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Reductive Electrophilic Substitution of Phthalans and Ring Expansion to Isochroman Derivatives

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Abstract: Reductive cleavage of phthalan, 1a, with Li metal in the presence of a catalytic amount of naphthalene leads to the formation of a stable aromatic dilithium compound. The adducts of the latter with CO₂, aldehydes or ketones undergo ring closure to isochroman derivatives, leading to ring expansion of the original heterocycle. The reductive electrophilic substitution procedure was successfully extended to the substituted phthalans 1b and 1c, to afford the corresponding isochroman-3-ones in satisfactory yields.

The reductive cleavage of alkyl arylmethyl ethers by electron transfer from alkali metals in ethereal solvents is a known reaction which results in the regioselective cleavage of the arylmethyl carbon-oxygen bond¹ and has found scant applications in the generation of arylmethyl carbonions.²⁻⁵

To improve the synthetic usefulness of this reaction we have investigated the behaviour of phthalan, Ia, under reductive electron-transfer conditions; indeed, reductive cleavage of Ia, which can be considered as an intramolecular diarylmethyl ether, should result in the formation of an arylmethyl carbanion bearing a methoxide group in the *ortho* position, potentially useful in the synthesis of substituted benzyl alcohols.



After several attempts, it was found that quantitative cleavage of 1a can be accomplished by reaction with Li powder (2.5 equiv) in the presence of a catalytic amount (3 mol%) of naphthalene⁶ in THF at 0 °C; formation

of the intermediate dianion 2 was evidenced by D_2O quenching. Once generated, the dianion is stable at 0 °C for several hours. Trapping of the carbanion with different electrophiles (alkyl halides, aldehydes, ketones, CO_2) was successful, affording compounds 3a-i in satisfactory yields (Scheme 1).⁷ The results are reported in the Table.

entry	EX (equiv)	T (°C)	t, min	product, $E =$	yield (%) ^b
1	D ₂ O ^c	0	30	3a , D	>95 ^d
2	CH ₃ I (1.2)	-10	60	3b , CH ₃	80
3	CH ₃ CH ₂ Br (1.2)	0	60	3c , CH ₃ CH ₂	90
4	(CH3)2CHBr (1.2)	0	60	3d, (CH3)2CH	63
5	PhCHO (1)	0	60	3e, PhCHOH	66
6	(CH3)3CHO (1)	0	60	3f, (CH ₃) ₃ CHOH	76
7	C ₂ H ₅ CHO (1)	-20	30	3g, C ₂ H ₅ CHOH	61
8	Ph ₂ CO (1)	0	60	3h, Ph ₂ COH	74
9	CO ₂ (gas) ^e	-40	5	3i, COO ^f	76

Table. Reductive Electrophilic Substitution of Compound 1a^a

^aThe reductive cleavage was performed with Li powder in the presence of a catalytic amount of naphthalene in THF at 0 °C during 2 h; see note 6. ^bIsolated yields after flash chromatography, unless otherwise indicated. ^c2 ml of D₂O were added. ^dAs determined by ¹H-NMR analysis by monitoring the percentage of deuterium incorporation in the arylmethyl position. ^cGaseous CO₂ was bubbled into the reaction mixture for 5 min. ^fLactonization occurred spontaneously during the acidic work up (see below).

Interestingly, reaction with CO_2 followed by acidic work up of the reaction mixture afforded directly isochroman-3-one, 3i, thus leading to ring expansion of 1a.

Scheme 2



This reaction was successfully extended to 1-phenylphthalan, **1b**, which afforded 4-phenylisochroman-3one, **3j**, and to 1,4-epoxy-1,2,3,4-tetrahydronaphthalene, **1c**, which afforded 1,4-ethyleneisochroman-3-one, **3k** (Scheme 2).⁸ It is interesting to observe that the reductive cleavage of **1b** is 100% regioselective, thus resembling the reductive cleavage of 1-phenyloxirane^{9,10} and 1-phenyloxetane.¹¹

A two-pot procedure allowed ring expansion of 1a to 3-substituted isochroman derivatives: the diols 3e, 3f and 3h, synthesized as reported above, were refluxed in 50% aqueous H₃PO₄ for several hours. Work up and flash-chromatography afforded the isochromans 4a-c in good to very good yields (Scheme 3).¹² It is interesting to observe that 50% aqueous H₃PO₄ proved superior both to H₂SO₄ and H₃PO₄ in glacial acetic acid in the cyclization reaction; indeed, under these conditions, isochroman 4a was obtained in 14 and 9% yield, respectively.¹³

Scheme 3



3e: $R_1 = H$, $R_2 = Ph$; **3f**: $R_1 = H$, $R_2 = (CH_3)_3C$; **3g**: $R_1 = H$, $R_2 = C_2H_5$; **3h**: $R_1 = Ph$, $R_2 = Ph$ **4a**: $R_1 = H$, $R_2 = Ph$, 70%; **4b**: $R_1 = H$, $R_2 = (CH_3)_3C$, 83%; **4c**: $R_1 = Ph$, $R_2 = Ph$, 92% **5a**: $R_1 = H$, $R_2 = (CH_3)_3C$, 75%; **5b**: $R_1 = H$, $R_2 = C_2H_5$, 69%

As a further elaboration, the diols 3f and 3g were regioselectively oxidized with aqueous KMnO₄ to afford, after acidic work up, the dihydroisocoumarins 5a and 5b, respectively, in satisfactory isolated yields (Scheme 3).^{14,15}

Our results provide a new and efficient synthesis of isochroman derivatives based on the ring expansion of phthalans *via* a reductive electrophilic substitution reaction. These results stress the usefulness of the reductive cleavage of arylmethyl ethers, showing its application to the generation of functionalized organolithium compounds valuable for the synthesis of 1,2-disubstituted aromatics. It is worth noting that isochroman-3-ones are useful intermediates for the synthesis of biologically active heterocyclic compounds, like isoquinolines and tetracyclines; furthermore, several dihydroisocumarines possess biological activity.¹⁶

From a mechanistic point of view, reductive cleavage reactions of carbon-heteroatom bonds involve transfer of an electron to the LUMO of the bond to be broken, followed by a dissociative cleavage step. Our results find therefore analogy in the work of Cohen *et al.*¹⁷ on the reductive cleavage of 2-vinyltetrahydrofuran, where the presence of a conjugated unsaturated system allows an easier formation of the σ radical anion of the C-O bond (dissociative electron transfer) through the intermediate formation π radical anion.

Further work is in progress in our laboratory to extend the synthetic usefulness and to enter into the mechanistic details of this reaction.^{18,19}

References and Notes

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- 7. The substrate (8 10 mmol) was added under Ar to a vigorously stirred suspension of 2.5 equiv of Li powder and naphthalene (3 mol%) in THF (30 ml) at 0 °C, and the mixture stirred for 2 h. To the mixture, chilled to the temperature reported in the Table, the appropriate electrophile, dissolved in a minimum amount of THF, was added dropwise. After stirring for the reported time, the mixture was quenched by slow dropwise of H₂O (*caution!*), the cold bath removed, and the resulting mixture extracted with Et₂O. CO₂ quenching was performed by bubbling the gaseous electrophile into the reaction mixture for 5 min., and work up as above. The crude products were purified by flash-chromatography.
- Reductive lithiation of 1b and 1c (according to note 6) followed by aqueous quenching afforded (2hydroxymethyl)phenyl-phenylmethane and 1-hydroxy-1,2,3,4-tetrahydronaphthalene, respectively, in quantitative yields. Quantitative intermediate formation of the corresponding carbanions was evidenced by D₂O quenching.
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- 12. The substrate (1 mmol) was dissolved in a minimum amount of THF and added under N₂ to 30 ml of a vigorously stirred 50% aqueous solution of H₃PO₄. The mixture was stirred at reflux temperature overnight. After cooling to r.t., the mixture was extracted with Et₂O, washed with saturated NaHCO₃ and dried (CaCl₂). The crude products were purified by flash-chromatography.
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- 14. The substrate (1 mmol) was added to a solution of KMnO4 (1.5 equiv) in 30 ml of H₂O and stirred at r.t. for 24 (synthesis of 5a) or 8 h (synthesis of 5b). After filtering, the mixture was acidified with concentrated H₂SO₄ and thoroughly extracted with CH₂Cl₂. The crude products were purified by flash-chromatography.
- For a recent application of the reductive lithiation procedure to the ring expansion of thiochroman and related systems, see: T. Cohen, F. Chen, T. Kulinski, S. Florio, V. Capriati, *Tetrahedron Lett.*, 1995, 36, 4459 and accompanying paper. We thank Prof. T. Cohen for a preprint copy of the manuscripts.
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- 1a and 1c are commercially available. 1b was synthesized according to: M. Barfield, R. J. Spear, S. Sternhell, J. Am. Chem. Soc., 1975, 97, 5160. All new compounds gave analytical and spectral (¹H and ¹³C NMR, IR) data in agreement with the assigned structures.
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