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Tandem Michael/Michael reactions mediated by phosphines or aryl thiolates

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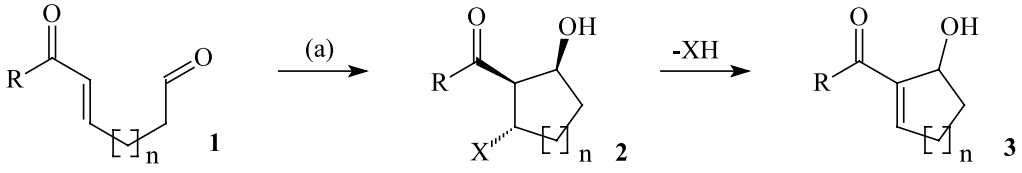
Abstract—*tri-n*-Butyl phosphine was found to effect tandem Michael/Michael cyclisations leading to the formation of cyclopentenes and cyclohexenes in good yields, whilst *p*-TolSH in conjunction with a catalytic amount of *p*-TolSNa effected cyclisation to the corresponding cyclopentanes and cyclohexanes. © 2002 Published by Elsevier Science Ltd.

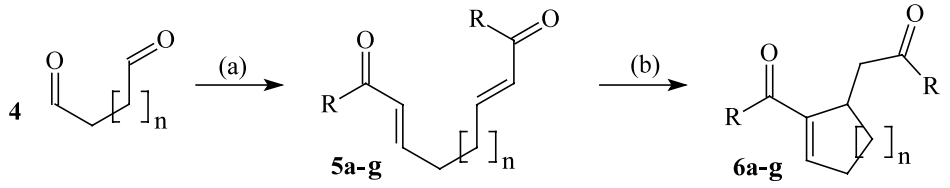
We have previously described[1] the ability of a range of nucleophiles, including secondary amines, thiols and phosphines to effect a tandem intramolecular Michael/aldol cyclisation of enones **1** leading to either the adducts **2** or the eliminated Baylis–Hillman type product **3**[1] (Scheme 1).

We wished to investigate potential developments of this reaction and envisaged that a similar Michael/Michael sequence might offer a flexible route to cycloalkenes. We are prompted to report our findings following the publication of related work by Roush et al. who have reported their studies on this reaction which they refer to as a '*vinylogous Morita–Baylis–Hillman reaction*' and Krische et al. who refer to this process as the '*intramolecular Rauhut–Currier reaction*'.[2] Tandem cyclisations of this type have also been previously reported using a range of carbanions,[3] metal thiolates[4] and metal amides[5] together with sequences initiated by free radicals.[6]

We began our investigation of this process by embarking on an investigation of the scope of the reaction with regards to the nature of the electron withdrawing group on the alkene and the ring size of the product formed. We thus prepared bis-enones **5a–g** from the aldehydes **4** using our previously reported Wittig methodology[1,7] and treated them with a catalytic amount of n-Bu_3P (0.2–0.6 equiv.) in chloroform at rt. (Scheme 2, Table 1). We were pleased to find that the phenyl enones **5a** and **5b** both underwent cyclisation to give the corresponding cyclopentene **6a** and cyclohexene **6b** in high



Scheme 1. *Reagents and conditions*: (a) R_2NH, R_3P, TolSH, $n=1$, 2; R = alkyl, Ph, OR; X = R_2N, R_3P^+, TolS.



Scheme 2. *Reagents and conditions*: (a) 2 equiv. RCOCH=PPh_3, 44–63% (see Refs. 1 and 7); (b) see Table 1.

Keywords: tandem reactions; Michael additions.

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Table 1.

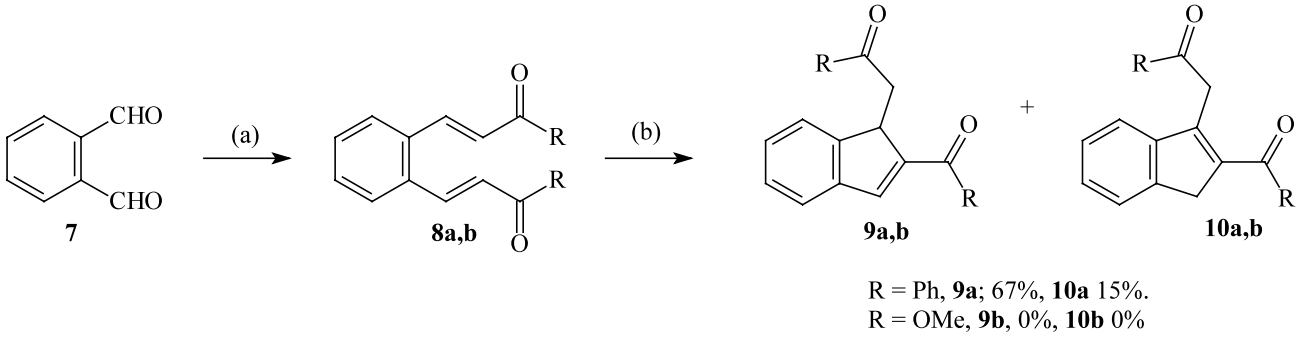
Entry	5	R=	*n*	Method[a]	6	Yield[b] (%)
1	**5a**	Ph	1	0.3 equiv., *n*-Bu_3P, 16 h	**6a**	80
2	**5b**	Ph	2	0.3 equiv., *n*-Bu_3P, 4 h	**6b**	68
3	**5c**	Ph	3	0.3 equiv., *n*-Bu_3P, 21 days[c]	**6c**	0
4	**5d**	OMe	1	0.3 equiv., *n*-Bu_3P, 4 days[d]	**6d**	0
5	**5e**	OMe	2	0.3 equiv., *n*-Bu_3P, 4 days[d]	**6e**	0
6	**5f**	Me	1	0.2 equiv., *n*-Bu_3P, 5 h	**6f**	66
7	**5g**	Me	2	0.2 equiv., *n*-Bu_3P, 16 h	**6g**	58

[a] Reactions were performed in chloroform (ca. 1–2 ml per mmol of substrate) at rt.
[b] All new compounds gave satisfactory analytical data.
[c] A further 0.3 equiv. of phosphine added after 1 week.
[d] A further 0.3 equiv. of phosphine added after 1 day and the reaction was refluxed for 16 h.

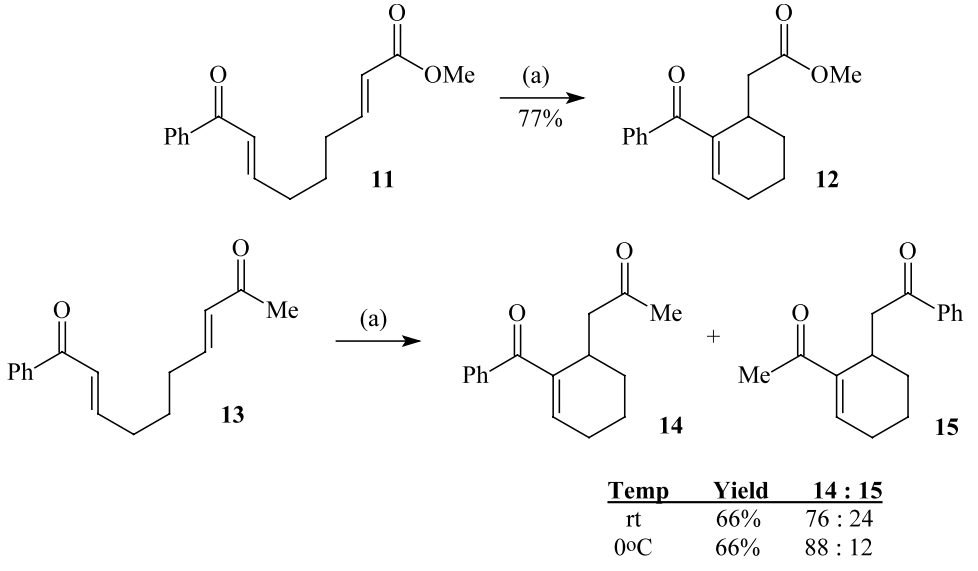
yield (entries 1, 2), whereas the substrate **5c**, which would generate a seven-membered product, was resistant to cyclisation under these conditions even after prolonged periods (entry 3). Similarly cyclisation of the enoate substrates **5d** and **5e** was also unsuccessful, possibly reflecting a low reactivity of enoates in Michael addition,[2] (entries 4, 5). We also investigated the methyl enones **5f** and **5g** and found that they also underwent cyclisation in good yield (entries 6, 7) (Scheme 2).

We also investigated the enone **8a** and enoate **8b** in which the two Michael acceptors are linked by an aromatic ring and found that these displayed similar reactivities to the previous examples. Thus, the enone substrate **8a** cyclised smoothly to give the isomeric indenes **9a** and **10a** in excellent overall yield, whilst the enoate **8b** was resistant to cyclisation under these conditions (Scheme 3).

We investigated the lack of reactivity of the enoate substrates in more detail and prepared the mixed sub-



Scheme 3. *Reagents and conditions*: (a) 2 equiv. RCOCH=PPh_3; 42% (**8a**), 85% (**8b**). (b) 0.3 equiv. *n*-Bu_3P, $CHCl_3$, rt, 16 h.

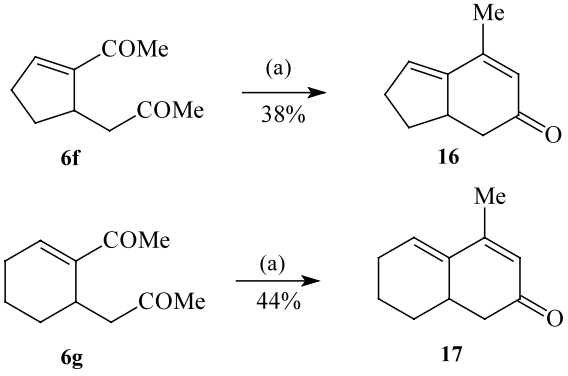


Scheme 4. *Reagents and conditions*: (a) 0.3 equiv. *n*-Bu_3P, $CHCl_3$, rt, or 0°C–rt, 16 h.

strates **11** and **13**. Treatment of **11** with n-Bu_3P under our standard conditions led to the formation of the cyclised product **12** as the only product, highlighting the low reactivity of the enoate to phosphine addition, but confirming that the enoate is a suitable acceptor for the cyclisation step of the tandem process. Substrate **13** allowed us to investigate the relative reactivity of the two enones we employed and not surprisingly we found that a 76:24 mixture of products **14** and **15** were formed in which the product **14** arising from initial Michael addition to the phenyl substituted enone was preferred. Repetition of the reaction at 0°C gave a slightly improved selectivity for the formation of **14** (Scheme 4).

We believe that products derived from these tandem processes have potential applications in synthesis and have initially investigated the aldol cyclisation of the enones **6f** and **6g**. We found that treatment of these under basic conditions led to the formation of the bicyclic products **16** and **17** in reasonable yields (Scheme 5).

We next investigated the thiol catalysed cyclisation of the substrates **5a**,**b**,**d**,**e** and **11** and were disappointed to find that all these substrates were resistant to cyclisation when treated with p-TolSH at rt or at reflux and only the products **20** of a single Michael addition of the thiol to the enone was observed. We next employed alternative conditions in which a catalytic amount of TolSNa was added to the reaction which was then heated at reflux in THF (Scheme 6). We were pleased to find that both the enone substrates **5a** and **5b** underwent cyclisation to the corresponding carbocycles **18a** and **18b** in good yield and as essentially single stereoisomers (entries 1 and 2). Structural determination was based on the presence of large *trans*-diaxial coupling constants for the methine proton at C-2 of the product **18b** ($J = 10.5$, 11 Hz) and corroborating NOE measurements. Similar reaction of the enoate substrates **5d** and **5e** were unsuccessful under all the conditions employed leading only to the Michael adducts **20d** and **20e**. However, when we treated the mixed enone/enoate substrate **11** under these conditions we were pleased to find that two cyclisation products **18f** and **19** were formed in high overall yield (entry 5). The reason for the formation of a mixture of products in this reaction and the predominance of **19** as the major product is unclear; however, the steric differences between the methyl ester and the aryl ketone may be a factor. This reaction does however demonstrate that an enone is required for an effective cyclisation, a factor that is probably associated with the ability to form an enol/enolate under the conditions employed (Scheme 6).



Scheme 5. *Reagents and conditions*: (a) KO^{t}Bu, ^{t}BuOH, rt, 16 h.

Table 2.

Entry	5	R =	R^1	n	18; %	19; %	20; %
1	**5a**	Ph	Ph	1	**18a**; 58	–	–
2	**5b**	Ph	Ph	2	**18b**; 59	–	–
3	**5d**	OMe	OMe	1	**18d**; 0	–	67
4	**5e**	OMe	OMe	2	**18e**; 0	–	40
5	**11**	Ph	OMe	2	**18f**; 14	56	–

In conclusion, we have found that the tandem Michael/Michael cyclisation of bis-enones is a viable process for the preparation of five- and six-membered carbocycles; however, it does not appear to be applicable to the synthesis of larger ring systems, a fact also largely apparent in our studies on tandem Michael/aldol reactions.[1] In addition the use of bis-enoates in these processes does not appear feasible, however they are suitable acceptor groups in mixed enone/enoate substrates. A general order of reactivity towards addition of phosphines was also established and appears to be Ph>Me>>>OR.

Acknowledgements

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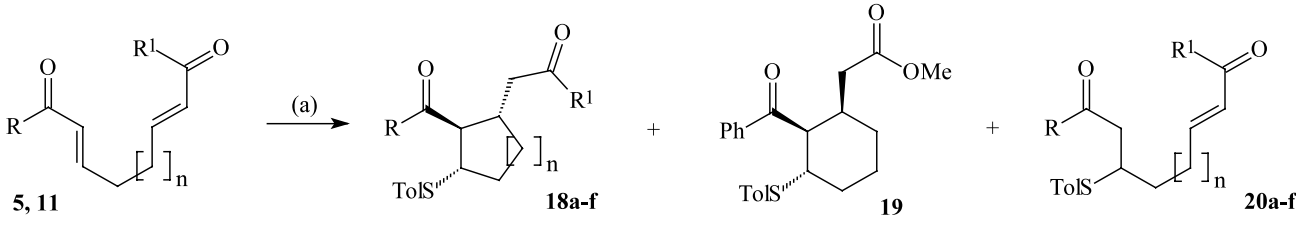

Scheme 6. *Reagents and conditions*: (a) 0.9 equiv. TolSH, 0.2 equiv. TolSNa, Δ, THF, 16 h and see Table 2.

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