SYNTHESIS OF SUBSTITUTED BENZOFURANS BY THE TANDEM ONE-POT INTRAMOLECULAR CARBOLITHIATION–CYCLIZATION–SUBSTITUTION SEQUENCE

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GRAPHICAL ABSTRACT

Abstract A convenient methodology for the synthesis of 3-substituted-2,3-dihydrobenzofurans was developed based on the tandem intramolecular carbolithiation–cyclization of 2-bromophenyl-3-phenylprop-2-enyl ether followed by trapping of the new lithiated intermediate by suitable electrophiles. Several electrophiles were tested, affording good to excellent yields. Alkyl bromides show better results than chlorides and when doubly halogenated alkyl chains are used as electrophiles only one position reacts, affording substituted benzofurans conveniently functionalized to undergo further reactions. The performance of both butyl and phenyllithium as lithiating agents was examined.

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Keywords Alkylation; benzofurans; intramolecular carbocyclization; intramolecular carbolithiation; organolithium

Received July 17, 2013.
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INTRODUCTION

Tandem sequences involving organolithium compounds continue to provide fascinating approaches to challenging synthetic issues.\textsuperscript{[1]} The subtle control of chemo-, regio-, and stereoselectivity achievable within carbolithiation points the way to exciting applications in carbocyclic, heterocyclic, alkene, and alkane synthesis.\textsuperscript{[2,3]} Carbolithiation reactions of vinyl, alkyl, and aryllithium to unactivated alkenes and alkynes are especially fruitful; the value of these transformations lies in their ability to regio- and stereoselectively construct carbon–carbon bonds in tandem with generating a new organolithium species.\textsuperscript{[1,2,4]} Particularly the intramolecular carbolithiation–electrophilic substitution tandem sequence is a well-suited, one-pot process for the building of cyclic structures.\textsuperscript{[5,6]} On the other hand, 2,3-dihydrobenzofuran (cumaran) is a basic skeleton found in a number of biologically interesting compounds, such as the neolignans.\textsuperscript{[7]} Attempts to build this skeleton using 2-bromophenyl-(E)-2-propenyl ether failed due to $\gamma$-elimination.\textsuperscript{[8]} A likely strategy to overcome the $\gamma$-elimination could be substitution by a phenyl moiety that could provide increased resonance stabilization to the cyclic lithium intermediate.\textsuperscript{[9]} We synthesized 2-bromophenyl-3-phenylprop-2-enyl ether, 1, and conditions were searched for the cyclization to occur in good yields.\textsuperscript{[10]} Based on the operational simplicity of this approach, we studied the scope of this tandem procedure in synthesis; herewith we report a convenient and efficient route to new 3-substituted 2,3-dihydrobenzofurans.

RESULTS AND DISCUSSION

The reaction of 1 with $n$-BuLi in tetrahydrofuran (THF), leads to the formation of three products, noted as 2, 3, and 4 in Scheme 1. The production of cyclic structures, like 3, were synthetically interesting, and reaction conditions were searched to increase its yield.

A detailed mechanistic study proved that the reaction occurs via a polar rather than a radical mechanism.\textsuperscript{[11]} The reaction mechanism giving rise to products 3 and 4 is outlined in Scheme 2. Organolithium 5 is assumed to be formed through an ate-complex intermediate, favored by the presence of Br and O in the substrate.\textsuperscript{[12]} The acyclic lithium intermediate 5 can then undergo cyclization to the new lithiated cyclic intermediate 6, which yields the substituted 2,3-dihydrobenzofuran 3, by

\begin{center}
\includegraphics[width=0.8\textwidth]{Scheme1.png}
\end{center}

**Scheme 1.** Reaction products of 2-bromo-phenyl-3-phenylprop-2-ethyl ether with $n$-BuLi.
further reaction with the \( n \)-butyl bromide previously generated in the halogen–metal exchange reaction. The new lithiated intermediate 6 is very reactive. In fact, when a methyl group replaces the phenyl moiety, an undesirably drawback is the \( \gamma \)-elimination, leading to cyclopropylphenol derivatives. In the present case, the phenyl group attached to the double bond provides stabilization to the cyclized carbanion, preventing the \( \gamma \)-elimination.

The experimental finding that deuterium is not incorporated at the aryl position when quenching with MeOD the by-product 4 suggests that the by product 4 should be formed via an intramolecular rearrangement of the carbanion 5 with the allylic protons, followed by isomerization to the more stable benzylic carbanion, which immediately reacts with the \( n \)-butyl bromide present in the reaction mixture. The (Z)-structure of the by-product 4 can be visualized through the intermediate 7, stabilized by Li/oxygen coordination. The formation of (Z)-N-(1-propenyl)benzamides observed in the reaction of \( N \)-allylbenzamides and \( n \)-BuLi has been explained by a similar coordination of the lithium atom to the nitrogen atom at the \( \gamma \)-carbon.\[13\]

Scheme 3 shows how substrate 1 can be transformed into conveniently substituted 2,3-dihydrobenzofuran derivatives, 8, by a fast tandem cyclization–\( \gamma \)-alkylation sequence, trapping the cyclic lithium intermediate 6 by an appropriate electrophile (E) in a 5 min reaction under very mild reaction conditions.

Table 1 summarizes the results obtained using several electrophiles. It is worthwhile to note that in all cases there is a competition between the added electrophile and the butyl bromide generated in situ in the first step of the reaction. Nevertheless, under the conditions described complete reaction of 1 occurs and good to excellent yields of functionalized 2,3-dihydrobenzofuran derivatives are obtained with a large variety of primary alkyl bromides. It can be observed that when two primary bromine atoms are present (entry g and h), only one position reacts; similarly, when
chlorine and bromine are present (entry f) the chlorine atom does not react under the present reaction conditions. In these cases, substituted 2,3-dihydrobenzofuran derivatives conveniently functionalized for further reactions are obtained, with good yields and conversions (~90%). Bromobenzene and methyl iodide did not afford a good yield of 4. Bromobenzene gave 80% of 3 and methyl iodide rendered 85% of 2-methylphenyl-(E)-2-propenyl ether.

To avoid the competitive reaction with butyl bromide the lithiation reagent was changed to PhLi. Several reaction conditions were tested. Finally by using a high [PhLi]–[1] ratio the reaction afforded different 2,3-dihydrofuran derivatives in good yield; complete conversion of 1 is observed for [PhLi]:[1] ≥ 3. As shown in Table 2 all the relative yields are improved compared to the same reaction using BuLi, although the diastereomer selectivity is slightly diminished.

An intriguing feature of this approach is the fact that a diastereomeric process is taking place. Although four diastereomers (two racemic pairs) can be formed, because the product contains two stereogenic centers, under the reaction conditions one of the pair is formed in a greater amount than the other. To search for a

| Entry | Electrophile | Yields (%) | 2 | 3 | 4 | 9 | 8 (dr %) |
|-------|--------------|------------|---|---|---|---|---------|
| a     | EtBr         | 0          | 9 | 0 | 9 | 3 | 79 (80:20) |
| b     | CH₃(CH₂)₂Br  | 0          | 9 | 3 | 15| 73 (97:3) |
| c     | CH₃(CH₂)₃Br  | 0          | — | — | 7 | 93 (60:40) |
| d     | CH₃(CH₂)₄Br  | 0          | 11| 4 | 11| 74 (83:17)|
| e     | CH₂=CHCH₂Br  | 32         | 3 | 4 | 0 | 61 (95:5) |
| f     | Br(CH₂)₂Cl   | 23         | 4 | 2 | 1 | 70 (98:2) |
| g     | Br(CH₂)₃Br   | 14         | 7 | 2 | 0 | 77 (98:2) |
| h     | Br(CH₂)₄Br   | 3          | 3 | 2 | 12| 80 (82:18)|

*1.5 equivalent BuLi was added to a solution of 1 at –85°C in THF. After 5 min the E was added. The reaction mixture was warmed up to rt, and then it was quenched with MeOH after 5 min.

*2Relative yields determined by NMR and GC.

*3In all cases 8 eq. of E were used.

*dr, determined by NMR.
plausible mechanistic interpretation for the observed stereoselectivity, theoretical
modeling of each one of all likely lithiated intermediates using B3LYP is in progress.

In conclusion, a variety of 3-sustituted-2,3-dihydrobenzofurans can be con-
veniently synthesized by the tandem intramolecular carbolithiation–cyclization of
2-bromophenyl-3-phenylprop-2-enyl ether, followed by in situ trapping of the new
lithiated intermediate by suitable electrophiles. This one-pot synthesis occurs under
mild reaction conditions and shows certain diastereoselectivity control.

EXPERIMENTAL

All reactions involving organolithium reagents were carried out by standard
techniques for the manipulation of air- and water-sensitive compounds.[14] NMR
spectra were determined using a Bruker AC200 MHz instrument The \(^1\)H chemical
shifts are referenced relative to tetramethylsilane (TMS), and the \(^13\)C-chemical shifts
are referenced relative to CDCl\(_3\) at \(\delta = 77\) ppm. The gas chromatographic (GC)
analyses were carried out on a 5890 Hewlett-Packard gas chromatograph, using a
HP-5 column and a FID detector. GC-MS were determined by a QP 5050A
Shimadzu a gas chromatograph mass spectrometer, using electron impact ionization
(EI, 70 eV).

Full Experimental Details for the General Procedure

n-Butyllithium and phenyllithium were prepared and titrated as previously
described.[15] 2-Bromophenyl 3-phenyl-2-propenyl ether, \(\mathbf{1}\), was prepared by reaction
of 2-bromophenol with cinnamyl bromide in acetone as previously described (yield
82%).[16] Compound \(\mathbf{1}\) (0.05 mol) in 10 mL of THF was placed in a two-necked,
septum-capped, round-bottomed flask equipped with a thermometer under a dry nitrogen atmosphere at $-85^\circ$C. Then 0.75 mL of 1.00 M n-BuLi in hexane was added dropwise via syringe in 1–2 min after 5 min at $-85^\circ$C, the electrophile (pure or as a solution in THF) was added rapidly via syringe. The reaction was immediately allowed to reach room temperature and stand for 5 min before quenching with MeOH. The reaction mixture was extracted with CH$_2$Cl$_2$, washed with aqueous 3 M NH$_4$Cl solution and brine, and dried with anhydrous MgSO$_4$ online. The reaction mixture was analyzed by $^1$H and $^{13}$C NMR, GC-FID, and GC-MS. The products were isolated by column chromatography or preparative thin-layer chromatography (TLC) using a mixture of 2% ethyl acetate, 70% cyclohexane, and 28% hexane as eluant. In some cases only the main diastereomer could be isolated. The pure compounds were characterized by $^1$H and $^{13}$C NMR and MS. Full data for key compounds are shown.

(2-d)-Phenyl (E)-3-phenyl-2-propenyl Ether (2)

Solid, mp 67.5–68.5$^\circ$C. $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 4.70 (dd, 2H, $J=5.7$ and 1.3 Hz), 6.42 (dt, 1H, $J=15.8$ and 5.7 Hz), 6.74 (d, 1H, $J=15.8$ Hz), 6.94–6.98 (m, 2H), 7.23–7.43 (m, 7H). MS $m/z$ (rel. ab.): 211(5) [M$^+$], 117 (100), 115 (83), 91 (60).

3-(1-Phenylpentyl)-2,3-dihydrobenzofuran (3)

Oil. Main diastereoisomer. $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 0.80 (t, 3H, $J=7.1$ Hz), 1.08 (m, 2H), 1.25 (m, 2H), 1.67 (m, 2H), 2.73 (m, 1H), 3.68 (dd, 1H, $J=6.2$ and 9.1 Hz), 4.44 (dd, 1H, $J=6.2$ and 9.1 Hz), 6.69 (d, 1H, $J=7.7$ Hz), 6.59 (dt, 1H, $J=1.0$ and 7.5 Hz), 6.71 (d, 1H, $J=8.0$ Hz), 7.09 (m, 3H), 7.26 (m, 3H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 13.85, 22.56, 29.48, 33.04, 48.05, 50.37, 75.06, 109.29, 119.80, 125.41, 126.57, 128.10, 128.34, 128.53, 129.07, 142.98, 160.34. Minor diastereomer. $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 0.79 (t, 3H, $J=7.1$ Hz), 1.08 (m, 2H), 1.25 (m, 2H), 1.67 (m, 2H), 2.73 (m, 1H), 3.55 (td, 1H, $J=4.0$ and 8.8 Hz), 4.17 (dd, 1H, $J=4.4$ and 9.1 Hz), 4.28 (dd, 1H, $J=8.8$ and 9.1 Hz), 6.76 (d, 1H, $J=8.8$ Hz), 6.85 (dt, 1H, $J=1.0$ and 7.5 Hz), 7.10 (m, 4H), 7.26 (m, 3H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 13.85, 22.66, 29.40, 32.48, 47.92, 49.94, 75.52, 109.72, 119.91, 125.97, 126.40, 128.34, 128.49, 128.53, 129.50, 143.06, 160.60. MS $m/z$ (rel. ab.): 266 (16) [M$^+$], 209 (22), 120 (32), 119 (100), 115 (36), 92 (27), 91 (50), 77 (19), 65 (30). Anal. calcd. for C$_{19}$H$_{22}$O: C, 85.67; H, 8.32. Found: C, 85.60; H, 8.34.

Phenyl-(Z)-3-phenyl-1-heptenyl Ether (4)

Oil. $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 0.86 (t, 3H, $J=6.6$ Hz), 1.32 (m, 4H), 1.72 (m, 2H), 3.94 (m, 1H), 4.96 (dd, 1H, $J=6.2$ and 9.9 Hz), 6.39 (d, 1H, $J=6.2$ Hz), 7.00 (m, 3H), 7.27 (m, 7H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 14.02, 22.58, 29.70, 36.21, 40.34, 116.38, 117.05, 122.49, 125.90, 127.30, 128.38, 129.52, 139.74, 145.53, 157.49. MS $m/z$ (rel. ab.): 266 (4) [M$^+$], 209 (50), 131 (13), 115 (100), 91 (12), 77 (18). Anal. calcd. for C$_{19}$H$_{22}$O: C, 85.67; H, 8.32. Found: C, 85.02; H, 8.16.
SUPPORTING INFORMATION

Full experimental detail and $^1$H and $^{13}$C NMR spectra can be found via the Supplementary Content section of this article’s webpage.

ACKNOWLEDGMENTS

The authors are grateful to Graciela Garcia. The financial support from the Agency for the Promotion of Science and Technology (ANPCyT) and the National Research Council of Argentine (CONICET) is gratefully acknowledged.

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