

REARRANGEMENT OF EPOXIDIZED BENZYNE/FURAN CYCLOADDUCTS: A CONVENIENT ROUTE TO α -FORMYL AND α -ACYL-2-INDANONES

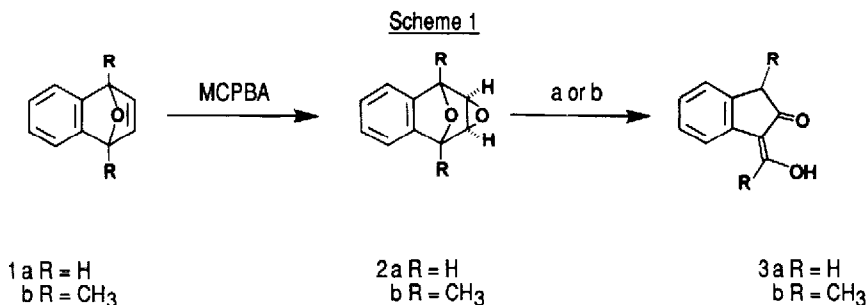
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Summary: The Lewis acids, LiClO_4 and $\text{BF}_3 \cdot \text{Et}_2\text{O}$, promote carbocation driven ring contracting rearrangements of epoxides derived from the Diels-Alder adducts of benzyne and furans. This unprecedented transformation provides moderate to excellent yields of novel α -formyl and α -acyl-2-indanones

From a synthetic standpoint, the import of furan Diels-Alder cycloaddition chemistry derives largely from the flexibility possible in subsequent manipulation of the cycloadducts.² The literature is replete with examples of fragmentation of the bicyclic adducts via endoxide fission and deoxygenation protocols affording 6-membered carbocyclic systems at various levels of unsaturation.³ Recently, the utility of these adducts as chiron equivalents for various natural and unnatural hexoses has been recognized and exploited.⁴ We have embarked on a methodology development program targeted at extending the synthetic utility of furan cycloadditions by devising ring contraction methods which would allow the oxanorbornenic cycloadducts to serve as vehicles for elaboration into 5-membered carbocycles. Specifically, we envisioned the generation of carbocationic intermediates from 7-oxabicyclo[2.2.1]hept-2-enes, 7-oxabicyclo[2.2.1]hepta-2,5-dienes, or their derivatives. Ring contraction via Wagner-Meerwein 1,2-alkyl or aryl shifts would afford oxonium ion intermediates subject to further rearrangement and/or nucleophilic trapping.⁵ If successful, the tandem furan cycloaddition/ring contraction strategy would afford an indirect means of applying the powerful Diels-Alder reaction to the synthesis of cyclopentanes and cyclopentenones. Herein, we detail the results of preliminary studies on the Lewis acid promoted ring contraction of benzyne/furan cycloadduct epoxides.

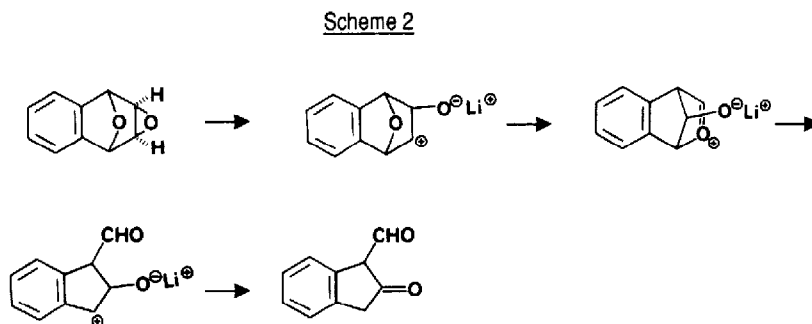
Very few examples of Wagner-Meerwein ring contraction of epoxidized furan cycloadducts have been reported.⁶ All incorporate either nucleophilic trapping or deprotonation steps affording low to moderate yields of rearranged solvolysis or elimination products. All but one have been promoted by strong protic acids, HSO_3F , H_2SO_4 , or $\text{CF}_3\text{CO}_2\text{H}$. Our initial objective was to investigate the feasibility of effecting Lewis acid mediated ring contractions of the cycloadduct epoxides in the absence of nucleophile/base. Attention was focused on LiClO_4 ⁷ and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ⁸, two efficient reagents for effecting epoxide ring opening to carbocationic intermediates.

Exo-1,4,2,3-diepoxy-1,2,3,4-tetrahydronaphthalene (**2a**) is obtained from commercially available 1,4-epoxy-1,4-dihydronaphthalene⁹ (**1a**) via MCPBA oxidation under biphasic conditions (CH_2Cl_2 , aqueous NaHCO_3)¹⁰ The epoxide (**2a**) rearranges affording α -hydroxymethylene-2-indanone (**3a**) in moderate yield upon refluxing in toluene solution over anhydrous LiClO_4 (Scheme 1; Table I). Surprisingly, the formylated 2-indanone has been heretofore inaccessible.¹¹ Claisen condensation of 2-indanone with ethylformate is reported to afford solely the α,α' -bisformylated product.¹² In our hands, Johnson's procedure¹³ for the formylation of 1-indanones similarly yields entirely diformylated material when applied to 2-indanone. Furthermore, Eaton's conditions¹⁴ for monoformylation of cyclopentanone (KH , HCO_2Et , Et_2O) provide a moderate yield of a mono- (36%) and bis-hydroxymethylene-2-indanone (64%) mixture as judged by integration of the ¹H NMR spectrum of the crude product mixture.



a) BF₃·Et₂O, benzene, 6-8°C; b) LiClO₄, toluene, reflux

Mechanistically, lithium ion promoted epoxide cleavage followed by a 1,2-aryl migration would afford a relatively stable oxonium ion. In the absence of nucleophile, this oxonium ion may cleave to provide a benzylic carbocation with subsequent 1,2-hydride shift affording the β-ketoaldehyde (Scheme 2). ¹H NMR spectroscopy indicates the dicarbonyl compound exists in deuteriochloroform solution exclusively as the *exo-Z*-enolic tautomer.



Attempts to bring about this transformation with BF₃·Et₂O catalysis proved problematic. Epoxide (**2a**) is rapidly consumed upon exposure to catalytic quantities of BF₃·Et₂O in cold benzene. However, only a small quantity (approximately 10%) of the desired rearrangement product could be isolated. Polymerizing condensations involving the reactive β-ketoaldehyde moiety in the presence of the strong Lewis acid is presumed to be responsible for the poor yield obtained. Attempts to improve these yields through changing parameters of time, temperature, solvent, and mole percent of catalyst were fruitless.

The bridgehead dimethyl substituted derivative (**2b**) can be prepared by epoxidation of cycloadduct (**1b**) obtained via reaction of benzyne with 2,5-dimethylfuran.¹⁵ Rearrangement to the corresponding α-acyl-2-indanone (**3b**) is effected in nearly quantitative yield when the epoxide is subjected to conditions of either LiClO₄ or BF₃·Et₂O catalysis. Again, the *exo-Z*-enol form is the sole tautomer in solution as evidenced by ¹H NMR spectroscopy.

TABLE I: Lewis Acid Catalyzed Epoxide Rearrangements¹⁶

Epoxide	Catalyst	Product	Yield	¹ H NMR (60 MHz, CDCl ₃)
2a	LiClO ₄	3a	57%	10.12 (br, 1H), 7.72 (s, 1H) 7.26 (m, 4H), 3.52 (s, 2H)
2a	BF ₃ ·Et ₂ O	3a	10%	
2b	LiClO ₄	3b	100%	14.25 (br, 1H), 7.25 (m, 4H) 3.42 (q, J=7.6 Hz, 1H), 2.38 (s, 3H), 1.40 (d, J=7.6 Hz, 3H)
2b	BF ₃ ·Et ₂ O	3b	99%	

This novel ring contraction offers an attractive route to formylated and acylated 2-indanone derivatives, compounds which have not been previously prepared. Investigations to assess the regioselectivity and scope of this rearrangement are currently underway including attempts to extend the transformation to epoxide substrates derived from non-benzynes/furan cycloadducts. Utilization of the functionalized 2-indanone products for the synthesis of indeno-fused heterocyclic systems is also being explored.

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16. Typical procedures are as follows. LiClO₄ catalyzed rearrangement To a solution of exo-1,4:2,3-diepoxy-1,4-dimethyl-1,2,3,4-tetrahydronaphthalene (**2b**) (.38 g, 2.0 mmol) in toluene (20 mL) was added anhydrous LiClO₄ (.38 g). The mixture was heated at reflux under CaCl₂ protection for 1h. After cooling, the solution was filtered and the residue rinsed with small portions of toluene. Evaporation of solvent under reduced pressure afforded .38 g (100%) of racemic 1-acetyl-3-methyl-2-indanone (**3b**) as a straw colored solid. Recrystallization from hexanes afforded white needles (m.p. 52°C). ¹H NMR (see Table) IR (film) 3324 broad, 1753, 1718, 1659 cm⁻¹. LRMS, m/z (relative intensity) 188 (M⁺, 73), 146 (42), 145 (39), 117 (22), 115 (36), 105 (21), 91 (14), 77 (14), 43 (100). HRMS calcd. for C₁₂H₁₂O₂ 188.0837, found 188.0836 BF₃·Et₂O catalyzed rearrangement To a solution of (**2b**) (.99 g, 5.3 mmol) in dry benzene (10 mL) stirring just above the freezing point in an ice bath under nitrogen was added BF₃·Et₂O (10 μL, 0.081 mmol) After stirring for 10 min, the reaction was quenched with water (25 mL). The aqueous layer was extracted with benzene (2 x 25 mL) and the combined organic layers dried (Na₂SO₄). Evaporation of solvent provided .98 g (99%) of (**3b**) as an oily solid judged to be pure by ¹H NMR spectroscopy

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