Intramolecular Arene Trapping of Pyran-4-one Derived Zwitterions: A Two-Step Synthesis of Tetrahydrobenz[*e*]inden-1-ones

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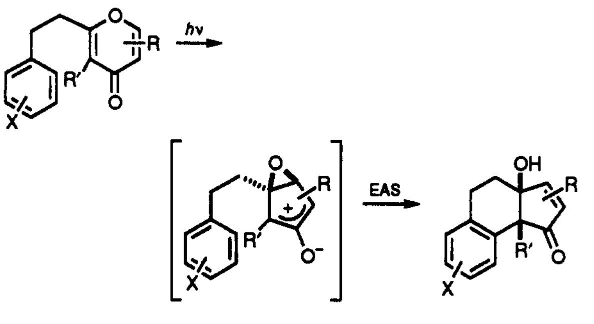
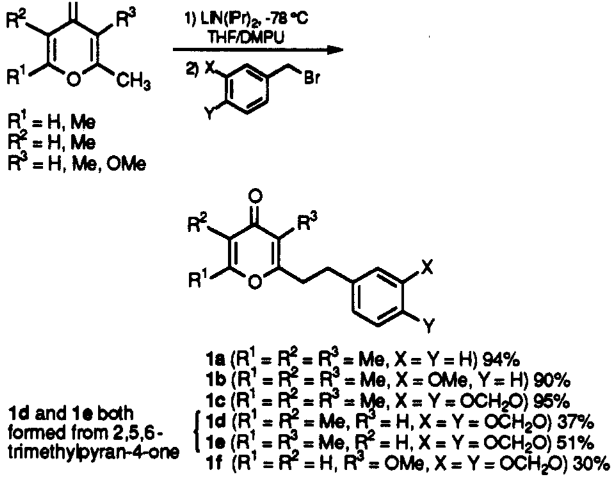
Summary: Pyran-4-ones bearing pendant arene traps undergo efficient photolytic conversion to transient oxyallyl zwitterions, which then cyclize onto the arene in an intramolecular electrophilic aromatic substitution to yield tetrahydrobenz[*e*]indenones.

The rapid assembly of polycyclic skeletons from simple precursors has for many years remained an important goal in synthesis. Examples abound of application of polycyclization reactions to the synthesis of steroids and triterpenes,[1] sesquiterpenes,[2] and alkaloids.[3] Recently, we have investigated the synthetic potential of the intriguing photochemical rearrangements of 4-pyrones.[4,5] We have previously reported that photochemically generated oxyallyl zwitterions can be efficiently trapped by pendant hydroxylic[5a] and olefinic[5b] nucleophiles, leading to bicyclic ethers, diquinanes, or hydrindans in a single step from simple precursors.[6] Aromatic rings would also be desirable internal carbon nucleophiles, since trapping ortho to the tether would lead directly to functionalized tricyclic skeletons corresponding to the steroid BCD rings (eq 1).[7] In addition to two strategic carbon–carbon bonds, two new carbocyclic rings would be formed. We report here our initial results in the area of intramolecular electrophilic aromatic substitution using photochemically generated oxyallyl electrophiles.



(1)

Substrate preparation could be effected in one step via benzylation at the C-2 methyl group of simple di-, tri-, or tetrasubstituted 4-pyrones (eq 2). Low-temperature



(2)

R^1 = H, Me
R^2 = H, Me
R^3 = H, Me, OMe

1a (R^1 = R^2 = R^3 = Me, X = Y = H) 94%
1b (R^1 = R^2 = R^3 = Me, X = OMe, Y = H) 90%
1c (R^1 = R^2 = R^3 = Me, X = Y = OCH_2O) 95%
1d (R^1 = R^2 = Me, R^3 = H, X = Y = OCH_2O) 37%
1e (R^1 = R^3 = Me, R^2 = H, X = Y = OCH_2O) 51%
1f (R^1 = R^2 = H, R^3 = OMe, X = Y = OCH_2O) 30%

1d and **1e** both formed from 2,5,6-trimethylpyran-4-one

γ-deprotonation[5,8] with lithium diisopropylamide in THF/DMPU, followed by alkylation with the requisite halides, gave **1a–f** with a two-carbon tether separating the arene and the incipient electrophile.

Photolyses were routinely carried out in trifluoroethanol solution at room temperature through quartz (Table I). In the case of phenyl-substituted 4-pyrone **1a**, a modest yield of nucleophilic trapping to give tricycle **2a** was observed, but the major products were isomeric 2-pyrones **3a** and **3a′** in a ca. 2.5:1 ratio. No evidence for solvent capture of the zwitterion was seen. Interestingly, the yield of **2a** proved to be concentration dependent (entries 1–3), with optimum levels of cyclization occurring when the starting

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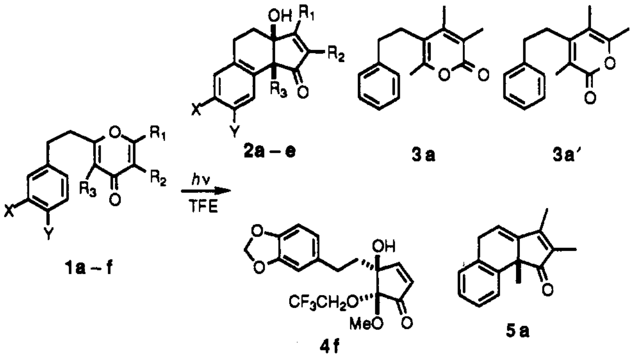
Table I. Photolysis of 2-Arylethylpyran-4-ones[a]



entry	substrate	R¹	R²	R³	X	Y	conditions[b]	yield 2^c (%)
1	1a	Me	Me	Me	H	H	A	32[d]
2	1a	Me	Me	Me	H	H	B	24[d]
3	1a	Me	Me	Me	H	H	C	21[d]
4	1b	Me	Me	Me	OMe	H	B	68
5	1c	Me	Me	Me	OCH_2O		B	75
6	1d	Me	Me	H	OCH_2O		A	57
7	1e	Me	H	Me	OCH_2O		B	11[e]
8	1f	H	H	OMe	OCH_2O		B	*f*
9	1a	Me	Me	Me	H	H	D	*g*

[a] Standard photolysis procedure: A solution of substrate in dry trifluoroethanol (TFE) was placed in a quartz tube and deoxygenated by bubbling a slow stream of dry N_2 gas through for 20 min. The reaction vessel was clamped 25 cm from a Hanovia 450 W medium-pressure Hg lamp and irradiated at ambient temperature for 0.5–5 h. [b] Conditions: (A) 0.015 M 1 in TFE; (B) 0.005 M 1 in TFE; (C) 0.025 M 1 in TFE. (D) 0.005 M 1 and 0.3 equiv of H_2SO_4 in TFE. [c] Isolated yields after chromatography. Satisfactory IR, ^1H and ^{13}C NMR, and combustion analysis or HRMS were obtained for all substrates and photolysis products. [d] 2-Pyrones **3a** and **3a′** were also isolated in varying quantities: 51% (entry 1), 48% (entry 2), and 62% (entry 3). [e] Starting material was recovered in the case of **1e** (50%). [f] Solvent adduct **4f** (36%) was the only zwitterion derived product isolated. [g] Dienone **5a** was isolated in 33% yield.

concentration of **1a** was 0.015 M. Since formation of **2a** and **3a**/**3a′** are both unimolecular processes, it is unclear why their apparent rates of formation should vary reproducibly with the concentration of **1a**. We are currently attempting to determine the origins of this surprising effect.

The isolation of substantial amounts of 2-pyrones[4] suggested that a simple, monosubstituted arene might not be sufficiently nucleophilic to effectively trap the transient intermediate prior to rearrangement. To test this notion, we then examined substrates **1b,c**, bearing more electron-rich arene traps (entries 4–5). In the event, trapping products **2b,c** were obtained in good yield, along with only trace amounts of **3**. It should be noted that optimum yields in these cases were obtained under the more dilute conditions.

While arene substitution is clearly important, pyrone ring substitution is also significant. When trisubstituted substrates **1d,e** were examined (entries 6–7), a dramatic difference in efficiency of conversion was observed. Thus, while irradiation of 2,5,6-trisubstituted pyrone **1d** led to tricycle **2d** in good yield, the isomeric 2,3,6-trisubstituted pyrone **1e** remained largely unconsumed even after extended photolysis, indicating an apparent barrier to formation of the zwitterion.[9] On the other hand, 2,3-disubstituted substrate **1f** was rapidly consumed (entry 8), perhaps as a result of substitution of the electron-releasing methoxy group on the incipient zwitterion, but furnished solvent adduct **4f** as the only zwitterion-derived product. The yield of trapping product under dilute conditions (5 mM) could be improved somewhat (33 vs 24%) in the case of **1a** by inclusion of 0.3 equiv of protic acid (entry 9). We reason that the acid may increase the electrophilicity of the zwitterion by oxygen protonation, leading to a greater preference for the cyclization pathway.[10] Under the acidic conditions, elimination of water occurred and dienone **5a** was the product isolated. Similar enhancements by catalytic acid were not apparent with other substrates.

In summary, we have reported a significant new class of cyclization reactions based upon intramolecular capture of transient, electrophilic oxyallyl zwitterions by pendant arenes. Easily prepared 4-pyrone substrates can be converted in one step to fused tricyclic products, in the process forming two strategic carbon–carbon bonds and greatly increasing molecular complexity.[11] The cyclization products may be useful precursors to natural or unnatural steroids. Further applications of 4-pyrone-based methodology will be reported elsewhere.

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Supplementary Material Available: Experimental procedures for the preparation and photolysis of substrates **1a–f** and physical data for **1a–f**, **2a–e**, **3a**, **4f**, and **5a** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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