemistry as that illustrated. (Fig 2).

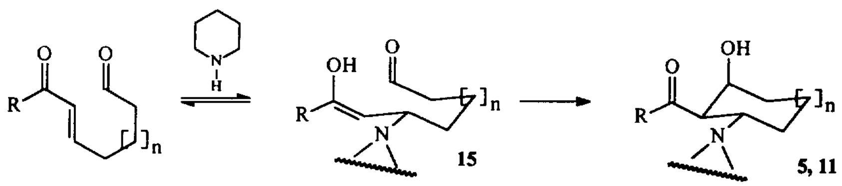


12 **13** **14**

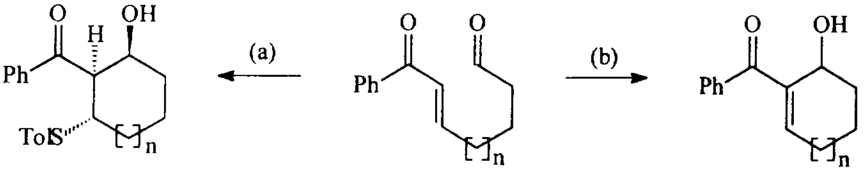
(a) 1.3 eqv.. piperidine, $CHCl_3$; 60%

It is worth emphasising that in all these reactions the Michael-addition/aldol cyclisation step proceeded to give a single diastereomer by nmr and as yet we have been unable to isolate any minor diastereomeric products.

All of these observations seem to suggest that the reaction indeed proceeds *via* a conjugate addition of the amine to the enone yielding an intermediate enol, followed by an intramolecular aldol cyclisation *via* the conformation shown (**15**, n = 0,1). This mechanism might explain the slow rate of formation of the Baylis-Hillman products from this reaction, as the key step must be the elimination of piperidine from intermediates **5** and **11**, which is obviously a stereoelectronically unfavourable process particularly in the case of the cyclohexane intermediate (n = 1).



With these result in hand we were keen to see if this cyclisation could be effected using other nucleophiles. It is known that metal thiolates and selenates,[8] or metallated amines[9] can be used in tandem Michael-aldol reactions, including some cyclisations,[10] and that phosphines can catalyse intramolecular Baylis-Hillman reactions,[11] albeit in poor isolated yield. We were thus pleased to find that the substrates **5** and **9** could be converted into either the adducts **16a,b** on treatment with excess *p*-tolylthiol or to the cyclic alkenols **3** and **6** by treatment with a catalytic amount of *n*-Bu_3P.



16a; n = 0, 77%
16b; n = 1, 93%

5; n = 0
9; n = 1

3; n = 0, 20%
6; n = 1, 75%

(a) 1.3 eqv. TolSH, $CHCl_3$, 16 hrs rt., (b) 0.05-0.2 eqv. n-Bu_3P, $CHCl_3$, 2-16 hrs, rt.

Again the reactions leading to **16a,b** proceed to a single diastereomer which can be equated to the amine case. The reaction involving the tri-*n*-butylphosphine proceeded well for the formation of the cyclohexene product **3**, however the corresponding cyclopentene case gave a somewhat disappointing yield, with a great deal of polymerisation being apparent. This may reflect differences in the conformation of the two intermediate enols at the point of cyclisation.

In conclusion, we have reported a mild, effective and potentially very versatile route to substituted cycloalkanes and alkenes, which is mediated in a predictable manner by a range of nucleophiles. We are currently developing this methodology to allow access to a range of substituted carbocycles and are assessing the scope of the reaction as a synthetic procedure.

Acknowledgements: Thanks are given to the ERASMUS (FD) and the European Social Fund (ER) for funding and to Mr E. Lewis for nmr studies; the EPSRC Mass spectrometry centre at Swansea is also acknowledged.

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2. Crystallographic measurements for both compounds were made using a FAST area detector diffractometer and Mo-K_α radiation (λ = 0.71069 Å), following previously described procedures.[3] The structures were solved by direct methods (SHELX-S)[4] and refined on F^2 by full-matrix least-squares (SHELXL-93)[5] using all unique data to final wR (on F^2) = 0.0897 (**7**) and 0.0641 (**14**) and R (on F) = 0.0423 (**7**) and 0.0323 (**14**) [hydrogen atoms riding on the parent atoms, non-H atoms anisotropic]. Full details of data collection and structure refinement, atomic co-ordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre.
   Crystal data for 7: $C_{17}H_{25}NO_2$, M_r = 275.38, orthorhombic $P2_12_12_1$, a = 5.6790(5), b = 13.1960(10), c = 20.1710(10) Å, U = 1511.6(2) Å^3, Z = 4, D_c = 1.210 g cm^{-3}, μ(Mo-Kα) = 0.78 cm^{-1}, F(000) = 600, T = 150K. *Crystal data for* **14**: $C_{26}H_{33}NO_3$, M_r = 407.53, triclinic P 1, a = 5.8680(10), b = 10.7490(10), c = 17.301(2) Å, α = 85.930 (9), β = 87.620(10), γ = 85.580(10)°, U = 1083.0(2) Å^3, Z = 2, D_c = 1.250 g cm^{-3}, μ(Mo-Kα) = 0.81 cm^{-1}, F(000) = 440, T = 150K.
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