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An N-Heterocyclic Carbene-Catalyzed [8 + 3] Annulation of Tropone and Enals via Homoenolate

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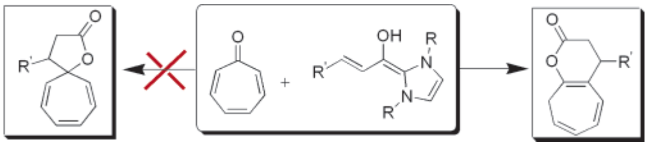
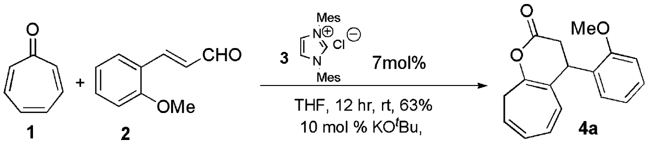


A novel protocol for the annulation of tropone to enals involving nucleophilic heterocyclic carbene (NHC) catalyzed homoenolate formation has been developed. Interestingly, the reaction led to bicyclic δ-lactones instead of the expected γ-spirolactones, presumably by the uncommon [8 + 3] annulation pathway. The strategy works well with a variety of enals.

Ever since the identification of tropolone moiety as a structural unit of colchicine, stipitatic acid, and hinokitiol,[1] and the recognition of its non-benzenoid aromatic character by Dewar,[2] the chemistry of tropone and its derivatives has attracted the attention of organic chemists from a synthetic and theoretical standpoint.[3] Troponoids have been viewed as convenient synthons of natural products[4] and as suitable partners in higher order cycloadditions.[5] Recently, triphenylphosphine-catalyzed [6 + 3] and [8 + 2] annulations of tropone with modified allylic compounds[6] and allenic esters/ketones[7] have been reported. Very recently Bode[8a,d] and Glorius[8b] have reported the NHC-catalyzed transformation of enals to homoenolates and the annulation of the latter to aldehydes leading to lactones. Our own work[9] in this area has led to the homoenolate annulation of cyclic 1,2-diones to afford γ-spiro butyrolactones. In this context, and in view of our sustained interest in NHC-mediated homoenolate reactions,[10] we have investigated the reaction of tropone with enals under NHC catalysis.[11] Our results revealing the [8 + 3] annulation of tropone and enals leading to the formation of cycloheptatriene-fused δ-lactones form the subject matter of this paper. To the best of our knowledge, there is only one [8 + 3] annulation of tropone reported,[5c] and this involves the addition of an oxyallyl cation generated from 2,4-dibromo-2,4-dimethylpentan-3-one using Fe$_2$(CO)$_9$.

SCHEME 1. Reaction of 2-Methoxycinnamaldehyde with Tropone



Our studies commenced with an experiment in which 2-methoxycinnamaldehyde **2** was exposed to tropone **1** in the presence of a catalytic amount of 1,3-dimesitylimidazol-2-ylidene (IMes), 7 mol % of **3**, and KO^{t}Bu in dry THF (Scheme 1). A facile reaction occurred to afford a colorless crystalline product in 63% yield. This was characterized as the δ-lactone **4a** presumably arising from the [8 + 3] annulation of tropone and the homoenolate of **2**.

The structure of the product was established by spectroscopic analysis. The IR spectrum of **4a** showed an absorption at 1771 cm^{-1} corresponding to the lactone carbonyl, which was sup-

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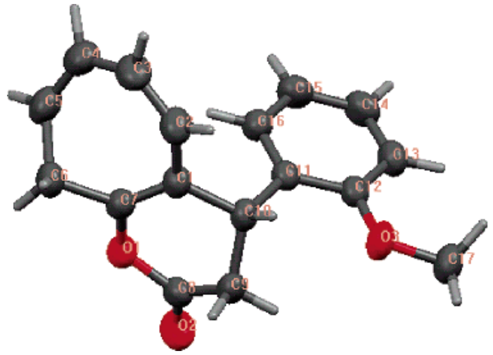
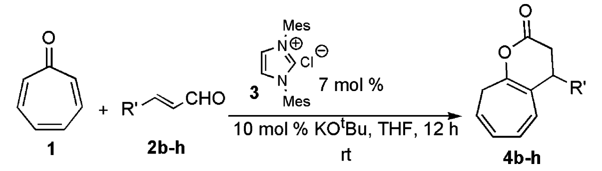


FIGURE 1. X-ray crystal structure of compound **4a**.

TABLE 1. One Pot Synthesis of Bicyclic δ-Lactones



entry	aldehyde	product	yield (%)
1	R′ = 4-methoxyphenyl	**4b**	62
2	R′ = cyclohexenyl	**4c**	61
3	R′ = 3,4-dimethoxyphenyl	**4d**	49
4	R′ = 2-methylphenyl	**4e**	48
5	R′ = 4-methylphenyl	**4f**	46
6	R′ = 4-chlorophenyl	**4g**	27
7	R′ = 3-methoxyphenyl	**4h**	39

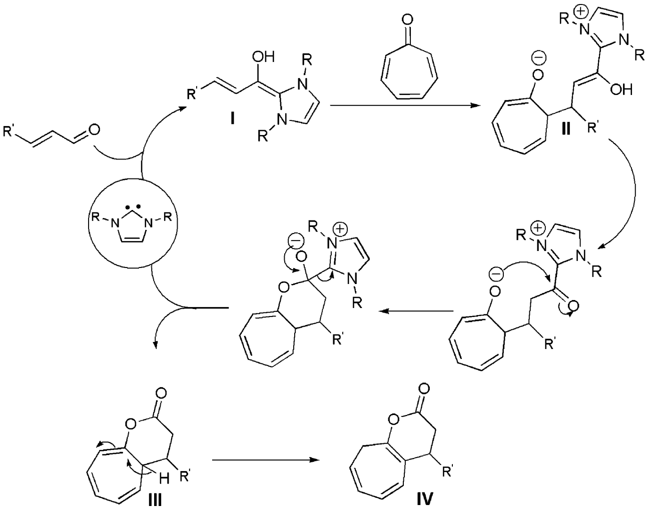
ported by the ^{13}C NMR signal at δ 167.8. Conclusive evidence for the structure of **4a** was obtained from single-crystal X-ray analysis (Figure 1).

The scope of this uncommon [8 + 3] annulation was investigated using a number of substituted cinnamaldehydes, and the results are presented in Table 1. Interestingly, the alicyclic dienal **2c** also underwent the annulation smoothly to afford the corresponding δ-lactone.

A mechanistic rationale for the reaction may be postulated as follows (Scheme 2).[12] The homoenol **I** formed by the reaction of IMes with enal conceivably undergoes conjugate addition to the tropone to generate the enolate **II**, which then cyclizes to afford **III** with the ejection of IMes, allowing the catalytic cycle to continue. The initially formed lactone **III** presumably undergoes isomerization to the more stable lactone **IV**.

In conclusion, we have successfully employed the organocatalyzed homoenolate chemistry for the functionalization of tropone, thereby leading to the formation of novel cycloheptatriene derivatives. To our knowledge, this is the first [8 + 3] annulation of tropone occurring via a homoenolate. It is conceivable that the strategy may be applicable to the synthesis of a variety of natural products containing bicyclic δ-lactone moiety.

SCHEME 2. Plausible Mechanism for the Formation of Bicyclic δ-Lactone from Tropone



Experimental Section

Typical Procedure for the Synthesis of Bicylic δ-Lactone Derivative 4a. KO^{t}Bu (12 mg, 10 mol %) was added to a suspension of the 1,3-dimesitylimidazolium chloride **3** (25 mg, 7 mol %) in 5 mL of dry THF under argon atmosphere. This was followed by the addition of 2-methoxycinnamaldehyde **2** (120 mg, 0.74 mmol) and tropone **1** (46 mg, 0.43 mmol), and the resulting solution was stirred for 12 h at room temperature (30 °C). The initial yellow color of the reaction mixture gradually changed to dark brown on completion of the reaction. The reaction mixture was then passed through a short pad of Celite. After removal of the solvent, the residue was subjected to chromatography on a silica gel (60−120 mesh) column using 95:5 hexane−ethyl acetate solvent mixture as eluent to afford **4a** (73 mg, 63%) as a white crystalline solid. CCDC file number for **4a**: 614942. Yield: 63%. White solid. Mp: 174−175 °C. IR (KBr) ν_{max}: 3002, 2934, 2841, 1771, 1652, 1599, 1490, 1243, 1191, 1125, 1027, 876, 755 cm^{-1}. ^{1}H NMR: δ 7.31−7.25 (m, 1H), 7.17 (d, J = 7.4 Hz, 1H), 7.02−6.98 (m, 1H),6.86 (d, J = 8.0 Hz, 1H), 6.51−6.46 (m, 2H), 6.13−6.07 (m, 2H), 5.11−5.06 (m, 1H), 3.95−3.91 (m, 1H), 3.77 (s, 3H), 3.03−2.87 (m, 2H), 2.58−2.54 (m,1H). ^{13}CNMR: δ 167.8, 156.7, 140.1, 129.3 128.6, 127.9, 127.1, 121.0, 120.7, 112.4, 110.5, 108.0, 96.1, 54.9, 35.9, 34.7, 30.6. HRMS (FAB): m/z calcd (M$^+$) for $C_{17}H_{16}O_3$ 268.11, found 268.01.

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Supporting Information Available: General experimental procedure and spectroscopic data for all compounds, ^{1}H and ^{13}C NMR spectra of all new compounds, and crystallographic data for **4a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] The mechanism outlined here is an adaptation of the one suggested independently by Bode and Glorius (ref 8a,b).