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6-(2-Haloethyl)-2,2-dimethyl-4*H*-1,3-dioxins: versatile haloethyl vinyl ketone equivalents for carbocycle construction

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Abstract—6-(2-Iodoethyl)-2,2-dimethyl-4*H*-1,3-dioxin has been prepared in five steps from ethyl acetoacetate. A variety of enolates were then alkylated with this iodide. The resulting 6-alkyl-4*H*-1,3-dioxins were either subjected to further transformations and/or heated (or subjected to a Lewis acid) to effect facile retrocycloaddition reactions. The resulting enones were found to smoothly participate in conjugate addition or olefin metathesis reactions to provide various carbocyclic ring systems. Collectively, these examples document the synthetic equivalency of dioxin **2** with iodoethyl vinyl ketone and, moreover, delineate a strategy for accomplishing the sequential reactions with nucleophiles at the β′, followed by the β electrophilic sites.

The discovery of more convenient and efficient strategies for hetero- and carbocyclic ring construction is an ongoing endeavor. For years, sequential reactions of doubly nucleophilic compounds with bis electrophiles have been a cornerstone method in achieving this goal.[1] Haloalkyl vinyl ketones represent a potentially valuable class of bis electrophiles that could be employed in this general strategy. However, only a few examples of this type of cyclization have been reported,[2] probably because of a lack of selectivity between the β enone and halocarbon electrophilic sites, and sensitivity of these compounds to basic reaction conditions conspire to render most strategies problematic. To circumvent these inherent problems, we recently reported the use of 6-bromomethyl-4*H*-1,3-dioxin (**1**)[3] as a bromomethyl vinyl ketone equivalent (Fig. 1), which permitted its unambiguous initial alkylation (including the use of highly basic nucleophiles) on the halocarbon electrophilic site vis-à-vis the β enone carbon. Following a mild thermal retrocycloaddition reaction of the 1,3-dioxin, the second nucleophilic site could then be activated to undergo a conjugate addition into the newly derived enone to furnish a variety of hetero- and carbocyclic compounds. We now wish to report the preparation and utility of the homologous reagent, 6-(2-iodoethyl)-2,2-dimethyl-4*H*-1,3-dioxin (**2**), as a haloethyl vinyl ketone equivalent for the construction of carbocyclic ring systems.

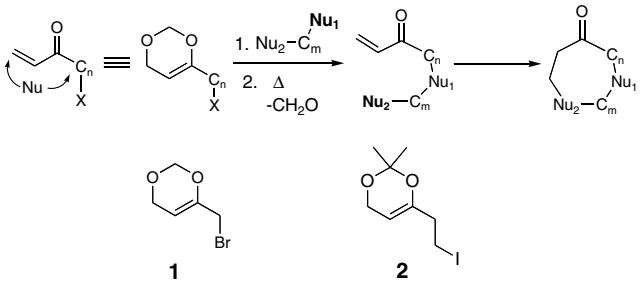
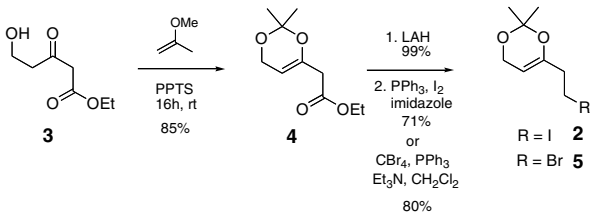


Figure 1.

The synthesis of iodide **2** (Scheme 1) commenced with cyclization of the known β-ketoester **3**[4] to the acetonide **4** upon treatment with 2-methoxypropene and pyridinium tosylate in THF. The acetonide is formed relatively quickly in this reaction (1–2 h); however, a large amount of the *exocyclic* conjugated ester is initially produced. Allowing the reaction to stir for an extended



Scheme 1.

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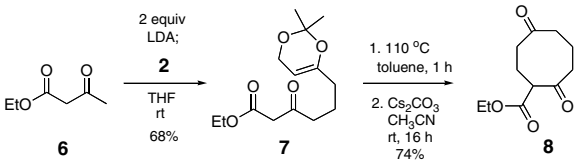
period of time produces almost exclusively the desired *endocyclic* isomer **4**. Next, reduction of the ester moiety with $LiAlH_4$, followed by Mitsunobu reaction (PPh_3, I_2, imidazole) of the resultant alcohol successfully produced iodoethyl dioxin **2** in good yield. It should be noted that this compound is not nearly as stable as bromomethyl dioxin **1**,[3] and it was found to readily polymerize if left on the benchtop for an extended period of time. It can, however, be stored in the freezer (−50 °C) for several months with no noticeable decomposition. The analogous bromide **5** was also prepared from the corresponding alcohol (CBr_4, PPh_3, Et_3N) in an attempt to obtain a more stable alkylating agent. However, bromide **5** seemed to decompose just as readily at room temperature as the iodide. Thus, once prepared, the haloethyl dioxins **2** and **5** were immediately stored in the freezer until ready for use.

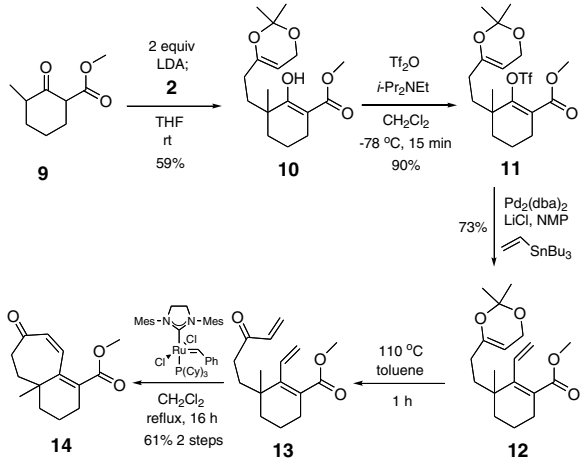
We first examined the alkylation reactions of iodide **2** with β-ketoester Weiler dianions.[5] Indeed, the dianion of ethyl acetoacetate (**6**) can be smoothly alkylated with iodide **2** to afford dioxin **7** (Scheme 2). Thermolysis of dioxin **7** effected a clean retrocycloaddition reaction to produce the desired enone, which was subsequently found to undergo a facile 8-*endo* conjugate addition reaction when subjected to conditions (0.2 equiv of Cs_2CO_3, CH_3CN)[6] we had previously employed for the related 7-*endo* ring closures of acyclic β-ketoesters.[3] To the best of our knowledge, this is the first example of an *endo*-Michael addition of an endocyclic enolate leading to an eight-membered ring.

In addition to the Michael addition reaction illustrated in Scheme 2, we have also found retrocycloaddition products to be useful substrates in olefin metathesis reactions (Scheme 3). To that end, iodide **2** was alkylated with the dianion prepared from β-ketoester **9**. Alkylation product **10**, which preferred to exist in its enol form, was easily sulfonylated with Tf_2O and Hünigs base to provide enol triflate **11**. Stille coupling with tributylvinyltin, followed by thermolysis of the resultant dienoate **12**, effected a facile retrocycloaddition (110 °C, 1 h) to give rise to the desired enone **13**. Finally, enone **13** underwent an olefin metathesis reaction to give the bicyclic dienone **14** in good yield using Grubb's second generation catalyst.[7]

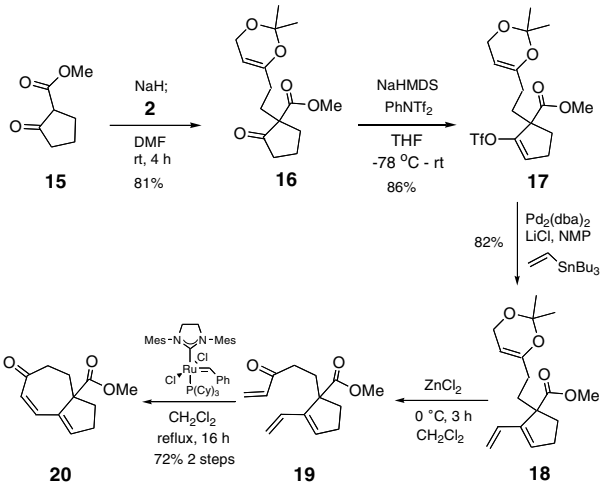
In a similar application, we have also been able to prepare tetrahydroazulenone **20** through olefin metathesis of its enone precursor **19** (Scheme 4). In this sequence, iodide **2** was successfully alkylated with the less reactive enolate of methyl cyclopentanone-2-carboxylate (**15**). In addition, we also found that retrocycloadducts could be obtained through treatment of the requisite dioxin with



Scheme 2.



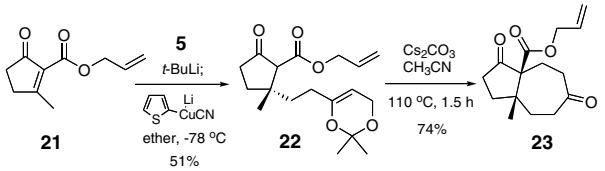
Scheme 3.



Scheme 4.

a Lewis acid. In this case, a competing thermally induced intramolecular cycloaddition reaction of enone **19** warranted the use of $ZnCl_2$ as a mild alternative in the retrocycloaddition reaction of dioxin **18**.

In addition to using the haloethyl dioxins as electrophiles in nucleophilic displacement reactions, we also examined their utility as nucleophiles in conjugate addition reactions (Scheme 5). We were pleased to find that the 2-thienylcyanocuprate reagent[8] of bromodioxin **5** could be prepared and used in a conjugate addition with the α,β-unsaturated ketoester **21**. The retrocycloaddition product derived from dioxin **22** was found to be unstable and could not be isolated. However, upon heating dioxin **22** in the presence of Cs_2CO_3, the β-ketoester



Scheme 5.

anion effectively trapped the enone intermediate, thus producing hydroazulene **23** in good yield. The *cis*-stereochemistry was assigned based on similar Michael addition reactions reported by Deslongchamps,[6] in which β-ketoesters were transformed to *cis*-hydroazulenes.

In conclusion, we have prepared 6-haloethyl-4*H*-1,3-dioxins and used them as haloethyl vinyl ketone equivalents for the construction of a variety of carbocyclic ring systems. The homoallylic halide moiety of iododioxin **2**[9] is sufficiently reactive to allow for facile substitution by a variety of nucleophiles. The 1,3-dioxin ring is quite robust and permits, if necessary, further multistep transformations of the alkylation products. The potentially sensitive enone moiety can then be released under mild, thermal or Lewis acid mediated conditions, and smoothly participates in a variety of ring closure reactions forming carbocyclic ring systems.

Acknowledgment

We appreciate the financial support provided by the National Institutes of Health (GM28553).

References and notes

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9. Preparation of dioxin **2**:
(2,2-Dimethyl-6H-[1,3]dioxin-4-yl)acetic acid ethyl ester (**4**). To a solution of alcohol **3**[4] (5.16 g, 32.2 mmol) in THF (105 mL) at 0 °C was added 2-methoxypropene (9.26 mL, 96.7 mmol), followed by pyridinium *p*-toluenesulfonate (2.43 g, 9.67 mmol). The resulting mixture was warmed to rt and stirred for 16 h. To the resulting solution was added solid Na_2CO_3 (10 g). The mixture was stirred at rt for 1 h, filtered, and concentrated. Purification by silica gel chromatography (ethyl acetate–hexanes, 1:4) provided dioxin **4** as a colorless oil (5.48 g, 85%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.25 (t, $J = 7.5$ Hz, 3H), 1.47 (s, 6H), 3.03 (s, 2H), 4.17 (q, $J = 7.5$ Hz, 2H), 4.20 (m, 2H), 4.78 (m, 1H).
2-(2,2-Dimethyl-6H-[1,3]dioxin-4-yl)ethanol. To a solution of $LiAlH_4$ (1.06 g, 28.0 mmol) in ether (215 mL) at 0 °C was added ester **4** (4.32 g, 21.6 mmol) in ether (15 mL) dropwise over 10 min. The mixture was stirred at 0 °C for 20 min. The resulting solution was quenched successively with H_2O (1.1 mL), 10% NaOH (1.7 mL), and H_2O (3.3 mL). The resulting mixture was filtered, washed with ether, and concentrated. Purification by silica gel chromatography (ethyl acetate–hexane, 2:3) provided the alcohol as a colorless oil (3.40 g, 99%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 6H), 2.28 (t, $J = 6.2$ Hz, 2H), 3.75 (m, 2H), 4.19 (m, 2H), 4.71 (t, $J = 2.7$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.0, 37.1, 58.9, 59.6, 95.4, 98.6, 148.4. HRMS (MH^+) calcd for $C_8H_{14}O_3$ 158.0937, found 158.0934.
6-(2-Iodoethyl)-2,2-dimethyl-4H-1,3-dioxin (**2**). To a solution of the above alcohol (611 mg, 3.86 mmol) in THF (38 mL) at 0 °C was added imidazole (605 mg, 8.89 mmol), PPh_3 (1.11 g, 4.25 mmol), and iodine (1.08 g, 4.25 mmol). The resulting solution was stirred at 0 °C for 1 h. The mixture was quenched with 10% aqueous $Na_2S_2O_3$ and extracted with ether. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (ethyl acetate–hexane, 1:19) afforded iodide **2** as a colorless oil (734 mg, 71%); ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 6H), 2.53 (t, $J = 7.1$ Hz, 2H), 3.22 (t, $J = 7.1$ Hz, 2H), 4.13 (m, 2H), 4.66 (t, $J = 2.6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 2.3, 24.3, 38.1, 58.9, 95.9, 98.8, 148.8. HRMS (MH^+) calcd for $C_8H_{13}IO_2$ 267.9955, found 267.9944.