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Formation of 3,4-dimethyl-2-pyrones from allene carboxylates and 2-silyloxydienes via 3-carboethoxyethylidene cyclobutanols

Michael E. Jung* and Aaron R. Novack

Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90095-1569, USA

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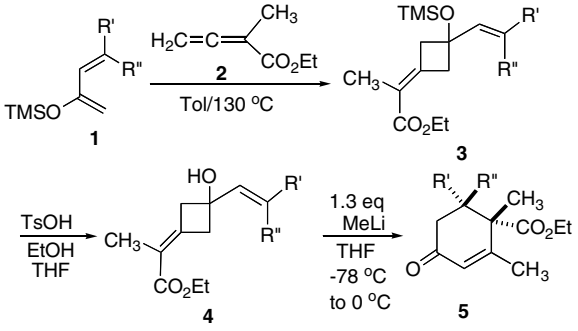
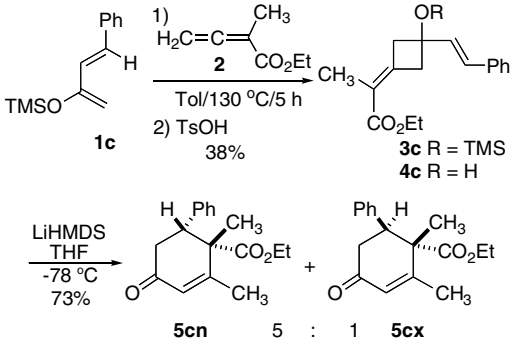
Abstract—The 3-carboethoxyethylidene cyclobutanols **4** are prepared in two steps via [2+2] cycloaddition of the 2-silyloxydienes **1** and the allene carboxylate **2** followed by acidic hydrolysis. Treatment of these cyclobutanols **4** with various bases affords good yields of the substituted 3,4-dimethyl-2-pyrones **6**. The proposed mechanism involves ring opening of the metal alkoxide **7** to give the carbanion **8**, which undergoes proton transfer to give the more stable carbanion **9** and double bond isomerization to give the enolate **10**, which then forms the pyrone ring **6** via attack on the ester via **11**.

Recently, we reported the formation (Scheme 1) of 1-alkenyl-3-carboethoxyethylidenecyclobutanols **4** via a two-step procedure involving first [2+2] cycloaddition of various 2-silyloxydienes **1** with ethyl 2-methylbuta-2,3-dienoate **2** to give the cyclobutyl silyl ethers **3** and then acidic hydrolysis of the silyl ethers to the alcohols **4**.[1] The dienes **2** were usually prepared from the corresponding enones via standard silyl enol ether formation. Treatment of these cyclobutanols **4** with lithium bases at low temperature led to a highly stereoselective rearrangement of the cyclobutane systems to the cyclohexenones **5**. For example, the 2-silyloxydiene **1c** derived from 4-phenyl-3-buten-2-one on heating with the allene carboxylate **2** in toluene at 130 °C for 5 h gave the [2+2] cycloadduct **3c**, which was hydrolyzed to the cyclobutanol **4c** in 38% overall yield for the two steps (Scheme 2).[2] Treatment of **4c** with lithium hexamethyldisilazide (LiHMDS) in THF at −78 °C afforded a 5:1 mixture of the *endo* and *exo* cyclohexenones **5cn** and **5cx** in 73% yield. We now report a different reaction pathway for the cyclobutanols **4** on treatment with different bases to produce not cyclohexenones **5** but rather the 6-substituted 3,4-dimethyl-2-pyrones **6** in good to excellent yields (Scheme 3). Since substituted 2-pyrones are compounds of interest both for their beneficial biological properties[3] and for their use in organic synthesis,[4] several routes have been devised for their synthesis.[5]



Scheme 1.



Scheme 2.

Keywords: 2-Pyrones; Cyclobutanols; Base-promoted rearrangement; Cyclobutanones.
* Corresponding author. Tel.: +1 3108257954; fax: +1 3102063722; e-mail: jung@chem.ucla.edu

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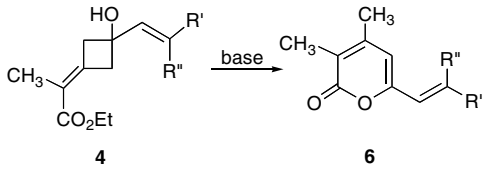


4 6

Scheme 3.

As reported herein, we have now developed a novel route to 2-pyrones from allene esters and silyl enol ethers via cyclobutanols.

The results are shown in Table 1. When the 1-(2-methylpropenyl)cyclobutanol **4a** was treated with sodium hydride, we isolated a 20% yield of the 2-pyrone **6a** as a white solid. The use of lithium hexamethyldisilazide (LiHMDS) converted **4a** into the pyrone **6a** in 63% yield. However, the best yield resulted when the cyclobutanol **4a** was treated with sodium hydride and an equiv of zinc dichloride was added; in this case a quantitative yield of the crystalline pyrone **6a** was isolated. The other 2,2-disubstituted alkenyl cyclobutanol **4b** also gave quite good yields of the pyrone **6b**. Sodium hydride afforded a 77% yield of **6b** while the use of *tert*-butyllithium as base furnished the desired pyrone as a white solid in 94% yield. The two *E* monosubstituted alkenylcyclobutanols **4c** and **4d** gave the corresponding pyrones **6c** and **6d** in yields of 60% and 64%, respectively. The 1-(cyclohexenyl)cyclobutanol **4e** afforded the pyrone **6e** in 62% yield. Finally, we also looked at a simple case in which no competing ring opening-intramolecular Michael addition (or anionic [3,3]-sigmatropic rearrangement) to give cyclohexenone products would be possible, namely the 1-phenyl derivative **4f**. Treatment of **4f** with LiHMDS gave the pyrone **6f** in 64% yield, while the use of potassium hydride and 18-Crown-6 afforded **6f** in 42% yield. Thus many different substituted 2-pyrones can be prepared by this route.[6]

We postulate that the formation of the 2-pyrones **6** from the cyclobutanols **4** proceeds via the mechanism shown in Figure 1. Deprotonation of the alcohol would give the alkoxide **7** with the metal counterion that was present in the base. We have already shown that very tight ion pairs are necessary for the ring opening-intramolecular Michael addition (or anionic [3,3]-sigmatropic rearrangement) to give cyclohexenones **5**.[1] We propose that the alkoxide opens the strained cyclobutane ring regiospecifically to give the carbanion *cis* to the ester

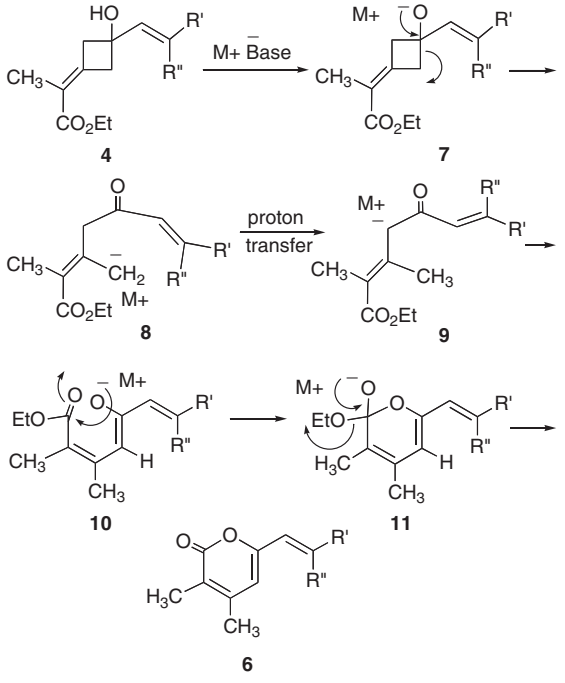
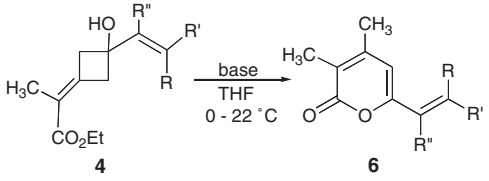
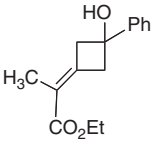
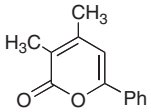


Figure 1. Mechanism for the conversion of the 3-carbo-ethoxyethylidenecyclobutanols **4** into 2-pyrones **6**.

Table 1. Formation of 6-substituted 3,4-dimethyl-2-pyrones **6** from cyclobutanols **4** on treatment with base



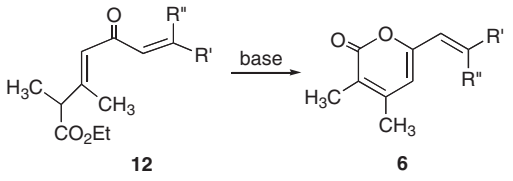
4 6

Cyclobutanol	R	R′	R″	Base	Pyrone	Yield (%)
4a	CH_3	CH_3	H	NaH	**6a**	20
4a	CH_3	CH_3	H	LiHMDS	**6a**	63
4a	CH_3	CH_3	H	$NaH/ZnCI_2$	**6a**	100
4b	CH_3	Ph	H	NaH	**6b**	77
4b	CH_3	Ph	H	*t*-BuLi	**6b**	94
4c	H	Ph	H	NaH	**6c**	60
4d	H	CH_3	H	NaH	**6d**	64
4e	H	$-(CH_2)_4-$		NaH	**6e**	62
4f				LiHMDS		64
				KH 18-C-6		42

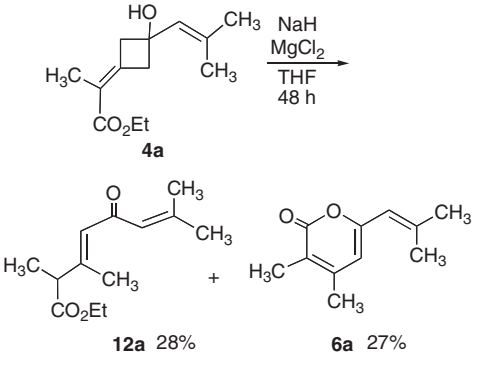
6f

8, since there is good literature precedent from Weiler that anions *cis* to esters are more stable than those *trans* to esters.[7] This anion, if the ion pair is tight, can undergo an intramolecular Michael addition to the enone to ultimately produce the cyclohexenones **5** as we have shown.[1] However, if the ion pair is not as tight, presumably a proton transfer can occur to convert the less stable carbanion **8**, stabilized via the allylic ester, into the more stable carbanion **9** stabilized by both the ketone and the allylic ester. Also at some point, via enolization–reprotonation, the double bond geometry of the tetrasubstituted olefin must switch from *E* to *Z* (or a mixture of the two since only the *Z* can react). Attack of the enolate on the ester as shown in **10** gives **11**, which then ejects ethoxide to give the observed product, the pyrone **6**. There is some evidence for at least part of this mechanism since Jeschke[8] (Scheme 4) showed that several keto esters **12**, which are the protonated forms of our suggested intermediates **9**, gave the 2-pyrones **6** on treatment with base. Thus, the anion of **12** (namely **9**) must lead to the pyrones. We have one additional piece of evidence that suggests that the formation of pyrones from the cyclobutanols proceeds as shown in Figure 1. Treatment of the cyclobutanol **4a** with sodium hydride with the subsequent addition of an equiv of magnesium chloride in THF at 22 °C for 48 h afforded two products, the expected pyrone **6a** in 27% yield and the dienone ester **12a** in 28% yield (Scheme 5). Thus, we have good evidence that the cyclobutanol **4a** opens in base to the diene ester **12**, which has already been shown to close to the pyrone in base.

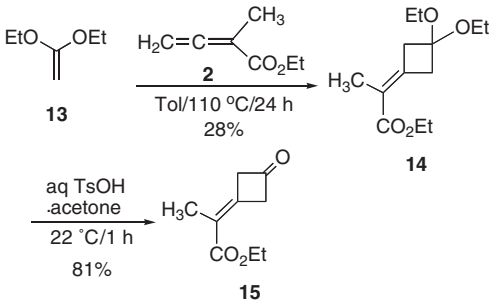
Finally, we wish to report a new method for the formation of these compounds that does not utilize the initial [2+2] cycloaddition of 2-silyloxydienes. Diethyl ketene acetal, **13**, prepared by the literature route,[9] was heated with the allene carboxylate **2** in toluene to give the



Scheme 4.



Scheme 5.



Scheme 6.

cyclobutanone ketal **14** in an unoptimized yield of 28% (Scheme 6). Acidic hydrolysis of the ketal in aqueous acetone afforded the 3-carboethoxyethylidene cyclobutanone **15** in 81% yield. Addition of nucleophiles to this reactive ketone would generate the same alkoxide intermediate shown in Figure 1 and thus should lead to the same pyrones, thereby streamlining the process somewhat.

In conclusion, we have developed a new method for the synthesis of 6-substituted 3,4-dimethyl-2-pyrones **6**, which involves the base-promoted rearrangement of 3-carbo-ethoxyethylidene cyclobutanols **4** and affords a series of pyrones in yields of 60–100%. A mechanism for this unusual transformation has been proposed and some evidence supporting it presented. Finally, a route to the reactive cyclobutanone **15** has been developed.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.091.

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