

Stability of the Dilithium Salts formed by the Reaction of Organolithium Derivatives with Lithium Salts of Aromatic Carboxylic Acids

By Philip Hodge,* Gordon M. Perry, and Paul Yates, Chemistry Department, University of Lancaster, Lancaster LA1, 4YA Lancashire

The dilithium salts $\text{PhCR}(\text{O-Li}^+)_2$, formed by the reaction of organolithium derivatives with lithium carboxylates, are stable in ether heated under reflux for 96 h when R = phenyl, 4-tolyl, or 4- or 2-methoxyphenyl, but decompose to give lithium benzoate and RLi when R = 2,6-dimethoxyphenyl, 2-thienyl, or 2-furyl. The dilithium salts react with water to give ketones; efficient methods for the synthesis of several substituted benzophenones, 2-benzoylthiophen, and 2-benzoylfuran are reported.

Base-induced cleavage of aromatic ketones is formally the reverse of the above reactions. Fluorenone, 2-chlorobenzophenone, 2,6-dimethoxybenzophenone, and 2-benzoylthiophen are cleaved readily when treated with potassium t-butoxide (10 equiv.) and water (3 equiv.) in ether but are unaffected by the analogous reagent prepared with lithium t-butoxide.

THE reaction of phenyl-lithium with lithium benzoate gives initially the dilithium salt (3), which during work-up reacts with water to give benzophenone.^{1,2} Other ketones can be prepared similarly.³⁻⁶ It has been suggested that the corresponding dipotassium salt (or the incipient salt) is an intermediate in the cleavage of benzophenone by a mixture of potassium t-butoxide and water in ether⁷⁻⁹ or 1,2-dimethoxyethane,^{8,10} and that the salt decomposes to phenylpotassium and potassium benzoate. This prompted us to investigate whether the dilithium salts generated in the synthesis of some aromatic ketones showed any tendency to break down to organolithium derivatives and lithium carboxylates, and we now report the results. Evidence for the breakdown of the dilithium salts has already been obtained in a few instances, but the reactions involved

halogenated aliphatic acids,^{2,11} triphenylacetic acid,¹² or phenylpropionic acid,¹³ or their salts.

We first investigated the reaction between lithium benzoate and phenyl-lithium.¹ Zook *et al.* isolated the dilithium salt (3) formed and showed that the dry salt can be heated for 12 h at 100 °C with negligible decomposition.² We have shown by tracer experiments that the salt is formed irreversibly under the various conditions summarised in Table 1. An excess of lithium [*ring*-¹⁴C]-benzoate was used in these reactions and, after work-up, the specific activity of the recovered benzoic acid was measured and compared with that of the acid used to prepare the labelled lithium benzoate. Had the dilithium salt broken down to starting materials, the recovered acid would have been less active than the initial acid, but in all the reactions studied the activity did not change. To investigate the effect of changing one or both counter ions, the remaining experiments in

¹ H. Gilman and P. R. Van Ess, *J. Amer. Chem. Soc.*, 1933, **55**, 1258.

² H. F. Bluhm, H. V. Donn, and H. D. Zook, *J. Amer. Chem. Soc.*, 1955, **77**, 4406.

³ M. J. Jorgensen, *Org. Reactions*, 1970, **18**, 1.

⁴ J. C. Floyd, *Tetrahedron Letters*, 1974, 2877.

⁵ R. Levine, M. J. Karten, and W. M. Kadunce, *J. Org. Chem.*, 1975, **40**, 1770.

⁶ H. O. House and T. M. Bare, *J. Org. Chem.*, 1968, **33**, 943; T. M. Bare and H. O. House, *Org. Synth.*, Coll. Vol. V, 1973, p. 775.

⁷ G. A. Swan, *J. Chem. Soc.*, 1948, 1408.

⁸ P. G. Gassman, J. T. Lumb, and F. V. Zalar, *J. Amer. Chem. Soc.*, 1967, **89**, 946.

⁹ G. Rawson and H. Wynberg, *Rec. Trav. chim.*, 1971, **90**, 46.

¹⁰ D. G. Davies, M. Derenberg, and P. Hodge, *J. Chem. Soc. (C)*, 1971, 455.

¹¹ T. F. McGrath and R. Levine, *J. Amer. Chem. Soc.*, 1955, **77**, 3634, 3656, and 4168; E. Jones and I. M. Moodie, *J. Chem. Soc. (C)*, 1968, 1195; R. V. Talalaeva, G. V. Kazennikova, and K. A. Kocheshkov, *J. Gen. Chem. (U.S.S.R.)*, 1959, **29**, 1566.

¹² P. Tomboulia and K. Stehower, *J. Org. Chem.*, 1968, **33**, 1509.

¹³ M. J. Jorgensen and A. F. Thacher, unpublished observations quoted in ref. 3.

Table 1 were carried out. In none of these was there any evidence for breakdown of the dianion, but only the reaction between phenyl-lithium and labelled potassium benzoate gave any benzophenone so the dianion might not have been formed in the other reactions, probably owing to the low solubility of both reactants.

TABLE 1

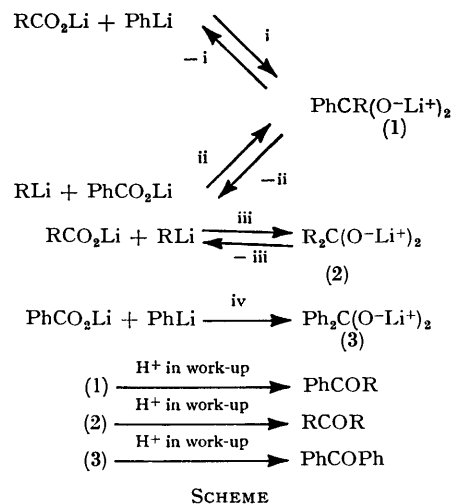
Action of phenyl-lithium, -potassium, and -sodium on the lithium potassium, and sodium salts of [*ring*-¹⁴C] benzoic acid ^a

M in PhCO ₂ M	M in PhM	Conditions			Ph ₂ CO (%)
		Solvent	Temp. (°C)	Time (h)	
Li	Li	Et ₂ O	35	10	83
Li	Li	Et ₂ O	35	192	79
Li	Li	DME ^b	85	40	72
Li	Li	BME ^b	110	40	36
Li	Li	BME ^b	150	3	19
K	Li	Et ₂ O	35	24	67
Li	K	THF ^b	65	70	0
K	K	THF ^b	65	70	0
Na	Na	C ₆ H ₆	78	6	0

^a In every case the benzoic acid recovered from the reaction had, within experimental error ($\pm 1.64\%$), the same specific activity as the benzoic acid used to prepare the salt. ^b DME = 1,2-dimethoxyethane; BME = bis-(2-methoxyethyl) ether; THF = tetrahydrofuran.

We next studied the reactions of phenyl-lithium with the lithium salts prepared from some substituted benzoic

were carried out for much longer periods than would normally be required in preparative work. Surprisingly,



the interaction of 2,6-dimethoxyphenyl-lithium with lithium benzoate gave no ketone. The results (Table 2) indicate that the dilithium salts (1) are stable when R = 4-tolyl or 4- or 2-methoxyphenyl but are unstable when R = 2,6-dimethoxyphenyl, 2-thienyl, or 2-furyl. The alternative explanation that the carboxylic acid salts undergo decarboxylation under the reaction

TABLE 2

Action of aryl-lithium derivatives on the lithium salts of aromatic carboxylic acids

Reaction ^a RCO ₂ Li + R'Li		Reaction time (h)	Yields of ketones (%) ^b			Composition of acid fraction (%) ^c	
R	R'		RCOR'	RCOR	R'COR'	RCO ₂ H	R'CO ₂ H
4-MeC ₆ H ₄	Ph	96	69	0	0	100	0
Ph	4-MeC ₆ H ₄	96	79	0	0	100	0
4-MeO-C ₆ H ₄	Ph	96	53	0	0	100	0
Ph	4-MeO-C ₆ H ₄	96	54	0	0	100	0
2-MeO-C ₆ H ₄	Ph	96	66	0	0	100	0
Ph	2-MeO-C ₆ H ₄	96	66	0	0	100	0
2,6-(MeO) ₂ C ₆ H ₃	Ph	{12	5	4	85	90	10
		{96	5	38	95	82	18
Ph	2,6-(MeO) ₂ C ₆ H ₃	{12	0	0	0	100	0
		{96	0	0	0	100	0
2-Thienyl	Ph	{12	41	4	16	100	0
		{96	52	10	36	100	0
Ph	2-Thienyl	{12	63	0	0	100	0
		{96	16	1	18	95	5
2-Furyl	Ph	{12	43	2	40	95	5
		{96	64	0	0	100	0

^a Reactions carried out in ether at reflux temperature. ^b Yields based on theoretical maximum amount for each ketone and determined by t.l.c. or g.l.c. analysis of the neutral products. The symmetrical ketones required for the analysis were prepared by analogous reactions with R = R'. Yields were as follows: 4,4'-dimethylbenzophenone (73%), 4,4'-dimethoxybenzophenone (55%), 2,2'-dimethoxybenzophenone (65%), bis-(2-thienyl) ketone (28%), bis-(2-furyl) ketone (30%). ^c Determined by g.l.c. analysis of the methylated (diazomethane) acid fraction.

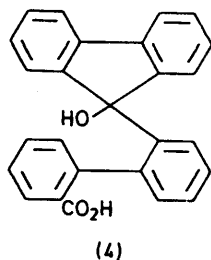
acids, from thiophen-2-carboxylic acid, and from furan-2-carboxylic acid, and the reactions of lithium benzoate with substituted phenyl-, 2-thienyl- and 2-furyl-lithium derivatives. Breakdown of the dilithium salts formed in these reactions could lead to the presence of three ketones and two acids in the products (Scheme). To facilitate the detection of any breakdown, the reactions

conditions and that the carbon dioxide released reacts efficiently with the organolithium derivatives present was eliminated by showing that the relevant carboxylate salts do not decompose in ether at 35 °C for 96 h.

Several conclusions can be drawn from the above results. First, if the proposed mechanism for the cleavage of benzophenones is essentially correct,⁸⁻¹⁰ the

dianion intermediates are much more stable when the counter ions are lithium rather than potassium. Secondly, the dilithium salts only break down when the leaving group [R in (1)] is a much more stable carbanion than benzenide ion. Thirdly, the dilithium salts (1; R = 2-thienyl, 2-furyl, or 2,6-dimethoxyphenyl) only break down by reaction —ii (Scheme) and not reaction —i. This is consistent with the fact that base-induced cleavages (see below) of 2-benzoylthiophen⁹ and 2,6-dimethoxybenzophenone give benzoic acid as the only acidic product, and explains why, for example, the reaction of phenyl-lithium with lithium thiophen-2-carboxylate yields three ketones, whereas that between 2-thienyl-lithium and lithium benzoate gives only one ketone. In reactions that give three ketones, reaction —ii must proceed at a rate that is at least comparable with that of reaction i. Fourthly, the great stability of the dilithium salt (3) means that phenyl-lithium and lithium benzoate are continually and irreversibly being removed from the system. As the reaction mixtures are heterogeneous, it is difficult to draw any other firm conclusions from the relative yields of the various products.

Finally, we treated several ketones with the cleavage reagent⁷⁻¹⁰ formed by adding water (3 equiv.) to potassium t-butoxide (10 equiv.) in ether and the analogous reagent prepared with lithium t-butoxide. Fluorenone, 2-chlorobenzophenone, 2,6-dimethoxybenzophenone, and 2-benzoylthiophen⁹ were readily cleaved by the former reagent at 21 °C but they were not cleaved when treated with the latter reagent at 35 °C for 12 h. Evidently the dianions are not formed in the latter reactions; it is known that those derived from 2,6-dimethoxybenzophenone or 2-benzoylthiophen would be cleaved under the reaction conditions. The fact that the reaction mixtures are heterogeneous (the insoluble material almost certainly being the appropriate metal hydroxide) again makes it difficult to draw firm conclusions, but it is interesting that Kenner *et al.*¹⁴ found that fluorenone reacts much more rapidly with powdered potassium hydroxide in toluene than it does with powdered sodium



hydroxide in toluene, and that with the former base biphenyl-2-carboxylic acid is obtained in high yield whereas with the latter, the hydroxy-acid (4) is obtained in high yield.

¹⁴ G. W. Kenner, M. J. T. Robinson, C. M. B. Tyler, and B. R. Webster, *J. Chem. Soc.*, 1962, 1756.

¹⁵ C. R. Harrison and P. Hodge, *J.C.S. Perkin I*, 1976, 605.

¹⁶ P. Hodge, E. R. H. Jones, and G. Lowe, *J. Chem. Soc. (C)*, 1966, 1216.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Organic solutions were dried with magnesium sulphate. Ether, 1,2-dimethoxyethane, bis-(2-methoxyethyl) ether, and t-butyl alcohol were distilled from calcium hydride and stored over molecular sieves. G.l.c. was carried out as previously.¹⁵ Scintillation counting of active compounds was performed by the procedure previously described.¹⁶

Preparation of Carboxylic Acid Salts.—The acid (1.02 equiv.) was treated with an aqueous solution of the appropriate metal hydroxide (1.00 equiv.) and the solution filtered. The filtrate was evaporated to dryness under reduced pressure and the residue dried to constant weight at 80 °C and 0.4 mmHg.

Reaction of Phenyl-lithium with Lithium [ring-¹⁴C]Benzoate.—(a) Bromobenzene (942 mg, 6.0 mmol) in ether (10 ml) was added dropwise over 45 min to a vigorously stirred mixture of lithium (84 mg, 12.0 mmol; freshly cut pieces) and lithium [ring-¹⁴C]benzoate (922 mg, 7.2 mmol; 1.07 $\mu\text{Ci g}^{-1}$) in ether (25 ml). The mixture was vigorously stirred and heated under reflux for 10 h. The cold mixture was slowly added with stirring to water (250 ml), then worked up to give neutral and acidic fractions. The neutral fraction was benzophenone (905 mg, 83%), m.p. 45–47° (lit.,¹⁷ 49°), free (t.l.c. and g.l.c.) from triphenylmethanol. The ketone was recrystallised from hexane to constant molar activity which, within experimental error, was the same as that of the labelled benzoic acid used to prepare the lithium benzoate. The acid fraction was benzoic acid (270 mg), m.p. 120–122°. The sample was recrystallised from water to constant specific activity which, within experimental error, was the same as that of the benzoic acid used to prepare the lithium benzoate.

(b) The other reactions between phenyl-lithium and metal carboxylates listed in Table 1 were carried out by a similar procedure. When solvents other than diethyl ether were used, the reactions were initially carried out with diethyl ether but after 4 h at 35 °C this was replaced by the other solvent.

Other Reactions listed in Table 1.—These were carried out similarly, the phenylpotassium being prepared *in situ* by the reaction of bromobenzene with potassium metal¹⁸ and the phenylsodium by the reaction of chlorobenzene with sodium wire.¹⁹ In all these reactions, the metal reacted completely and no halogenobenzene was recovered from the neutral fractions despite careful removal of the ether. By i.r. and u.v. spectroscopic analysis, the neutral fractions (4–9% of the mass expected if benzophenone had been formed quantitatively) contained traces of biphenyl, but little or no benzophenone (<2%) or triphenylmethanol (<1%). After recrystallisation to constant activity, the recovered benzoic acid (80–88%) had an activity within 2% of that of the benzoic acid used to prepare the benzoate salts.

Reaction of Phenyl-lithium with Lithium 2,6-Dimethoxybenzoate.—(a) Bromobenzene (20.9 g, 133 mmol) in ether (50 ml) was added dropwise over 45 min to a vigorously stirred mixture of lithium (1.86 g) and lithium 2,6-dimethoxybenzoate (27.5 g, 146 mmol) in ether (250 ml) and the mixture was heated under reflux for 96 h. Addition of the cold mixture to water (2.5 l) gave a white precipitate,

¹⁷ 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1965.

¹⁸ G. M. Pickles and F. G. Thorpe, *J. Organometallic Chem.*, 1974, **76**, C23.

¹⁹ G. Erhart, *Chem. Ber.*, 1963, **96**, 2042.

which was identified as 2,2',6,6'-tetramethoxybenzophenone (8.30 g, 38%), m.p. 212–214° (lit.,²⁰ 204°), ν_{\max} (Nujol) 1675 cm^{-1} , m/e 302 (M^+). Neutral and acidic fractions were isolated as usual.

The neutral fraction (16.7 g) was fractionally distilled under reduced pressure. Fraction 1, b.p. 41° at 0.2 mmHg, was identified as 1,3-dimethoxybenzene (3.01 g) by ^1H n.m.r. and mass spectral analysis (comparison with an authentic sample). Fraction 2, b.p. 101° at 0.4 mmHg, was identified as benzophenone (11.5 g, 95%), m.p. 46–47° (from hexane), by i.r. and ^1H n.m.r. spectral comparison with an authentic sample. Fraction 3, the residue (2.1 g), was crystallised from methanol to give 2,6-dimethoxybenzophenone (1.60 g, 5%), m.p. 96–98° (lit.,²¹ 99°).

The acidic fraction (4.5 g) was treated with diazomethane in ether and the ester mixture analysed by g.l.c. This showed the presence of methyl benzoate (18%) and methyl 2,6-dimethoxybenzoate (82%).

(b) The reaction was repeated but with a reaction time of 12 h. The results are summarised in Table 2.

Other Reactions summarised in Table 2.—Except as indicated below, these reactions were carried out essentially like those above, the neutral fractions being analysed by t.l.c. or g.l.c. comparison with authentic samples of the possible ketone products. When only one ketone was produced, it was isolated and shown to have an m.p. or b.p. in good agreement with the literature value.

2-Chloro-1,3-dimethoxybenzene, prepared by methylating²² 2-chloro-1,3-dihydroxybenzene prepared²³ from cyclohexane-1,3-dione, was treated with lithium in the presence of lithium benzoate; work-up gave 1,3-dimethoxybenzene (87%). G.l.c. and i.r. analysis of the neutral fraction indicated that no ketone was formed. Benzoic acid was recovered (98%).

²⁰ H. Gilman, B. H. Willis, T. H. Cook, F. J. Webb, and R. N. Meals, *J. Amer. Chem. Soc.*, 1940, **62**, 667.

²¹ D. B. Limaye, *Chem. Ber.*, 1934, **67**, 12, 15.

²² P. Kovacic and M. E. Kurz, *J. Org. Chem.*, 1966, **31**, 2459.

²³ N. Schamp and M. Versele, *Bull. Soc. chim. belges*, 1964, **73**, 81.

Solutions of 2-thienyl-lithium were prepared²⁴ by treating thiophen in ether with 0.95 mol. equiv. of n-butyl-lithium (1.8M in hexane) and stirring the mixture at 20 °C for 30 min. This solution was then added dropwise to a suspension of the lithium carboxylate in ether. Solutions of 2-furyllithium were prepared and used similarly.²⁵

Action of Potassium t-Butoxide–Water on Various Ketones.—Fluorenone, 2-chlorobenzophenone, 2,6-dimethoxybenzophenone, and 2-benzoylthiophen were treated with the reagent by the usual procedures,¹⁰ the reactions being carried out for 5 min in ether at 21 °C. Fluorenone gave biphenyl-2-carboxylic acid (55%). Benzoic acid was the sole acid product in every other case, the yields being 67, 96, and 100%, respectively.

Action of Lithium t-Butoxide–Water on Various Ketones.—Lithium t-butoxide was prepared²⁶ by adding lithium to dry t-butyl alcohol and heating the mixture under reflux under nitrogen for 4 h. Evaporation gave the crude alkoxide as a white solid which was purified by sublimation (120° and 0.1 mmHg). The sublimate was 98% pure (by titration with 0.1N-hydrochloric acid).

Fluorenone, 2-chlorobenzophenone, 2,6-dimethoxybenzophenone, and 2-benzoylthiophen were treated with lithium t-butoxide and water in ether by the procedure used previously with potassium t-butoxide and water.¹⁰ After being heated under reflux for 12 h, the mixtures were worked up as usual. In each case the starting ketone was recovered quantitatively.

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²⁴ H. Gilman and D. A. Shirley, *J. Amer. Chem. Soc.*, 1949, **71**, 1870.

²⁵ C. H. Heathcock, L. G. Gulick, and T. Dehlinger, *J. Heterocyclic Chem.*, 1969, **6**, 141.

²⁶ M. S. Bains, *Canad. J. Chem.*, 1964, **42**, 945.