One-pot Annulation of Enones with Lithiated Allyl Phenyl Sulfone

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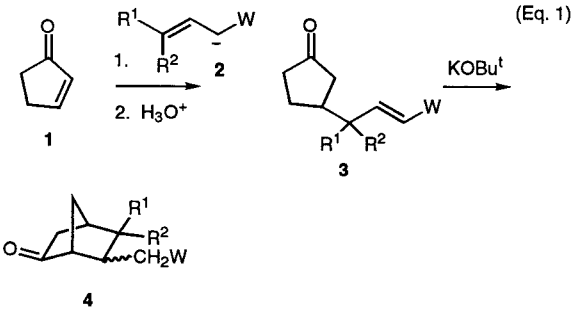
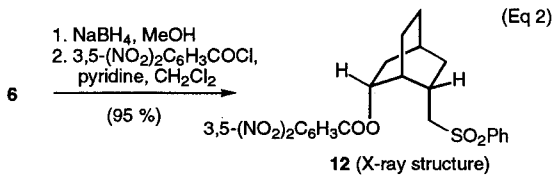
Abstract: A one-pot method of converting five and six membered cyclic enones to their respective bicyclo[2.2.1]heptanones and bicyclo[2.2.2]octanones, respectively, and acyclic enones to cyclohex-3-enols is reported.

The cyclization of the neutral Michael adducts **3**, that are formed from the reaction of cyclopent-2-enone **1** with the allylic sulfone,[1] sulfoxide[2] and phosphine oxide[2] carbanions **2**, has been reported to give the bicyclo[2.2.1]heptanones **4**. The stereochemistry of the bicyclic products **4** when W = SO_2Ph or SOPh has not been elucidated. We report here a one-pot method of converting five and six membered cyclic enones to their respective bicyclo[2.2.1]heptanones and bicyclo-[2.2.2]octanones, respectively, and acyclic enones to cyclohex-3-enols with lithiated allyl phenyl sulfone **2a**. The stereochemistry of these annulation products has been elucidated by ^1H NMR and X-ray crystallographic studies.



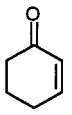
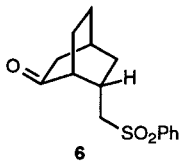
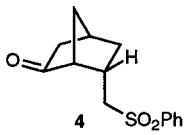
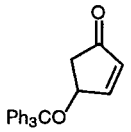
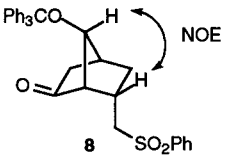
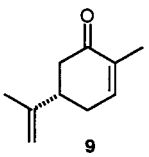
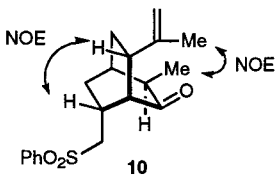
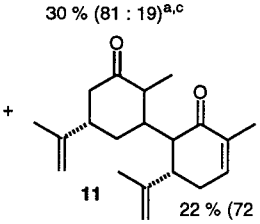
[**a**, W = SO_2Ph, $R^1 = R^2 = H$; **b**, W = SOPh, $R^1 = R^2 = Me$; **c**; W = $P(O)Ph_2$, $R^1 = Me$, $R^2 = H$]

Treatment of cyclohex-2-enone **5** with lithiated allyl phenyl sulfone **2a** (1 equiv.) in THF initially at -78° C followed by warming to room temperature (rt) and then stirring at rt for 1 hr gave, after aqueous work-up and column chromatography, the bicyclo[2.2.2]octan-2-one **6** in 49 % yield (Table 1). A significant amount (26 %) of the 1,4-α-adduct between **2a** and **5** was also isolated. The modest yield of **6** is compensated by the formation of two carbon-carbon sigma bonds in a single one-pot procedure. Furthermore, this yield compares favourably with the 53 % overall yield of **4b** (W = SOPh) in the two step procedure (Eq. 1) that required a reaction time of over 72 hr. The structure of **6** was secured by a single crystal X-ray structural analysis of its 3,5-dinitrobenzoate ester **12**[3] that was prepared from **6** in a straight forward and completely stereoselective manner and in high overall yield (Eq 2).



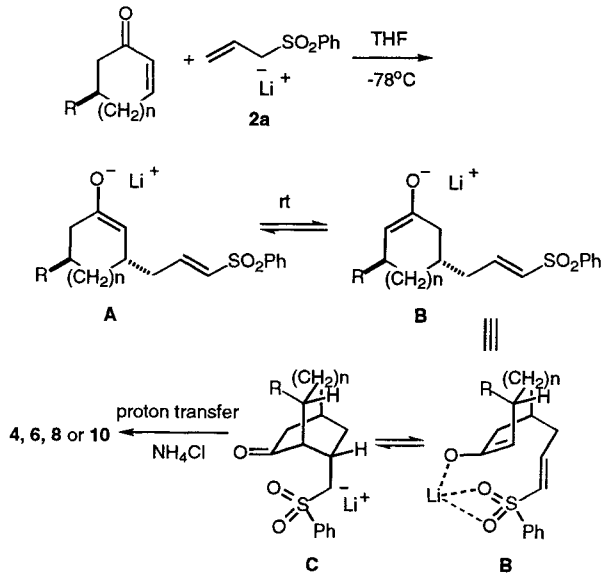
This one-pot procedure was found to be useful for the synthesis of the bicyclo[2.2.1]heptanones **4** and **8** from the reaction of **2a** with the cyclopent-2-enones **1** and **7**[4] (Table 1). The bicyclic compound **8** was a mixture (86 : 14) of diastereoisomers. The stereochemistry of the major diastereoisomer is that shown in Table 1 from NOESY experiments. The formation of **8** is surprising since a competing β-elimination of the trityloxy group might have been expected to have been more likely (from intermediate **B** (R = Ph_3CO) in Scheme 1) than the second Michael cyclization reaction. The reaction of **2a** and (*S*)-(+)-carvone gave the bicyclo[2.2.2]octanone derivative **10** in low yield (30 %) as a 81 : 19 mixture of diastereoisomers and the Michael adduct **11**. The stereochemistry of the major diastereoisomer of **10** is that shown in Table 1 from NOESY experiments that showed strong cross-peaks between the two methyl groups and between the methine protons indicated in structure **10**. The stereochemistry of the major diastereoisomer of **8** and **10** is that expected from addition of **2a** to the face of the enone that is *anti* to the β-substituent (R in Scheme 1).

Table 1. Products from the reaction of lithiated **2a** and cyclic enones

enone	product(s) yield / (d. r.)
 **5**	 **6** 49 % (> 98 : < 2)[a,b]
 **1**	 **4** 43 % (> 98 : < 2)[a,b]
 **7**	 **8** 46 % (86 : 14)[b]
 **9**	 **10** 30 % (81 : 19)[a,c]
	 **11** 22 % (72 : 28)

[a] 1,4-α-adducts and their isomeric vinyl sulfones were also isolated [b] Reaction time 1 hr at rt. [c] Reaction time 12 hr at rt.

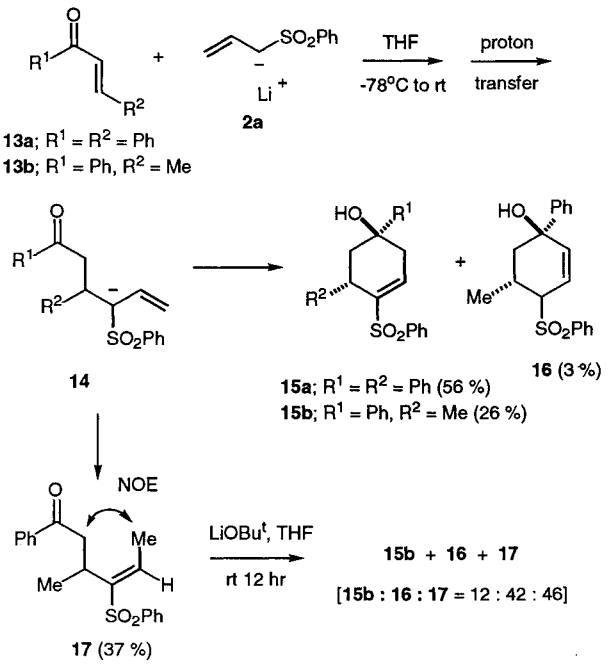
A mechanistic scheme for the formation of the bicyclic compounds **4**, **6**, **8** and **10** is shown in Scheme 1. Conjugate addition of **2a** to the cyclic enones at -78° C gives the 1,4-γ anionic adduct **A**, as the kinetically favoured adduct,[5] that upon warming to rt would be expected to be in equilibrium with its isomeric enolate **B** *via* intermolecular proton transfer mechanisms. Cyclization of **B** would give **C** that upon intermolecular / intramolecular proton transfer and finally protonation upon work-up would give the observed bicyclic products. The possible chelated intermediate shown in **B** may be responsible for the high level of stereochemical control in the cyclization step. While the intermolecular[6-8] and intramolecular[9] conjugate addition of enolate anions to vinyl sulfones under aprotic conditions has been reported, the double Michael addition sequence involved in the formation of **4**, **6**, **8** and **10** from the reaction of cyclic enones and **2a** is new.[10]



Scheme 1

Treatment of the acyclic enones **13a** or **13b** with lithiated allyl phenyl sulfone **2a** in THF at -78° C followed by warming to rt and then stirring for 12 hr at rt gave, after aqueous work-up and column chromatography, the cyclohex-3-enols **15a** or **15b** as single diastereoisomers in 56 and 26 % yield, respectively (Scheme 2). In the latter reaction a small amount (3 %) of the isomeric allylic sulfone **16** was also isolated and the major product (37 %) was the vinyl sulfone **17**. The geometry of the alkene group in **17** was established by NOESY experiments that showed a cross-peak between the vinyl methyl group and the protons α to the carbonyl group. The stereochemistry of **15a** was established by a single crystal X-ray structural analysis that showed the two phenyl substituents had the thermodynamically more stable 1,3-*cis*-stereochemical relationship (di-pseudo-equatorial conformation).[3] The cyclic products **15a,b** arise from a tandem Michael reaction-intramolecular aldol sequence *via* the anionic intermediate **14** derived from the initially formed, and kinetically favoured,[11] 1,4-α-adduct. Treatment of **17** with lithium *tert*-butoxide (1.2 equiv.) in THF at rt for 12 hr gave a 12 : 42 : 46 mixture of **15b**, **16** and **17**, respectively, from which **15b**, **16** and **17** could be isolated in 7 %, 33 % and 43 % yields, respectively, after column chromatography.

In conclusion, we have developed a one-pot method of converting five and six membered cyclic enones to their respective bicyclo[2.2.1]heptanones and bicyclo[2.2.2]octanones, respectively, and acyclic enones to cyclohex-3-enols. This one-pot method gives comparable yields to the previous method that required two sequential steps and is much more convenient in terms of shorter reaction times.



Scheme 2

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References and Notes

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4. Obtained from Dr. Simone C. Vonwiller, School of Chemistry, University of Sydney.
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