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A novel synthesis of bicyclo[3.3.0]oct-1-en-3-ones from cyclobutanones through [chloro(*p*-tolylsulfinyl)-methylidene]cyclobutanes with ring expansion

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Abstract—Treatment of [chloro(*p*-tolylsulfinyl)methylidene]cyclobutanes, which were synthesized from cyclobutanones and chloromethyl *p*-tolyl sulfoxide in three steps in high overall yields, with excess cyanomethyllithium gave enaminonitriles in high yields. Heating of these enaminonitriles with H_3PO_4 in acetic acid gave 2-cyanobicyclo[3.3.0]oct-1-en-3-ones in good yield. On the other hand, treatment of the [chloro(*p*-tolylsulfinyl)methylidene]cyclobutanes with cyanomethyllithium followed by lithium carbanion of the homologues of acetonitrile afforded enaminonitriles having a substituent at the 3-position. Heating of the enaminonitriles with H_3PO_4 in acetic acid gave 2-substituted bicyclo[3.3.0]oct-1-en-3-ones in good to high yields. This method offers a novel and versatile procedure for synthesis of 2-substituted bicyclo[3.3.0]oct-1-en-3-ones from cyclobutanones in good overall yields.

The bicyclo[3.3.0]octane ring system is one of the most widely distributed carbon structures in natural and unnatural organic compounds. Especially, cyclopentanoid natural products such as angular triquinanes and linear triquinanes contain bicyclo[3.3.0]octane rings in their structure.[1] Many methods have already been reported for the construction of the bicyclo[3.3.0]octane ring system and for the total synthesis of cyclopentanoid natural products,[2] including Nazarov cyclization[3] and Pauson–Khand reaction;[4] however, in view of the importance of the bicyclo[3.3.0]octane ring system, new methods are still eagerly sought.

Previously, we reported a new synthesis of spiro[4.*n*]-alkenones from three components: cyclic ketones, chloromethyl *p*-tolyl sulfoxide and acetonitrile.[5] In continuation of our interest in the development of new synthetic methods by using chloromethyl *p*-tolyl sulfoxide as a one-carbon homologating agent, we recently investigated the above-mentioned reaction with cyclobutanones and it was found that the reaction proved to be a novel method for construction of 2-substituted bicyclo[3.3.0]oct-1-en-3-ones in good overall yields.

Thus, [chloro(*p*-tolylsulfinyl)methylidene]cyclobutane **2** was synthesized from cyclobutanone **1** in three steps in quantitative yield. Treatment of this vinyl sulfoxide **2** with 5 equiv of cyanomethyllithium gave enaminonitrile **3** in high yield. The enaminonitrile **3** was heated in acetic acid containing H_3PO_4 and water to give 2-cyanobicyclo[3.3.0]oct-1-en-3-one **4** with ring expansion of the cyclobutane ring (Scheme 1). The vinyl sulfoxide **2** was first treated with cyanomethyllithium at −78 °C to give the adduct **5** in quantitative yield. The adduct was then treated with LDA followed by lithium α-carbanion of the homologue of acetonitrile to give 3-substituted enaminonitrile **6** in high yield.[6] Finally, heating of **6** in acetic acid containing H_3PO_4 and water resulted in the formation of 2-substituted bicyclo[3.3.0]oct-1-en-3-ones **7** in good yield. These reactions offer a novel and versatile procedure for the preparation of various bicyclo[3.3.0]oct-1-en-3-ones from cyclobutanones in good overall yield.

A representative example of the synthesis of 2-cyanobicyclo[3.3.0]oct-1-en-3-one **4a** starting from cyclobutanone **1a** is reported as an example (Scheme 2). [Chloro(*p*-tolylsulfinyl)methylidene]cyclobutane **2a** was synthesized from cyclobutanone **1a** and chloromethyl

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Keywords: Cyclobutanone; Sulfoxide; Ring expansion; Bicyclo-[3.3.0]octane; Bicyclo[3.3.0]oct-1-en-3-one.

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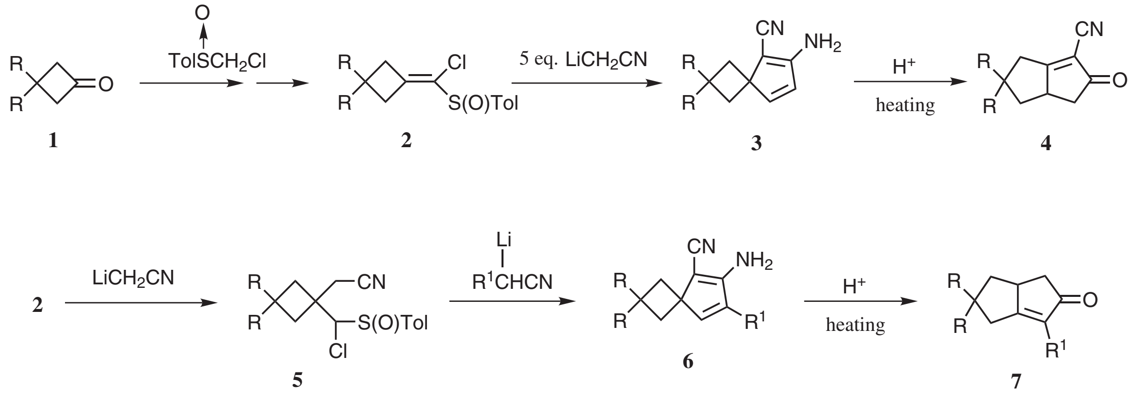
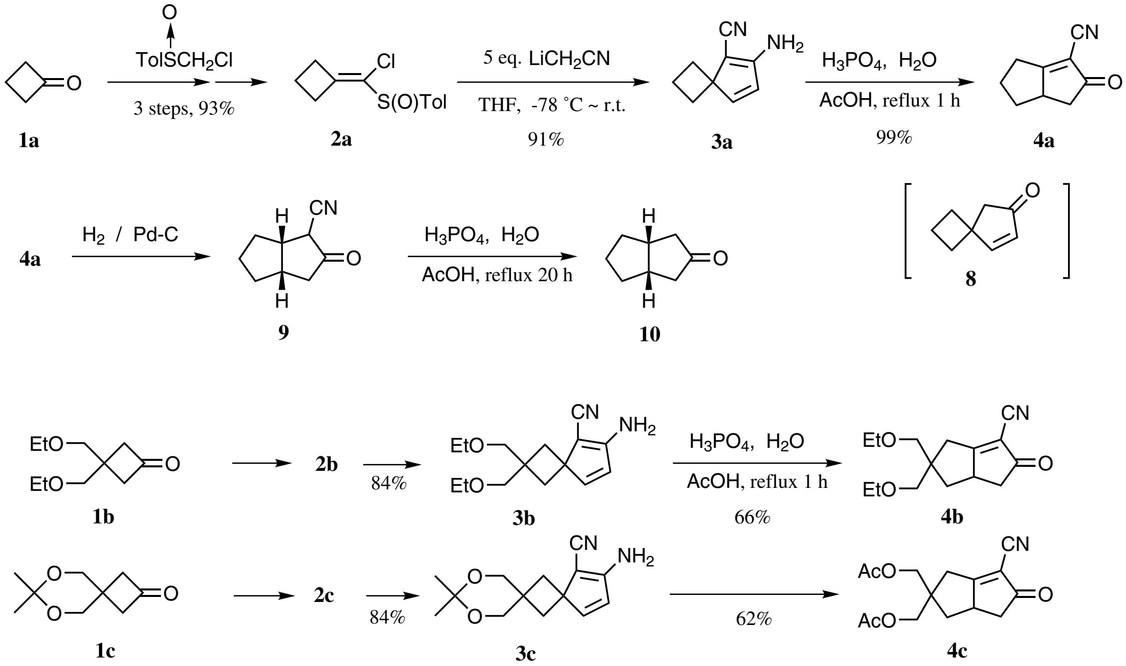


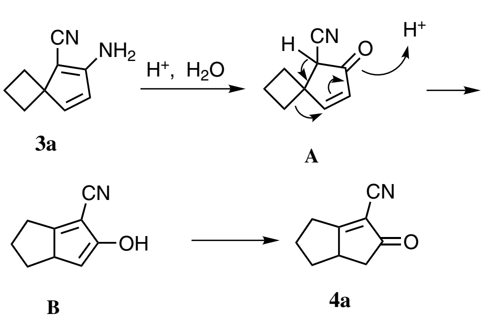
Scheme 1.



Scheme 2.

p-tolyl sulfoxide in three steps in 93% overall yield.[5] The vinyl sulfoxide **2a** was treated with 5 equiv of cyanomethyllithium in THF to give the enaminonitrile **3a** in 91% yield.[5] The enaminonitrile was treated with H_3PO_4 in the presence of water in acetic acid to give the bicyclooctenone **4a** in 99% yield.

We expected that this reaction would give spiro[3.4] alkenone **8** at first;[5] however, the product obtained had no olefinic hydrogen. The product showed 147 as the molecular weight and the presence of a nitrile group (2229 cm^{-1}) and a carbonyl group (1724 cm^{-1}) in its IR spectrum. From the ^1H and ^{13}C NMR, the product was presumed to be 2-cyanobicyclo[3.3.0]oct-1-en-3-one **4a**. In order to confirm the structure, **4a** was hydrogenated to **9** and the product was hydrolyzed and decarboxylated to give the known bicyclo[3.3.0]octan-3-one **10**.[7]



Scheme 3. Presumed mechanism for the formation of bicyclo-[3.3.0]oct-1-en-3-one **4a** from the enaminonitrile **3a** by the treatment with acid.

The presumed mechanism of this reaction is illustrated in Scheme 3. Thus, acidic hydrolysis of the enaminonitrile **3a** gives the enone **A**. Protonation of the carbonyl oxygen of the enone **A** followed by the ring expansion of the cyclobutane ring would give bicyclo[3.3.0]octane

B. Tautomerization of the enol **B** gives the product enone **4a**.

Generality of this reaction was investigated with two cyclobutanones **1b** and **1c**[8] and the results are shown in Scheme 2. The enaminonitriles **3b** and **3c** were synthesized from the cyclobutanones **1b** and **1c** via the vinyl sulfoxides **2b** and **2c** in high overall yields by the same procedure as described above. The acidic treatment of the enaminonitriles gave the expected 7,7-disubstituted 2-cyanobicyclo[3.3.0]oct-1-en-3-ones **4b** and **4c** in somewhat variable yields.

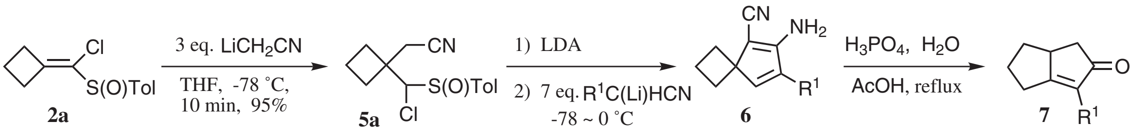
We previously reported a novel synthesis of 2,4,4-trisubstituted 2-cyclopentenones from 1-chlorovinyl *p*-tolyl sulfoxides by consecutive reaction with acetonitrile and its homologues.[6] We applied this methodology to the [chloro(*p*-tolylsulfinyl)methylidene]cyclobutane **2a** and quite interesting results were obtained (Table 1).

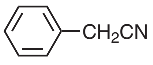
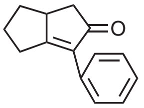
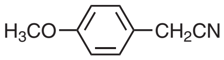
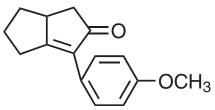
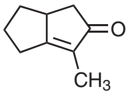
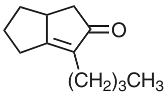
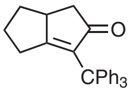
First, **2a** was treated with 3 equiv of cyanomethyllithium in THF at −78 °C for 10 min to give the adduct **5a** in 95% yield. The adduct **5a** was treated with LDA at −78 °C followed by lithium α-carbanion of phenylacetonitrile (7 equiv). The reaction mixture was slowly allowed to warm to −40 °C and the reaction was quenched to afford enaminonitrile **6a** (Table 1, entry 1) in 78% yield. Finally, **6a** was heated under reflux in acetic acid containing H_3PO_4 and water for 12 h to give the product in 99% yield. Somewhat surprisingly, the product was not the expected 2-cyano-4-phenylbicyclo[3.3.0]oct-1-en-3-one but 2-phenylbicyclo[3.3.0]oct-1-en-3-one **7a**. All the spectral data of **7a** was highly consistent with those reported.[9]

A presumed mechanism of this reaction is as follows (Scheme 4). At first, acidic hydrolysis of the enaminonitrile **6a** would give the enone **C**, then the rearrangement (ring expansion) takes place as described in Scheme 3 to afford 2-cyano-4-phenylbicyclo[3.3.0]oct-1-en-3-one **D**. Migration of the double bond under acidic conditions proceeds to give 4-cyano-2-phenylbicyclo[3.3.0]oct-1-en-3-one **E**. Finally, the cyano group is hydrolyzed and decarboxylated to give **7a**.

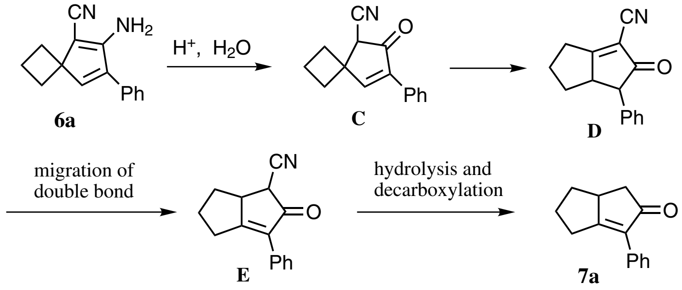
As this procedure is quite an interesting new method for synthesis of various 2-substituted bicyclo[3.3.0]oct-1-en-3-ones, we investigated the generality of the substituents at the 2-position and the results are summarized in Table 1. The reaction with 4-methoxyphenylacetonitrile gave also **7b** in good overall yield (entry 2). Entries 3 and 4 show that the alkyl groups can be introduced at the 2-position of the bicyclo[3.3.0]oct-1-en-3-one system in high yields. Interestingly, it was found that the enaminonitriles having alkyl groups need much longer time for the acidic hydrolysis compared with those having aryl groups (compare entries 1 and 2 with 3 and 4). A sterically highly bulky group, a triphenylmethyl group, can

Table 1. Synthesis of 2-substituted bicyclo[3.3.0]oct-1-en-3-one **7** from the vinyl sulfoxide **2a** with acetonitrile and its homologues through enaminonitriles **6**



Entry	R^1CH_2CN	Enaminonitrile **6**, yield (%)	Conditions for the hydrolysis	2-Substituted bicyclo[3.3.0]oct-1-en-3-one **7** (yield, %)
1		**6a**, 78[a]	12 h	**7a**  (99)
2		**6b**, 99	14 h	**7b**  (75)
3	CH_3CH_2CN	**6c**, 97	65 h	**7c**  (78)
4	$CH_3(CH_2)_3CH_2CN$	**6d**, 95	85 h	**7d**  (83)
5	Ph_3CCH_2CN	**6e**, 64	50 h	**7e**  (53)

[a] Conditions: −78 to −40 °C and −40 °C for 1.5 h.



Scheme 4. Presumed mechanism for the formation of 2-phenylbicyclo[3.3.0]oct-1-en-3-one **7a** from the enaminonitrile **6a** by the treatment with acid.

be introduced at the 2-position by this procedure to give **7e**, though the overall yield was not satisfactory (entry 5).

It is worth noting that when cycloalkanones having larger than five-membered ring were used in this reaction, the ring expansion did not proceed.[5] The relief of strain associated with the cyclobutane ring must be the driving force of this reaction.[10]

In conclusion, we have discovered a novel procedure for synthesis of 2-cyanobicyclo[3.3.0]oct-1-en-3-ones and 2-substituted bicyclo[3.3.0]oct-1-en-3-ones from three components: cyclobutanones, chloromethyl *p*-tolyl sulfoxide and nitriles, in good overall yields. We are continuing to study the scope and limitations of this procedure and its application to total synthesis of cyclopentanoid natural products.

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