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An Intramolecular Baylis-Hillman Reaction Catalysed by Secondary Amines

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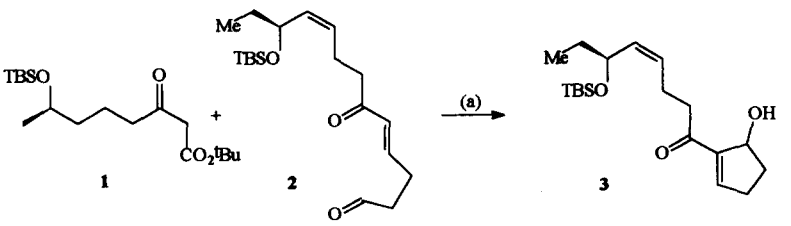
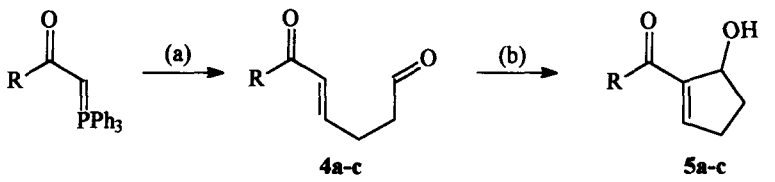
Abstract: Treatment of enonealdehydes **4** or **7** with a catalytic amount of a secondary amine lead to the formation of the cyclopentenol **5** or cyclohexenol **8** respectively. Piperidine proved to be the most effective catalyst for this process. © 1997 Published by Elsevier Science Ltd.

In the course of studies directed towards the synthesis of marine natural products,[1] we found it necessary to investigate the Knoevenagel condensation of β-ketoester **1** and the aldehyde **2**. Using a technique described in some previous literature[2] we were surprised to find that when the suggested catalysts for this procedure (piperidine, piperidinium acetate or morpholine) were employed, a considerable quantity (15-40%) of the aldehyde **2** was converted into the cyclopentenol **3**, in a process somewhat reminiscent of the Baylis-Hillman reaction.[3]



(a) Morpholine, piperidine or piperidinium acetate/DCM/ -20 - 0°C 24-48 hrs

We were intrigued by this process and in order to investigate it further prepared three potential substrates **4a-c** from succinaldehyde[4] and the corresponding phosphoranes. These substrates were then treated with a range of catalysts to effect the formation of the cyclopentenols **5a-c**.[5]



4a-c 5a-c

(a) 1.4 eqv. Succinaldehyde/DCM/48hrs. (b) Catalyst, 30 mol % (**Table 1**)/$CDCl_3$.

Table 1

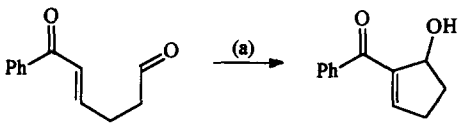
	R	yield 4	yield 5[a]		
			Pip	Pip.HOAc	DABCO
4a	C_9H_{19}	67%	50% (30 hrs)	45% (30 hrs)	no reaction
4b	Ph	48%	50% (144 hrs)	28% (72 hrs)	no reaction
4c	OEt	58%	(b)	(b)	no reaction

(a) Isolated. (b) Only products of aldol condensation and polymerisation were observed.

As can be seen the yields for this process are reasonable for the ketonic substrates **4a** and **4b**, when either piperidinium acetate or piperidine are employed as the catalyst, with the latter giving the best yield in both cases. Interestingly, the ester substrate **4c** gave only products of aldol condensation and polymerisation on treatment with either catalyst. The common Baylis-Hillman catalyst DABCO gave no reaction for any of the three examples, even after prolonged periods of time (30 days).

In order to investigate the reaction further we investigated the reaction of substrate **4b** with a series of secondary amines (**table 2**).

Table 2



4b **5b**

Amine[i]	**% conversion**	**% yield 5b**[ii]
Piperidine	93%	55 (50)%
2-methylpiperidine	97%	30 (26)%
2,6-dimethylpiperidine	75%	0
Morpholine	74%	16%
Piperazine	94%	28%
N-methylpiperazine	83%	21%
Pyrrolidine	82%	15%
di-*n*-butylamine	100%	15%

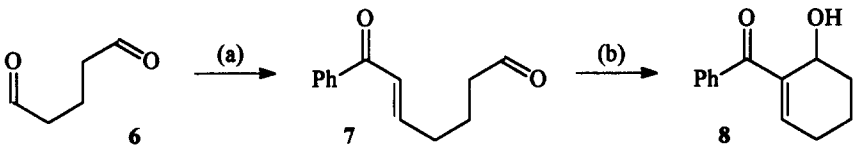
(i) Conditions: catalyst, 30 mol %/$CDCl_3$ (0.35M)/rt.., 7 Days.

(ii) Yields (+/- 5%) are calculated from ^1H nmr data; yields in brackets are isolated yields.

As can be seen, with the exception of the hindered 2,6-dimethylpiperidine, all the secondary amines gave the expected cyclised product, however none of the catalysts showed an improvement in yield compared to

piperidine. In addition a trend was observed in the series piperidine, 2-methylpiperidine and 2,6-dimethylpiperidine, in that the yield of product decreases as steric bulk of the amine increases. To further investigate this reaction, we performed a series of experiments in which the concentration of substrate **4b** was varied. The previous experiments were all performed at a concentration of 0.35M, on repeating at 0.18M and 0.09M a slight increase in yield (ca 5% for 0.09M) was observed for the formation of **5b**, however reaction time was increased for both reactions (10 and 15 days for 95% conversion respectively).

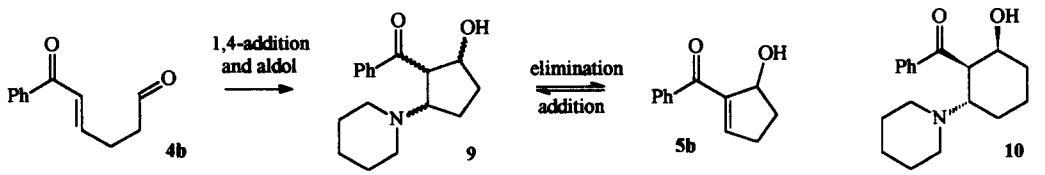
In order to study the effects of ring size on this reaction, pentane-1,5-dialdehyde **6** (formed from the ozonolysis of cyclopentene) was converted to the adduct **7** in 70% yield, which on treatment with piperidine under identical conditions gave the cyclohexenol **8**[5] in 24% yield (0.38 M 95% conversion, 14 days). Once again the yield could be increased slightly (30%) by performing the reaction at a higher dilution (0.19 M) but the time scale for the reaction is increased to 28 days for 95% conversion. Despite these yields the transformation demonstrates that the method has potential for the formation of a range of carbocycles.



6 7 8

(a) $PhCOCH{=}PPh_3$/DCM/48hrs. 70%, (b) Piperidine (30 mol%)/$CDCl_3$/r.t 14 days, 24%

The observation that the hindered base 2,6-dimethylpiperidine failed to give the cyclisation product **5b** may suggest that from a mechanistic viewpoint, 1,4-addition of the amine to the substrate precedes any cyclisation step. Indeed close observation of the piperidine catalysed reaction (nmr) illustrates that consumption of the catalyst is rapid (ca 10 min) and that an intermediate **9**[6] is present in the reaction mixture. In addition, it is also possible to form this intermediate quantitatively by treatment with excess piperidine (10 min, room temperature). Upon standing for a few days, **9** undergoes slow decomposition leading to a small quantity (ca 5%) of the previously isolated **5b**, and a considerable number of unidentified by-products. From this information, it is thus possible to suggest that the reaction mechanism involves a fast 1,4-addition/intramolecular aldol step, leading to **9** and a slow, possibly reversible, elimination step to yield **5b**. The reaction appears to be concentration dependent which may suggest a bimolecular mechanism for the elimination step.



4b 9 5b 10

Interestingly the intermediate **9** is present as primarily one diastereomer (>90% by nmr), as is a similar intermediate, identified (nmr) as **10**,[6] formed in the reaction of **7**. The stereoselective nature of the formation of **9** and **10** may offer hope for an asymmetric version of this reaction. The mechanism of the piperidinium acetate catalysed reaction appears to follow a similar course with the rapid consumption of the substrate **4b**, followed by the formation the product **5b**, at a slightly faster rate.

Two previous examples of the intramolecular variant of the traditional DABCO catalysed Baylis-Hillman reaction have been reported,[7] however these have displayed both limited scope and applicability. This new

method opens the way for the investigation of variants of this reaction with potential for controlling the stereochemistry of the cyclisation using both internal and external stereocontrol, with applications in the synthesis of larger carbocyclic and also heterocyclic systems being possible. Work is currently in progress to achieve these goals and to assess the applicability of these reactions in synthesis and elucidate further the mechanistic details.

Acknowledgements

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5. All new compounds displayed satisfactory analytical data. Selected data:
   5a: Rf: 0.11 (20 % diethyl ether/petroleum ether). **^{1}H nmr**: (300MHz) δ = 0.87 (t, 3H, J = 6.2Hz, CH_3), 1.2-1.3 (bs, 12H), 1.62 (m, 2H), 1.82 (m, 1H), 2.30 (m, 2H), 2.46 (m, 1H), 2.68 (t, 2H, J = 8.0Hz, CH_2), 3.13 (s, 1H, OH), 5.12 (bt, 1H, J = 7.3Hz, CHOH), 6.84 (t, 1H, J = 2.6Hz =CH). **^{13}C nmr**: (62.5MHz) δ = 14.01 (CH_3), 22.57 (CH_2), 24.32 (CH_2), 29.23 (CH_2), 29.34 (CH_2), 30.99 (CH_2), 31.25 (CH_2), 31.78 (CH_2), 38.97 (CH_2), 75.55 (CH), 145.49 (CH), 145.74 (CH), 200.82 (C). **IR**: ν_{max} = 3472 (O-H) 2925, 2854 (C-H), 1663 (C=O), 1618 (C=C) cm^{-1}. **MS (CI)**: 256 (100% $[M+NH_4]^+$), 239 (70% $[M+H]^+$), 238 (75% $[M+NH_4-H_2O]^+$), 221 (75% $[M-H_2O]^+$), **HRMS**: $C_{15}H_{30}NO_2$ ($[M+NH_4]^+$) requires 256.2277, found 256.2277.
   5b: Rf: 0.10 (50 % diethyl ether/petroleum ether). **^{1}H nmr**: (250MHz) δ = 1.94 (m, 1H, CH), 2.30-2.85 (m. 3H, 3 x CH), 3.33 (br s 1H, OH) 5.30 (m, 1H, CHOH), 6.71, (t, 1H, J = 1.5 Hz, vinyl CH), 7.42-7.78 (m, 5H, Ph). **^{13}C nmr**: (62.5MHz) δ = 31.40 (CH_2), 31.74 (CH_2), 76.51 (CH) 128.35 (2 x CH), 128.92 (2 x CH), 132.44 (CH), 138.13 (C), 144.54 (C) 149.05 (CH), 194.86 (C=O). **IR**: ν_{max} = 3460 (O-H), 3058, 2940 (C-H), 1639 (C=O) cm^{-1}. **MS (CI)**: 189 (100%, $[M+H]^+$), 206 (45%, $[M+NH_4]^+$). **HRMS**: $C_{12}H_{13}O_2$ ($[M+H]^+$) requires 189.0916, found 189.0916.
   8: **Rf**: 0.11 (25 % diethyl ether/petroleum), **^{1}H nmr**: (250MHz) δ = 1.67 (m, 1H, CH), 1.90 (m. 3H, 3 x CH), 2.31 (m, 2H, 2 x CH) 3.53 (br s 1H, OH) 4.75 (m, 1H, CHOH), 6.73, (t, 1H, J = 4.0 Hz, vinyl CH), 7.40-7.68 (m, 5H, Ph). **^{13}C nmr**: (62.5MHz) δ = 17.29 (CH_2), 26.23 (CH_2), 29.60 (CH_2), 63.83 (CH), 128.03 (2 x CH), 129.10 (2 x CH), 131.77 (CH), 137.69 (C), 140.00 (C) 146.79 (CH), 199.38 (C=O). **IR**: ν_{max} = 3436 (O-H) 3058, 2938, 2864 (C-H), 1636 (C=O) cm^{-1}. **MS (CI)**: 202 (35%, $[M]^+$), 203 (100%, $[M+H]^+$), 220 (15%, $[M+NH_4]^+$). **HRMS**: $C_{13}H_{15}O_2$ ($[M+H]^+$) requires 203.1072, found 203.1072.
6. Both intermediates were identified by analysis of nmr data obtained from the reaction mixtures. Efforts are underway to isolate and determine the exact relative stereochemistry of **9** and to confirm the nmr structural assignment of **10**.
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