

How the by-products hint at mechanisms and suggest new synthetic routes in some organolithium reactions†

Norma Sbarbati Nudelman,^{1*} Graciela V. García¹ and Susana Velurtas²

¹Depto. Química Orgánica, Facultad de Ciencias Exactas, Universidad de Buenos Aires, Ciudad Universitaria, 1428 Buenos Aires, Argentina

²Depto. de Química, Facultad de Ciencias Exactas, Universidad Nacional de Mar del Plata, Ciudad Universitaria, 1428 Buenos Aires, Argentina

Received 19 November 2001; revised 17 December 2001; accepted 24 January 2002

ABSTRACT: The recent proliferation of structural studies of organolithium reagents has led to an extended knowledge of the aggregation state of these pervasive synthetic intermediates. Nevertheless, detailed investigations of organolithium reaction mechanisms are still very limited. The most popular techniques in the relatively few reported studies are UV, EPR and NMR spectroscopy, the use of radical clocks and investigation of the stereochemical course of the reaction when applied. This paper describes how the search for minor products can be an additional mechanistic tool. Metal–halogen exchange was studied with a new suitable fast radical clock bearing a phenyl group at the alkene C-terminus, even when the probe was able to trap very short-lived radical intermediates, the results showed that the reaction proceeds through an open lithiated intermediate. In another study, radicals of benzil were generated on the lithium surface and their reactions studied in THF. Characterization of the minor products, the rates of decay of the reagent and formation of products, and also periodical EPR of the reaction mixture, allowed the proposal of the whole reaction mechanism. In both reactions studied, the detailed understanding of the reaction mechanisms based on the side-products provided new more economical and environmentally friendly alternatives for the synthesis of substituted 2,3-dihydrobenzo[*b*]furans and aromatic esters. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: organolithium; halogen–lithium exchange; lithium surface reactions; anionic cyclization; ate complex; Li/oxygen carbenoid.

INTRODUCTION

Although organolithium compounds are powerful reagents in organic synthesis,^{1,2} in only a few cases have the reaction intermediates been isolated and fully characterized;^{3–5} for most of the reactions the mechanisms by which they proceed remain unclear or poorly understood. As an example, the mechanism of one of the most powerful methods for the preparation of organolithium compounds, halogen–metal exchange, is still controversial.⁶ Bailey and Patricia reviewed the data and they noted, as do most recent workers in the field, that the pathway followed may be dependent on the reactants and reaction conditions.⁷

Reactions with radical probes^{8,9} and the trapping of carbanionic intermediates by deuteration^{10,11} have been used as tools for deciding between the two most preferred

mechanisms for organolithium reactions. It has been shown recently that many addition reactions of organolithium reagents to carbonyl compounds proceed via an ET mechanism^{11–13} Previous studies in our laboratory on the reaction of phenyllithium with carbon monoxide by EPR and ¹³C NMR spectroscopy have provided evidence that the reaction occurs through the intermediacy of paramagnetic species.¹⁴ The UV and/or EPR spectroscopic observation of a radical intermediate does not necessarily mean that a radical is involved in the major reaction pathway, because both techniques detect intermediates at very low concentrations,⁸ but a developed ¹³C NMR methodology allowed quantitative determinations of the radical concentrations up to nearly 1 M,^{14b} and elucidation of the reaction mechanism.¹⁵ The top end of the alkyl radical kinetic scale has been recently adjusted by laser flash photolysis calibrations of fast radical clocks.¹⁶

On the other hand, it has been shown recently that the first step in the addition of aryllithiums to α,β -unsaturated aldehydes is electron transfer from the organolithium reagent to the carbonyl moiety.¹⁷ The main addition product of PhLi, to (*E*)-cinnamaldehyde is the alcohol (*E*)-1,3-diphenyl-2-propen-1-ol, as expected, but a careful investigation of by-products showed the presence of

*Correspondence to: N. S. Nudelman, Depto. Química Orgánica, Facultad de Ciencias Exactas, Universidad de Buenos Aires, Ciudad Universitaria, 1428 Buenos Aires, Argentina.

E-mail: nudelman@qo.fcen.uba.ar

†Presented in part at the Sixth Latin American Conference on Physical Organic Chemistry (CLAFQO-6), held at Isla Margarita, Venezuela, during December 2001.

Contract/grant sponsor: Universidad de Buenos Aires.

Contract/grant sponsor: CONICET.

(*E*)-chalcone and 1,3-diphenyl-1-propanone in minor amounts. The remarkable feature in that reaction is the coordination of a second lithium atom to the β -carbon in the 1,2-adduct, leading to a β -lithiated cyclic adduct whose structure determined by ^{13}C NMR showed an η^3 -coordination of the lithium atom,¹⁸ as has been shown recently by other organolithiums in solution.¹⁹

The knowledge of the reaction mechanism suggested a new tandem strategy for the synthesis of interesting β -alkyl-substituted dihydrochalcones, in good to excellent yields.^{18,20} Tandem reactions have recently been of interest in organic synthesis because they constitute a convenient, economical and environmentally friendly synthetic alternative when compared with conventional stepwise reactions.²¹

In our recent research involving organolithium reactions, we have observed that a careful search of the minor by-products formed in the different steps under varying reactions conditions could be an additional useful tool for the elucidation of the mechanisms of their reaction and the suggestion of original convenient synthetic routes. In this paper, the reactions of organolithiums with aryl halides and the generation of radicals on lithium surface are discussed.

EXPERIMENTAL

General methods. All reactions involving organolithium reagents were carried out by using standard techniques for the manipulation of air- and water-sensitive compounds.²² All compounds reported here were fully characterized by melting point (when applicable), mass spectrometry (using a QP 5050A gas chromatograph-mass spectrometer, Shimadzu) and nuclear magnetic resonance spectroscopy (determined on a Bruker Model 200, 300 or 500 spectrometer operating at 200, 300 or 500 MHz for ^1H and 50, 75 or 125 MHz for ^{13}C). The ^1H chemical shifts are referenced relative to TMS and the ^{13}C chemical shifts are referenced relative to CDCl_3 at $\delta = 77.0$ ppm. EPR spectra were determined on a Bruker EPR 200D (X band) TE102 cavity using procedures similar to those described for the reactions of phenyllithium with CO .^{14a} High-resolution mass spectra were measured on a ZAB-SEQ4F mass spectrometer. GC analyses were carried out on a Hewlett-Packard Model 5890 gas chromatograph using an HP-5 column.

Materials. Tetrahydrofuran and hexane were purified as described previously;²³ they were distilled from dark-blue solutions of sodium benzophenone ketyl under nitrogen immediately prior to use. Lithium wire (Merck, >99%, 3 mm diameter) was weighed under ligroin, washed with hexane and cut into small portions over a reaction flask containing warm solvent. *n*-BuLi was prepared as described previously;²⁴ its concentration was determined by the double titration method described

before.²⁵ Benzil was prepared by reported methods and crystallized from ethanol, m.p. 94–95 °C (lit.²⁴ 94–95 °C). Alkyl halides were commercial or prepared by reported methods and purified by distillation immediately prior to use. All glassware, syringes and needles were dried in a vacuum oven and cooled in a desiccator. 2-Bromophenyl 3-phenyl-2-propenyl ether, **4**, was prepared by reaction of 2-bromophenolate with cinnamyl bromide in acetone as described previously (yield 82%), m.p. 55–56 °C (ethanol).²⁶ An authentic sample of phenyl (*E*)-3-phenyl-2-propenyl ether was prepared according to the literature.²⁷

General procedure for the reaction of 4 with *n*-BuLi. A solution of 0.05 mmol of **4** in 10 ml of THF (0.05 M) was cooled to –85 °C under a blanket of dry nitrogen and 1.5 equiv. of *n*-BuLi as a solution in hexane was added dropwise via syringe over a 1–2 min period. The temperature was maintained at –80 °C during a chosen time and the reaction mixture was quenched with 0.2 ml of MeOH. The reaction mixture was washed with aqueous NH_4Cl solution, extracted with Et_2O and dried (MgSO_4). The organic layer was analysed by GC and ^1H NMR. GC–MS of the reaction mixture was carried out after 5 min of reaction.

[2- ^2H]Phenyl (*E*)-3-phenyl-2-propenyl ether, 5- d_1 . M.p. 67.5–68.5 °C. ^1H NMR (200 MHz, CDCl_3), δ 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), 6.96 (m, 2H), 7.33 (m, 7H). MS, m/z (rel. abs.) 211 (5), 118 (45), 117 (100), 116 (25), 115 (70), 91 (27), 78 (6), 77 (5), 66 (8), 65 (7), 51 (8).

3-(1-Phenylpentyl)-2,3-dihydrobenzo[*b*]furan, **6**. Compound **6** is obtained as a mixture of two diastereoisomers, diastereomeric ratio (dr) = 80:20. The diastereomeric ratio was determined by ^1H NMR and GC analysis. Main diastereoisomer: ^1H NMR (200 MHz, CDCl_3), δ 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 8.8 Hz), 4.44 (dd, 1H, $J = 6.2$ and 9.1 Hz), 4.61 (dd, 1H, $J = 8.8$ and 9.1 Hz), 6.26 (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), δ 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 diastereoisomer: ^1H NMR (200 MHz, CDCl_3), δ 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 (ddd, 1H, $J = 4.0$, 8.8 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), δ 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. abs.) 266 (16), 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, 7. Oil. 1H NMR (200 MHz, $CDCl_3$), δ 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, $CDCl_3$), δ 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. abs.) 266 (4), 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%.

^{13}C NMR spectrum of the reaction mixture of 4 with RLi in THF- d_8 . Taking into account that the *n*-BuLi should be prepared in hexane and that the butyl moiety is incorporated in intermediate 10, the reaction to investigate likely intermediates by ^{13}C NMR was carried out using PhLi as a more suitable RLi reagent for this purpose. To a 5 mm NMR tube capped with a septum at $-90^\circ C$ under a nitrogen atmosphere containing 96.3 mg (0.3 mmol) of 2-bromophenyl 3-phenyl-2-propenyl ether, 4, in 0.5 ml of THF- d_8 , a solution of 84 mg (1 mmol) of PhLi in 0.5 ml of THF- d_8 was added. The mixture was shaken, to ensure complete mixing, for 5 min at $-90^\circ C$. Then it was allowed to warm to $-50^\circ C$, and the 1H decoupled ^{13}C NMR spectrum was determined. The center peak of the downfield quintet of the THF- d_8 was used as the reference peak and was set at δ 67.50 ppm. A signal at δ 148.1 ppm, that was not present at the beginning or at the end of the reaction, was observed. That signal is easily assigned to the *ipso*-carbon of the aromatic ring bonded to the lithium-bearing carbon atom.

General procedure for the synthesis of 2,3-dihydrobenzo[b]furans. The organolithium derived from 4 was generated as described above. After 5 min at $-80^\circ C$, the electrophile, pure or as a solution in THF, was added rapidly via a syringe. The reaction mixture was immediately allowed to reach $0^\circ C$ and to stand for 5 min before quenching with MeOH. After work-up, the products were isolated by TLC and identified by melting point, 1H and ^{13}C NMR. The diastereomers were separated by chromatography over silica gel with a mixture of 2% ethyl acetate, 70% cyclohexane and 28% hexane as eluent. The compounds were isolated and fully characterized.

3-(1-Phenylpropyl)-2,3-dihydrobenzo[b]furan. Oil, dr = 80:20. Main diastereoisomer: 1H NMR (200 MHz, $CDCl_3$), δ 0.75 (t, 3H, $J = 7.1$ Hz), 1.70 (m, 2H), 2.65 (dt, 1H, $J = 5.5$ and 9.1 Hz), 3.69 (dt, 1H, $J = 6.2$ and 9.1 Hz), 4.43 (dd, 1H, $J = 6.2$ and 9.1 Hz), 4.61 (dd, 1H, $J = 9.1$ Hz), 6.28 (d, 1H, $J = 7.3$ Hz), 6.59 (t, 1H, $J = 7.3$ Hz), 6.71 (d, 1H, $J = 8.0$ Hz), 7.12 (m, 3H), 7.26 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ 11.99, 26.22,

47.81, 52.28, 75.03, 109.29, 119.83, 125.41, 126.59, 128.10, 128.34, 128.59, 129.10, 142.60, 160.31. Minor diastereoisomer: 1H NMR (200 MHz, $CDCl_3$), δ 0.71 (t, 3H, $J = 7.3$ Hz), 1.67 (m, 2H), 2.65 (dt, 1H, $J = 4.4$ and 9.1 Hz), 3.56 (ddd, 1H, $J = 4.0$, 4.4 and 8.8 Hz), 4.17 (dd, 1H, $J = 4.0$ and 9.1 Hz), 4.28 (dd, 1H, $J = 8.8$ and 9.1 Hz), 6.76 (d, 1H, $J = 7.3$ Hz), 6.85 (t, 1H, $J = 7.3$ Hz), 7.12 (m, 4H), 7.26 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ 11.75, 25.68, 47.65, 51.66, 75.60, 109.72, 119.91, 126.00, 126.46, 128.34, 128.40, 128.51, 129.52, 142.74, 160.52. MS, m/z (rel. abs.) 238 (25), 120 (33), 119 (100), 91 (51), 65 (33).

3-(1-Phenylheptyl)-2,3-dihydrobenzo[b]furan. M.p. $76-78^\circ C$, dr = 83:17. Main diastereoisomer: 1H NMR (200 MHz, $CDCl_3$), δ 0.83 (t, 3H, $J = 5.9$ Hz), 1.18 (m, 8H), 1.66 (m, 2H), 2.72 (m, 1H), 3.67 (dd, 1H, $J = 6.6$ and 8.8 Hz), 4.43 (dd, 1H, $J = 6.6$ and 9.1 Hz), 4.61 (dd, 1H, $J = 8.8$ and 9.1 Hz), 6.25 (d, 1H, $J = 7.3$ Hz), 6.59 (dt, 1H, $J = 1.0$ and 7.3 Hz), 6.71 (d, 1H, $J = 8.0$ Hz), 7.12 (m, 3H), 7.26 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ 13.96, 22.56, 27.22, 29.19, 31.64, 33.34, 48.03, 50.37, 75.06, 109.29, 119.80, 125.41, 126.57, 128.10, 128.32, 128.51, 129.07, 142.98, 160.31. Minor diastereoisomer: 1H NMR (200 MHz, $CDCl_3$), δ 0.82 (t, 3H, $J = 5.1$ Hz), 1.18 (m, 8H), 1.66 (m, 2H), 2.72 (m, 1H), 3.54 (ddd, 1H, $J = 4.0$, 8.4 and 8.8 Hz), 4.17 (dd, 1H, $J = 4.0$ and 9.1 Hz), 4.29 (dd, 1H, $J = 8.4$ and 9.1 Hz), 6.76 (d, 1H, $J = 8.8$ Hz), 6.86 (dt, 1H, $J = 1.0$ and 7.3 Hz), 7.01 (m, 3H), 7.26 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ 13.96, 22.56, 27.22, 29.29, 31.64, 32.82, 47.89, 49.94, 75.52, 109.72, 119.91, 125.97, 126.40, 128.32, 128.43, 128.51, 129.50, 143.06, 160.55. MS, m/z (rel. abs.) 294 (14), 120 (28), 119 (100), 118 (72), 92 (30), 91 (80), 65 (20).

General procedure for the reaction of benzil with lithium wire in THF. Lithium wire was weighed under ligroin, washed with THF and cut into small pieces in a reaction flask containing a small portion of warm THF, under a stream of dry argon. Preliminary runs cutting the wire in very tiny pieces, or even working with lithium suspension, showed that these changes of the lithium surface seemed not to have a significant influence. The reaction flask was capped with an 'air-tight' stopper and alternatively evacuated and flushed with nitrogen several times. This is a common technique in our laboratory and it has been found that by carrying out the procedure fairly fast, no complication with any lithium reaction with dinitrogen giving the gray lithium nitride is observed. A solution of benzil of the desired concentration in THF was transferred by syringe, and allowed to reach the working temperature (no significant temperature effect was observed in the range $0-50^\circ C$, therefore most of the reactions were carried out at room temperature). Aliquots of 0.2 ml of the reaction mixture were taken at time intervals, quenched with MeOH and analysed by GC, using benzophenone as internal standard. Since this is a

heterogeneous reaction, runs were made at least in triplicate and the reproducibility was satisfactory.

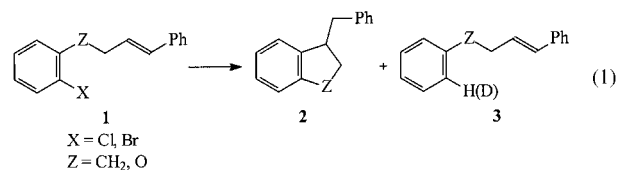
EPR spectra. The independently prepared radical anion solutions or the reaction mixtures in preparative concentrations (0.2–1.5 M) were diluted to nearly 10^{-5} M with THF. Optimization of the final concentration was adjusted in each case. The temperature was kept constant using a Dewar cavity with a thermostated stream of air; calibration was carried out at different modulation amplitudes using a THF solution of galvinoxyl.

RESULTS AND DISCUSSION

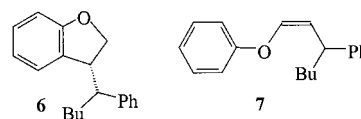
The halogen–lithium exchange reaction is of one of the most powerful methods for the preparation of organolithium compounds, but although widely used, its mechanism is still controversial. Up to now, four different mechanisms have been suggested, each of which has its adherents and all possibilities appear in the recent literature.^{6,7} The earliest suggestions of a concerted S_N2 displacement and an ‘ate complex’ intermediate were made by Sunthakar and Gilman²⁸ and Wittig and Schöllkopf,²⁹ respectively. A ‘four-center’ mechanism¹ was initially suggested to explain retention of configuration when the reaction was carried out with asymmetric halides; nevertheless, more recent studies established that the percentage retention of configuration observed can be easily accommodated within mechanisms involving other intermediates.³⁰ Intermediates such as ate complexes have been firmly established in the aryllithium–aryl iodide exchange³¹ and recently correlated with theoretical studies.³² Beak and co-workers^{6,33} have shown that evolution of the transition structure geometry for reaction of aryl bromide with alkyllithium is consistent with a trigonal bipyramid structure of a ‘10-Br-2-ate complex’ or an S_N2 transition state; recent kinetic studies of organolithium–aryl bromide exchange have been also interpreted in terms of an S_N2 mechanism.³⁴ On the other hand, evidence for a single electron transfer mechanism has been afforded by running ESR³⁵ and NMR³⁶ spectroscopy, and more recently it has been strongly supported by the observation of coupling^{11,24} and rearranged products,^{37,38} especially from radical probes. The UV and/or EPR spectroscopic observation of a radical intermediate does not necessarily mean that a radical is involved in the major reaction pathway leading to products, because both techniques detect intermediates at very low concentrations.⁸

To afford some new elements for the alkyllithium–aryl bromide exchange reaction, we synthesized a new suitable fast radical clock, **1**, bearing a phenyl group at the alkene C-terminus, able to trap very short-lived radical intermediates. The kinetic accelerating effect of aryl group substitution in the opening and closing of carbonyl radicals has been used recently in intramolecular

probe reactions.³⁹ The finding of cyclized products, **2**, is usually interpreted as evidence for a radical mechanism, while open-chain products, **3**, indicate that carbanionic intermediates are involved [Eqn (1)].

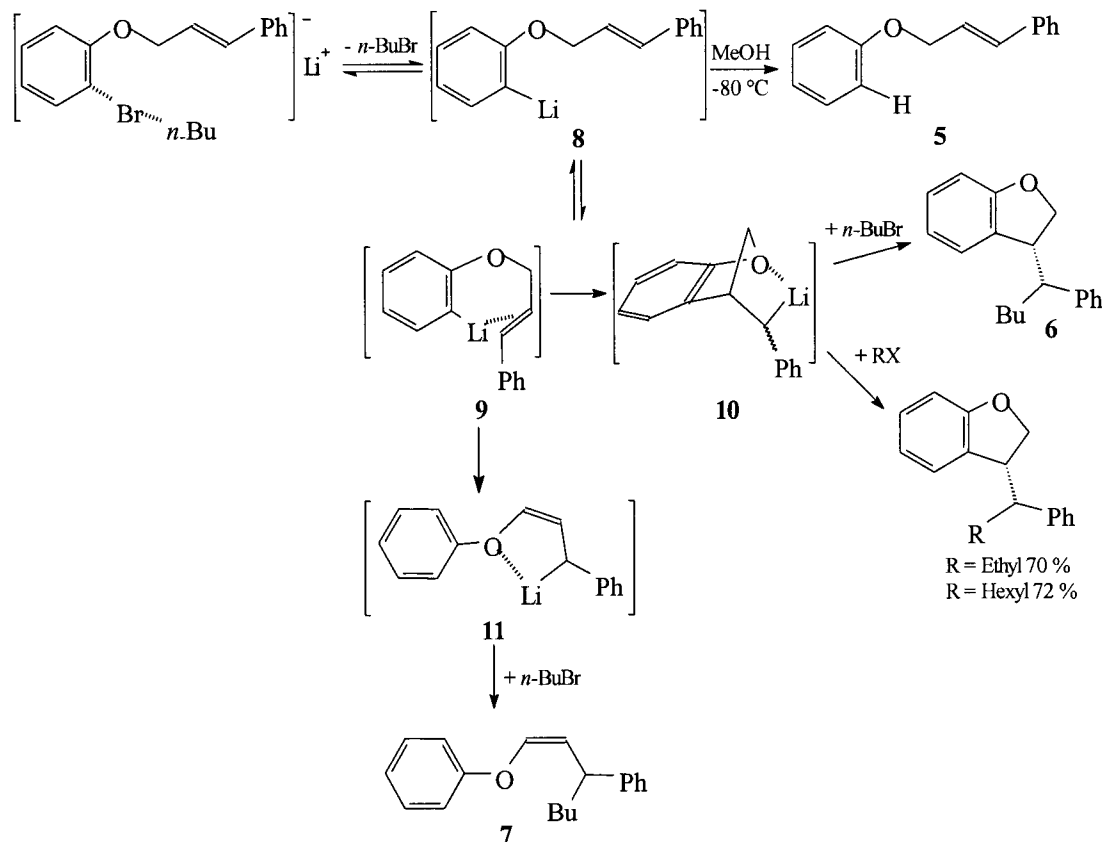


It should also be noted, however, that the finding of open-chain products from radical probes does not definitely rule out a radical intermediate during the formation of the aryl carbanions. Indeed, the radical probe could not be efficient enough to trap a very short-lived aryl radical through a fast radical cyclization. In the case of $\text{X} = \text{Br}$ and $\text{Z} = \text{O}$ the intramolecular cyclization of the radical derived from the 2-bromophenyl 3-phenylprop-2-enyl ether, **4**, was recently found to be $k_C > 8.1 \times 10^9 \text{ s}^{-1}$, 30°C ⁴⁰ (Ref. 40a corrects the value initially given by Johnston *et al.*^{40b}). This radical probe has been used recently to establish the participation of radicals during the formation of aryl Grignard reagents.⁴¹ The main product of the reaction of **4** with *n*-BuLi in THF at -80°C is an open-chain product, **5**, which has a structure similar to **3** with $\text{Z} = \text{O}$, plus two unexpected by-products, **6** and **7**.



The products were isolated and fully characterized by spectroscopic determinations and independent synthesis. By quenching the reaction mixture after 5 min at -80°C with MeOD, high deuterium incorporation ($>95\%$) was observed in the 2-position of the open product **5**, indicating the structure of the open lithiated intermediate **8** (Scheme 1). Efforts were then concentrated on improving the yields of the by-products **6** and **7**, to obtain insights into the mechanisms of their formation. By allowing longer reaction times, the yields of **6** and **7** increase at the expense of **5**; the yield of **6** especially increases (up to 47% after 60 min of reaction), suggesting that **8** could be the precursor of **6** (Table 1, entries 1 and 2). To confirm this assumption, the effect of increasing the temperature of the reaction was examined. Each experiment was performed at least three times, and reproducible yields of products were obtained. Entries 3–5 in Table 1 summarize the drastic effect of temperature upon the yield of **5**. Warming the solution from -80°C to various temperatures leads to complete isomerization of the intermediate, yielding **5** in only 5 mins at temperatures $\geq -50^\circ\text{C}$.

Scheme 1 shows the whole reaction mechanism, outlined on the basis of the experimental findings. The



R = Ethyl 70 %
R = Hexyl 72 %

Scheme 1

Scheme 1

Scheme 1

Scheme 1

Scheme 1

Scheme 1

Scheme 1

Scheme 1

Scheme 1

bromophenol as by-product is not observed, whereas in the reaction of magnesium with **4** under the same conditions (temperature and solvent), where an ET from magnesium to **4** is generally accepted, *o*-bromophenol is regularly formed as a by-product.⁴¹ All these observations converge to suggest the absence of radicals in the reaction of *n*-BuLi with **4**.

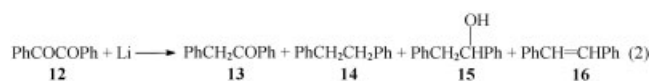
Regarding the by-product **7**, GC–MS of the crude mixture revealed no deuterium incorporation at the aryl C-2 position. Furthermore, results of experiments 4 and 5 in Table 1, and particularly the yield of **4**, are identical when 1.5 or 4 equiv. of *n*-BuLi are used. These experimental facts hint that product **7** is formed via intramolecular rearrangement of the carbanionic intermediate **9** with the allylic protons (Scheme 1), followed by isomerization to the more stable benzilic carbanion and then reaction with *n*-BuBr. The *cis* structure of the by-product **7** indicates the resonance **9** $\leftrightarrow$ **11** shown in Scheme 1; formation of **7** can be visualized through an intermediate **11**, stabilized by Li–oxygen coordination. The crystal structure of [2-lithio-3-bromobenzofuran diisopropyl ether]₂, an α -lithiated ether, has recently been determined.⁴⁴ The structure shows that lithium bridges C and O. Calculations on simpler lithiated ethers at a high level are consistent with Li–oxygen carbenoid structures.⁴⁵

The finding of the route **4** $\rightarrow$ **9** $\rightarrow$ **10** $\rightarrow$ **6** also suggests a likely route for the synthesis of other substituted 2,3-dihydrobenzo[*b*]furans. The study of a synthetic methodology based on the anionic cyclization of **10** in the presence of suitable electrophiles, thus providing a convenient tandem sequence for the synthesis of alkyl-substituted 2,3-dihydrobenzo[*b*]furans, is in progress with successful preliminary results for ethyl and hexyl bromide (see yields in Scheme 1). Taking into account the present and previous results, we envisage the lithium–halogen exchange as a mechanistic spectrum with radical and carbanion in each extreme, the precise structure/s of the transition state(s) prevailing in any case depending on the substrate structure, the nature of the halogen, the solvent and any other reaction conditions.

Organolithium-derived radicals can also be generated by the reaction of suitable substrates with lithium metal. We have recently published a study of the reactions in THF of benzaldehyde on a lithium surface.⁴⁶ As expected, the main reaction product is benzil alcohol, but determinations of minor products (e.g. benzoin and benzil) proved to be mechanistically significant. In fact, they suggested the intermediacy of a benzoyl radical, that could be trapped by CCl₄. The rate of disappearance of benzaldehyde, α and the rate of formation of the three products, were measured and the kinetics of all the reactions pathways involved were determined.^{46a} The first step was proved to be an ET from lithium to benzaldehyde producing a radical anion–lithium cation pair.

The knowledge of the whole reaction scheme based on

the minor products suggested a new synthetic route for the synthesis of benzil benzoate, which is a highly convenient, economic and environmentally friendly alternative for the quantitative synthesis of the highly pure ester.^{46b}



We have now studied the reactions of benzil, **12**, with lithium metal. The rates of decay of **12** and of the formation of products and by-products were followed by GC as a function of time. Most of the reaction occurs in the first 60 min but the reaction is complete in 15–24 h depending on the temperature, the concentration of **12** and the mass of lithium. The main reaction products are: 1,2-diphenylacetophenone, **13**, and 1,2-diphenylethane, **14**, but careful searching for other products showed the presence of by-products, 1,2-diphenyl-1-ethanol, **15**, and 1,2-diphenyl-1-ethene, **16**, in very tiny amounts, that, together with other evidence, give an insight into the full reaction mechanism. No reaction was detected by the quantitative GC determinations in the first 10–15 min, depending on the temperature and reagent concentration. The induction period for the decay of **12** was the same as that for the appearance of **13**; almost 90% of **13** is formed in the first 60 min of reaction; in contrast, **14** appears only after 20 min (as traces) and reaches its final yield after nearly 10 h of reaction.

EPR of the reaction mixture was performed periodically as a probe for the involvement of radicals as reaction intermediates. Signals appear after 12–15 min of reaction depending on the reaction conditions. The EPR spectrum of the reaction mixture in THF ([**12**] = 0.2 M, Li = 428 mg) at 298 K after 20 min of reaction is shown in Fig. 1. The total spectral width is $\Delta a = 7.64$ G and it shows hyperfine structure fully consistent with the dibenzoyl anion [coupling constants: $a_{\text{H}} = 0.99$ G (4), 0.36 G (4) and 1.12 G (2) for the *ortho*, *meta* and *para*-H, respectively. The reported frequencies for the dibenzoyl anion chemically generated in THF are 0.90; 0.41 and 0.90, respectively, $\Delta a = 7.0$ G].¹² A close correspondence was found between the induction period

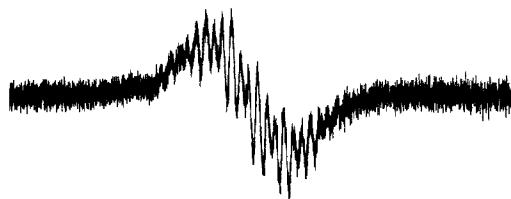
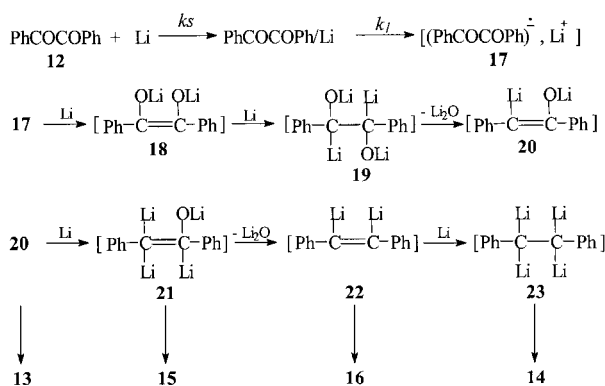


Figure 1. EPR of the reaction of benzil, **12**, with lithium in THF at 298 K, [**12**] = 0.2 M; M_{Li} = 428 mg. Details of the EPR conditions: $\nu = 9.57$ Hz; field control 3436.5 G; span width $\Delta G = 20$ G; modulation = 0.16 Gp; $\tau = 200$ ns; scanning rate = 2 ks



Scheme 2

shown by the EPR signal appearance and that observed for the decay of **12** by GC, indicating that formation of the radical could be the first reaction step.

All the evidence obtained is consistent with the overall reaction mechanism shown in Scheme 2. Adsorption of the reagent on the lithium surface was found to be the initial slow step in the reaction of benzaldehyde with Li, and it also occurs in the reaction of **12** (all adsorption phenomena are symbolized by k_s in the Scheme 2). These are followed by a slow one-electron transfer from the lithium surface to the adsorbed **12**, measured by k_1 , forming the radical anion (**17**)–lithium cation pair; **17** partially escapes the surface and can be detected by EPR of the THF reaction mixture. Further successive reductions of **17** by lithium metal gives intermediates **18** → **19**, and the latter by loss of lithium oxide gives intermediate **20**, precursor of **13**, one of the main products (24% yield in the first 60 min, final yield 35%). Similar reactions afford intermediates **21**, **22** and **23**, that are the precursors of the other isolated products (only 5% of **14** is produced in the first 60 min of reaction; yields of **14**, **15** and **16** after 24 h of reaction are 24, 5 and 6%, respectively). Treatment of the reaction mixture after 24 h with deuterated water showed the disappearance of the aliphatic protons of **13** and **14** in the ^1H NMR spectrum of the reaction mixture. Traces of pinacol were detected by periodical HPLC of the reaction mixture: its formation shows a similar induction period to that of **13**; it reaches the maximum yield after about 40 min of reaction and then decreases to almost negligible amounts after 60 min. This is further evidence of the reaction sequence **18** → **19** → **20**, which should be faster than the others shown in Scheme 2 on the basis of the relative yields of products observed as a function of time.

The reasons for the induction period are not yet clear. Adsorption of the reagent on the lithium surface was proved to occur: strong interaction between the adsorbate and the metal causes the formation of a layer (detected by GC at the metal surface). Nevertheless, the long induction period could be related to additional surface processes. In the Grignard reagent formation on magne-

sium surface, induction periods are very well known, and plausible hypotheses abound,⁴⁷ but there is no comprehensive, documented understanding of the factors that create the induction period or constitute initiation.⁴⁸

CONCLUSIONS

This paper has described how the careful investigation of the by-products formed in tiny amounts in some organolithiums reactions and the survey of the different parameters that influence their formation can provide insights into the specific mechanisms involved. They also afforded important clues on the likely transition states and reaction intermediates, indicating that both radical and carbanionic mechanisms are possible and that the pathways followed are strongly dependent on the reactants and reaction conditions. Finally, a thorough knowledge of the reaction mechanism could suggest new convenient, economical and environmentally friendly synthetic methodologies for the preparation of alkyl-substituted 2,3-dihydrobenzo[*b*]furan and of aryl esters, with important advantages over the usual conventional, stepwise reactions.

Acknowledgements

Financial support from the Universidad de Buenos Aires and CONICET is gratefully acknowledged.

REFERENCES

- Wakefield BJ. *Organolithium Methods*. Academic Press: London, 1988.
- Jamison TF, Shambayati S, Crowe WE, Schreiber SL. *J. Am. Chem. Soc.* 1997; **119**: 4353–4363.
- Hilmersson G, Arvidsson PI, Davidsson Ö, Håkansson M. *Organometallics* 1997; **16**: 3352–3358.
- Adler M, Marsh M, Nudelman NS, Boche G. *Angew. Chem., Int. Ed. Engl.* 1999; **38**: 1261–1262.
- (a) Nudelman NS, García Liñares GE. *J. Org. Chem.* 2000; **65**: 1629–1635; (b) Nudelman NS, Schulz HG, García Liñares GE, Bonatti AE, Boche G. *Organometallics* 1998; **17**: 146–150.
- Beak P, Allen DJ. *J. Am. Chem. Soc.* 1992; **114**: 3420–3425.
- Bailey WF, Patricia JJ. *J. Organomet. Chem.* 1988; **352**: 1–46.
- (a) Ashby EC, Park B, Patil GS, Gadru K, Gurumurthy R. *J. Org. Chem.* 1993; **58**: 424–437; (b) Ashby EC. *Acc. Chem. Res.* 1988; **21**: 414–422.
- (a) Newcomb M, Williams WG, Crumacker EL. *Tetrahedron Lett.* 1985; **26**: 1183; (b) Bailey WF, Patricia JJ, Nurmi TT, Wang W. *Tetrahedron Lett.* 1986; **27**: 1861–1864; (c) Bailey WF, Patricia JJ, Nurmi TT, Wang W. *Tetrahedron Lett.* 1986; **27**: 1865–1868.
- Boche G, Lohrenz JCW, Opel A. In *Lithium Chemistry: a Theoretical and Experimental Overview*, Sapse A-M, Schleyer PvR (eds). Wiley: New York, 1995; Chapt. 7.
- Ashby EC, Pham T. *J. Org. Chem.* 1987; **52**: 1292–1300.
- (a) Maruyama K, Katagiri T. *J. Phys. Org. Chem.* 1991; **4**: 381; (b) Maruyama K, Katagiri T. *J. Phys. Org. Chem.* 1991; **4**: 158, and references cited therein.
- (a) Yamataka H, Miyano N, Hanafusa T. *J. Org. Chem.* 1991; **56**: 2573; (b) Yamataka H, Fujimura N, Kawafuji Y, Hanafusa T. *J. Phys. Org. Chem.* 2002; **15**: 903–910.

- Am. Chem. Soc.* 1987; **109**: 4305–4308; (c) Matsuyama T, Yamataka H, Hanafusa T. *Chem. Lett.* 1988; 1367–1368.
14. (a) Nudelman NS, Doctorovich F, Amorin G. *Tetrahedron Lett.* 1990; **31**: 2553; (b) Doctorovich F, Nudelman NS. *Magn. Reson. Chem.* 1990; **28**: 576–579.
15. Nudelman NS, Doctorovich F. *Tetrahedron* 1994; **50**: 4651–4666.
16. Newcomb M, Choi S-Y, Horner JH. *J. Org. Chem.* 1999; **64**: 1225–1231.
17. Nudelman NS, Schulz HG, García GV. *J. Phys. Org. Chem.* 1998; **11**: 1–9.
18. Nudelman NS, García GV. *J. Org. Chem.* 2001; **66**: 1387–1394.
19. Ahlbrecht H, Harbach J, Kalinowski HO, Lang A, Maier G. *Chem. Ber.* 1997; **130**: 683–686.
20. Nudelman NS, García GV, Schulz HG. *J. Org. Chem.* 1998; **63**: 5730–5731.
21. Tietze LF. *Chem. Rev.* 1996; **96**: 139–148.
22. Shriver DF. *The Manipulation of Air Sensitive Compounds*. Wiley: New York, 1989.
23. Pérez DG, Nudelman NS. *J. Org. Chem.* 1988; **53**: 408–413.
24. Vitale AA, Doctorovich F, Nudelman NS. *J. Organomet. Chem.* 1987; **332**: 9–18.
25. Trzuppek LS, Newirth TL, Kelly EG, Nudelman NS, Whitesides GM. *J. Am. Chem. Soc.* 1973; **95**: 8118–8133.
26. Moody CJ, Doyle KJ, Elliot MC, Mowlem TJ. *J. Chem. Soc., Perkin Trans. 1* 1997; 2413–2417.
27. White WN, Fife WK. *J. Am. Chem. Soc.* 1961; **83**: 3846–3853.
28. Sunthakar SV, Gilman H. *J. Org. Chem.* 1951; **16**: 8–16.
29. (a) Wittig G, Schöllkopf V. *Tetrahedron* 1958; **3**: 91; (b) Wittig G. *Angew. Chem.* 1958; **70**: 65.
30. Boche G, Walborsky HM. In *The Chemistry of the Cyclopropyl Group*, Rappaport Z (ed). Wiley: Chichester, 1987; 701.
31. Reich HJ, Green DP, Phillips NH. *J. Am. Chem. Soc.* 1991; **113**: 1414–1416.
32. Boche G, Schimeczek M, Cioslowski J, Piskorz P. *Eur. J. Org. Chem.* 1998; 1851–1860.
33. Beak P, Allen DJ, Lee WK. *J. Am. Chem. Soc.* 1990; **112**: 1629–1630.
34. (a) Rogers HR, Houk J. *J. Am. Chem. Soc.* 1982; **104**: 522–525; (b) Winkler HJS, Winkler H. *J. Am. Chem. Soc.* 1966; **88**: 964–969; (c) Winkler HJS, Winkler H. *J. Am. Chem. Soc.* 1966; **88**: 969–974.
35. (a) Fischer H. *J. Phys. Chem.* 1969; **73**: 3834; (b) Russell GA, Lamson DW. *J. Am. Chem. Soc.* 1969; **91**: 3967–3968.
36. (a) Ward HR. *Acc. Chem. Res.* 1972; **5**: 18; (b) Lawler RG. *Acc. Chem. Res.* 1972; **5**: 25–32.
37. Ashby EC, Coleman D, Gamasa M. *J. Org. Chem.* 1987; **52**: 4079.
38. Jenneskens LW, de Boer HJR, de Wolf WH, Bickelhaupt F. *J. Am. Chem. Soc.* 1990; **112**: 8941–8949.
39. Horner JH, Musa OM, Bouvier A, Newcomb M. *J. Phys. Org. Chem.* 2000; **13**: 688–692.
40. (a) Garden SJ, Avila DV, Beckwith ALJ, Ingold KU, Luszyk J. *J. Org. Chem.* 1996; **61**: 805–809; (b) Johnston LJ, Luszyk J, Wayner DDM, Abeywickreyma AN, Beckwith ALJ, Scaiano JC, Ingold KU. *J. Am. Chem. Soc.* 1985; **107**: 4594–4596.
41. (a) Bodineau N, Mattalia J-M, Thimokhin V, Handoo K, Négrel J-C, Chanon M. *Org. Lett.* 2000; **2**: 2301–2304; (b) Bodineau N, Nudelman NS, García GV, Mattalia J-M, Rogério M, Arbelot M, Chanon M. *ARKIVOC* 2002; **5**: 139–150.
42. Jedlicka B, Crabtree RH, Siegbahn EM. *Organometallics* 1997; **16**: 6021–6025.
43. Farnham WB, Calabrese JC. *J. Am. Chem. Soc.* 1986; **108**: 2449–2451.
44. (a) Boche G, Bosold F, Zulauf P, Marsch M, Harms K, Lohrenz J. *Angew. Chem. Int. Ed. Engl.* 1991; **30**: 1455; (b) Boche G, Opel A, Marsch M, Harms K, Haller F, Lohrenz J, Thummler C, Koch W. *Chem. Ber.* 1992; **125**: 2265.
45. Viruela-Martin P, Viruela-Martin R, Tomás F, Nudelman NS. *J. Am. Chem. Soc.* 1994; **116**: 10110–10116.
46. (a) Nudelman NS, Mendiara S. *J. Phys. Org. Chem.* 1997; **10**: 233–237; (b) Nudelman NS, Mendiara S. *Tetrahedron Lett.* 1997; **38**: 2245–2248.
47. Silverman GS, Rakita PE. In *Handbook of Grignard Reagents*, Heinemann H (ed). Marcel Dekker: New York, 1996.
48. Garst JF, Ungvary F. In *Grignard Reagents: New Developments*, Richey HG (ed). Wiley: Chichester, 2000; Chapt. 7, 222–260.