REARRANGEMENT OF EXO-1,4:2,3-DIEPOXY-1,2,3,4-TETRAHYDRONAPHTHALENE: FORMATION OF A NOVEL ISOCHROMENE VIA GROB FRAGMENTATION[1]

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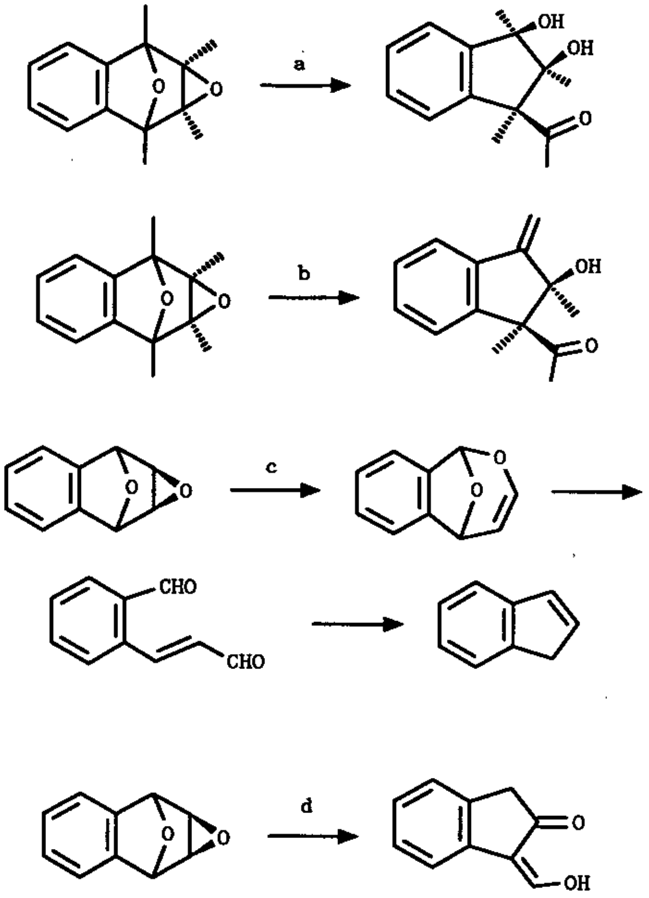
Abstract - The suitability of various acid catalysts for effecting the ring contracting rearrangement of an epoxidized benzyne/furan cycloadduct (**1b**) to α-formyl-2-indanone (**7**) was investigated. Nafion-H was demonstrated to be an effective catalyst for this transformation. Competing rearrangement pathways were evident under catalysis by acidic alumina and led to the formation of the novel 1*H*-2-benzopyran-1-carboxaldehyde (**9**) in addition to the expected product.

The 1,4:2,3-diepoxy-1,2,3,4-tetrahydronaphthalene system (**1**) has been shown to undergo a number of intriguing skeletal reorganizations under conditions which effect epoxide ring opening (Scheme 1). Hart demonstrated that the 1,2,3,4-tetramethyl derivative (**1a**) yields a ring contracted keto-2,3-diol (**2**) upon acidic solvolysis and an unsaturated ß-ketoalcohol elimination product (**3**) when subjected to acidic conditions in a non-nucleophilic medium.[2] Each of these rearrangements proceeds by way of Wagner-Meerwein phenyl migration to a carbocation generated by epoxide ring opening; shifts facilitated by the formation of a relatively stable oxonium ion intermediate. Solvolytic trapping yields a strained bicyclic acetal which affords (**2**) upon workup. In the absence of a nucleophile, deprotonation of a bridgehead methyl group results in the formation of 3.

Lewars identified indene (**4**) and *o*-formylcinnamaldehyde (**5**) as the predominate flash vacuum thermolysis products of the unsubstituted parent system (**1b**).[3] A mechanistic hypothesis in which both products derive from 6,7-benzo-2,9-dioxabicyclo[3.2.1]oct-3-ene (**6**) was postulated. More recently, we have demonstrated that these diepoxynaphthalenes undergo carbocation driven ring contracting rearrangements (**1b** to **7**) when treated with the Lewis acids, lithium perchlorate and boron trifluoride etherate.[4] These reactions afford moderate to excellent yields of otherwise difficultly accessible α-formyl- and α-acyl-2-indanones and constitute our first successful realization of a strategy for 5-membered carbocycle construction based upon the manipulation of furan Diels-Alder cycloadducts.[5]

Scheme 1

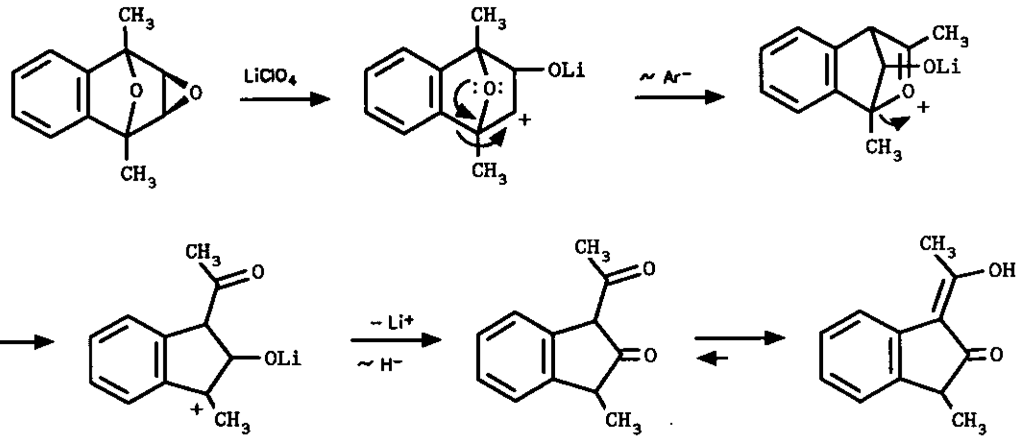


a) TFA/CH$_2$Cl$_2$/MeOH   b) TFA/CH$_2$Cl$_2$

b) 600 °C, 10^{-3} mm   d) LiClO$_4$ or BF$_3$Et$_2$O

Exo-1,4:2,3-diepoxy-1,4-dimethyl-1,2,3,4-tetrahydronaphthalene (1c) underwent quantitative conversion into racemic 1-acetyl-3-methyl-2-indanone (8) upon treatment with lithium perchlorate in refluxing toluene. As in the reactions observed by Hart,[2] epoxide opening and 1,2-phenyl migration would afford an oxonium ion. In the absence of nucleophile/base, oxonium ion carbon-oxygen bond cleavage to a benzylic carbocation and subsequent 1,2-hydride shift represents a plausible mechanistic interpretation of the reaction (Scheme 2).[15]

Scheme 2



In this note, we detail results of a study designed to gauge the efficacy of various acid catalysts in promoting this rearrangement. These studies were prompted in part by the mediocre yields obtained in the reactions of the unsubstituted (1b) in the preliminary work. In addition, we describe an alternate rearrangement which emerged during the course of this investigation which affords a novel isochromene derivative (9).

RESULTS AND DISCUSSION.

The two Lewis acid catalysts examined in our initial studies were less than ideal for ring contraction of the unsubstituted parent (1b) which produces a somewhat unstable 1,3-ketoaldehyde as the hydroxymethylene tautomer (7). With the powerful Lewis acid, boron trifluoride etherate in benzene at 6-8°C, a very low yield (10%) of α-formyl-2-indanone (7) could be extracted from a crude product mixture which was devoid of epoxide starting material. Boron trifluoride promoted self-condensations of the product are believed to be responsible for the low yield. We sought to minimize such polymerizing condensations by attempting the rearrangement at lower temperatures and by quenching after shorter reaction times but could not augment the yield (Table 1, 1-4).

Epoxide solubilized lithium cations possess sufficient Lewis acidity to promote epoxide ring opening. Lithium perchlorate in aromatic hydrocarbon solvents efficiently effects epoxide to carbonyl rearrangement under mild conditions compatible with aldehyde production; and advantage not associated with the use of strong protic acids in this capacity.[6] In refluxing benzene over lithium perchlorate, complete consumption of (1b) required 6 hours and product destruction again proved problematic (Table 1, 5). A moderate yield of 7 (57%) was achieved in refluxing toluene for a shorter period of time (Table 1, 6).

We then endeavored to assess the utility of an array of heterogeneous acid catalysts in the rearrangement with the goal of improving this yield. Attention was focused on the use of Nafion-H, a perfluorinated sulfonic acid resin, Amberlyst 15, a strongly acidic ion exchange resin, and acidic, neutral, and basic alumina.

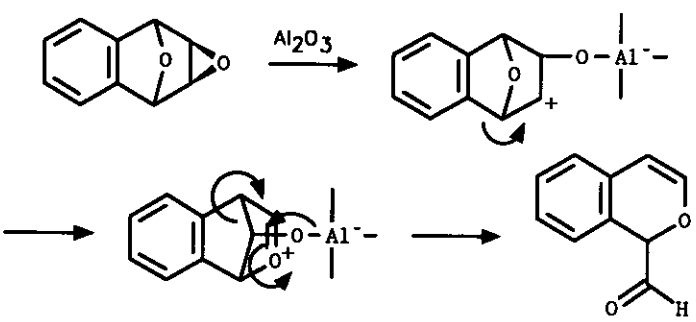
Nafion-H is reported to catalyze solvolytic opening of epoxides with trans diastereoselectivity.[7] It is also efficacious in promoting three classes of synthetically important carbocation rearrangements; the pinacol-pinacolone, Fries, and Rupe reactions.[8] Refluxing a solution of epoxide (1b) in benzene in the presence of Nafion-H beads brought about very slow conversion into the desired indanone (7) (Table 1, 7). When refluxed in toluene over Nafion-H for 28 hours, a 62% yield of rearranged material could be extracted from a gummy red residue with boiling hexanes (Table 1, 8). Incremental addition of the catalyst over the course of the reaction appears beneficial as catalytic efficiency diminishes with the deposition of a black film on the surface of beads during the course of the reaction.

Amberlyst 15 has proven to be an effective and versatile acid catalyst particularly in applications where stronger mineral acids can not be tolerated. Unfortunately, attempts to mediate our epoxide rearrangement with this reagent were entirely unsuccessful and yielded predominately uncharacterizable tars and only traces of (7) (Table 1, 9).

An unusual result was obtained in the alumina promoted reaction. On an exploratory scale, a solution of the epoxide in benzene was heated at reflux in the presence of acidic alumina. After 5 hours, ^{1}H nmr spectroscopy revealed a 67% conversion of starting material into a roughly 1:1 mixture of two products; the expected 2-indanone (7) and a compound incorporating an aldehydic proton (s, δ = 9.70), two vicinal olefinic protons (d, δ = 6.5, J = 6 Hz), (d, δ = 5.72, J = 6 Hz), a single proton (s, δ = 5.34) and aromatic protons. Interpretation of the NMR data suggested that the unexpected product was 1H-2-benzopyran-1-carboxaldehyde (9). The unsubstituted isochromene is reported to display two doublets (δ = 6.5 and δ = 5.7, J = 6 Hz) for its alkene protons and a singlet (δ = 4.9) for the benzyloxymethylene protons in addition to aromatic resonances in its proton spectrum.[9]

A mechanistic rationale (Scheme 3) for the formation of this isochromene derivative commences with epoxide ring opening and aryl migration to the incipient carbocation as in the formation of 7. At this juncture, Grob-type carbon-carbon bond fission can compete with carbon-oxygen oxonium ion cleavage and result in the formation of 9. In so much as this mechanism involves a discreet carbocation intermediate, the stringent geometrical constraints for bond breaking imposed in the concerted version of the Grob fragmentation are obviated.[15] A number of alumina catalyzed epoxide rearrangements are known.[10] Among the reported examples are several in which epoxidized di- and sesquiterpene substrates yield complex product mixtures which include Grob derived aldehydes and ketones.[11]

Scheme 3



Reproducing this reaction on a larger scale enabled isolation and complete characterization of the novel heterocycle. Thus, a solution of the epoxide (3 mmol) in benzene refluxed with 1.0 gram of acidic alumina for 6 hours returned a 50% yield of a 6:5 mixture of isochromene (9) and 2-indanone (7) which was readily separable by flash chromatography on silica. The α-alkoxyaldehyde is somewhat sensitive and prone to hydration. The solid 2,4-DNP derivative was prepared for purposes of elemental analysis. An attempt to characterize (9) as its carboxylic acid failed when treatment with Jones reagent led to over oxidation.

Both rearrangements were found to proceed at a much slower rate in the presence of neutral alumina. Basic alumina was found to be ineffectual.

Of the acid catalysts surveyed, Nafion-H and lithium perchlorate are effective catalysts for the conversion of exo-1,4:2,3-diepoxy-1,2,3,4-tetrahydronaphthalene (1b) to α-formyl-2-indanone (7). A divergent rearrangement cascade is operative in the acidic alumina catalyzed reaction and affords a Grob fragmentation product in addition to the expected compound. At the present time, the basis for the disparate behavior of the alumina catalyst remains uncertain.

Table 1: Acid Catalyzed Rearrangements of 1,4:2,3-Diepoxy-1,2,3,4-tetrahydronaphthalene.

entry	catalyst		conditions	yield	
		(cat. quant., sub. quant.)		(7)	(9)
1	$BF_3 \cdot Et_2O$	(20 μL, .48 g)	benzene, 6-8 °C, 30 min	10%	-
2	$BF_3 \cdot Et_2O$	(10 μL, .32 g)	CH_2Cl_2, -40 °C, 20 min	no rxn	
3	$BF_3 \cdot Et_2O$	(5 μL, .16 g)	CCl_4, -15 °C, 30	10%	
4	$BF_3 \cdot Et_2O$	(10 μL, .31 g)	CH_2Cl_2, 0 °C, 5 min	5%	
5	$LiClO_4$	(.80 g, .80 g)	benzene, 80 °C, 6 h	36%	
6	$LiClO_4$	(.80 g, .80 g)	toluene, 110 °C, 90 min	57%	
7	Nafion-H	(.06 g, .32 g)	benzene, 80 °C, 24 h	17%	
8	Nafion-H	(1.44 g, .48 g)	toluene, 110 °C, 28 h	62%	
9	Amberlyst-15	(.09 g, .32 g)	CH_2Cl_2, 20 °C, 6 h	5%	
10	Al_2O_3 (H^+)	(1.00 g, .48 g)	benzene, 80 °C, 6 h	25%	25%

EXPERIMENTAL

Exo-1,4:2,3-Diepoxy-1,2,3,4-tetrahydronaphthalene (1b).

To a mixture of 1,4-epoxy-1,4-dihydronaphthalene (1.44 g, 10.0 mmol),[12] sodium dihydrogen phosphate (12.4 g, 87.3 mmol) and urea/hydrogen peroxide 1:1 complex monohydrate (4.75 g, 50.5 mmol) stirring in methylene chloride (60 ml) at 0 °C was added acetic anhydride (2.55 g, 23.6 mmol) dropwise over 10 min. The reaction mixture was allowed to slowly warm to room temperature while stirring for 24 h.[13] Saturated sodium bicarbonate (100 ml) and additional methylene chloride (40 ml) were added. The aqueous layer was extracted with methylene chloride (100 ml) and the organic layers washed with water (100 ml) and dried over sodium sulfate. Solvent was removed by rotary evaporation after checking for complete destruction of any unreacted peroxide to afford 1b (1.56 g, 97%) as a light yellow crystalline solid. Recrystallization from hexanes/ethyl acetate provided highly pure 1b (1.18 g, 74%) as colorless plates: mp 90-92 °C; lit.,[14] 91-92 °C ; ^{1}H nmr ($CDCl_3$) δ 6.9-7.3 (m, 4H), 5.20 (s, 2H), 3.50 (s, 2H).

α-Formyl-2-indanone (7).

Lithium perchlorate induced rearrangement.

A solution of exo-1,4:2,3-diepoxy-1,2,3,4-tetrahydronaphthalene (**1b**) (0.80 g, 5.0 mmol) in toluene (50 ml) over anhydrous lithium perchlorate (0.80 g) was heated at reflux under calcium chloride protection for 90 min. The reaction mixture was filtered while hot and the solvent removed by rotary evaporation to provide 0.56 g of a red solid. This residue was extracted with boiling hexanes (2 X 50 ml). Evaporation of solvent under reduced pressure afforded 7 (0.46 g, 57%) as a light pink solid: *mp* 112-120 °C *(decomp.)*; ^{1}*H nmr* (CDCl$_3$) δ 10.12 (broad, 1H, enol O*H*), 7.72 (s, 1H, vinyl C*H*), 6.9-7.3 (m, 4H), 3.52 (s, 2H); ir (thin film) 3030, 2950, 2800-2400 broad H-bonded O-H stretch, 1710, 1700, 1600 cm^{-1}; LRMS m/z (relative intensity) 160 (M$^+$,100), 132 (32), 131 (67), 103 (39), 77 (27); Anal. Calcd for $C_{10}H_8O_2$: C, 74.98; H, 5.03. Found: C, 74.97; H, 5.15.

Nafion-H induced rearrangement.

A solution of **1b** (0.48 g, 3.0 mmol) in toluene (15 ml) over Nafion-H (0.24 g) was heated at reflux under calcium chloride protection. Five additional 0.24 g portions of catalyst were added over the course of the 28 h reflux period. The reaction mixture was filtered while hot and toluene was removed by rotary evaporation. Extraction with boiling hexanes and subsequent solvent removal afforded 7 (0.30 g, 62%).

Boron trifluoride etherate induced rearrangement.

To a solution of epoxide (**1b**) (0.48 g, 3.0 mmol) in benzene (15 ml) stirring near the freezing point under nitrogen was added boron trifluoride etherate (20 μl). The reaction was quenched with water (15 ml) after 30 min. The organic layer was dried over sodium sulfate and the solvent was removed by rotary evaporation. Extraction of the resulting dark red residue provided 7 (0.06 g, 10%).

1H-2-Benzopyrano-1-carboxaldehyde (9).

A solution of epoxide (**1b**) (0.48 g, 3.0 mmol) in benzene (15 ml) over oven dried acidic alumina (1.00 g, Brockmann I) was heated at reflux under calcium chloride protection for 6 h. Removal of solvent and hexane extraction of the residue provided 0.24 g of a mixture of 9 and 7 in a 6:5 ratio as indicated by integration of the ^{1}H nmr. Flash chromatography on silica gel eluting with 20% ethyl acetate/hexanes afforded isochromene(9) (0.12 g, 25%) as a pale yellow oil (the enol (7) does not elute): ^1H nmr ($CDCl_3$) δ 9.70 (s, 1H, CHO), 6.9-7.4 (m, 4H), 6.67 (d, 1H, J = 6 Hz, OC*H*=CH), 5.72 (d, 1H, J = 6 Hz, OCH=C*H*), 5.35 (s, 1H); ir (thin film) 3450 (broad, weak, hydrated aldehyde), 3030, 2970, 2930, 2830, 1737, 1629, 1054 cm^{-1}; LRMS m/z (relative intensity) 160 (M^+, 5), 132 (9), 131 (100), 103 (22), 77 (33). The 2,4-dinitrophenylhydrazone was prepared and recrystallized from methanol/water to provide an orange-red solid, mp 123-125 °C for combustion analysis: Anal. Calcd for $C_{16}H_{12}N_4O_5$: C, 56.47; H, 3.55; N, 16.46. Found: C, 56.05; H, 3.79; N, 16.32.

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12. Apparently this material is no longer commercially available. We have found the procedure of Newman for benzyne generation from anthranilic acid and isoamyl nitrite in the presence of furan diene to be a convenient route to substituted derivatives and should be suitable for preparation of the parent compound. M. S. Newman and J. A. Cella, *J. Org. Chem.*, 1973, 38, 3484.
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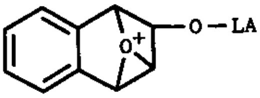
15. *Note added in proof.* A reviewer has pointed out that oxygen bridging is conceivable in the

carbocationic intermediate **(10)** formed upon epoxide ring opening in the reactions leading to the 2-indanones (Scheme 2) and 1H-2-benzopyran-1-carboxaldehyde (Scheme 3). This would not be of conseqence in the outcome of the 2-indanone generating rearrangment. However, we believe that significant carbocation bridging of the type suggested may provide an alternate mechanistic course for the production of Grob fragmentation products which does not involve Wagner-Meerwein phenyl migration. We intend to search for evidence of such a pathway by examining the acidic alumina promoted rearrangement of appropriately substitued substrates.



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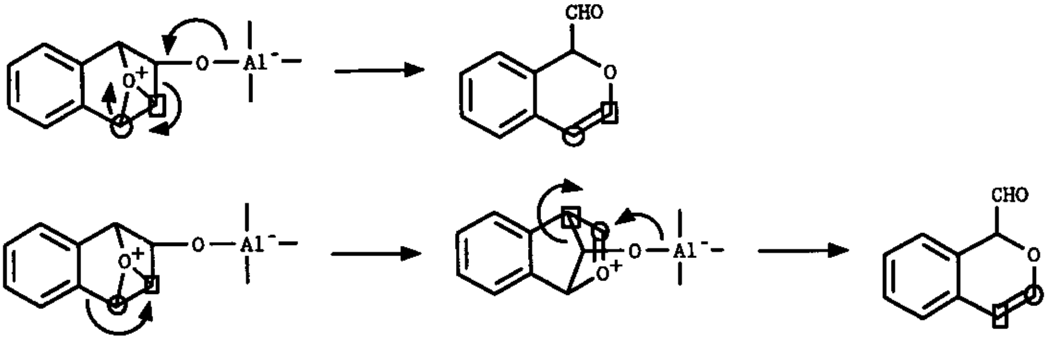

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