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A [3+2] Annulation Procedure for Methylenecyclopentanes

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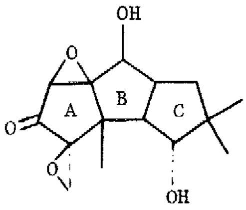
Summary: A two step sequence converts certain cyclic enones to fused methylenecyclopentanes using the annulation reagent 2-chloromethyl-3-trimethylsilylpropene.

A profitable method for the construction of fused carbocycles has been the [4+2], [2+2], or [1+2] cycloaddition of a cyclic enone to a reagent of appropriate chain length and functionality. For example, a diene may be used for the Diels-Alder reaction, an alkene for photochemical [2+2] cycloaddition, and a sulfoxonium ylide for cyclopropanation. In contrast, efficient procedures for [3+2] annulation of enones have not been generally available.[2,3] Because of our interest in the synthesis of the antitumor agent coriolin (**1**)[2,4], we sought a [3+2] annulation procedure for fusing five membered rings, shown schematically as **2**+**3** → **4**.



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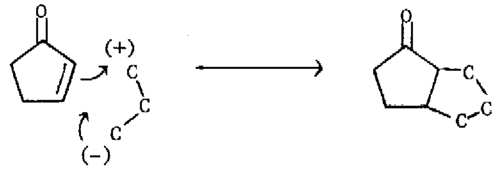
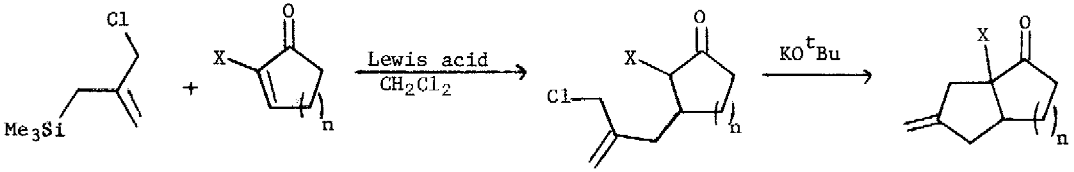


2 **3** **4**

The annulation reagent should possess a nucleophilic end and a compatible electrophilic end in a three carbon chain.[5] Because of the nucleophilicity of allylsilanes toward enones in the presence of a Lewis acid[6], 2-chloromethyl-3-trimethylsilylpropene (**5**) has the requisite properties. We wish to report that [3+2] annulation of cyclic enones in this manner by **5** has been achieved (Scheme 1).

Annulation reagent **5** was prepared from iodomethyltrimethylsilane[7] by a short sequence: 1) CH$_2$(CO$_2$Et)$_2$, NaOEt, EtOH, reflux; 2) NaH, THF, LiAlH$_4$, reflux[8,9]; 3) MeSO$_2$Cl, LiCl, DMF, collidine, 0°.[10] Treatment of a dichloromethane solution of the titanium tetrachloride complex of cyclohexenone (**6a**)[6] with 1.6 equiv. of **5** at -78° followed by warming to -20° (0.5h) gave the product of conjugate addition, **7a**[11], in 80% yield after chromatography. Cyclization to **8a** does not occur under these conditions, but can be induced by treatment of **7a** with 1.1 equiv of

Scheme 1. [3+2] Annulation of Cyclic Enones



5 6 7 8

6	7	8
a. n=2, X=H	a. 80%	a. 60%
b. n=1, X=H	b. 8%	b. –
c. n=2, X=SPh	c. 80%	c. 79%
d. n=1, X=SPh	d. 63%	d. 73%

potassium tert-butoxide in tert-butanol for 3h at 25°. The product 8a[3] was obtained as a 3:1 mixture of ring fusion isomers after chromatography. Thus the two step procedure constitutes an overall [3+2] annulation of 6a in satisfactory yield.

Similar treatment of cyclopentenone (6b) with 5 resulted in a low yield of conjugate addition product 7b. Apparently 6b is polymerizing under these conditions. Conjugate addition of 5 to 3-methylcyclopentenone, carvone, isophorone, and 1-acetylcyclohexene also gave low yields of conjugate addition, although in these cases substantial amounts of starting ketones were obtained. Since allyltrimethylsilane adds to these enones[6,12], the chloromethyl group of 5 is exerting an inductive, and possibly steric, effect in reducing its reactivity.

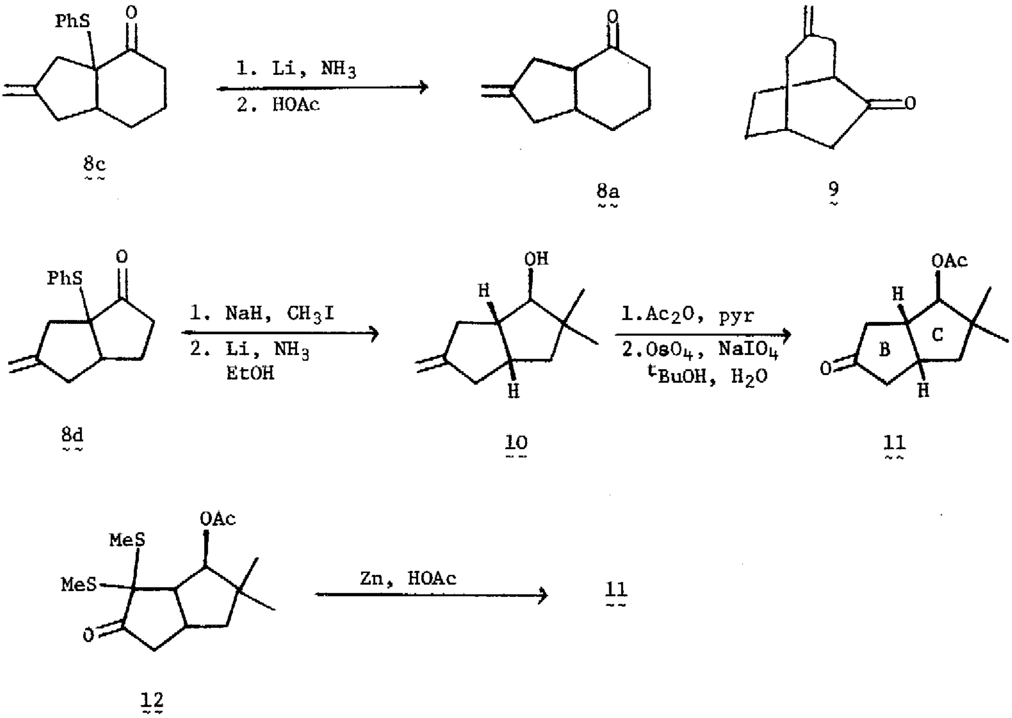
By using the 2-phenylthioenones, the conjugate addition reactions can be improved. Thus 2-phenylthiocyclohexenone (6c)[13] and 2-phenylthiocyclopentenone (6d)[14] reacted with 5 to give 7c and 7d, respectively. In the case of 6d, an improvement in yield was realized if ethylaluminum dichloride was used instead of titanium tetrachloride, although the same substitution lowered the yields in the other cases. Cyclization of 7c and 7d occurred smoothly upon treatment with 1.1 equiv of potassium tert-butoxide in 2:1 tetrahydrofuran: tert-butanol at 0°.

The structure of 8a has been verified by its synthesis from 8c using lithium in ammonia/ether at -78° (Scheme 2). The same 3:1 mixture of isomers of 8a was obtained (NMR, IR, gc, tlc). Evidently cyclization of 7a occurs mainly in the fused mode, since the ketone expected from bridged mode cyclization, 9, is not observed.

Annulation product 8d has been transformed by a four step sequence (Scheme 2) to 11, a compound which represents the BC rings of coriolin (1). The structure of 11 (and thus 8d) is confirmed by its preparation from 12, which we had synthesized in related work.[15]

The [3+2] annulation of cyclic enones is therefore a practical route to fused carbocycles which may be of use in the synthesis of complex natural products. Further extension of this method using annulation reagents related to 5 is presently under investigation.

Scheme 2. Transformations of Annulation Products



Acknowledgment. This investigation was supported by Grant Number CA-24747, awarded by the National Cancer Institute, DHEW.

References and Notes

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