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Unusual, Strained Heterocycles: 3-Alkylidene-2-methyleneoxetanes from Morita–Baylis–Hillman-type Adducts†

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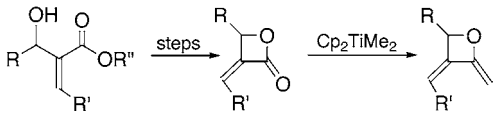
ABSTRACT



3-Alkylidene-2-methyleneoxetanes have been prepared by treating α-alkylidene-β-lactones, derived from Morita–Baylis–Hillman-type adducts, with dimethyltitanocene. Preliminary studies of the reactivity of these little known, strained heterocycles are also described.

The high reactivity and tremendous potential for acting as chiral templates have made strained heterocyclic systems attractive targets for synthetic development. Our interest in such systems has centered on the exploitation of the little investigated 2-methyleneoxetanes. We developed a straightforward entry into this class of compounds by the methylenation of β-lactones with dimethyltitanocene.[1] Our anticipation of the flexibility of 2-methyleneoxetanes has been confirmed by their conversion to homopropargylic alcohols,[2] functionalized ketones,[3,4] and 1,5-dioxaspiro[3.2]hexanes,[5] the latter representing useful strained heterocyclic systems.[6,7] In studying these transformations, it occurred to us that the presence of unsaturation at the 3-position of the 2-methyleneoxetane (cf. **11**) would provide additional flexibility and utility. In this communication, we describe our approach to 3-alkylidene-2-methyleneoxetanes and preliminary studies of their reactivity. Also highlighted is an unexpected formation of electron-rich aryl allenes.

To our knowledge, there are two examples (compounds **1** and **2**)[8,9] of 2,3-dialkylidene oxetanes in the literature.[10] Compound **1** was a byproduct isolated in 17% yield from the reaction between 1,3-dimethylallene and bis(trifluoromethyl)ketene.[8] Compound **2**, isolated in 25% yield, ultimately resulted from a partial decomposition of 4-hydroxy-4-methylpentynenitrile in the presence of sodium azide.[9] Neither approach is broadly applicable, and we sought a more general entry to 2,3-dialkylidene oxetanes. Because of our success with methylenating β-lactones, our targeted entry into 2,3-dimethyleneoxetanes (or the related 3-alkylidene-

† Dedicated to the memory of Joseph D. Emch, a NSF REU student from The Ohio State University who died suddenly on January 6, 2001.

(1) Dollinger, L. M.; Ndakala, A. J.; Hashemzadeh, M.; Wang, G.; Wang, Y.; Martinez, I.; Arcari, J. T.; Galluzzo, D. J.; Howell, A. R.; Rheingold, A. L.; Figuero, J. S. *J. Org. Chem.* **1999**, *64*, 7074−7080.

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(10) There are a number of reports in the literature of 3,4-dialkylideneoxetan-2-ones, which do contain a 2,3-dialkylideneoxetane substructure. However, these compounds will have a fundamentally different reactivity than the targeted dialkylideneoxetanes. For examples of the structurally related oxetanones, see: (a) Masters, A. P.; Sorensen, T. S. *Tetrahedron Lett.* **1989**, *30*, 5869−5872. (b) Zhidkova, T. A.; Vakulova, L. A.; Yanotovskii, M. T.; Svetlaeva, V. M.; Filippova, T. M. *Pharm. Chem. J. (Engl. Transl.)* **1983**, *17*, 344−346. (c) Baxter, G. J.; Brown, R. F. C.; Eastwood, F. W.; Gatehouse, B. M.; Nesbit, M. C. *Aust. J. Chem.* **1978**, *31*, 1757−1767. (d) Payne, G. B. *J. Org. Chem.* **1966**, *31*, 718−721.

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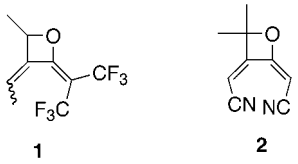
2-methyleneoxetanes) was via methylenation of α-methylene(or α-alkylidene)-β-lactones **3**.



A number of approaches to α-alkylidene-β-lactones have been reported.[11−19] The most straightforward and general strategies for α-methylene-β-lactones are a phenyselenation/oxidation/elimination of α-methyl-β-lactones **4**, utilized by Danheiser and co-workers,[14] and a cyclization of α-methylene-β-hydroxy acids **5** (Figure 1). From **4**, the late-stage

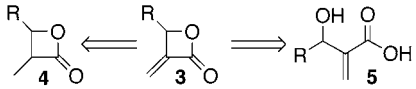
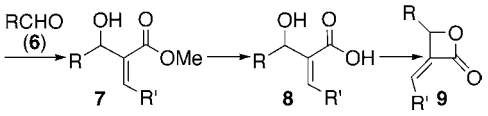


Figure 1. Potential strategies for α-methylene-β-lactones

introduction of the double bond utilizing a strong base and oxidative conditions represented a potential problem of intolerance of some functional groups.

The lactonization of α-alkylidene-β-hydroxy acids **5** is precedented.[11,15−17] Although these cyclizations are not specifically related to Morita−Baylis−Hillman reaction adducts, we recognized that this reaction[20] represented an ideal entry into α-methylene-β-hydroxy acids. Morita−Baylis−Hillman reactions are generally limited to α-methylene, rather than α-alkylidene-β-hydroxy esters; however, similarly efficient procedures for the synthesis of α-alkylidene-β-hydroxy esters have been recently described.[17,21,22] Our results for the preparation of α-alkylidene-β-lactones via Morita−Baylis−Hillman-type adducts **7** are shown in Table 1.

Table 1.[a,b]



entry	R	R′	% yield of **7**	% yield of **8**	% yield of **9**
a	$PhCH_2CH_2$	H		74[c]	77
b	Ph_2CH	H	84	88	51
c	isopropyl	I	66		55[c]
d	*tert*-butyl	I	96		68[c]
e	methyl	Ph			51[d]
f	isopropyl	Ph			35[d]

[a] See Supporting Information for experimental procedures. [b] All yields are isolated, purified yields. [c] Yield over two steps. [d] Yield over three steps.

Acids **8a**,**b**,**g**−**i** were prepared by the traditional Morita−Baylis−Hillman reaction, followed by hydrolysis with KOH in methanol. Optimization of lactonization conditions was examined with **8a**. Benzenesulfonyl chloride, a common promoter of lactonization of β-hydroxy acids, did not produce **9a**. Both *p*-toluenesulfonyl chloride and methanesulfonyl chloride gave **9a** in 20−30% yield. However, *o*-nitrobenzenesulfonyl chloride provided **9a** in good yield and was used in the preparation of all of the lactones except **9c** and **9d**.

The syntheses of lactones **9c** and **9d** have been previously described.[17] Iodozirconation of methyl propiolate and in situ condensation with isobutyraldehyde and pivaldehyde, respectively, provided esters **7c** and **7d**. Hydrolysis with LiOH, followed by methanesulfonyl chloride-promoted cyclization, provided the lactones.

Morita−Baylis−Hillman adducts **7e** and **7f** were prepared by a one-pot hydroalumination−condensation procedure described by Ramachandran et al.[21] Hydrolysis and cyclization provided **9e** and **9f**. It is noteworthy that these lactones were prepared without purification of the intermediates. We are confident that these overall yields can be improved.

An unexpected outcome resulted when the preparation of simple 4-aryl-substituted β-lactones was attempted. Upon exposure to *o*-nitrobenzenesulfonyl chloride, the Morita−Baylis−Hillman-derived acid **8g** was converted directly to aryl allene **10g**, rather than to the desired α-methylene-β-lactone **9g** (Table 2). Although the isolated yield was low (28%), the allene was the only product observed in ^{1}H NMR spectra of the reaction mixture. A similar outcome was observed for the Morita−Baylis−Hillman-derived acid **8h**. The thermal decarboxylations of 4-alkyl-substituted 3-alkylidene-2-oxetanones have been previously reported, with decarboxylations occurring at temperatures above 110 °C to produce allenes.[14,23] In contrast, these aryl allenes were formed at room temperature. No attempts were made to optimize the yields of **10g** and **10h**; moreover, the yields may reflect the volatility of the allenes. We were interested

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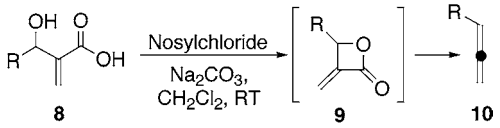
Table 2.[a]



entry	R	% yield of **9**	% yield of **10**
g	phenyl		28
h	*p*-tolyl		34
i	(*o*)-nitrophenyl	46	

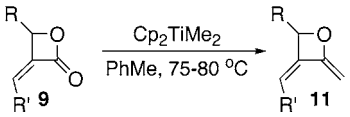
[a] See Supporting Information for experimental procedures.

in having 4-aryl-substituted α-methylene-*β*-lactones as substrates for methylenation and wondered if decarboxylation could be suppressed.

Cossio and co-workers had reported the results of computational studies on structural and solvent effects on the mechanism of the thermal decarboxylation of 2-oxetanones.[24] Their calculations suggested that *π* donors at C4 decreased the activation energy for decarboxylation. Consequently, an electron-deficient aromatic aldehyde, *o*-nitrobenzaldehyde, was employed to prepare acid **8i**, which was successfully converted to α-methylene-*β*-lactone **9i**. Although the yield of the lactonization was not high, no allene was observed in ^{1}H NMR spectra of the reaction mixture.

Results for the preparation of 3-alkylidene-2-methyleneoxetanes **11** via the methylenation of lactones **9** are presented in Table 3. The lactones were dissolved in a solution of

Table 3.[a]



entry	R	R′	% yield of **11**[b]
a	$PhCH_2CH_2$	H	35[d]
b	Ph_2CH	H	55[c]
c	isopropyl	I	70[d]
d	*tert*-butyl	I	75[b]
e	methyl	Ph	28[d]
f	isopropyl	Ph	60[d]
i	(*o*)-nitrophenyl	H	see text

[a] See Supporting Information for experimental procedures. [b] Isolated, purified yields. [c] Petasis (1.5−2 equiv), 0.5 M, 80 °C. [d] Petasis (4 equiv), 0.25 M, 75 °C.

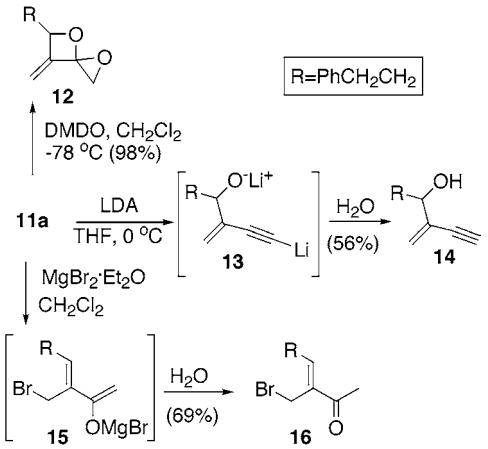
dimethyltitanocene in toluene and heated under N_2 in the dark until the starting material disappeared. At the beginning of the investigation, conditions similar to those we employed to prepare 2-methyleneoxetanes were used.[1] However, oxetanes **11** are more sensitive and less stable than simple 2-methyleneoxetanes. Increasing the number of equivalents of the Petasis reagent and decreasing the concentration and temperature increased the rates of reaction and improved the yields for most of these substrates. Neither sonication nor microwave methods enhanced the yields. As with 2-methyleneoxetanes, the Tebbe reagent provided products, but in lower isolated yields.

Initial methylenation studies were conducted with hydrocinnamaldehyde-derived lactone **9a**. Disappointingly, no matter how the reaction conditions were modified, the yield of **11a** never exceeded 35%. Careful monitoring of the reaction never revealed any lactone-related material other than the reactant and the product. Running the reaction in the presence of an internal standard (1,3,5-*tri*-*tert*-butylbenzene) demonstrated that the isolated yield was consistent with the yield based on the internal standard. On the other hand, lactone **9d**, the next lactone prepared, gave high yields. Low yields were also observed with lactone **9e**. It appeared that steric effects at C4 might be playing a role, with bulkier substituents at C4 leading to higher yields. In support of this, lactones **9b**, **9c**, and **9f** all provided higher yields of the corresponding 3-alkylidene-2-methyleneoxetanes. The reaction of **9i** with dimethyltitanocene was problematic. ^{1}H NMR spectra of reaction mixtures were messy, but showed some **11i**; however, product isolation was not successful. We did not see evidence of allene formation in the ^{1}H NMR spectra. Other 4-aryl-substituted 3-alkylidene-2-oxetanones would need to be prepared before generalizations about the methylenations of these systems could be made.

The difference in stability between 2-methyleneoxetanes and 3-alkylidene-2-methyleneoxetanes is noteworthy. The former can be stored in the freezer for extended periods. 3-Alkylidene-2-methyleneoxetanes decompose within days. Also, there is substantially more product loss with repeated purification of 3-alkylidene-2-methyleneoxetanes in comparison to what was observed with 2-methyleneoxetanes.

We decided to compare the reactivity of 3-alkylidene-2-methyleneoxetanes with that of 2-methyleneoxetanes. The enol ether of **11a** was oxidized chemoselectively with DMDO to provide 1,5-dioxaspiro[3.2]hexane **12**, as a ∼3:2 mixture of diastereomers, in excellent yield (Scheme 1).

Scheme 1



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Compound **12** was far less stable than any of the 1,5-dioxaspirohexanes that we previously prepared.[3] In the presence of LDA, **11a** was converted to enynol **14** in 56% yield. Further functionalization of the dianionic intermediate **13** should be possible, as we found for 2-methyleneoxetanes.[2] Moreover, enynols are useful synthetic intermediates. For example, they are direct precursors of highly substituted furans.[25−28]

We were interested in the potential of 3-alkylidene-2-methyleneoxetanes as electron-rich dienes in Diels−Alder reactions. Experimental evidence and computational studies suggest that, as the 1,4-distance in outer ring dienes increases, the Diels−Alder reactivity drops.[29,30] Nevertheless, 1,2-dimethylenecyclobutanes undergo Diels−Alder reactions with a wide range of dienophiles.[31−37] An initial investigation involved the reaction of **11a** with methyl acrylate in the presence of $MgBr_2$. Allylic bromide **16**, presumably arising from a S_N2'-like attack by bromide, was the sole product observed and isolated. This result could be reproduced by exposing **11a** to magnesium bromide diethyl etherate in dichloromethane (Scheme 1). The conversion of **11a** to **16**, which presumably proceeded through magnesium enolate **15**, offers the potential for tandem reactions that should yield highly functionalized products that are useful intermediates for further transformation.

In summary, we have described a general method for the synthesis of 3-alkylidene-2-methyleneoxetanes **11** by the methylenation of 3-alkylidene-2-oxetanones **9**; these lactones have been readily prepared from Morita−Baylis−Hillman-type adducts. Preliminary investigations of the reactivity of these unusual, strained heterocyclic compounds using **11a** have demonstrated their potential as synthetic scaffolds. The conversion of electron-rich 3-aryl-2-methylene-3-hydroxy acids to give electron-rich aryl allenes at room-temperature represents an unanticipated transformation that may have synthetic utility.

Acknowledgment. Helpful discussions about the hydroalumination procedure with Israel Figueroa are gratefully acknowledged, as are discussions on the potential Diels−Alder reactivity of **11** with Prof. Jeff Winkler and Dr. Sithamalli Chandramouli. We thank Daniel R. Clark for preliminary studies. This material is based upon work supported by the National Science Foundation (NSF) under Grant CHE-0111522. We thank the NSF/REU (CHE-9732366) Program at the University of Connecticut for support of J. D. Emch, Bristol-Myers-Squibb for support of A. E. Andrews via an undergraduate summer fellowship, and the NIH for a predoctoral fellowship to I. Martinez.

Supporting Information Available: Experimental details and characterization data for all compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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