The Sonochemical Barbier Reaction applied to Carboxylates. Study of a Model Case

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Sonication of a *n*-butyl halide, lithium benzoate and lithium metal in THF at room temperature provides the expected ketone and/or benzil in yields depending on the nature of the halogen.

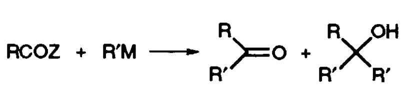
The transformation of carboxylic acids or their derivatives, chlorides, esters and amides, to ketones using organometallic reagents has been extensively studied (Scheme 1).[1] This type of reaction is rather demanding. The more readily accessible organo-lithium or -magnesium compounds generally give mixtures of ketones and tertiary alcohols unless precise experimental conditions are fulfilled.

There has recently been some discussion concerning the presence of the tertiary alcohols in cases where the starting materials are carboxylic acids.[2] Use of carboxylate alkali salts instead of free acids was proposed by several authors as a convenient method for diminishing the formation of the alcohol and successful applications, in particular in amino acid chemistry,[3] were developed. Running the reacton in the presence of cerium chloride also seems to optimize the ketone yield.[4]

Because of the experimental simplicity of the sonochemical Barbier procedure, its extension to carboxylate salts would be a simple method to achieve the desired transformation.[5] To investigate its mechanism with a view to synthetic development, experiments were conducted with lithium benzoate **1** taken as a model (Scheme 2). A mixture of this salt, lithium (2.2 equiv.) and *n*-butyl halides (1.1 equiv.) in dry THF was sonicated at room temperature in an ultrasonic bath (Kerry Ultrasonics Pulsatron 250, 38 kHz) until the metal disappears. After work-up, the reaction products were analysed and the results are shown in Table 1.

A high selectivity in favour of the ketone results from the use of the salt rather than the carboxylic acid (entries 1 and 7), illustrating the preceding discussion. More importantly, the results show the importance of the halide to the reaction outcome. The bromo-, and especially the iodo- compounds react much more slowly, and product **2** is formed in smaller amounts, or is entirely absent (entries 3 and 5). Unexpectedly, substantial amounts of the α-diketone **4** are obtained. This result, similar to that described by Fry *et al.* (formation of **4** after sonication for 160 h of lithium or sodium benzoate with lithium metal), is indicative of the presence of the ketyl radical anion of **1**.[6] The reaction of lithium *o*-allylbenzoate **6**[7] was expected to provide further evidence for the existence of reactive intermediates. Sonication of **6** in the presence of lithium metal gives a mixture of the α-diketone **7** (33%) and 2-methylindanone **8** (22%), both compounds resulting from an inter- or intra-molecular reaction of the carboxylate ketyl (Scheme 3). However, sonication in the presence of lithium and iodobutane leaves the initial acid quantitatively unchanged, but octane is detected by VPC (vapour phase chromatography) of the crude mixture. The same reaction run with chlorobutane leads to a mixture of the starting material and the acid **9** (*ca.* 50%), the formation of which can be explained by the rapid formation of butyllithium, deprotonation of the allyl group and alkylation by excess butyl chloride.†

In previous work on the Barbier reaction,[8] it was concluded that the presence of alkyl chlorides leads to the rapid formation of the alkyl lithium reagent. The addition of the organometallic to non-enolisable carboxylates is known to be rapid even at low temperatures.[1] The selectivity observed in this work in favour of the ketone is most probably due to the

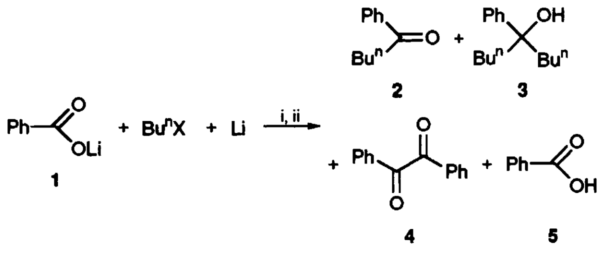


Scheme 1

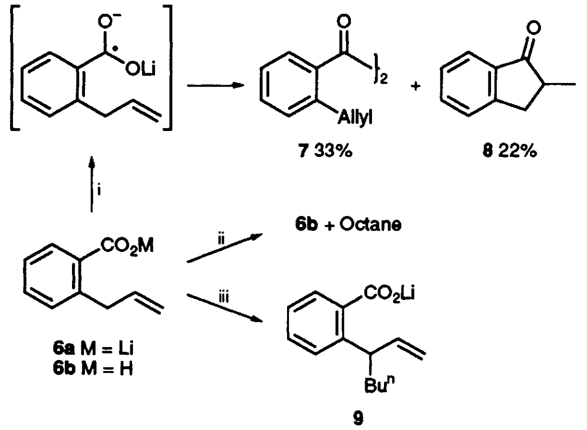
Table 1 Barbier reaction from lithium benzoate

Entry	X	Sonication *t*/min	Reaction product[a] **2**	**3**	**4**	**5**
1	Cl	45	94	0	0	3
2	Cl	0[b]	77	0	0	23
3	Br	120	66	0	12	22
4	Br	0[c]	0	0	0	83
5	I	190	0	0	41	40
6	I	0[d]	0	0	19	67
7	Cl[e]	90	66	18	0	10
8	Br[f]	95	49	0	18	25
9	I[f]	360	0	0	0	93

[a] VPC yields (%). [b] Stirring for 2.5 h. [c] Stirring for 6 days. [d] Stirring for 3 days. [e] Starting material was benzoic acid. [f] Sonication at 400 kHz.



Scheme 2 *Reagents*: i, THF,)))), room temp; ii, H_3O^+



Scheme 3 *Reagents and conditions*: i, **6a**, Li, THF, room temp.,)))), 2 h; ii, Bu^{n}I, Li, THF,)))), room temp., 0.5 h; iii, Bu^{n}Cl, Li, THF,)))), room temp., 0.25 h

low concentration of butyllithium in the medium and the stability of the rapidly formed intermediate *gem*-dialkoxide. At the end of the process all the reagents have been consumed and no overalkylation to the tertiary alcohol can occur. In the case of iodides, the reaction with lithium is much slower and gives radical (or radical–anion) intermediates. Competition can thus take place between electron transfer from the metal to the carboxylate, Wurtz coupling (the relative efficiencies of which depend on the structure of the carboxylate) and formation of the organometallic. Incidentally, from comparison between entries 5 and 9, Wurtz coupling seems to be strongly reinforced when sonication is carried out at higher frequencies, since the only reaction product from irradiation at 400 kHz is octane.

In conclusion, the sonochemical Barbier procedure applied to lithium carboxylates should offer a simple and easy method for ketone synthesis with minimal side reactions provided the rate of organometallic formation is high, which requires the preferential use of chloro precursors. These results also show that the mechanistic hypotheses of Barbier reactions, proceeding through an alkylation of the ketyl radical-anion, or coupling of two radical species (ketyl and $[R–X]^{\cdot -}$), are not valid in the case described here.[5]

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Footnote

† Reaction of **6a** with *n*-butyllithium yields small amounts of 1-[2-(prop-1-enyl)]-phenyl-1-pentanone, 22% of α-naphthol, and many unidentified products.

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