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Synthesis of bicyclo[2.2.2]oct-5-en-2-ones via a tandem intermolecular Michael addition intramolecular aldol process (a bridged Robinson annulation)

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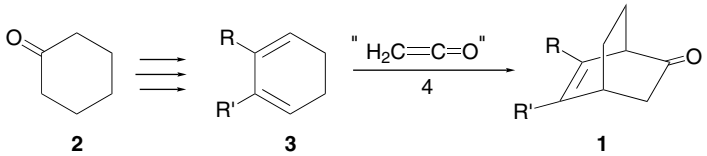
Abstract—A novel one-pot synthesis of the several bicyclo[2.2.2]oct-5-en-2-ones **19** has been developed in which a cyclic or acyclic ketone **18** is reacted with a cyclic enone **6** in the presence of strong acid to give the bicyclic enone product **19**. Alternatively, the intermediate diketone **21** can be prepared separately and subjected to the reaction conditions to give the bicyclic enones **19** in good yields.

Substituted bicyclo[2.2.2]oct-5-en-2-ones **1** are very useful building blocks in organic chemistry, which serve as substrates for anionic oxy-Cope rearrangements[1] and retro-Diels–Alder procedures.[2] They are prepared by several synthetic methods, most commonly by a multistep approach (Scheme 1) using an initial Diels–Alder reaction of a substituted cyclohexadiene **3** (itself prepared from a cyclohexanone **2** or an aromatic precursor) and any of several ketene equivalents **4** as dienophiles[3] or by other Diels–Alder cycloadditions.[4] Although this method has been successfully applied to the synthesis of various bicyclooctenones, there is still a need for a simpler preparation of such systems requiring fewer steps and higher generality. We report herein a novel synthesis of such compounds via a tandem intermolecular Michael addition–intramolecular aldol condensation process that affords the desired substituted bicyclo[2.2.2]oct-5-en-2-ones **1** in good yields in a single multi-step one-pot operation.

When a 1:3 mixture of a ketone and a cyclic enone is heated in the presence of 3 equiv of trifluoromethanesulfonic (triflic) acid in dichloromethane either in a microwave reactor[5] or under standard conditions, one isolates the corresponding bicyclic enones in fair to good yields. For example, when a solution of cyclohexanone **5** and cyclohex-2-enone **6** in dichloromethane is heated at 40 °C for 8 h in a standard microwave reactor, the tricyclic enone **7** is produced in 57% isolated yield (Scheme 2). A proposed mechanism for the reaction is given in Scheme 3, namely a Michael addition of the enol of cyclohexanone **8** to the protonated cyclohexenone **9** to give the enol **10**, which could condense directly in an aldol fashion to give the β-hydroxyketone product **11**,



Scheme 1.

Keywords: Robinson annulation; Bicyclo[2.2.2]oct-5-en-2-ones; Michael-aldol process.
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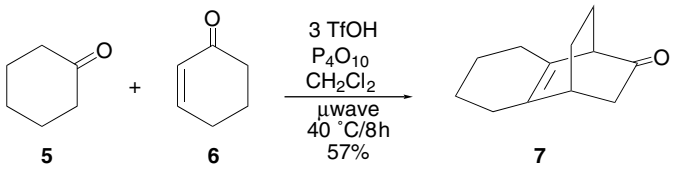
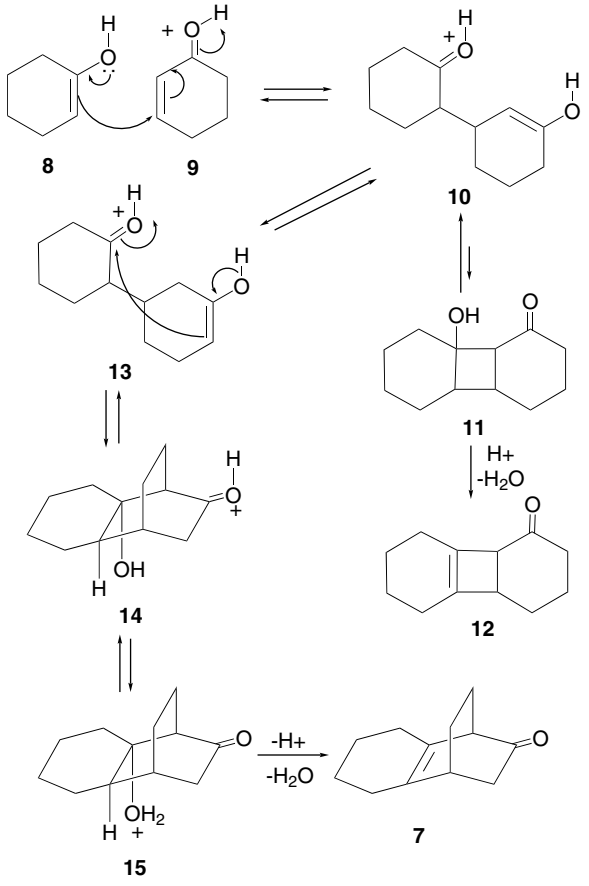


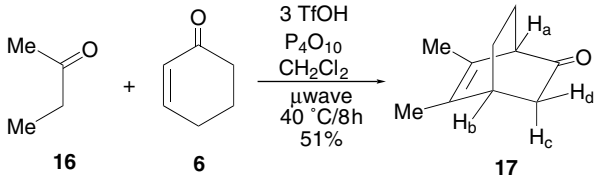
Scheme 2.



Scheme 3.

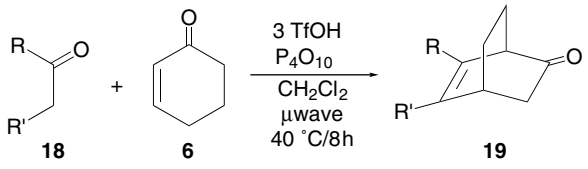
which could then eliminate water to give the cyclobutene **12**. Although such ring systems are known, they are normally prepared via [2+2] photoadditions and are almost certainly too strained to be formed by an intramolecular aldol condensation.[6] Instead the initially formed enol **10** presumably isomerizes via the ketone to a second enol **13** and an intramolecular aldol condensation occurs to generate, via the intermediates **14** and **15**, the non-conjugated enone **7**. By examining the reaction before completion by gas chromatography, one can see evidence for the formation of the diketone corresponding to **10**. This reaction is essentially a bridged Robinson annulation, an initial Michael addition, enol isomerization, and intramolecular aldol condensation with a bridged non-conjugated enone being produced. Even though the Robinson annulation has been known for almost 70 years,[7] as far as we can tell, there have been no previous examples of such a bridged Robinson annulation, namely the condensation of a ketone on to a cyclic enone to give the bicyclic enone products.

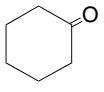
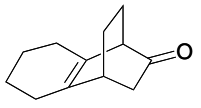
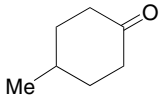
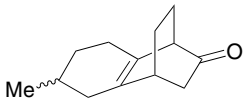
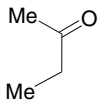
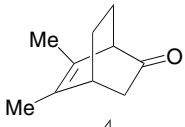
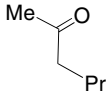
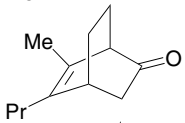
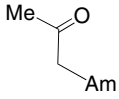
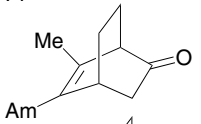
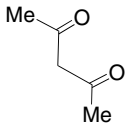
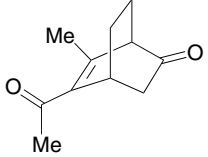
Like the Robinson annulation, the reaction is fairly general with a number of cyclic and acyclic ketones and cyclohexenone participating. For example, heating a solution of 2-butanone **16** and cyclohexenone **6** for 8 h at 40 °C gave the analogous bicyclic enone **17** in 51% yield (Scheme 4). Analysis of the high field proton



Scheme 4.

Table 1. Synthesis of bicyclic enones **19** from **18** and **6**



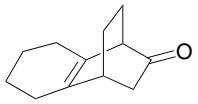
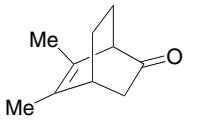
Entry	Ketone **18**	Enone **19**	Yield (%)
1			57
2			50[a]
3			51
4			32
5			31
6			40

[a] A ~1.5:1 mixture of diastereomers.

NMR spectrum of **17** allowed the determination of the structure of these bicyclic enones. In particular the protons α to the ketone displayed the expected couplings constants with H_c being a ddd, $J = 18.2$, 3.0, 3.0 Hz with the third doublet being due to a relatively large W coupling while H_d is a dd, $J = 18.2$, 2.1 Hz.[8]

We examined the reaction and found it to be fairly general. As shown in Table 1, several other ketones **18** can be used with cyclohexenone **6** in this process with fair to good yields of the corresponding enones **19**. 4-Methylcyclohexanone (entry 2) afforded a ~1.5:1 mixture of diastereomers at the methyl group while alkyl methyl ketones (entries 4 and 5) produced the disubstituted bicyclic enones in fair yield. An interesting example is the use of pentane-2,4-dione (entry 6) to give a 40% yield of the enedione.[9] Although we have used microwave conditions for this process, the reaction is not limited to this method. We also examined (Table 2) conventional heating of the reaction mixture in a normal reflux apparatus (Method B) and obtained similar results with a slight reduction in the isolated yields. One can even carry out the reaction at room temperature (Method C) for a longer period of time with a somewhat larger reduction in the yield. Thus the process is quite general and does not require microwave conditions.

Table 2. Effect of reaction conditions on yield of **19**

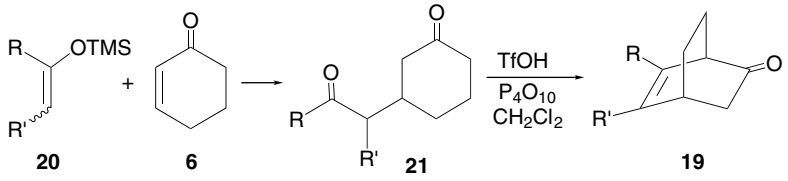
Enone	Method A[a]	Method B[b]	Method C[c]
	57%	55%	46%
	51%	40%	33%

[a] A mixture of 1 mmol ketone, 3 mmol enone, 3 mmol TfOH and 0.4 mmol P_4O_{10} in 4 ml anhydrous DCM was microwaved for 8 h at 40 °C.
[b] Same as A but the mixture was heated using a conventional reflux apparatus for 8 h at an oil bath temperature of 48–50 °C.
[c] Same as A but the mixture was stirred for 24 h at room temperature.

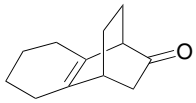
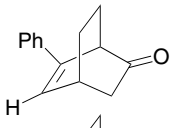
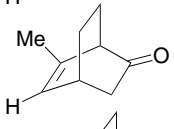
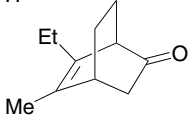
It is important to point out that when the conventional Robinson annulation is carried out under acidic conditions to produce fused bicyclic enones, the yields are generally quite similar to those reported here, for example, 40–60% (e.g., 2-methylcyclohexanone and methyl vinyl ketone gave the octalone in 49–55% yield).[10] The sterically hindered enone, 4,4-dimethylcyclohexenone, did not give good yields of the corresponding bicyclooctenones, presumably due to the steric hindrance in the Michael addition.

Since simple methyl ketones, for example, acetone and acetophenone, give poor yields in this one-step process, presumably because of a slow initial Michael addition due to the fact that the formation of the unsubstituted enol would not be favored, we therefore developed a two-step method for the preparation of the bicyclic enones (Table 3). Thus one can prepare and isolate the 1,5-diketones **21** in 70–93% yields by the

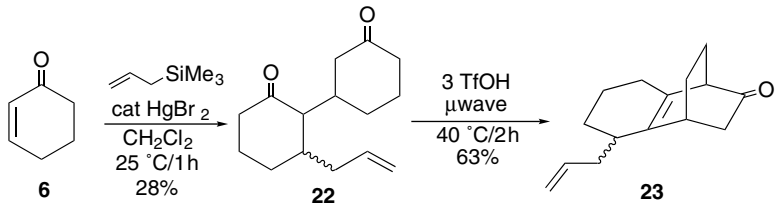
Table 3. Two-step synthesis of bicyclic enones **19** from **20** and **6** via diones **21**



20 **6** **21** **19**

20 R, R′	**21**	Enone **19**	Cond.	**19**
$(CH_2)_4$	70%[a]		Microwave/40 °C/2 h	82%
Ph, H	92%[b]		0 °C/30 min; 23 °C/45 min	78%
Me, H	78%[b]		0 °C/1 h; 23 °C/40 min	51%
Et, Me	93%[c]		Microwave/40 °C/8 h	40%

[a] Ref. 11.
[b] Ref. 12.
[c] Ref. 13.



Scheme 5.

Mukaiyama–Michael addition of the silyl enol ethers **20** to cyclohexenone **6** using various catalysts.[11–13] Cyclization of these 1,5-diketones using triflic acid is much easier and proceeds under milder conditions and in higher isolated yields, 40–82%. Even though both of the cyclic ketones can enolize in two ways, the one which leads to the bicyclic enone **19** predominates, presumably since it is the only one which can eliminate easily to give an alkene (the others would give cyclobutenes or anti-Bredt's rule alkenes). Thus one can prepare the 6-monosubstituted bicyclo[2.2.2]oct-5-en-2-ones **19** as well as the disubstituted analogues by this two step approach, thereby increasing the scope of the process.

Finally a tandem Sakurai allylation[14]–Michael addition can also give the intermediate diketone, for example, **22**, from cyclohexenone **6** and allyltrimethylsilane.[15] Treatment of **22** under normal conditions gave an approximate 2:1 diastereomeric mixture of the product **23** in an unoptimized 63% yield (Scheme 5).

In conclusion, we have shown that one can prepare substituted bicyclo[2.2.2]oct-5-en-2-ones in a multi-step one-pot process from simple ketones and diones and cyclic enones under acidic conditions by using either microwave or conventional heating and even at room temperature. We have also demonstrated that this process can be carried out in a two-step sequence via the intermediate 1,5-diketones. Further work in the preparation of other similar compounds and their use in the synthesis of interesting natural products are underway and will be reported in due course.

Acknowledgements

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5. The microwave reactions were carried out using a CEM Focused Microwave System, Model Discover, set at an initial power setting of 300 W. In a representative procedure, phosphorus pentoxide was suspended in 4 ml anhydrous dichloromethane, and the ketone, followed by 2-cyclohexen-1-one, was added at room temperature. The suspension was cooled to 0 °C and the trifluoromethanesulfonic acid was added. The suspension was warmed to room temperature and heated with stirring in a microwave reactor for 8 h at 40 °C. The dark suspension was cooled to 0 °C and 0.55 ml (399.3 mg, 3.9 mmol) triethylamine was added dropwise with stirring. After complete addition of the triethylamine, the reaction mixture was stirred for 5 min at room temperature, and a reddish-yellow suspension was obtained. The suspension was filtered, the residue washed thoroughly twice with 5 ml dichloromethane, and the volume of the filtrate reduced. The reddish oil obtained was directly subjected to flash column chromatography using silica without aqueous workup. The oily products obtained were dried under weak vacuum (30 mm Hg) until the weight was constant (approx. 15–20 min).
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8. The analogous peaks in the tricyclic enone **7** are obscured and thus less informative for structure determination.
9. The byproducts formed in these reactions are mostly higher oligomers resulting from Michael addition of the initially formed enol, for example, **10**, on another molecule of the protonated starting enone, for example, **9**. The structures of these products were assigned only by GC and MS and the compounds were not isolated or purified. We have not observed the formation of any regioisomeric products in entries 3–6 of Table 1 since enolization toward the methyl group is very unfavorable under these conditions.
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15. For an alternate preparation of **22**, see: Cossy, J.; Lutz, F.; Alauze, V.; Meyer, C. *Synlett* **2002**, 45–48.