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THE REACTION OF *n*-BUTYLLITHIUM WITH BENZOIC ACID: IS NUCLEOPHILIC ADDITION COMPETITIVE WITH DEPROTONATION?†

PETER BEAK* AND LANCE A. PFEIFER

Department of Chemistry, University of Illinois, Urbana, Illinois 61801, USA

An evaluation of a branching vs sequential mechanism for the reaction of benzoic acid with *n*-butyllithium favors the latter. © 1997 John Wiley & Sons, Ltd.

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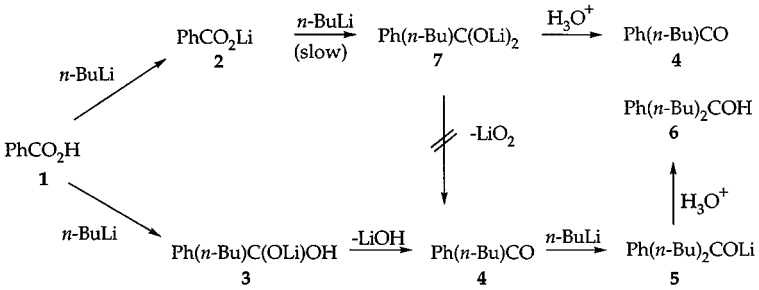
INTRODUCTION

The reaction of carboxylic acids with organolithium reagents to provide ketones and alcohols is well known.[1] The first step in the reaction has been considered to be formation of a lithium carboxylate, which subsequently undergoes nucleophilic addition by the organolithium reagent.[2] In 1991, however, it was proposed that nucleophilic addition to benzoic acid by *n*-butyllithium is competitive with deprotonation.[3] The classic mechanism is sequential whereas the more recent mechanism involves branching from benzoic acid. If the later mechanism were to be correct, we believe it would be the first case of transfer of a highly acidic proton being slower than nucleophilic addition in organolithium chemistry.

We have investigated reactions of organolithium reagents for which deprotonation and bromine lithium exchange were claimed to be competitive. Our experiments showed, however, that deprotonation precedes bromine lithium exchange at the molecular level.[4] Because of our interest in this type of reaction, we have reinvestigated the reaction of *n*-butyllithium with benzoic acid. We report that we are unable to find the compelling evidence that we believe would be needed to support the branching mechanism.

The branching pathway for reaction of benzoic acid and *n*-butyllithium which was proposed in 1991 is shown in Scheme 1.[3] In one branch acid **1** reacts with *n*-butyllithium to give carboxylate salt **2**, which subsequently reacts slowly with *n*-butyllithium to give **7**. In the other branch, nucleophilic addition of *n*-butyllithium to benzoic acid gives adduct **3**, which is also a precursor of the ketone **4**. The ketone reacts with *n*-butyllithium before quenching to provide **5**, the precursor to alcohol **6**. Under this mechanism, ketone **4** that is produced from **7** arises only on exposure to aqueous acid. Consequently, alcohol **6** should be produced only from **3** under the reaction conditions. In the paper proposing this mechanism, it was stated that '18% of *n*-butyllithium has been used in the nucleophilic pathway' and that control experiments have shown that 'the



Scheme 1

* *Correspondence to:* P. Beak.

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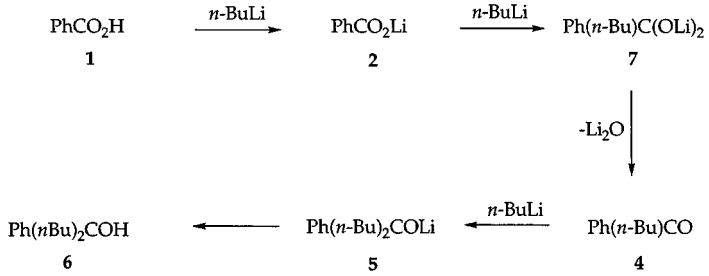


Scheme 2

latter (*n*-butyllithium) adds to the carboxylate (**2** in Scheme 1) with a relatively slow rate in comparison to other reactions and we can consider that the bis-lithium alkoxide (**7** in Scheme 1) is virtually absent from the reaction mixture.'[3]

The sequential reaction pathway is shown in Scheme 2 with the lithium carboxylate **2** being the precursor of **4** and **5**.

We sought experimental data would distinguish the branching and sequential pathways. In evaluating the alternative mechanisms, we made the assumption that Scheme 2 is the simpler process. The reaction of Scheme 1 has more species and more steps than Scheme 2. Under the logic of processing experimental facts by Ockham's razor, Scheme 2 should be preferred unless there is compelling experimental evidence to rule it out.[5]

RESULTS AND DISCUSSION

The reaction of benzoic acid with *n*-butyllithium was carried out in THF and found to provide the acid, the ketone **4** and the alcohol **6** as expected.[3] The yields and ratios of products were a function of the reaction conditions as described (see below).[3] We note that the reactions can be heterogeneous, a factor which may complicate the interpretation of both the reaction and control experiments.

The necessity for the branching pathways of Scheme 1 is stated to be based in part of the assessment (see above) that the carboxylate salt **2** reacts with *n*-butyllithium too slowly to account for the products.[3] In particular, if Scheme 1 is correct, the alcohol **6** should not be produced from **2** under the reaction conditions.

We investigated the reaction of *n*-butyllithium with lithium benzoate (**2**). The lithium carboxylate was prepared from **1** and 1·15 equiv. of lithium hydride and exposed to *n*-butyllithium before the reaction was quenched after 30 s with methanol and the ratio of ketone **4** and alcohol **6** determined. The results of these experiments are given in Table 1.

The results in Table 1 show that the reaction of the lithium carboxylate **2** with butyllithium leads to both the ketone **4** and the alcohol **6**. The salt **2** was fairly reactive when the reactions were carried out at room temperature and under conditions where the carboxylate was more soluble. When either the temperature was lowered or the amount of solvent was decreased, the amounts of addition products decreased substantially, although they were still detectable.

$$\mathbf{2} \xrightarrow[(2)\ H_3O^+]{(1)\ n\text{-BuLi}} \mathbf{4+6}$$

We note that neither our experiments nor other control experiments which would use preformed **2** may be perfect mimics of the reaction. The lithium carboxylate that is produced *in situ* from *n*-butyllithium and benzoic acid could be part of an aggregate that could have different reactivity than exogenous lithium benzoate. Indeed **2**, **3**, **5** and **7** formed in the presence of *n*-butyllithium might be parts of aggregates which would also involve *n*-butyllithium that would have a different reactivity from *n*-butyllithium added to preformed **2**. Although we have not been able to make rate comparisons, we note that if these results are taken to show that **2** can give rise to **4** and **6** under the reaction conditions in which **1** provides **4** and **6**, the pathway in Scheme 1 should be rejected. Under Scheme 1 the alcohol **6** can arise only via **3**, which is not available from **2**.

However, this interpretation is open to challenge. Rubottom and Kim[6] have shown that the amounts of tertiary alcohols arising from the reaction of methyllithium with carboxylic acids can be a function of the quenching reagent

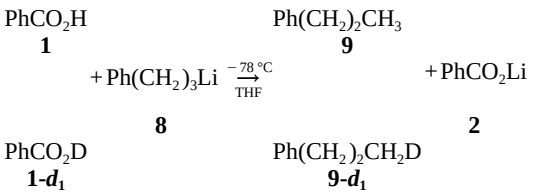
Table 1. Reaction of **2** with *n*-butyllithium

n-BuLi (equiv.)	Temperature (°C)	THF solvent (ml)	Addition as % of *n*-BuLi	**4**:**6** ratio
0·5	− 78	40	7·8	0·7
0·5	20	40	73	1·5
0·5	20	5	18	0·2
0·2	20	5	18	0·6

(quenching with trimethylsilyl chloride greatly reduced, but did not necessarily eliminate, the amount of tertiary alcohol relative to quenching with aqueous ammonium chloride). Such results suggest that the alcohol **6** might be an artifact arising after the initial reaction and during the quenching. This criticism could be applicable to a work-up with any quenching reagent.[6]

Accordingly, we carried out a second series of experiments in which the amount of alcohol formed during the reaction should be different under the reaction pathways in Schemes 1 and 2. The relative rates of the reaction of benzoic acid (**1**) and of benzoic acid-d_1 (**1-*d*$_1$**) with *n*-butyllithium could be different. In this case, under the mechanism in Scheme 2, the reaction would proceed via **2** from either **1** and **1-*d*$_1$** and the ratios of products **4** and **6** would be the same from either reactant. However, the mechanism in Scheme 1 should give different product ratios for the reactions of **1** and **1-*d*$_1$**. In this case a hydrogen–deuterium isotope effect would favor the formation of **3** over **2** for the reaction of **1-*d*$_1$** relative to **1**. The subsequent reactions of **3** should give a product profile for **4** and **6** which is different from that in which **2** provides **4**. The relative amount of **6** would be expected to be greater for the reaction of **1-*d*$_1$** than for **1** since in Scheme 1 **3** provides the only pathway to **6**.

In order for this experimental test to be valid, the reaction of **1-*d*** with *n*-butyllithium must show a significant primary hydrogen–deuterium isotope effect (the hydrogen deuterium isotope effect for deprotonation of a carboxylic acid by an alkyl lithium could be small if the reaction was diffusion controlled or the transfer highly asymmetric[7]). We evaluated the isotope effect by the reaction of mixtures of fivefold excesses of **1** and of **1-*d*** with 3-phenylpropyl lithium (**8**).[4] The products of the reaction, 1-phenylpropane (**9**) and 1-phenylpropane-3-d_1 (**9-*d*$_1$**), were analyzed by GC–MS and by MS.



The product ratios in Table 2 show there is an experimentally significant isotope effect for the reaction of **1** and **1-*d*$_1$** with **8**. There appears to be a substantially greater nominal isotope effect for the reaction of the 1:4 ratio than for the 1:1 ratio of **1**:**1-*d*$_1$**, however, extraction of a quantitative isotope effect from these data is not warranted. Reaction variables include the presence of **9** in **8** and possible exposure to small amounts of atmospheric water. The organolithium reagent **8** was shown by reaction with deuterium oxide to contain about one third **9** (we presume this results from the reaction of **8** with *tert*-butyl bromide formed in the preparation of **8** from 1-phenyl-3-bromopropane with *tert*-butyllithium). Nonetheless the present data are sufficient to suggest that if **8** is a model for *n*-butyllithium a hydrogen–deuterium isotope effect of at least 5:1 can be expected for the reaction of benzoic acid with *n*-butyllithium under these reaction conditions. Thus, if 18% of the reaction of **1** were to proceed by addition of *n*-butyllithium to give **3** from **1** and *n*-butyllithium, then at least 90% of the reaction of **1-*d*$_1$** with *n*-butyllithium should proceed via **3**.

Table 2. Reactions of mixtures of **1** and **1-*d*$_1$** to give **1-*d*$_1$** and **9-*d*$_1$**

Reactant ratio: **1**:**1-*d*$_1$**	Product ratio: **9**:**9-*d*$_1$**
1:4	4:1[a]
1:1	6:1[a]

[a] Corrected for natural isotopes and for the presence of **9** in **8**.

Table 3. Reactions of **1** and **1-*d*$_1$** with *n*-butyllithium in THF at −78 °C to give **4** and **6**

Reactant	*n*-BuLi (equiv.)	*n*-BuLi addition (%)	**4**:**6** ratio
1	1·0	4·5	1:2·4
1-*d*$_1$	1·0	4·2	1:2

The products **4** and **6** from the reactions of **1** and **1-*d*$_1$** with *n*-butyllithium are shown in Table 3. The results show that these reactants afforded product yields and **4**:**6** ratios which are very similar. Indeed, the slight differences, a higher yield of addition products which contained a larger amount of the alcohol **6** relative to **4** from **1** is the opposite of what would be expected if **3** is the only precursor of **6** and if more **3** is formed from **1-*d*$_1$** than from **1**. Accordingly, these results discount Scheme 1 as compared with Scheme 2.

In summary, we have carried out two experiments to evaluate the possibility that nucleophilic addition to benzoic acid by *n*-butyllithium is competitive with deprotonation. We do not find compelling evidence to support the mechanism of Scheme 1 and suggest the data to be consistent with the more prosaic mechanism of deprotonation preceding nucleophilic addition. This preferred reaction pathway as illustrated in Scheme 2 is as originally suggested.[1, 2]

EXPERIMENTAL

General. ^{1}H NMR spectra were obtained using a QE 300 MHz spectrometer. Chemical shifts are reported in parts per million downfield from either tetramethylsilane (TMS) or relative to CH_2Cl_2 as an internal standard and $CDCl_3$ or CD_2Cl_2 as solvent. When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; and br, broadened. Mass spectra were measured by Dr R. Milberg and co-workers (Noyes

Laboratory, University of Illinois, Urbana, IL, USA) on a Finnigan MAT 731 mass spectrometer. Elemental analysis was performed by the University of Illinois Microanalytic Laboratory. Analytical gas chromatography (GC) was performed on a Hewlett-Packard Model 5890 gas chromatographer with a Hewlett-Packard Model 3396A integrator and a 25 m HP-5 capillary column. GC–electron impact ionization mass spectrometry (GC–MS) was carried out on a Hewlett-Packard model 5890 GC–MS workstation. For reactions with air-sensitive reagents, all glassware was oven dried prior to use and all reactions were performed under a nitrogen atmosphere.

Materials. Diethyl ether (Et_2O), pentane and tetrahydrofuran (THF) were distilled from sodium and benzophenone under a nitrogen atmosphere immediately preceding their use. 3-Phenylpropyl bromide was distilled from calcium chloride at 58–60 °C and 0·15 Torr. *n*-Butyllithium and *tert*-butyllithium were purchased from Aldrich (1·5 M) and titrated prior to use.[8]

Isotopic ratios. The isotopic distribution was calculated by the standard matrix method with respect to the molecular ion region in the GC–MS trace of the corresponding unlabeled compound.[9] The isotopic distribution for an intermolecular reaction was calculated based on the actual spectra obtained minus the background spectra.

Preparation of 1-phenylpentanone (4).[10] To a solution of benzonitrile (4·85 mmol) in diethyl ether under nitrogen at −10 °C was added 1·0 equiv. of *n*-butyllithium dropwise over 5 min. The reaction mixture was stirred at this temperature for 5 min, then warmed to room temperature and stirred for an additional 3 h. The reaction mixture was then poured into 50 ml of an ice–water mixture and warmed to room temperature. The aqueous layer was extracted three times with diethyl ether. The organic extracts were then combined and washed once with brine. The organic layer was dried over anhydrous sodium sulfate and concentrated, giving a yellow oil. The crude product was purified on a silica column with 10% ethyl acetate–hexane as eluent to give 0·490 g (62%) of the product **4** as a non-viscous slightly yellow oil of >95% purity. ^{1}H NMR (TMS, $CDCl_3$): δ 7·98 (d, 2H, ARH), 7·35–7·60 (m, 3H, ArH), 2·97 (t, 2H, $COCH_2$), 1·70 (m, 2H, CH_2), 1·4 (m, 2H, CH_2), 0·95 (t, 3H, CH_3). GC retention times: 2·78 min (benzonitrile, 2%), 5·43 min (product, 95%) and 11·05 min (impurity, 3%).

Preparation of dibutylphenyl alcohol (6).[11] To a solution of nonan-5-one (2·13 mmol) in 25 ml of THF at 0 °C under nitrogen was added 1·1 equiv. of phenylmagnesium bromide over 2 min. The solution turned light yellow and was stirred at 0 °C for 1 h, then warmed to room temperature and stirred for another 30 min. The solution was quenched in 1 M HCl and immediately extracted three times with diethyl ether. The organic extracts were combined and washed once each with water and brine. The organic layer was dried under anhydrous sodium sulfate and chromatographed on a silica column with 10% ethyl acetate–hexane as eluent to give 0·380 g (82%, 95% pure) of **6**. The alcohol **6** was a clear, viscous oil. ^{1}H NMR: (TMS, $CDCl_3$), δ 7·36 (m, 3H, ArH), 7·22 (m, 2H, ARH), 1·80 (m, 4H, $COHCH_2$), 1·28 (m, 4H, CH_2), 1·05 (m, 4H, CH_2), 0·92 (m, 6H, CH_3). GC retention times: 4·26 min (impurity, 5%) and 7·07 min (alcohol, 95%).

A T_1 relaxation experiment for a known mixture of ketone **4** and alcohol **6** was carried out to establish that the relaxation times would allow accurate detection of the product ratios by integration of an NMR spectrum of the mixture. The experiment was performed using a known 1:1·3 ratio of the ketone to alcohol, and integration of the spectrum after the T_1 experiment showed a 1:1·2 ratio of the ketone to alcohol. This experiment showed that accurate (<10% error) integrations of the ketone and alcohol products could be obtained under standard NMR data acquisition conditions.

Preparation of deuterated benzoic acid (1-d_1*).* Benzoic acid was stirred in 99·8% pure D_2O for 1 h under nitrogen. The solution was then concentrated until a small amount of D_2O remained (*ca* 1 ml). The deuterated acid was dried under vacuum for 1 h at 50 °C, at which time the amount of deuterated acid was reweighed (some sublimation had occurred) and used immediately in the following steps. Analysis: calculated for $C_6H_5O_2D$, C 68·29, H 4·91; found, C 68·28, H 4·87%; calculated for $C_6H_5O_2H$, C, 68·84, H 4·95; found, C, 68·85, H 4·96%.

Reaction of benzoic acid with n-butyllithium (−78 °C). To a solution of the acid (5 mmol) in 40 ml of THF under nitrogen was added *n*-butyllithium (5 mmol) at a rate of 1 ml/min^{-1}. The solution was stirred at −78 °C for 30 min, then quenched with a few milliliters of methanol at −78 °C. The solution was concentrated, producing a white solid, which was dissolved in a mixture of ethyl acetate and 0·1 M KOH. The oranic layer was extracted three times with 40 ml of the potassium hydroxide solution, then the aqueous layers were combined and extracted once with ethyl acetate. The organic layers were combined and washed twice with water and once with brine. The organic layer was dried over anhydrous sodium sulfate and concentrated, giving a light yellow oil. ^{1}H NMR (CD_2Cl_2), **4**+**6**: **4**, δ 7·98 (d, 2H, ArH), 7·35–7·60 (m, 3H, ArH), 2·97 (t, 2H, $COCH_2$), 1·70 (m, 2H, CH_2), 1·4 (m, 2H, CH_2), 0·95 (t, 3H, CH_3); **6**, δ 7·36 (m, 3H, ArH), 7·22 (m, 2H, ArH), 1·80 (m, 4H, $COHCH_2$), 1·28 (m, 4H, CH_2), 1·05 (m, 4H, CH_2), 0·92 (m, 6H, CH_3). GC retention times: 5·45 min (ketone) and 7·07 min (alcohol). The ratios of the ketone and alcohol were determined by measuring the relative peak heights of the respective protons. Control experiments in which known amounts of the ketone and alcohol were mixed and analyzed showed a maximum error of 10% using this method of analysis. The aqueous layer was reacidified with 6–HCL and extracted with ethyl acetate twice. The organic layers were combined and washed twice with water and once with brine, yielding recovered benzoic acid. ^{1}H NMR (TMS, $CDCl_3$): δ

12·2–12·8 (s, br, 1H, COOH), 8·12 (d, 2H, ArH), 7·6 (t, ArH), 7·47 (t, ArH).

Preparation and reaction of lithium carboxylate (2). To a solution of 5 mmol of benzoic acid in 40 ml of THF at room temperature under nitrogen was added 1·15 equiv. of lithium hydride. The solution was heated at 50–60 °C on a hot water-bath for 1 h, during which time a white precipitate formed. Bubbling of hydrogen gas was vigorous for the first several minutes but was undetectable after 30 min. The solution was concentrated, THF was added and the solution was cooled to the desired temperature for reaction of the carboxylate salt (20 or −78 °C) before the appropriate amount of *n*-butyllithium (0·2 or 0·5 equiv.) was added at a rate of 1 ml min^{-1}. The solution was stirred for 30 s, at which time it was quenched with 5 ml of methanol, stirred for several minutes and then warmed, if needed, to room temperature. The solution was concentrated, partitioned between 0·1 M KOH and ethyl acetate and separated. The organic layer was extracted twice more with 30 ml of the hydroxide solution. The aqueous layers were combined and extracted once with ethyl acetate (40 ml). The organic layers were combined and washed once with water and twice with brine, dried over anhydrous sodium sulfate and concentrated, giving a light yellow oil. NMR data were taken on the mixture of ketone **4** and alcohol **6** by comparing the integration of the α-protons on the ketone with the phenyl protons. ^{1}H NMR (CD_2Cl_2), **4**+**6**: **4**, δ 7·98 (d, 2H, ArH), 7·35–7·60 (m, 3H, ArH), 2·97 (t, 2H, $COCH_2$), 1·70 (m, 2H, CH_2), 1·4 (m, 2H, CH_2), 0·95 (t, 3H, CH_3); **6**, δ 7·36 (m, 3H, ArH), 7·22 (m, 2H, ArH), 1·80 (m, 4H, $COHCH_2$), 1·28 (m, 4H, CH_2), 1·05 (m, 4H, CH_2), 0·92 (m, 6H, CH_3). GC retention times: 5·51 min (ketone) and 7·05 min (alcohol). The aqueous layer was reacidified using 5 ml of 6 M HCl and extracted twice with ethyl acetate. The organic layers were combined and washed twice with water and once with brine, yielding recovered benzoic acid. ^{1}H NMR (TMS, $CDCl_3$), recovered benzoic acid (**1**): δ 12·2–12·8 (s, br, 1H, COOH(, 8·12 (d, 2H, ArH), 7·6 (t, ArH), 7·47 (t, ArH).

Preparation of 3-phenylpropyllithium (8).[12] To 25 ml of diethyl ether at −78 °C were added 31·5 mmol (2·1 equiv.) of *tert*-butyllithium over 8 min. The solution was stirred for 10 min, during which time a faint yellow color developed. Neat 3-phenylpropyl bromide (15 mmol) was added by syringe over 3 min, turning the solution bright yellow. The solution was stirred for 45 min at −78 °C. A white precipitate formed after 30 min of stirring. The diethyl ether was evaporated using the Schlenk technique at −40 °C and 0·2 Torr (1 Torr = 133·3 Pa) for 2 h, then 25 ml of pentane were added by the Schlenk technique and the solution was filtered through a dry Celite column, yielding an orange solution of the lithium reagent.

Standardization of 3-phenylpropyllithium (8). To 10 ml of 99·8% D_2O at room temperature under nitrogen were added 2 mmol of **8**. The reagent became colorless immediately. The recovered deuterated phenylpropane was analyzed by GC–MS and MS. GC–MS data: background of phenylpropane standard, *m*/*z* 120 (100), 121 (10), 122 (0·5)l; product for D_2O: *m*/*z* 120 (57), 121 (100), 122 (10) for the phenylpropane peak. MS data: background of phenylpropane standard, *m*/*z* 120 (100), 121 (10), 122 (0·4); product for D_2O, *m*/*z* 118 (7), 119 (23), 120 (69), 121 (100), 122 (10).

Reaction of 3-phenylpropyllithium (8) with benzoic acid (1). To the mixture of **1**-d_1 and **1** totaling 5 mmol in 40 ml of THF was added 1 mmol of **8** at −78 °C. The solution was stirred for 30 min, then quenched with methanol at −78 °C. The solution was then partitioned between 0·1 M KOH and diethyl ether. The aqueous layer was extracted twice with diethyl ether. The ether extracts were combined and washed twice with water and once with brine to afford **9** and **9**-d_1. GC–MS and MS data were obtained. GC–MS data: 80:20 D:H, *m*/*z* 120 (100), 121 (26), 122 (2) for the phenylpropane peak; 50:50 D:H, *m*/*z* 120 (100), 121 (19), 122 (1) for the phenylpropane peak. MS data: 50:50 D:H, *m*/*z* 119 (1), 120 (100), 121 (17), 122 (1).

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