

Regiochemistry in the reductive opening of phthalan derivatives

Francisco Foubelo,* Daniel García, Benjamín Moreno and Miguel Yus*

Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

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Dedicated to Professor Vicente Gotor on the occasion of his 60th birthday

Abstract—The lithiation of phthalan derivatives **4**, **9** and **12** with an excess of lithium in the presence of a catalytic amount of 4,4'-*tert*-butylbiphenyl (DTBB) in THF at $-78\text{ }^{\circ}\text{C}$ gives dianionic intermediates **5**, **10** and **13**, respectively, which by reaction with different electrophiles [H_2O , *t*-BuCHO, Me_2CO , $(\text{EtO})_2\text{CO}$] at the same temperature, followed by hydrolysis, leads to regioselective functionalised naphthalenes **7**, and biphenyls **11** and **14**. The reductive opening takes place with high or total regioselectivity and can be explained considering the electron density in the dianion or in the radical anion, which are formed previous to the carbon–oxygen bond excision. The lithiation of the dihydrofurophthalan derivative **18** with the same reaction mixture but at higher temperature ($0\text{ }^{\circ}\text{C}$) leads to intermediates **19** and **20**, resulting from a single and a double reductive cleavage, respectively, which after addition of H_2O and benzaldehyde as electrophiles gives a mixture of compounds **21** and **22**.

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Functionalised organolithium¹ compounds can be achieved following classical procedures (i.e. halogen–lithium exchange or tin–lithium transmetallation)² or, in some cases, through new methodologies, among them the reductive opening of different appropriate oxygen-, nitrogen- and sulfur-containing heterocycles.³ The interest of functionalised organolithium compounds lies in their applicability in organic synthesis, due to the fact that by reaction with electrophiles, polyfunctionalised molecules are obtained in a single synthetic operation. Lithium metal itself or in the presence of a stoichiometric or catalytic amount of an arene [naphthalene, 4, 4'-*di-tert*-butylbiphenyl (DTBB), biphenyl, 1-(*N,N*-dimethylamino)naphthalene being the most commonly used] have been used as the lithiating reagents in the reductive opening of heterocycles.³ Only small heterocycles (three and four membered-rings), which are prone to release the strain energy, and heterocycles with activated bonds can undergo a reductive opening lithiation. For instance, benzylic carbon–oxygen bonds are susceptible to suffering reductive cleavage by means of a lithiating reagent to generate benzylic organolithium compounds.

Keywords: Reductive ring opening; Phthalans; DTBB-catalysed lithiation; Electrophilic substitution; Substituted naphthalenes; Substituted biphenyls.

* Corresponding authors. Fax: +34 965 903549 (F.F.); e-mail addresses: foubelo@ua.es; yus@ua.es

Phthalan (**1a**, $\text{R}^1 = \text{R}^2 = \text{H}$) is a special kind of cyclic benzyl ether and is opened reductively with an excess of lithium in the presence of a substoichiometric amount of DTBB⁴ or naphthalene⁵ to give the dianionic intermediate **2a** (in this case it is the same as **3a**, $\text{R}^1 = \text{R}^2 = \text{H}$), which has shown a wide use in organic synthesis. For instance, the reaction of **2a** with keto derivatives of some protected monosaccharides (glucose and fructose),⁶ as well as steroids (estrone and cholestanone)⁷ gives the expected selectively functionalised natural products. Intermediate **2a** has also been transformed into the corresponding functionalised organozinc derivative by a lithium–zinc transmetallation process with zinc bromide, and its reaction with allylic bromides,⁸ aryl halides in the presence of palladium,^{9,10} electrophilic olefins^{11,12} and acylating reagents was studied. Azzena and co-workers also studied the regiochemistry of the reductive opening of several substituted phthalans **1b–g** and the synthetic usefulness of the resulting intermediates. They observed that the most stable carbanions are the exclusive (**2b** and **2c**) or main (**3d–f**) intermediates of these processes,¹³ in spite of that the most stable carbanions **3d–f** are formed via the less stable carbon radicals. This behaviour has been explained on the basis of theoretical calculations considering that the greater stability of the more-branched oxyanion outweighs the lesser stability of the less substituted carbon radical.¹⁴ With these antecedents, we considered that it would be of interest to

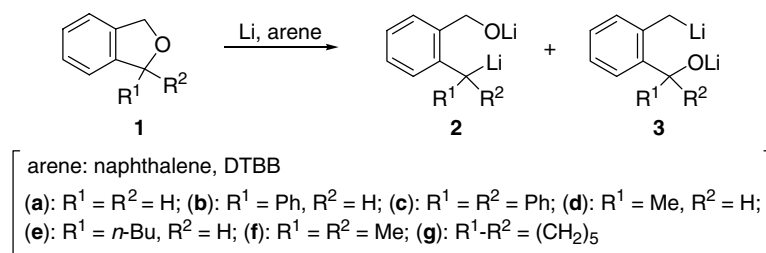
study the regiochemistry of the reductive opening of different nonsymmetrical phthalan derivatives **4**, **9** and **12** by an arene-catalysed lithiation in order to know how the aromatic moiety of these compounds affects the process **Scheme 1**.

Starting material **4** was prepared from commercially available 1,2-dimethylnaphthalene in only two steps and in 49% overall yield: first, radical benzylic bromination with *N*-bromosuccinimide in the presence of AIBN¹⁵ gave 1,2-bis(bromomethyl)naphthalene and finally, double nucleophilic substitution by treatment with a 5 M NaOH aqueous solution in dioxane in the presence of 2,6-lutidine¹⁶ afforded the 1,3-dihydronaphtho[1,2-*c*]furan (**4**). The reaction of benzophthalan **4** with an excess of lithium (1/10 molar ratio) in the presence of a catalytic amount of DTBB (5 mol%) in THF at temperatures ranging from -78 to -50 °C for 3 h, followed by addition of different electrophiles [H_2O , *t*-BuCHO, Me_2CO , $(\text{EtO})_2\text{CO}$] at -78 °C and final hydrolysis, led to a mixture of functionalised alcohols **7** and **8** (**Scheme 2** and **Table 1**). A 6:1 mixture (based on the study of the ^1H NMR spectrum of the crude product) of alcohols **7a** and **8a** was obtained when H_2O was used as electrophile (**Table 1**, entry 1). The structure of the reaction products was unambiguously determined by comparison of the ^1H and ^{13}C NMR spectra of 1-hydroxymethyl-2-methylnaphthalene (**8a**) (prepared from commercially available 1-chloromethyl-2-methylnaphthalene after treatment with tetrabutylammonium hydroxide in quantitative yield) with those corresponding to the minor isomer, both being identical. Two reductive cleavages in the starting heterocycle **4** can occur under these reaction conditions: the major one leads to intermediate **5** and the minor one to intermediate **6** through the two possible benzylic carbon–oxygen bond cleavages. Diols **7b,c** and lactone **7d** derived from intermediate **5** were the only reaction products isolated and characterised when *t*-BuCHO, Me_2CO and $(\text{EtO})_2\text{CO}$

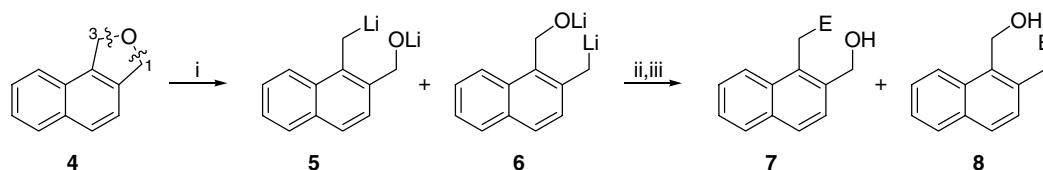
were, respectively, used as electrophiles (**Table 1**, entries 2–4).

Phenyl substituted phthalans **9** and **12** were prepared following different methodologies. Thus, 5-phenylphthalan (**9**) was obtained in a one-pot process from commercially available phenyl acetylene and dipropargyl ether through a cycloaromatization mediated by the Wilkinson catalyst in 60% yield.¹⁷ On the other hand, 4-phenylphthalan (**12**) was prepared from 3-bromo-*o*-xylene in a three-step process: first, radical benzylic bromination with *N*-bromosuccinimide in the presence of AIBN¹⁵ [to give 3-bromo-1,2-bis(bromomethyl)benzene], followed by double nucleophilic substitution by treatment with tetrabutylammonium hydroxide in dioxane and finally palladium catalysed coupling of the resulting 4-bromophthalan with benzenboronic acid in 25% overall yield. The reaction of phenylphthalans **9** and **12** with an excess of lithium (1/10 molar ratio) in the presence of a catalytic amount of DTBB (5 mol%)¹⁸ in THF at -78 °C for 3 h, followed by addition of H_2O and pivaldehyde as electrophiles at -78 °C and final hydrolysis, led to regioselective functionalised biphenyls **11** and **14**, respectively (**Scheme 3**, **Table 1**, entries 5–7). The structure of these compounds was elucidated based on NOESY experiments. In the case of 5-phenylphthalan (**9**) the reductive cleavage takes place at C(1)–O benzylic bond leading to intermediate **10**, meanwhile, the reductive cleavage in 4-phenylphthalan (**12**) occurs at C(3)–O benzylic carbon–oxygen bond giving the dianionic intermediate **13** (**Scheme 3**).

The experimental results obtained in the reductive cleavage of phthalan derivatives **4**, **9** and **12** can be rationalised by considering the electron density in the aromatic systems of the resulting anionic intermediates through a single electron-transfer (SET) from the reducing reagent to the substrate. The reductive cleavage at the benzylic carbon–oxygen bond takes place at the

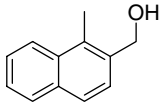
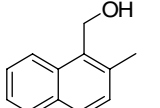
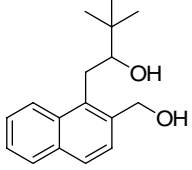
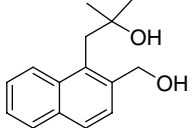
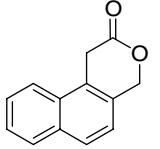
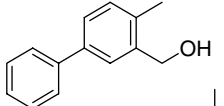
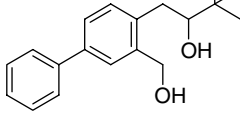
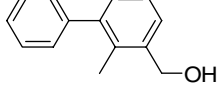
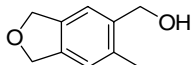
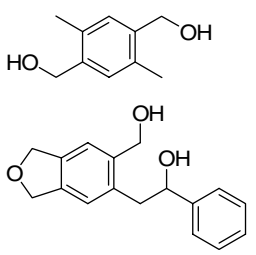
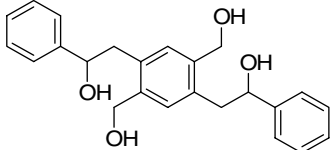


Scheme 1.



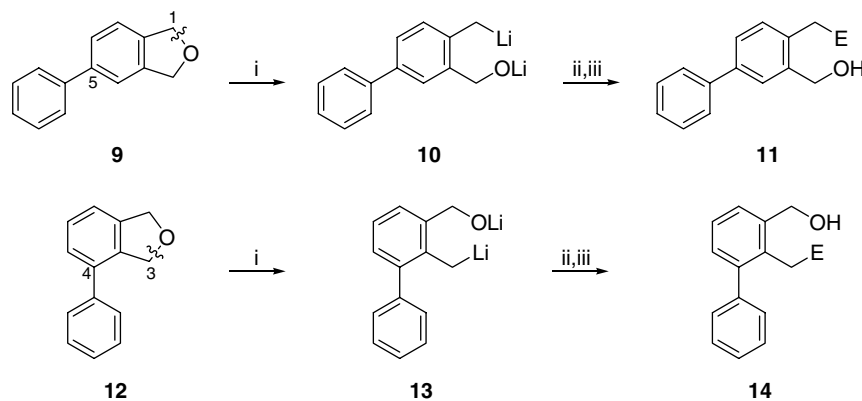
Scheme 2. Reagents and conditions: (i) Li, DTBB (5 mol%), THF, -78 to -50 °C, 3 h; (ii) $\text{E}^+ = \text{H}_2\text{O}$, *t*-BuCHO, Me_2CO , $(\text{EtO})_2\text{CO}$, -78 °C, 15 min; and (iii) H_2O -78 to 20 °C.

Table 1. Preparation of compounds **7**, **8**, **11**, **14**, **21** and **22**

Entry	Starting material	E ⁺	Product ^a		
			No.	Structure	Yield (%) ^b
1	4	H ₂ O	7a		85
			8a		14
2	4	<i>t</i> -BuCHO	7b		61
3	4	Me ₂ CO	7c		50
4	4	(EtO) ₂ CO	7d		42
5	9	H ₂ O	11a		75
6	9	<i>t</i> -BuCHO	11b		60
7	12	H ₂ O	14a		77
8	18	H ₂ O	21a		42
			21b		21
9	18	PhCHO	22b		9

^a Products **7**, **8**, **11**, **14**, **21** and **22** were $\geq 95\%$ pure (GLC and 300 MHz ¹H NMR) and were fully characterised by spectroscopic means (IR, ¹H, and ¹³C NMR and LRMS/HRMS).

^b Yield based on the corresponding starting material.



Scheme 3. Reagents and conditions: (i) Li, DTBB (5 mol%), THF, $-78\text{ }^{\circ}\text{C}$, 3 h; (ii) $\text{E}^+ = \text{H}_2\text{O}$, $t\text{-BuCHO}$, $-78\text{ }^{\circ}\text{C}$, 30 min; and (iii) H_2O -78 to $20\text{ }^{\circ}\text{C}$.

position bonded to the carbon of the aromatic ring with the higher electron density in the intermediate anion radical (one electron transfer) or dianion (two electron transfer).¹⁹ The semiempirical PM3 calculation of the Mulliken charge of dianions **15**–**17** (Chart 1) resulting from a two-electron transfer to compounds **4**, **9** and **12**, respectively, are shown in Chart 1. The reductive cleavage in dianion **15** occurs predominantly at C(3) (attached to the aromatic carbon atom with the highest electron density: -0.475) instead of at C(1) (in this case: -0.284) to yield an alkoxide (see **15'**), which, after aromatization, gives dianionic intermediate **5** (Scheme 2). In dianion **16** [resulting from 5-phenylphthalan (**9**)], the reductive cleavage occurs exclusively at C(1) (attached to the aromatic carbon atom with the highest electron density: -0.606) instead of at C(3) (in this case: -0.054) to give intermediate **10** (see **16'** and Scheme 3). Finally, in dianion **17** [resulting from 4-phenylphthalan (**12**)], the reductive cleavage takes place at C(3) (attached to the aromatic carbon atom with the highest electron density: -0.449) [in the case of C(1): -0.032] of the biphenyl moiety leading to alcoholate **13** (see **17'** and Scheme 3). The semiempirical calculated (PM3) electron density of the corresponding radical anions resulting from the transfer of one electron to phthalan derivatives **4**, **9** and **12** are shown in parenthesis in Chart 1: the calculated values are in concordance with

those for the corresponding dianions **15**–**17**. So, taking into account the electron density both in the dianion and in the radical anion (which are in agreement), it is possible to explain the regiochemistry of the reductive opening lithiation of phthalan derivatives **4**, **9** and **12**.

In order to continue our study on the reductive opening of phthalan derivatives, dihydrofurophthalan **18** was prepared starting from commercially available 1,2,4,5-tetrakis(bromomethyl)benzene in 30% yield through a double nucleophilic substitution after treatment with tetrabutylammonium hydroxide in dioxane. The reaction of dehydrofurophthalan **18** with an excess of lithium (1/10 molar ratio) in the presence of a catalytic amount of DTBB (2.5 mol%) in THF at $-78\text{ }^{\circ}\text{C}$ for 30 min and then for 2 h at $0\text{ }^{\circ}\text{C}$, followed by addition of H_2O and benzaldehyde as electrophiles at $-78\text{ }^{\circ}\text{C}$ and final hydrolysis, led to a mixture of functionalised alcohols **21** and diols **22** (Scheme 4, Table 1, entries 8 and 9). According to these results, intermediates **19** and **20** are involved in this process. Thus, after reductive cleavage of compound **18** (the four benzylic carbon–oxygen bonds are equivalent), dianion **19** is formed and undergoes a second and selective reductive cleavage, at $0\text{ }^{\circ}\text{C}$ in the highly reductive reaction medium, leading to dialkoxide **20**. When the reaction is performed for longer reaction time or at higher temperatures in order

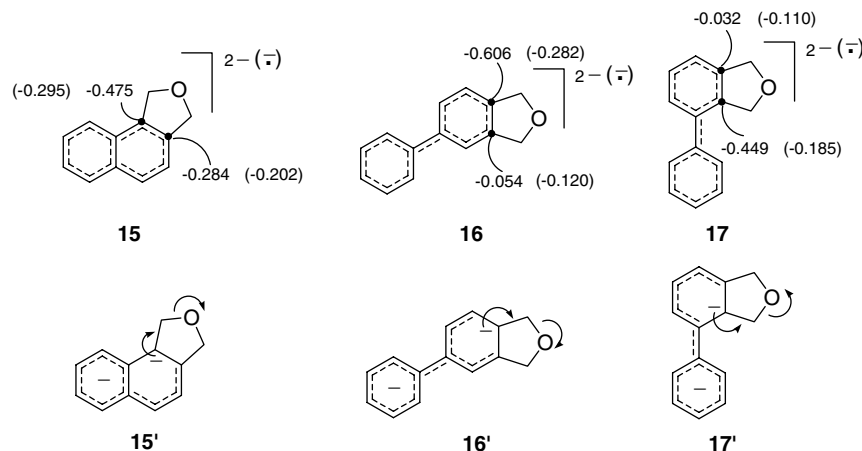
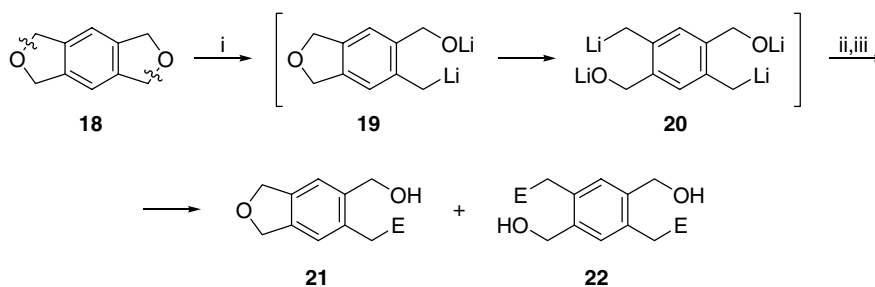


Chart 1.



Scheme 4. Reagents and conditions: (i) Li, DTBB (2.5 mol%), THF, $-78\text{ }^{\circ}\text{C}$, 30 min, then $0\text{ }^{\circ}\text{C}$, 2 h; (ii) $\text{E}^+ = \text{H}_2\text{O}$, PhCHO, $-78\text{ }^{\circ}\text{C}$, 30 min; and (iii) H_2O , -78 to $20\text{ }^{\circ}\text{C}$.

to complete the transformation of intermediate **19** into **20**, yields become significantly lower and variable amounts of 1,2,4,5-trimethylbenzene are detected by GC/MS (Scheme 4).

In conclusion, we report here that the reductive opening of different phthalan derivatives **4**, **9** and **12** with an excess of lithium in the presence of a catalytic amount of DTBB at different temperatures takes place in a regioselectivity fashion. The regiochemistry of the process can be explained taking into account the electron density of either the dianion or the radical anion, which undergoes the reductive cleavage. The reaction of the resulting intermediates with electrophiles allows the preparation of regioselectively functionalised naphthalene and biphenyl derivatives **7**, **11** and **14**.

Acknowledgements

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