HOMOLOGATION OF HETEROCYCLES BY A SEQUENTIAL REDUCTIVE OPENING LITHIATION – S_E – CYCLIZATION

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I. Introduction

The development of new methodologies for the conversion of simple reactants into more complex compounds is the main goal of synthetic organic chemistry (99MI1). For instance, transforming readily available small heterocycles into much less common medium-sized rings would be of great interest, because many biological active compounds possess medium-sized heterocyclic units in their structure (91MI2). Thus, synthetic approaches to heterocyclic compounds require the development of methodology for easily repeatable heterocycle homologation and multicarbon ring expansion.

I.A. Methods for homologation of heterocycles

Many methodologies have been developed for the ring expansion of heterocycles involving different reaction intermediates such as carbenes, nitrenes, radicals and a large

The reaction of epoxides (**1**) with trimethylsulfoxonium ylide leads to oxetanes (**2**) in high yields through a nucleophilic ring opening followed by intramolecular dimethylsulfoxide elimination (Eq. (1)) (83JOC5133). This is probably the simplest homologation reaction of a three-membered heterocycle.

SCHEME 1

The reaction of sodium azide with chloromethyl heterocycles (8) derived from morpholine, thiazine, piperazine and piperidine gave the ring-expanded compounds (11) along with the normally substituted compounds (10) *via* the postulated aziridinium intermediate (9) (Scheme 2) (94JCS(P1)2565).

SCHEME 2

Palladium(0)-catalyzed one-atom ring expansion of various hydroxyl methoxyallenylisoindolinones (12) proceeded in the presence of aryl and vinyl halides to give the corresponding isoquinolinediones (13) in various yields (Eq. (3)). Tandem intramolecular carbo-palladation-heterocyclic ring expansion reaction of compound (12) was also achieved to give a tetracyclic compound. (02SL480, 98TL8677).

The treatment of phenylselenomethyl nitrogen-, oxygen and sulphur-containing heterocyclic β -keto esters with tri-*n*-butyltin hydride leads to smooth one-carbon ring expansion through the corresponding radical intermediate. Thus, in the case of piperidine β -ketoester derivative (**14**), the expected azetidine (**15**) was obtained in 15% yield along with the undesired direct reduction product (**16**) in 26% yield (Eq. (4)) (91T4847).

Copper catalysts promote the ring expansion of oxetanes (**2**) to tetrahydrofurans (**17**) by reacting with diazocarbonyl compounds. The stereochemistry of these processes can be controlled by performing the reactions in the presence of chiral ligands. For this purpose, C_2 -symmetric bipyridine (96T3905) as well as bisazaferrocene ligands have been used (Eq. (5)) (01T2621).

Carbenes, generated from thermolysis of α -oxacyclo- and α -azacyclo-*N*-aziridinylimines in refluxing toluene, underwent also ring expansion via insertion of alkyl carbenes into carbon-carbon bonds and intramolecular ammonium ylide formations, respectively. Ring expansion reaction of α -oxetanyl-*N*-aziridinylimines occurred via alkylidenecarbene intermediates, whereas thermal reaction of α -azetidiny-*N*-aziridinylimines afforded α -aminoacetylene compounds via 1,2-H migration of alkylidenecarbene intermediates (00S1622). Fischer carbene complexes react with some 1,2-dithiole-3-thiones to

give cyclohexadithiine derivatives by insertion of the carbene ligand into the C3-C4 bond of the heterocycle (02TL8037).

The introduction of a carbonyl moiety into an organic molecule using carbon monoxide requires the presence of transition metal complex functioning as a catalyst or as a stoichiometric reactant. The insertion of carbon monoxide into a carbon-heteroatom bond of a heterocyclic compound comprises a simultaneous ring expansion and functionalization of a heterocyclic substrate. The carbonylation reaction provides a very convenient and effective one-step procedure for ring homologation (95ACR414).

The ring expansion of heterocycles can be performed to produce new heterocycles with two (bishomologation), three or even more carbons or heteroatoms in the ring unit. Thus, the palladium-catalyzed ring-opening cycloaddition reactions of vinyloxiranes (97JA3709, 98JOC6229), vinyloxetanes (99JOC4152), vinylaziridines (00JOC5887) and 2-vinylthiiranes (01JOC3502) with heterocumulenes leads to the regio- and stereoselective formation of five- and six-membered heterocycles (Eq. (6)).

A three carbon ring expansion of α -vinyltetrahydrothiophene and 2-vinyl-*N*-benzylpyrrolidine was accomplished by conversion to these heterocycles into the corresponding ylides by alkylation followed by deprotonation which underwent a [2,3]sigmatropic shift, the corresponding eight-membered heterocycles being obtained in this way (78JOC1185).

I.A. Reductive opening of heterocycles as a source of functionalized organolithium compounds

Functionalized organolithium compounds (91MI3, 95OPP383, 97MI4, 03T9255, 04CRV2667) are of great interest in organic synthesis because polyfunctionalized molecules are obtained in a single synthetic operation by reaction with electrophilic reagents.(95MI5, 02MI6) Functionalized organolithium compounds can be prepared by halogen-lithium exchange, metal-lithium exchange, direct deprotonation, addition of organolithium compounds to unsaturated systems, and also by reductive opening of different appropriate oxygen-, nitrogen- and sulfur-containing heterocycles (97RHA73, 02MI7). The last methodology being probably the most elegant and direct strategy considering atom economy as well. Since most functionalized organolithium compounds are very unstable molecules, they have to be prepared at low temperature in order to avoid their decomposition. For that purpose, in the last few years a methodology consisting in the use of an excess of lithium in the presence of a catalytic amount of an arene has been developed as lithiating agent, naphthalene and 4,4'-di-*tert*-butylbiphenyl (DTBB) being the most commonly used (96CSR155, 00EJO225, 01SL1197). Some requirements should be accomplished in order to get the reductive opening of a heterocycle: (a) Small heterocycles (three and four membered-rings) due to a release of strain energy and (b) heterocycles with activated bonds that can be reductively broken by means of the lithiating reagent, as in the case of compounds with allylic (98JA2534, 98TL3303, 00T1745, 00TL1661) and benzylic (95TL5641, 97MI8, 97T16205) carbon-heteroatom bonds as well as cyclic aryl ethers (87AGE972, 89JA8640, 00JOC322, 90JOC5386, 92JOC1444) and thioethers (78JOC1064, 79JOC713, 89ACR152).

Specically interesting is the reaction of functionalized organolithium compounds resulting from the reductive opening of heterocycles with a carbonyl compound because, after

hydrolysis, functionalized alcohols are obtained. These polyfunctionalized molecules can undergo intramolecular dehydration to afford a new regioselectively substituted heterocycle which is homologous of the starting heterocycle (Scheme (3)). A compilation of most of the heterocycle homologation processes which have been reported in the literature by the tandem reductive opening lithiation - electrophilic substitution by reaction with a carbonyl compound - dehydration, follows.

SCHEME 3

II. Homologation of four-membered heterocycles

II.A. Oxetanes

Cohen and Mudryk reported for the first time in 1989 on the reductive opening of oxetanes (89JOC5657). Thus, treatment of oxetanes **2** with lithium and a stoichiometric amount of DTBB in THF at 0 °C gave dianionic species **18**, which by reaction with electrophiles and final hydrolysis yielded functionalized alcohols **19** (Scheme (4)). Regarding the regiochemistry of the process for unsymmetrical substituted oxetanes, reductive opening takes place always to give the most stable organolithium compound **18**, which are the less substituted except in the case of the benzyl derivative (**18d**) (Scheme (4)).

SCHEME 4

When reductive opening of unsymmetrical oxetanes takes place in the presence of a Lewis acid such as AlEt_3 , the regiochemistry of the ring cleavage is the opposite to that commented above, this strategy being complementary to the former one (Scheme (5)) (91JOC5760).

SCHEME 5

Enantiomerically pure functionalized alcohols **19** are obtained from chiral oxetanes (**2f**)-(**2i**), derived from menthone and glycidol, when the reductive opening is performed with lithium and a substoichiometric amount of DTBB in THF at 0 °C, followed by reaction with electrophiles and final hydrolysis with water (Scheme (6)) (97TA2633).

SCHEME 6

The above shown methodology has found wide application in organic synthesis. For instance, the reaction of carbonyl compounds with intermediates **18** gives 1,4-diols which undergo cyclization leading to tetrahydrofurans (**20**) under acidic conditions (Eq. (7)) (Table 1).

TABLE 1. Preparation of tetrahydrofurans (**20**) from oxetanes (**2**).

Entry	Starting		Product					Yield (%)
	Oxetane	No	R ¹	R ²	R ³	R ⁴	R ⁵	
1	(2a)	(20a)	H	H	H	H	<i>p</i> -MeOC ₆ H ₄	93 ^a
2	(2a)	(20b)	H	H	H	H	PhSCH=CH	76 ^a
3	(2a)	(20c)	H	H	H		(CH ₂) ₅	85 ^a
4	(2a)	(20d)	H	H	H		CH=CH(CH ₂) ₃	76 ^a
5	(2h)	(20e)	Me	Me	H	H	CH ₃ C=CHCH ₃	57 ^b
6	(2h)	(20f)	H	THPOCH ₂	H		(CH ₂) ₅	95 ^a
7	(2i)	(20g)	H	THPOCH ₂	H		(CH ₂) ₅	95 ^a

^a Based on the diol (**19**)

^b Based on the starting oxetane (**2**)

In the case of using lactones as electrophiles in the presence of cerium trichloride, spiroketals are obtained after acidic work-up (90JA6389). Also cyclic Fischer-type chromium carbene complexes **17** have been prepared when hexacarbonyl chromium was added first, followed by treatment with trimethyloxonium tetrafluoroborate (Scheme (7)) (92JCS(CC)1623).

SCHEME 7

II.B. Thietanes

Oxetanes (**2**) undergo reductive opening by means of alkali metals in the presence of an arene, but thietane itself or alkyl substituted thietanes are stable compounds towards the same reductive reagents because they are less strained heterocycles due to the longer carbon-heteroatom bond distances. However, 2-phenylthietane (**22**) can be reductively opened with lithium in the presence of a catalytic amount of DTBB at low temperature. In this case a phenyl group at 2-position is necessary for the reductive opening to take place in order to stabilize the γ -thiofunctionalized organolithium compound (**23**). The reaction of (**23**) with electrophiles gave after acidic hydrolysis functionalized thiols (**24**). When 3-pentanone and

cyclopentanone were used as electrophiles, the resulting thiols (**24**) underwent acidic cyclization to give in good yields tetrahydrothiophenes (**25**) (Scheme (8)) (97T5563).

SCHEME 8

III. Homologation of five-membered heterocycles

III.A. Tetrahydrofurans

In sharp contrast to the behaviour of epoxides and oxetanes, tetrahydrofuran (**26a**) do not undergo reductive opening by means of lithium metal itself and in the presence of arenes as electron carriers at low temperatures. However, it is also possible to carry out this process at low temperature but necessarily in the presence of boron trifluoride etherate. Thus, treatment of the complex resulting from (**26a**) and the Lewis acid with lithium and DTBB in a stoichiometric ratio at $-78\text{ }^\circ\text{C}$ leads to δ -oxygenofunctionalized organolithium compound (**27a**) which after reaction with electrophiles and final hydrolysis with water gives functionalized alcohols (**28a**) (Scheme (9)) (91JA1866). The same process can be performed using an excess of lithium and a catalytic amount of naphthalene as lithiating mixture (Scheme 22) (92T3585). In the case of 2-methyltetrahydrofuran (**26b**), reductive ring opening leads to the formation of the more substituted organolithium derivative (**27b**) in a similar way as for oxetanes (see above) (Scheme (9)) (91JA1866). Acidic hydrolysis gives tetrahydropyran derivatives (**29**) (Scheme (9)).

SCHEME 9

III.B. Tetrahydrothiophenes

Reductive opening of 2-phenyltetrahydrothiophene (**30**) takes place by treatment with lithium in the presence of a catalytic amount of DTBB at low temperature to give the benzylic dianion (**31**) in a similar way as for thietane (**22**) (e.g., see section II.B.). The reaction with electrophiles followed by hydrolysis gives functionalized thiols (**32**). The treatment of the sulfanyl alcohol obtained by addition of acetone as electrophile with 85% phosphoric acid leads to the expected tetrahydrothiopyran (**33**) (Scheme (10)) (97T5563).

SCHEME 10

III.C. Phthalane: a versatile starting material

Phthalan (**34**) is opened reductively with lithium and a catalytic amount of DTBB at 0 °C to afford dianion (**35**) which have shown a wide use in organic synthesis, giving by

reaction with electrophiles at $-78\text{ }^{\circ}\text{C}$ and final hydrolysis functionalized alcohols (**36**) (Scheme (11)) (95T3351). The lithiation of (**34**) can be directed to the introduction of two different electrophiles at both benzylic positions in a sequential manner. After addition of the first electrophile, the resulting alcoholate is stirred in the presence of the excess of lithiating mixture at room temperature for four additional hours to give a new organolithium intermediate (**37**), which finally reacts with a second electrophile to yield difunctionalised products (**38**) (Scheme (11)). Diols (**36**) derived from the reaction of intermediate (**35**) with carbonyl compounds ($E_1^+ = R^1R^2CO$), are easily cyclized under acidic conditions to give the corresponding six-membered benzocondensed cyclic ethers (**39**) (Scheme (11)) (Table (II)), meanwhile, diols (**38**) derived from the reaction with two carbonyl compounds ($E_1^+ = R^1R^2CO$, $E_2^+ = R^3R^4CO$) under acidic conditions leads to tetrahydrobenzoxepines (**40**) (Scheme (11)) (Table (II)).

SCHEME 11

TABLE 2. Preparation of isochromans (**39**) and tetrahydrobenzoxepines (**40**).

Entry	Product					Yield (%)
	No	R ¹	R ²	R ³	R ⁴	
1	(39a)	H	Bu ^t	--	--	82
2	(39b)	H	Ph	--	--	90
3	(39c)	Et	Et	--	--	83
4	(39d)	(CH ₂) ₅		--	--	96
5	(39e)	Ph	Me	--	--	94
6	(40a)	H	Bu ^t	(CH ₂) ₅		68
7	(40b)	Me	Me	H	Et	71
8	(40c)	Et	Et	H	Et	52
9	(40d)	(CH ₂) ₄		H	Et	61

Using *N*-silylaldimines as electrophiles, aminoalcohols (**41**) are obtained as reaction products, which after chlorination followed by cyclization under basic conditions lead to the formation of tetrahydroisoquinolines (**42**) (Figure (1)) (00JHC1061). When ketones derived from D-fructose, and D-glucose, as well as *O*-ethoxymethylsubstituted estrone and (-)-menthone are used as electrophiles, diols (**36f**)-(36i) (00TA493, 01TA801, 04S1115) are obtained as reaction products (Figure (1)). The transformation of these compounds into the expected isochroman derivatives (**39f**)-(39i) (98TA3939, 00TA2063, 04S1115) is easily achieved under typical Mitsunobu reaction conditions (Figure (1)).

III.D. Thiophthalane

As it could be expected by considering the reactivity of phthalan (**34**), thiophthalan (**43**) is reductively opened with lithium and a catalytic amount of DTBB at -78 °C (instead of 0 °C for (**34**)) in order to avoid undesired side reactions. The reaction of the resulting dianionic intermediates (**44**) with different electrophiles leads to compounds (**45**), after acidic hydrolysis (Scheme (12)) (96JOC1859). In a similar manner to phthalan (**34**) (see Scheme

FIGURE 1

(11)), in the case of thiophthalan (43), two electrophilic fragments can be introduced at both benzylic positions by a double sequential lithiation reaction with electrophiles to give difunctionalized compounds (38). Thiols (45) derived from the reaction of intermediate (44) with carbonyl compounds ($E_1^+=R^1R^2CO$), cyclize under acidic conditions to give thioisochromans (46) (Scheme (12)) (Table (III)).

SCHEME 12

TABLE 3. Preparation of thioisochromans (46).

Entry	Product			
	No	R ¹	R ²	Yield (%)
1	(46a)	H	Pr ⁱ	51
2	(46b)	H	Bu ^t	35
3	(46c)	H	Ph	97
4	(46d)	Me	Me	89
5	(46e)	(CH ₂) ₄		85
6	(46f)	Me	Ph	94

III.E. 2,3-Dihydrobenzofuran

Cyclic alkyl aryl ethers lead also to functionalised organolithium compounds by reductive carbon-oxygen bond cleavage in arene catalyzed lithiation process. Thus, the treatment of 2,3-dihydrobenzofuran (47) with an excess of lithium in the presence of a catalytic amount of DTBB in THF at 0 °C gives the dianion (48) which after reaction with different carbonyl compounds and final hydrolysis with water leads to diols (49) (Scheme

(13)) (98TL7759, 02T4907). Dehydration under acidic conditions of compounds **(49)** leads to chromans **(50)** (Scheme (13)) (Table 4).

SCHEME 13

TABLE 4. Preparation of chromans **(50)**.

Entry	Product			Yield (%)
	No	R^1	R^2	
1	(50a)	H	Ph	>95
2	(50b)	Et	Et	92
3	(50c)	$(CH_2)_5$		>95
4	(50d)	$(CH_2)_7$		68

III.F. 2,3-Dihydrobenzothiophene

Screttas and Micha-Screttas (78JOC1064, 79JOC713) developed a methodology for the preparation of organolithium compounds starting from phenylthioethers, being an alternative to the use of chlorinated materials as precursors of this intermediates. Since then, the cleavage of the carbon-sulfur bond in phenylthioethers using either the stoichiometric or the catalytic version of the arene-mediated lithiation has been extensively used to generate organolithium compounds by sulfur-lithium exchange. The reductive cleavage of benzodihydrothiophene **(51)** with lithium di-*tert*-butylbiphenylide takes place at 0 °C to give the dilithium intermediate **(52)** which reacted with electrophiles to give compounds **(53)**.

When *o*-methoxybenzaldehyde was used as electrophile, the resulting sulfanyl alcohol underwent acidic cyclization to yield the thiochroman (**54**) in good yield (Scheme (14)) (95TL4459).

SCHEME 14

III.G. 2,3-Benzofuran

In the case of 2,3-benzofuran (**55**), a stereoselective ring opening lithiation takes place under the same reaction conditions as for 2,3-dihydrobenzofuran (**47**) shown on Scheme (13), yielding the (*Z*)-organolithium intermediate (**56**) which, by reaction with different electrophiles and final acidic hydrolysis, gives the expected (*Z*)-products (**57**). Cyclization of the products obtained by reaction with carbonyl compounds under acidic conditions, affords the expected substituted 2*H*-chromenes (**58**) (Scheme (14)) (01EJO2809).

SCHEME 14

IV. Homologation of six-membered heterocycles

IV.A. Isochroman

Isochroman (**59**) undergoes reductive opening lithiation with lithium and a catalytic amount of DTBB at 20 °C to afford dianion (**60**) which after reaction with electrophiles and final hydrolysis leads to alcohols (**61**). Dehydration of these alcohols with H₃PO₄ allows the preparation of tetrahydrobenzoxepines (**62**). The whole process represents the homologation of the oxygen-containing six-membered starting heterocycle (**59**) (Scheme (15)) (Table (5)) (95T3365).

SCHEME 15

TABLE 5. Preparation of benzoxepines (**62**).

Entry	Product			Yield (%)
	No	R ¹	R ²	
1	(62a)	H	Ph	67
2	(62b)	Me	Me	72
3	(62c)	Et	Et	79
4	(62d)	(CH ₂) ₄		69
5	(62e)	(CH ₂) ₇		68
6	(62f)	Me	Ph	72

Similarly to phthalan (**34**) (see Figure (1)), when ketones derived from D-fructose, and D-glucose, *O*-ethoxymethylsubstituted estrone and (-)-menthone are used as electrophiles, the resulting diols (00TA493, 01TA801, 04S1115) were transformed by dehydration to benzooxepines (**62g**)-(**62j**) (98TA3939, 00TA2063, 04S1115) (Figure (2)). On the other hand, when *N*-silylaldimines is used as electrophiles, the resulting aminoalcohols can be easily transformed into benzoazepines (**63**) (Figure (2)) (00JHC1061).

FIGURE 2

IV.B. Thioisochroman

Applying to thioisochromans (**64**) the same methodology than to isochroman (**59**) (see above), it was possible to transform them into tetrahydrobenzothiepins (**67**) (Scheme (16)) (96JOC1859) which are their homologous heterocycles. The only different is that in this case, the reductive opening lithiation should be performed at -78 °C instead of 20 °C.

SCHEME 16

IV.C. 4-Heterosubstituted dibenzothiins: phenoxathiin, phenothiazine, and thianthrene

The DTBB-catalyzed lithiation of 4-hetero-substituted dibenzothiins (**68**), such as phenoxathiin (**68a**), phenothiazine (**68b**), and thianthrene (**68c**), at low temperature gives the corresponding functionalized organolithium intermediates (**69**), which by reaction with different electrophiles afford the expected functionalized thiols (**70**), after hydrolysis. The cyclization of some carbonyl compound derivatives under acidic conditions gives the corresponding homologous seven-membered dibenzo heterocycles (**71**) (Scheme (17)) (Table 6) (02CL726). Again, from a synthetic point of view, the whole process (**68**)→(**71**) represents a homologation of the starting materials (**68**). In the case of thianthrene (**68c**), all the reactions should be performed at −90 °C in order to avoid undesired side processes.

SCHEME 17

TABLE 6. Preparation of seven-membered heterocycles (71).

Entry	Product				
	No	X	R ¹	R ²	Yield (%)
1	(71a)	O	H	Ph	78
2	(71b)	O	Et	Et	85
3	(71c)	S	H	Bu ^t	74
4	(71d)	S	H	Ph	97

IV.D. 1*H*,3*H*-Benzo[*de*]isochromene

The reductive opening lithiation of benzoisochromene (72) to give intermediate (73) should be performed at -50 °C for 6 h with an excess of lithium in the presence of a catalytic amount of DTBB. At higher temperatures a double carbon-oxygen bond reductive cleavage takes place leading to 1,8-bis(lithiomethyl)naphthalene. The reaction of (73) with electrophiles yields after hydrolysis functionalized alcohols of type (74). Dehydration under acidic conditions of diols (74) resulting from the reaction with a carbonyl compound as electrophile leads to dihydronaphthooxepines (75) (Scheme (18)) (Table (7)) (04T4655).

{E⁺ = H₂O, D₂O, Bu^tCHO, PhCHO, Me₂CO, Et₂CO, [CH₃(CH₂)₄]₂CO, (CH₂)₅CO, (CH₂)₇CO}

SCHEME 18

TABLE 7. Preparation of dihydronaphthooxepines (75).

Entry	Product			
	No	R ¹	R ²	Yield (%)
1	(75a)	Me	Me	95
2	(75b)	Et	Et	95
3	(75c)	CH ₃ (CH ₂) ₄	CH ₃ (CH ₂) ₄	89
4	(75d)		(CH ₂) ₅	95
5	(75e)		(CH ₂) ₇	56

V. Homologation of seven-membered heterocycles

V.A. 2,7-Dihydrodibenzothiepine

Applying the same strategy as for phthalan (34) and thiophthalan (43), the lithiation of 2,7-dihydrodibenzothiepin (76) can be directed either to the formation of sulfanyl alcohols (79) or to the introduction of two different electrophiles at both benzylic positions in a sequential manner, to yield difunctionalised biphenyls (80). Thus, the treatment of compound (76) with an excess of lithium and a catalytic amount of DTBB at -78 °C leads to intermediate (77), which reacts with carbonyl compounds to give alkoxides (78), and after acidic hydrolysis to the afore mentioned sulfanyl alcohols (79). However, when alkoxides (78) are stirred at room temperature in the presence of the excess of the lithiating mixture, the

remaining benzylic carbon-sulfur bond is cleaved and after reaction with a second electrophile and final hydrolysis with water lead to polyfunctionalized compounds (**80**) (Scheme (19)) (01TL2469). Compounds (**79**) can be cyclized under acidic conditions as is exemplified for the benzaldehyde derivative ((**79**), $R^1 = H$, $R^2 = Ph$). Treatment of this compound with 85% phosphoric acid under toluene reflux yields the dihydrodibenzothiocine (**81**) (Scheme (19)) (05T9082).

SCHEME 19

VI. Related processes

VI.A. Benzodioxane and benzooxathiane

Reductive opening lithiation of heterocycles has also been employed in processes which allow the synthesis of new heterocycles but different for those previously mentioned homologation methodologies. For instance, starting from six-membered heterocycles

benzo[*c*]-1,3-dioxane and 1,3-oxathiane derivatives (**82**), it is possible to prepare five-membered heterocycles 2,3-dihydro-2-substituted benzofurans or thiophenes (**84**). The whole process (**82**)→(**84**) represents a ring contraction instead of a ring expansion. Thus, the treatment of heterocycles (**82**) with excess of lithium and a catalytic amount of DTBB at 20 °C for dioxanes ((**82**), X = O) or at −78 °C for oxathianes ((**82**), X = S) followed by hydrolysis, leads to the formation of 2-substituted homobenzylic alcohols (**83**). Cyclization of these alcohols either under acidic conditions in refluxing toluene or under Mitsunobu-type reaction conditions gives 2,3-dihydro-2-substituted benzofurans or thiophenes (**84**) (Scheme (20)) (Table 8) (97T17373). Starting heterocycles (**82**) are easily prepared by ketalization of carbonyl compounds with *o*-(hydroxymethyl)phenol or *o*-(hydroxymethyl)thiophenol (**85**) (Scheme (20)). In this process, a benzylic carbon-oxygen bond cleavage takes place first leading to dianionic alcoholates (**86**), which undergo β-elimination giving benzylic dianions (**87**) together with the carbonyl compound used for the preparation of the starting heterocycles. These species react immediately to give (**88**), which after hydrolysis with hydrochloric acid, lead to final compounds (**83**) (Scheme 20) (97T17373).

VI.B. Double lithiation of thianthrene

The reductive opening of thianthrene (**68c**) has been reported in (Section IV.D) for homologation purposes, however the lithiation of (**68c**) and reaction with appropriate electrophiles lead to interesting organic compounds. Thus, after the reductive opening lithiation of (**68c**) and reaction with a carbonyl compound as the first electrophile, the resulting intermediate (**89**) is allowed to react with the excess of the lithiation mixture present in the reaction medium, a new intermediate (**90**) is formed. The addition of carbon dioxide as the second electrophile gives phthalides (**91**) after acidic work-up (Scheme (21)) (Table 9)

SCHEME 20

TABLE 8. Preparation of 2,3-dihydrobenzo-furans or -thiophenes (**84**).

Entry	Product				
	No	X	R ¹	R ²	Yield (%)
1	(84a)	O	H	Me	57
2	(84b)	S	H	Me	66
3	(84c)	O	Me	Me	65
4	(84d)	S	Me	Me	62
5	(84e)	O	H	Pr ⁱ	66
6	(84f)	S	H	Pr ⁱ	74
7	(84g)	O	H	Bu ⁱ	69
8	(84h)	S	H	Bu ⁱ	70
9	(84i)	O	H	Bu ^t	52
10	(84j)	S	H	Bu ^t	19
11	(84k)	O	(CH ₂) ₅		79
12	(84l)	S	(CH ₂) ₅		83
13	(84m)	O	H	Ph(CH ₂) ₂	68
14	(84n)	S	H	Ph(CH ₂) ₂	61

(02TL7205, 03T2083). Meanwhile, the addition of a second carbonyl compound as electrophile leads to diols (**92**) after hydrolysis. This diols undergo acidic cyclization in almost quantitative yield to give phthalans (**93**) (Scheme (21)) (Table 9) (02TL7205, 03T2083).

SCHEME 21

TABLE 9. Preparation of phthalides (**91**) and phthalans (**93**) from thianthrene (**68c**).

Entry	Product					
	No	R ¹	R ²	R ³	R ⁴	Yield (%)
1	(91a)	H	Me	--	--	58
2	(91b)	H	Bu ⁿ	--	--	78
3	(91c)	H	Me(CH ₂) ₇	--	--	38
4	(91d)	H	Ph	--	--	58
5	(91e)	Me	Me	--	--	59
6	(91f)	Me	Et	--	--	78
7	(91g)	(CH ₂) ₅	--	--	--	39
8	(93a)	Me	Me	H	Ph(CH ₂) ₂	>95
9	(93b)	Me	Me	Me	Me	>95
10	(93c)	Me	Me	(CH ₂) ₅	--	>95
11	(93d)	Et	Et	Et	Et	>95
12	(93e)	(CH ₂) ₅	--	(CH ₂) ₅	--	>95

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