Electron-Transfer-Induced Reductive Cleavage of Phthalans: Reactivity and Synthetic Applications

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The behavior of phthalan (**1a**) was investigated under conditions of electron transfer from alkali metals in aprotic solvents. Reaction with lithium in the presence of a catalytic amount of naphthalene in THF led to the reductive cleavage of an arylmethyl carbon−oxygen bond, with formation of a stable dilithium compound. Trapping of this intermediate with several electrophiles (alkyl halides, carbonyl derivatives, CO_2) was successful. The extension of this procedure to several substituted phthalans (**1b**−**i**) was investigated, and the regiochemistry as well as the synthetic usefulness of these reactions are discussed.

The reductive cleavage of arylmethyl alkyl ethers by electron-transfer from alkali metals results in the regioselective cleavage of the arylmethyl carbon−oxygen bond.[1,2] Under suitable conditions, this reaction allows the generation of arylmethyl carbanions; we have recently reported on the synthetic usefulness of this procedure.[3]

To further extend the scope of the reaction, we have investigated the behavior under reductive electron-transfer conditions of 1,3-dihydroisobenzofuran (phthalan, **1a**); indeed, this compound can be considered as an intramolecular diarylmethyl ether, *i.e.*, its reductive cleavage should result in the generation of an arylmethyl carbanion ortho functionalized with a methoxide group (Scheme 1).

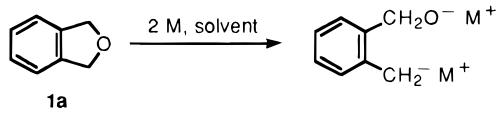
Accordingly, we have developed a new and efficient synthesis of ortho-substituted arylmethyl alcohols. We have also investigated the reductive cleavage of the substituted phthalans **1b**−**i** (Chart 1), and wish to report on the regioselectivity as well as on the synthetic usefulness of their cleavage reaction.

A preliminary report concerning the reductive cleavage of **1a** has already appeared;[4] when this paper was in preparation, we became aware of a recent paper by Yus *et al.* on the single- and double-reductive electrophilic substitution of **1a** under similar reaction conditions.[5]

Results

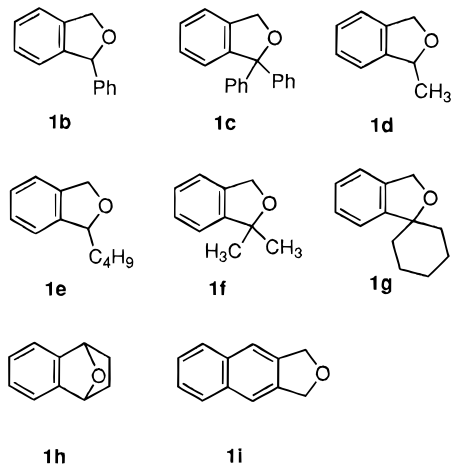
Starting Materials. Compounds **1a** and **1h** are commercially available. Compounds **1b**,[6] **1g**,[7] and **1i**[8] were prepared according to described procedures. Compounds **1c** and **1f** were obtained in 55% and 71% overall yield, respectively, by reaction of phthalide with 2 equiv of the appropriate Grignard reagent, followed by cyclization of the resulting diols in refluxing 50% H_3PO_4.

Scheme 1



1a

Chart 1



1b **1c** **1d** **1e** **1f** **1g** **1h** **1i**

Compound **1d** was obtained in 52% yield by metalation of **1a** with *sec*-BuLi in THF at −40 °C, followed by quenching with CH_3I. According to the same procedure, compound **1e** was obtained in 77% yield by trapping the intermediate carbanion with *n*-BuBr.

Reductive Cleavage Reactions. The reduction of **1a**, taken as a model compound, was carried out under Ar with different alkali metals in tetrahydrofuran (THF). The results are reported in Table 1. The results of D_2O quenching experiments, carried out to check the formation of carbanionic intermediates, are also reported in Table 1.

The reductive cleavage of **1a** with 2.5−5 equiv of Li metal was investigated in THF both at room temperature and at 0 °C; besides the expected 2-(methylphenyl)-methanol (**2**) variable amounts of 1,2-bis(2-hydroxymethyl)diphenylethane (**3**) were obtained (Table 1, entries 1−3) (eq 1).

Exclusive formation of **2** was obtained by the action of Li metal in the presence of a catalytic amount of naphthalene[9] (3 mol %) in THF at 0 °C; under these conditions, quantitative formation of the intermediate carbanion was evidenced by D_2O quenching, even after

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(3) Azzena, U.; Demartis, S.; Fiori, M. G.; Melloni, G.; Pisano, L. *Tetrahedron Lett.* **1995**, *36*, 5641.
(4) Azzena, U.; Demartis, S.; Fiori, M. G.; Melloni, G.; Pisano, L. *Tetrahedron Lett.* **1995**, *36*, 8123.
(5) Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1995**, *51*, 3351; we thank Prof. M. Yus for calling our attention on this paper.
(6) Barfield, M.; Spear, R. J.; Sternhell, S. *J. Am. Chem. Soc.* **1975**, *97*, 5160.
(7) Meyer, N.; Seebach, D. *Chem. Ber.* **1980**, *113*, 1304.
(8) Bartlett, A. J.; Laird, T.; Ollis, W. D. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1315.

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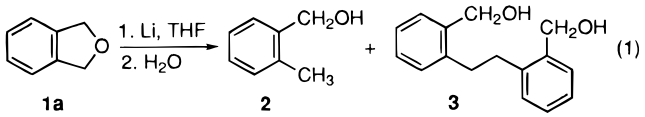
Table 1. Reductive Cleavage of Compound 1a in THF

entry	metal (equiv)	naphthalene mol %	*T*, °C	*t*, h	**2**, yield[a] %	% D[b]
1	Li (5)	−	20	3	65[c]	ND[d]
2	Li (2.5)	−	0	4	78[e]	ND[d]
3	Li (5)	−	0	3	81[f]	90
4	Li (2.5)	3	0	2	73[g]	ND[d]
5	Li (2.5)	3	0	4	>95	>95
6	Li (5)	3	0	1.5	>95	>95
7	Li (5)	3	0	22	>95	>95
8	Na (2.5)	3	20	16	15[h]	*i*
9	K (2.5)	−	20	16	40[j]	ND[d]
10	Na/K[k] (2.5)	−	0	3	60[l]	ND[d]

[a] Determined by ^{1}H NMR, unless otherwise indicated. [b] Determined by ^{1}H NMR, by monitoring the percentage of deuterium incorporation in the arylmethyl position of recovered **2**. [c] 35% of **3** was also obtained. [d] ND = not determined. [e] 22% of **3** was also obtained. [f] Determined on products isolated by flash chromatography. 16% of **3** was also obtained. [g] 27% of **1a** was also recovered. [h] 78% of **1a** was also recovered; unidentified byproducts also formed. [i] No deuterium incorporation was detected. [j] 45% of **1a** was also recovered; unidentified byproducts also formed. [k] 1:5 w/w. [l] 32% of **1a** was also recovered; unidentified byproducts also formed.

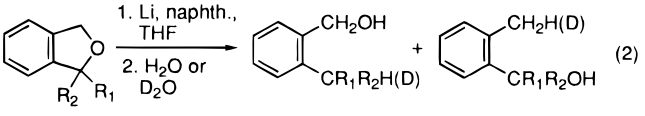


a prolonged reaction time (Table 1, entries 5−7). It is also to observe that the use of a large excess of metal resulted in a shorter reaction time (Table 1, entry 4 *vs* entries 5 and 6).

Reductive cleavages of **1a** with Na (in the presence of 3 mol % of naphthalene) or with K sand at room temperature were by far less effective and led to the recovery of the starting material to a high extent, as well as to the formation of byproducts (Table 1, entries 8 and 9). The use of larger amounts of Na or K did not significantly improve these results. Somewhat better results were obtained employing a Na/K alloy (1:5 w/w) as a reducing agent at 0 °C (Table 1, entry 10).

Attempts to perform the reductive cleavage of **1a** with Li metal in Et_2O or isooctane were unsuccessful.

To improve the usefulness of the reaction and to obtain more information on its mechanistic details, we have investigated the reductive cleavage of the substituted phthalans **1b**−**g** with Li metal (5 equiv) in the presence of 3 mol % of naphthalene in THF; the results are reported in Table 2, together with the results of D_2O quenching experiments (eq 2).



1b, **4b**: R_1 = C_6H_5, R_2 = H; **1c**, **4c**: R_1 = R_2 = C_6H_5; **1d**, **4da**, **4db**: R_1 = CH_3, R_2 = H; **1e**, **4ea**, **4eb**: R_1 = C_4H_9, R_2 = H; **1f**, **4fa**, **4fb**: R_1 = R_2 = CH_3; **1g**: R_1 = R_2 = -$(CH_2)_4$-

1-Phenyl- and 1,1-diphenylphthalan (**1b** and **1c**) underwent highly regioselective cleavage reactions to afford alcohols **4b** and **4c**, respectively, as the only products (Table 2, entries 1 and 2).

(9) Yus, M.; Ramón, D. J. *J. Chem. Soc., Chem. Commun.* **1991**, 398.

Table 2. Reductive Cleavage of 1-Substituted Phthalans 1b−f[a]

entry	compd	*T*, °C	*t*, h	products (% yield)[b]	products (% D)[c]
1	**1b**	0	3.5	**4b** (>95)	**4b** (>95)
2	**1c**	0	1	**4c** (>95)	**4c** (>95)
3	**1d**	0	3	**4da** (30), **4db** (70)	**4da** (>95), **4db** (>95)
4	**1d**	−40	6	**4da** (28), **4db** (72)	ND[d]
5	**1e**	0	5	**4ea** (20), **4eb** (80)	**4ea** (>95), **4eb** (>95)
6	**1f**	−20	12	**4fa** (25), **4fb** (75)	**4fa** (85), **4fb** (>95)
7	**1f**	−20 to rt	22[e]	**4fa** (25), **4fb** (75)	**4fa** (50), **4fb** (>95)

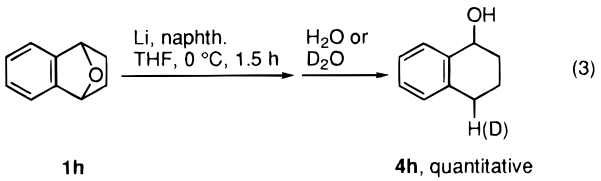
[a] All reactions run with 5 equiv of Li in the presence of 3 mol % of naphthalene. [b] Determined by ^{1}H NMR. [c] Determined by ^{1}H NMR, by monitoring the percentage of deuterium incorporation in the arylmethyl position of crude products. [d] ND = not determined. [e] 12 h at −20 °C and 10 h at rt.

Reductive cleavage of 1-methylphthalan (**1d**) at 0 °C afforded a 30:70 mixture of the isomeric alcohols **4da** and **4db**. Lowering the temperature to −40 °C gave an almost identical result (Table 2, entries 3 and 4). Comparable results were obtained in the reductive cleavage of 1-butylphthalan (**1e**) (Table 2, entry 5) and 1,1-dimethylphthalan (**1f**) (Table 2, entry 6). In the last case, however, the reductive cleavage reaction was performed at −20 °C, in order to avoid the formation of unidentified byproducts.

Interestingly, D_2O quenching experiments evidenced the quantitative intermediate formation of carbanions in all cases but one. The notable exception is the intermediate in the synthesis of alcohol **4fa**. Indeed, recovered **4fa** showed only 85% incorporation of deuterium in the arylmethyl position (Table 2, entry 6). This percentage lowered to 50% when D_2O quenching was performed after a more prolonged reaction time, thus suggesting decay of the intermediate tertiary carbanion (Table 2, entry 7).

At variance with the above reported results, the spiro-[cyclohexane-1,1′-phthalan] (**1g**), although affording a deep yellow colored solution, was quantitatively recovered after 6 h reaction time at 0 °C; at room temperature it reacted sluggishly to afford a complex reaction mixture (not reported in Table 2).

We have also investigated the reductive cleavage of 1,4-epoxy-1,2,3,4-tetrahydronaphthalene (**1h**), which does not pose regioselectivity problems. This polycyclic ether underwent a clean ring opening to 1-hydroxy-1,2,3,4-tetrahydronaphthalene (**4h**); D_2O quenching showed quantitative formation of the intermediate carbanion (eq 3).



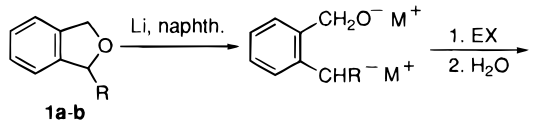
Reductive Electrophilic Substitution of 1a and 1b. Due to the results obtained in the reductive cleavage reactions, reductive electrophilic substitution reactions of **1a** and **1b** were performed using 5 equiv of Li metal in the presence of a catalytic amount of naphthalene (3 mol %) in THF at 0 °C. The results are reported in Table 3 (eq 4).

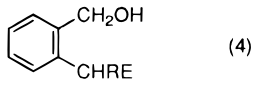
Alkylation of the intermediate carbanion generated in the reductive cleavage of **1a** was achieved with primary

Table 3. Reductive Electrophilic Substitution of Compounds 1a,b[a]

entry	compd	EX (equiv)	*T*, °C	*t*, min	product, E =	% yield[b]
1	**1a**	CH_3I (1.2)	0	60	**4da**, CH_3	80
2	**1a**	C_4H_9Br (1.2)	0	60	**4ea**, C_4H_9	81
3	**1a**	CH_3CH_2Br (1.2)	0	60	**5a**, CH_3CH_2	90
4	**1a**	$(CH_3)_2CHBr$ (1.2)	0	60	**5b**, $(CH_3)_2CH$	63
5	**1a**	C_6H_5CHO (1)	0	60	**5c**, C_6H_5CHOH	66
6	**1a**	ArCHO[c] (1)	0	60	**5d**, ArCHOH[c]	78
7	**1a**	$(CH_3)_3CCHO$ (1)	0	60	**5e**, $(CH_3)_3CCHOH$	76
8	**1a**	$(C_6H_5)_2CO$ (1)	0	60	**5f**, $(C_6H_5)_2COH$	74
9	**1a**	C_2H_5CHO (1)	−20	30	**5g**, C_2H_5CHOH	61
10	**1a**	C_6H_5COAlk[d] (1)	−40	60	**5h**, $C_6H_5COHAlk$[d]	54
11	**1b**	C_4H_9Cl (1.2)	0	60	**5i**, C_4H_9	62
12	**1b**	$(CH_3)_2CO$ (1)	−40	30	**5j**, $(CH_3)_2COH$	64

[a] The reductive cleavage reactions were performed with 5 equiv of Li in the presence of a catalytic amount of naphthalene in THF at 0 °C, for the time reported in Table 1 or 2. [b] Determined on isolated products. [c] Ar = 3-methoxyphenyl. [d] Alk = $(CH_2)_2N(CH_3)_2$.





(4)

4da, **4ea**, **5a-j**

1a, R = H; **1b**, R = C_6H_5; **4da**, R = H, E = CH_3; **4ea**, R = H, E = C_4H_9; **5a**, R = H, E = C_2H_5; **5b**, R = H, E = $CH(CH_3)_2$; **5c**, R = H, E = C_6H_5CHOH; **5d**, R = H, E = 3-$CH_3O(C_6H_4)CHOH$; **5e**, R = H, E = $(CH_3)_3CCHOH$; **5f**, R = H, E = $(C_6H_5)_2COH$; **5g**, R = H, E = C_2H_5CHOH; **5h**, R = H, E = $C_6H_5COH(CH_2)_2N(CH_3)_2$; **5i**, R = C_6H_5, E = C_4H_9; **5j**, R = C_6H_5, E = $(CH_3)_2COH$.

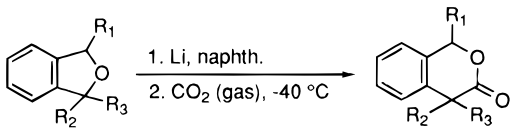
and secondary alkyl halides under mild conditions: a slight excess (1.2 equiv) of the alkyl halide was added to the reaction mixture at 0 °C; after 1 h stirring at this temperature, standard workup afforded good yields of the alkylated products **4da**, **4ea**, **5a**, and **5b**, together with minor amounts of the product of reductive cleavage (Table 3, entries 1−4).

Several carbonyl derivatives were tested as electrophiles. The addition reaction of the Li carbanion to the carbonyl of nonenolizable aldehydes or ketones occurred readily at 0 °C within 1 h (Table 3, entries 5−8). Satisfactory results were obtained also with enolizable aldehydes or ketones, performing the addition reactions at subzero temperatures (Table 3, entries 9 and 10).

Similar satisfactory results were obtained in the reductive electrophilic substitution of **1b** (Table 3, entries 11 and 12).

Synthesis of Isochroman-3-ones. As an application of the reductive electrophilic substitution of phthalans, we have investigated their ring expansion to substituted 1,4-dihydro-3*H*-2-benzopyran-3-ones (substituted isochroman-3-ones), which are useful intermediates in the synthesis of biologically active heterocyclic compounds.[10,11]

According to the procedure reported above, ethers **1a**−**c** and **1h** were reduced with Li in the presence of naphthalene; the corresponding carbanions were reacted at −40 °C with gaseous CO_2 to afford, after acidic workup, the isochroman-3-ones **6a**−**d** (eq 5).

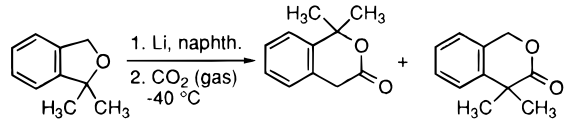


(5)

1a, **6a**: $R_1 = R_2 = R_3$ = H, 76% yield; **1b**, **6b**: $R_1 = R_2$ = H, $R_3 = C_6H_5$, 66% yield; **1c**, **6c**: R_1 = H, $R_2 = R_3 = C_6H_5$, 77% yield; **1h**, **6d**: $R_1 = R_2 = (CH_2)_2$, R_3 = H, 43% yield

The same procedure was applied to the dimethyl derivative **1f**, which afforded a 85:15 mixture of two isomeric dimethyl-substituted isochroman-3-ones, **6e** and **6f**, in 77% overall yield. Although it was possible to isolate **6e** by repeated, careful, column chromatographies of this mixture, we investigated the possibility to obtain only **6e**, avoiding the tedious purification step. Accordingly, the reaction mixture obtained by the reductive cleavage of **1f** at −20 °C was stirred at room temperature for 30 h before CO_2 quenching. To our delight, under such conditions only the isochroman-3-one **6e** was formed (eq 6).

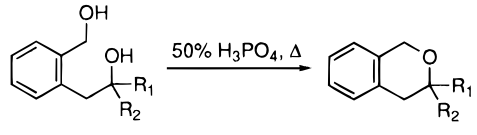
This finding further supports the observation that the intermediate tertiary carbanion decays under the reaction conditions. It is therefore interesting to note that the reductive electrophilic substitution of **1f** is made regioselective by virtue of the different stability of the two carbanions generated in the reductive cleavage step.



(6)

reduction conditions: 12h, -20 °C: **6e**/**6f** = 85:15, by ^{1}H NMR (77% yield)
12h, -20 °C, then 30 h at rt: **6e** = 47% yield, **6f** = not observed

Synthesis of Isochromans. The diols **5c**−**f**, obtained by the reductive electrophilic substitution of **1a** with aldehydes or ketones, are suitable starting materials for the synthesis of 3-substituted 3,4-dihydro-1*H*-2-benzopyrans (3-substituted isochromans) by a dehydration procedure (eq 7).



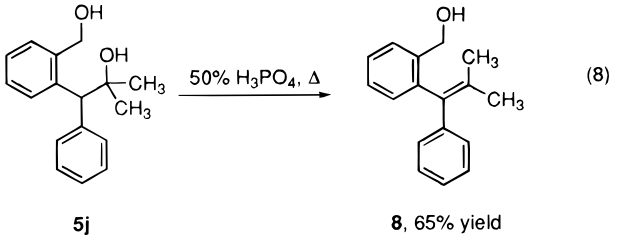
(7)

5c, **7a**, R_1 = H, $R_2 = C_6H_5$, 70% yield; **5d**, **7b**, R_1 = H, R_2 = 3-$(CH_3O)C_6H_4$, 75% yield; **5e**, **7c**, R_1 = H, $R_2 = (CH_3)_3C$, 83% yield; **5f**, **7d**, $R_1 = R_2 = C_6H_5$, 92% yield

Accordingly, the above mentioned diols were refluxed in 50% aqueous H_3PO_4 for several hours. Workup and flash chromatography afforded the 3-substituted-isochromans **7a** (70%), **7b** (75%), **7c** (83%), and **7d** (92%) in good to very good yields. An attempt to cyclize compound **5j** under similar reaction conditions was unsuccessful, leading to 1-[2-(hydroxymethyl)phenyl]-1-phenyl-2-methylpropene (**8**), as the main reaction product (65% isolated yield) (eq 8).

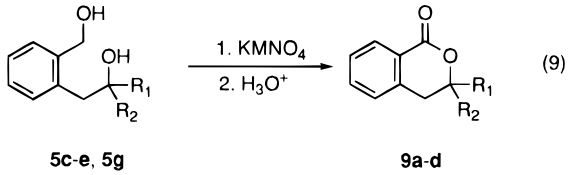
(10) Narasimhan, N. S.; Mali, R. S. *Top. Curr. Chem.* **1987**, *138*, 63.

(11) For a recent synthesis of lactones **6**, see: Kobayashi, K.; Mannami, T.; Kawakita, M.; Tokimatsu, J.; Konishi, H. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 582.



Synthesis of Dihydroisocoumarins. As a further application, we have developed a simple procedure allowing the transformation of the diols obtained by the reductive electrophilic substitution of **1a** with aldehydes into 3-substituted 3,4-dihydro-1*H*-2-benzopyran-1-ones (dihydroisocoumarins), a class of compounds which can be found in several plants and, due to their potential biological activity, are the subject of continuous synthetic efforts.[10,12]

Accordingly, diols **5e** and **5g** were regioselectively oxidized with aqueous $KMnO_4$ at room temperature for 24 h to afford, after acidic workup and flash chromatography, the dihydroisocoumarins **9c** (75%) and **9d** (69%) in good yields (eq 9).



5c, **9a**, R_1 = H, R_2 = C_6H_5 , 56% yield; **5d**, **9b**, R_1 = H, R_2 = 3-$(CH_3O)C_6H_4$, 71% yield; **5e**, **9c**, R_1 = H, R_2 = $(CH_3)_3C$, 75% yield; **5g**, **9d**, R_1 = H, R_2 = C_2H_5, 69% yield

The same procedure applied to diols bearing an aromatic substituent at both the hydroxyl functionalities (compounds **5c** and **5d**) was not so effective, affording complex reaction mixtures from which the desired dihydroisocoumarins **9a** and **9b** were isolated in poor yields. However, when the oxidation reactions were performed at 0 °C, acidic workup and flash chromatography allowed the clean isolation of the dihydroisocoumarins as well as the recovery of unreacted starting materials. Taking into account the relative amount of recovered diols, compounds **9a** and **9b** were obtained in 56% and 71% isolated yields, respectively. The dihydroisocoumarin **9b** is the methyl ether of the aglycon of (±)-dihydrohomalicine, a naturally occurring glycoside.[10]

Reductive Cleavage of Phthalan 1i. Due to the peculiar reactivity of 1,3-dihydronaphtho[2,3-*c*]furan (**1i**), the results pertaining to the reductive cleavage of this substrate are presented separately.

Depending upon the reaction conditions, reductive cleavage of **1i** afforded, besides the expected 2-(hydroxymethyl)-3-methylnaphthalene (**4i**), variable amounts of 2,3-dimethylnaphthalene (**10**) (eq 10).

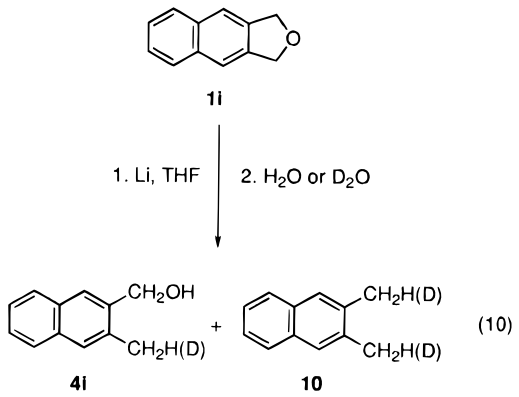
As the reaction run at room temperature led to the formation of some unidentified byproducts, most reactions were carried out at −15 °C; selected results are reported in Table 4.

Reductive cleavage of **1i** in the presence of 2.2 equiv of Li metal and 5 mol % of naphthalene was very sluggish

Table 4. Reductive Cleavage of Compound 1i in THF[a]

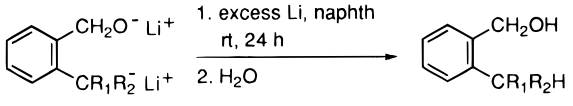
			product (% yield)[b]		product (% D)[c]	
entry	equiv of Li	*t*, h	**4i**	**10**	**4i**	**10**
1	2.2	10	62[e]	5	ND[d]	ND[d]
2	4	4	85[f]	<5	>95	ND[d]
3	6	2	62	38	ND[d]	ND[d]
4	6	6	41	59	ND[d]	ND[d]
5	6	19	37	63	>95	85
6	10	2	35	65	ND[d]	ND[d]
7	10	10		>95		88

[a] All reactions were run at −15 °C in the presence of 5 mol % of naphthalene. [b] Determined by ^{1}H NMR. [c] Determined by ^{1}H NMR, by monitoring the percentage of deuterium incorporation in the arylmethyl position of crude **4i** or **10**; in case of **10**, 100% refers to quantitative mono-deuteriation at both arylmethyl carbon atoms. [d] ND = not determined. [e] 33% of **1i** was also recovered. [f] 11% of **1i** was also recovered.



and led to the formation of the alcohol **4i** as the main reaction product (Table 4, entry 1). An increase in the relative amount of Li metal increased the rate of the first cleavage reaction and led to the formation of significant amounts of the hydrocarbon **10**. Indeed, the hydrocarbon **10** became the main product in the reactions described in Table 4, entries 4−7, which were carried out in the presence of 6−10 equivs of Li metal. A comparison of the distribution of the products obtained at different reaction times shows that **10** formed as the alcohol **4i** disappeared from the reaction mixtures (Table 4, entry 3 *vs* entries 4 and 5, and entry 6 *vs* entry 7). Furthermore, D_2O quenching experiments suggested formation of **10** *via* an intermediate dicarbanion. These observations strongly support formation of **10** *via* two successive reductive cleavage reactions.

From this point of view, the reactivity of the ether **1i** is unique: indeed, under similar conditions, the intermediate carbanions generated in the reductive cleavage of **1a** and **1c** did not undergo further reduction (eq 11).

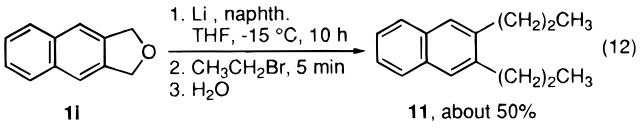


1a, R_1 = R_2 = H; **1c**, R_1 = R_2 = C_6H_5

Formation of a dianion in the reductive cleavage of **4i** with an excess (10 equivs) of Li metal was further confirmed by quenching of the reaction mixture with 2 equiv of ethyl bromide, immediately followed by aqueous workup.

Careful fractional distillation of the complex reaction mixture, although not leading to a pure compound,

(12) For recent syntheses of lactones **9**, see: (a) Kanda, T.; Kato, S.; Sugino, T. , Kambe, N.; Ogawa, A.; Sonoda, N. *Synthesis* **1995**, 1102. (b) Bertelli, L.; Fiaschi, R.; Napolitano, E. *Gazz. Chim. Ital.* **1993**, *123*, 669.



(12)

1i **11**, about 50%

allowed us to ascertain that the main reaction product was 2,3-dipropylnaphthalene (**11**, about 50% yield, as determined by ^{1}H NMR, eq 12); this product was mainly contaminated byproducts of reduction of the naphthalene ring, as evidenced by ^{1}H NMR analysis of the crude mixture.

Discussion

The results obtained in the present work provided further evidence of the versatility of the phthalan system in reductive electron transfer reactions.

From a practical point of view, good results were obtained performing the reactions with an excess of Li metal in the presence of a catalytic amount of naphthalene in THF under mild conditions (from 0 °C to −20 °C). The carbanions generated according to this procedure reacted readily with several electrophiles, leading to the preparation of arylmethyl alcohols bearing various substituents in the ortho position; some of the resulting products were easily transformed into different classes of isochroman derivatives, including potentially biologically active compounds.

Significant results, supporting the mechanistic picture generally accepted for the reductive cleavage of carbon−heteroatom bonds conjugated with an unsaturated system, were also obtained. According to this picture, a first electron transfer from the metal to the substrate generates a π^* radical anion, which transfers the electron to the σ^* orbital of the bond to be broken.The σ^* radical anion thus formed undergoes fragmentation to afford a carbon radical and an anion. The carbon radical is reduced to a carbanion in a subsequent electron transfer step.[1,13−15]

This scheme helps to rationalize the formation of **3**, a dimeric diol formed as a byproduct of the Li-mediated reductive cleavage of **1a**. Indeed, diol **3** likely derives from the coupling reaction of two arylmethyl radicals, generated according to the above picture; this assumption is corroborated by the quantitative reduction of the arylmethyl radical to the corresponding carbanion observed in the reactions performed in the presence of naphthalene; the latter, acting as an homogeneous electron transfer agent, speeds up the second electron transfer step and avoids radical recombination.[9,16]

Also the regioselectivity observed in the reductive cleavage of the 1-substituted phthalans **1b**−**f** deserves some comments. Our results show that the most stable carbanions are the exclusive (from **1b** and **1c**) or main (from **1d**−**f**) final intermediates of our reactions. From this point of view, while the results obtained for the aryl-substituted phthalans **1b** and **1c** are straightforward,[17] there is an apparent discrepancy in the results observed in the case of the alkyl-substituted ethers **1d**−**f**; indeed, the alkyl-substituted derivatives form the most stable carbanions *via* the intermediate formation of the least stable carbon radicals.

Interestingly, our results are in perfect agreement with the results reported by Bartmann,[18] and by Cohen *et al.*,[13,19,20] on the reductive lithiation of alkyl-substituted oxiranes and oxetanes. These results were rationalized by Cohen *et al.* which, on the basis of theoretical calculations, proposed that the greater stability of the more-branched oxyanion, relative to the less-branched one, outweighs the lesser stability of the less substituted carbon radical, relative to the more substituted one.[13]

It is also interesting to observe that substitution at the arylmethyl position does not affect the reductive cleavage reaction of the mono- and disubstituted phthalans **1b**−**f** and **1h**; at variance with these results, the spirocyclohexyl derivative **1g** is almost unreactive. As a possible rationalization of this result, we can assume that the conformational equilibrium of the sterically hindered spirocyclohexyl derivative affects the ease of the intramolecular electron transfer from the π^* radical anion to the σ^* orbital of the breaking bond. Although bending vibrations of the breaking bond usually overcome the orbital simmetry restrictions to this intramolecular electron transfer step,[21] the low reactivity of 1-spirocyclohexyl phthalan recalls the lowering in the cleavage rate which has been observed for the radical anions of some sterically hindered arylmethyl halides.[21,22]

A final interesting result was obtained in the reactions of the naphthalene derivative **1i**. Indeed, at variance with what observed for the analogous benzene derivatives,[23] **1i** underwent a double reductive cleavage with formation of a dicarbanion. This is probably due to the ease with which naphthalene derivatives undergo formation of π^* radical anions, in spite of the presence of a negative charge in the arylmethyl position.

Experimental Section

General Procedures. Boiling and melting points are uncorrected; the air bath temperatures recorded on bulb-to-bulb distillation are given as boiling points. Starting materials were of the highest commercial quality and were further purified by distillation or recrystallization. Deuterium oxide was 99.8% isotopic purity. Solvents were distilled from Na under N_2 immediately prior to use. Compounds **1b**[6], **1g**[7], and **1i**[8] were prepared according to literature procedures. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR at 75 MHz in $CDCl_3$ (unless otherwise indicated) with $SiMe_4$ as internal standard. Deuterium incorporation was calculated by monitoring the ^{1}H NMR spectra of the products of reductive cleavage reactions and comparing the integration of the signal corresponding to the proton(s) in the arylmethyl position with the integrals of the ArCHRO protons. IR spectra were recorded in CCl_4 solution, unless otherwise indicated. Elemental analyses were performed by the Microanalytical Laboratory of the Dipartimento di Chimica, Università di Sassari.

Preparation of 1,1-Disubstituted Phthalans 1c and 1f. A solution of phthalide (8 g, 60 mmol) in 40 mL of dry THF

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(17) In the case of the aryl-substituted phthalans **1b** and **1c**, the possibility that the first electron transfer could involve the π^* orbitals of the substituent(s) must also be taken into account.[18]
(18) Bartmann, E. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 653.
(19) Mudryk, B.; Cohen, T. *J. Org. Chem.* **1989**, *54*, 5657.
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(21) Adcock, W.; Andrieux, C. P.; Clark, C. I.; Neudeck, A.; Savéant, J.-M.; Tardy, C. *J. Am. Chem. Soc.* **1995**, *117*, 8285.
(22) Norris, R. K.; Barker, S. D.; Neta, P. *J. Am. Chem. Soc.* **1984**, *106*, 3140.
(23) A stepwise, one-pot, double reductive cleavage of phthalan, **1a**, was reported by Yus *et al.*[5] In that case, however, quenching of the first intermediate dianion is needed to generate an arylmethyl alkoxide which underwent further reduction.

was added dropwise to a well stirred suspension of the appropriate Grignard reagent (from 4 g, 165 mmol, of Mg and 150 mmol of CH_3I or C_6H_5Br) in 50 mL of Et_2O under N_2. The mixture was stirred at rt for 12 h and then chilled to 0 °C. Saturated aqueous NH_4Cl was added dropwise until a white precipitate formed. The mixture was filtered, the precipitate washed with Et_2O (3 × 20 mL), the organic phase washed with saturated NH_4Cl and dried (Na_2SO_4), and the solvent evaporated. The crude product was suspended in 60 mL of 50% H_3PO_4 and the mixture stirred at reflux temperature under N_2 for 4 h. The mixture was chilled to rt and extracted with Et_2O (3 × 20 mL). The collected organic fractions were washed with H_2O (50 mL) and saturated $NaHCO_3$ (50 mL), and dried (Na_2SO_4). Evaporation of the solvent and vacuum distillation afforded the pure products, which were characterized as follows.

1,1-Diphenylphthalan (1c). Isolated in 91% yield by recrystallization from EtOH, mp 95−97 °C; ^{1}H NMR δ 5.18 (s, 2H), 7.20−7.37 (m, 14H); ^{13}C NMR δ 71.45, 93.01, 121.07, 123.84, 127.21, 127.33, 127.64, 127.96, 139.57, 144.10, 144.61; ^{1}H and ^{13}C NMR in perfect agreement with the literature.[24]

Preparation of 1-Substituted Phthalans 1d and 1e. A solution of **1a** (2 g, 16.5 mmol) in 30 mL of THF was chilled to −40 °C under dry N_2. To this mixture, 14 mL (1.1 equiv) of a 1.3 M solution of *sec*-BuLi in cyclohexane was added dropwise, and the mixture was stirred for 2 h, before adding to it 1.2 equiv of the appropriate alkyl halide dissolved in 2 mL of THF. After 1 h stirring, the reaction was quenched by slow dropwise addition of H_2O (10 mL) (*caution!*), the cold bath removed, and the resulting mixture extracted with Et_2O (3 × 30 mL). The organic fractions were collected, washed with H_2O (30 mL), and dried ($CaCl_2$), and the solvent was evaporated. Crude products were purified by fractional distillation and were characterized as follows.

1-Methylphthalan (1d). Bp 80 °C/20 mmHg (lit.[6] 94−95 °C/25 mmHg); ^{1}H NMR δ 1.50 (d, J = 6.3, 3H), 4.98−5.08 (m, 1H), 5.13 (dd, J = 12.3, J = 2.4, 1H), 5.26−5.38 (m, 1H), 7.10−7.30 (m, 4H).

General Procedure for the Reductive Cleavage of Compounds 1. Li metal (42 mg atom, 0.96 g of a 30% wt. dispersion in mineral oil, 5 equiv)[26] was placed under Ar in a two-necked flask equipped with reflux condenser and magnetic stirrer, washed with THF (3 × 10 mL), and suspended in 30 mL of THF. In some cases, 30 mg (0.2 mmol) of naphthalene were added to the suspension of the metal, and the mixture was stirred until a dark green color appeared. The mixture was chilled to the temperature reported in Table 1 or 2, and a solution of the appropriate substrate (8 mmol) in 5 mL of THF was added. After stirring for the reported time, the reaction was quenched by slow dropwise addition of H_2O (10 mL, *caution!*), and the resulting mixture was extracted with Et_2O (3 × 30 mL). The organic phase was dried (Na_2SO_4) and the solvent evaporated. D_2O-quenching was performed as described in ref 14. Crude products were characterized as follows.

(2-Methylphenyl)methanol (2). Bp 120 °C/20 mmHg (lit.[7] 115 °C/20 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (br s, 1H), 2.36 (s, 3H), 4.69 (s, 2H), 7.10−7.30 (m, 3H), 7.30−7.40 (m, 1H); IR 3613, 3367 cm^{-1}.

1,2-Bis[2-(hydroxymethyl)phenyl]ethane (3). Mp 151−152 °C (acetone); ^{1}H NMR δ 2.05 (br s, 1H), 3.02 (s, 4H), 4.64 (s, 4H), 7.15−7.40 (m, 8H); ^{13}C NMR (DMSO-d_6) δ 33.38 (t), 60.87 (t), 125.80 (d), 126.93 (d), 127.53 (d), 128.95 (d), 139.35 (s), 139.78 (s); IR (KBr) 3333, 3244 cm^{-1}. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.29; H,7.51. Found: C, 79.11; H, 7.38.

[2-(Hydroxymethyl)phenyl]phenylmethane (4b). Bp 155 °C/1 mmHg (lit.[27] bp 147−148 °C/1 mmHg); ^{1}H NMR δ 1.80 (br s, 1H), 4.04 (s, 2H), 4.58 (s, 2H), 7.07−7.30 (m, 8H), 7.33−7.40 (m, 1H); IR 3612, 3459 cm^{-1}.

General Procedure for the Reductive Electrophilic Substitution of Compounds 1. The appropriate substrate was reduced according to the general procedure reported above in the presence of a catalytic amount of naphthalene, and the reaction mixture was chilled to the temperature reported in Table 3. The appropriate amount of electrophile dissolved in THF (5 mL) was slowly added, and the mixture was stirred for the reported time. Crude products were purified and characterized as follows.

[2-(Hydroxymethyl)phenyl]ethane (4da). Purified by flash chromatography (AcOEt/hexane = 3:7); bp 150 °C/20 mmHg (lit.[29] bp 229 °C/760 mmHg); ^{1}H NMR δ 1.24 (t, J = 7.5 Hz, 3H), 1.59 (br s, 1H), 2.72 (q, J = 7.5 Hz, 2H), 4.73 (s, 2H), 7.17−7.31 (m, 3H), 7.37 (d, J = 7.5 Hz, 1H); ^{13}C NMR δ 15.34, 25.16, 63.12, 126.03, 128.02, 128.07, 128.59, 138.02, 142.22; IR 3612, 3458 cm^{-1}.

1-[2-(Hydroxymethyl)phenyl]-1-phenylpentane (5i). Purified by flash chromatography (AcOEt/hexane = 3:7); bp 190 °C/1 mmHg; ^{1}H NMR δ 0.86 (t, J = 6.9 Hz, 3H), 1.30−1.45 (m, 4H), 1.57 (br s, 1H), 2.02 (q, J = 7.8 Hz, 2H), 4.25 (t, J = 7.5 Hz, 1H), 4.66 (dd, J = 12.9 Hz, J = 5.1 Hz, 1H), 4.72 (dd, J = 12.9 Hz, J = 6.3 Hz, 1H), 7.12−7.37 (m, 8H), 7.40−7.45 (m, 1H); ^{13}C NMR δ 13.97, 22.75, 30.22, 36.18, 45.87, 63.19, 126.01, 126.29, 127.15, 127.97, 127.99, 128.38, 128.54, 138.49, 142.79, 145.06; IR 3611 cm^{-1}. Anal. Calcd for $C_{18}H_{22}O$: C, 84.98; H, 8.73. Found: C, 84.87; H, 8.91.

General Procedure for the Synthesis of Substituted Isochroman-3-ones 6. The appropriate substrate was reduced according to the general procedure reported above in the presence of a catalytic amount of naphthalene, and the reaction mixture was stirred for the reported time. Gaseous CO_2 was bubbled for 5 min into the reaction mixture chilled to −40 °C. The reaction mixture was quenched by slow dropwise addition of H_2O (10 mL, *caution!*), acidified with concd HCl, and worked up as reported above. Crude products were purified and characterized as follows.

Isochroman-3-one (6a). Purified by flash chromatography (AcOEt/hexane = 1:1); mp 80−81 °C (CH_3OH/H_2O) (lit.[38] mp 82−83 °C, benzene) ^{1}H NMR δ 3.72 (s, 2H), 5.32 (s, 2H), 7.18−7.39 (m, 4H); IR (KBr) 1745 cm^{-1}.

General Procedure for the Synthesis of 3-Substituted-Isochromans 7. The substrate (1 mmol) was dissolved in a minimum amount of THF and the solution added under N_2 to 30 mL of a vigorously stirred 50% aqueous solution of H_3PO_4. The mixture was stirred at reflux temperature overnight. After cooling to rt, the mixture was extracted with Et_2O (3 × 10 mL), and the organic phase was washed with saturated $NaHCO_3$ (20 mL), H_2O (20 mL), and dried ($CaCl_2$). The solvent was evaporated, and the crude products were purified and characterized as follows.

3-Phenylisochroman (7a). Purified by recrystallization, mp 74−75 °C (EtOH) (lit.[37] 76−77 °C, EtOH); ^{1}H NMR δ 2.96 (dd, J = 16.3 Hz, J = 3.6 Hz, 1H), 3.08 (dd, J = 16.3 Hz, J = 10.8 Hz, 1H), 4.72 (dd, J = 10.8 Hz, J = 3.6 Hz, 1H), 5.00 (s, 2H), 6.98−7.52 (m, 9H); ^{13}C NMR δ 36.08, 68.70, 76.84, 124.19, 125.87, 126.17, 126.46, 127.67, 128.46, 128.77, 133.48, 134.51, 142.11.

General Procedure for the Synthesis of Dihydroisocoumarins 9. The substrate (1 mmol) was added to a solution of $KMnO_4$ (320 mg, 2 mmol) dissolved in 30 mL of H_2O and

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the mixture stirred (compounds **5e** and **5g**: rt, 24 h; compounds **5c** and **5d**: 0 °C, 30 h). The mixture was filtered, acidified with concentrated H_2SO_4, and extracted with CH_2Cl_2 (4 × 20 mL). The organic phase was dried ($CaCl_2$) and the solvent evaporated. The crude products were purified and characterized as follows.

3-Phenyldihydroisocoumarin (9a). Purified by flash chromatography (AcOEt/hexane = 1:1); mp 87−88 °C (2-propanol) (lit.[39] mp 88−90 °C, 2-propanol); ^{1}H NMR δ 3.13 (dd, J = 16.5 Hz, J =3.3 Hz, 1H), 3.34 (dd, J = 16.5 Hz, J =12.0 Hz, 1H), 5.56 (dd, J = 12.0 Hz, J =3.3 Hz, 1H), 7.26−7.32 (m, 1H), 7.32−7.52 (m, 6H), 7.58 (td, J = 7.5 Hz, J = 1.2 Hz, 1H), 8.12−8.19 (m, 1H); ^{13}C NMR δ 35.50, 79.88, 125.03, 126.04, 127.30, 127.79, 128.57, 128.60, 130.32, 133.86, 138.47, 138.87, 165.25; IR 1737 cm^{-1}.

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Supporting Information Available: Characterization (^{1}H and ^{13}C NMR, IR, bp's or mp's, literature references, or analytical data) of compounds **1e**, **1f**, **4c**, **4ea**, and **4fa**, **4db**−**4fb**, **4h**, **4i**, **5a**−**5h**, **5j**, **6b**−**e**, **7b**−**d**, **8**, **9b**−**d**, **10**, and **11** (7 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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