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STABILIZED CARBANIONS BY ALKYLLITHIUM-INDUCED DECARBOXYLATION OF NON-ENOLIZABLE CARBOXYLIC ACIDS. AN ANIONIC EQUIVALENT TO THE HUNSDIECKER REACTION

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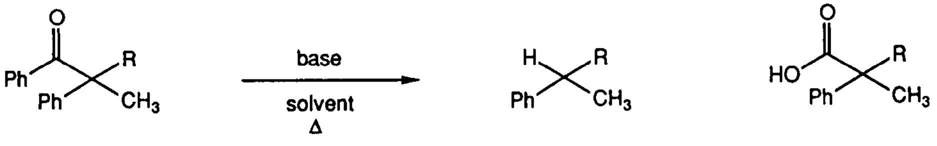
Summary: Intermediate dianions formed by nucleophilic attack of methyllithium on α-phenyl or α-phenylthio carboxylate salts fragment in highly coordinating solvents to produce stabilized carbanions. Once formed, these anions may be conveniently functionalized with various electrophilic reagents.

Carbon-carbon bond cleavage of non-enolizable ketones (1) by means of the Haller-Bauer reaction[1] proceeds efficiently under strongly basic conditions *in refluxing solvent.*[2] We

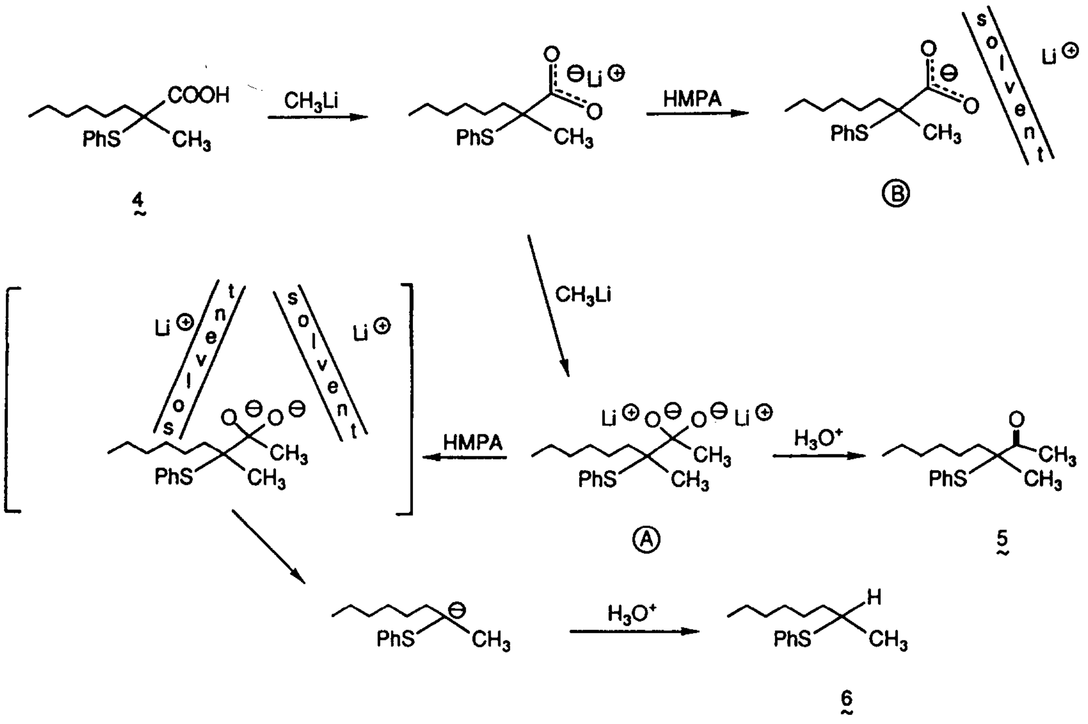


1 2 3

now report that the corresponding acids 3 undergo a similar fragmentation upon treatment with methyllithium under appropriate solvent conditions at much lower temperature (0 °C → room temp). Decarboxylations of this type have been noted as undesirable side-reactions during conversion of a few highly fluorinated[3] or phenylated carboxylic acids[4] to ketones.[5]

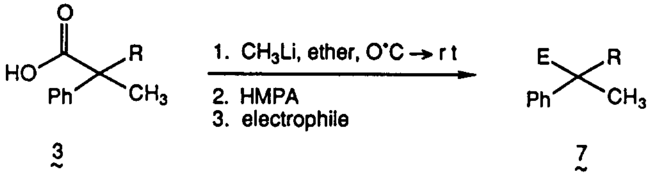
Compound 4 constitutes a prototypical example. Its exposure to methyllithium in ether afforded 5 (98%) after aqueous acidic work-up. Similar reaction in HMPA returned only unreacted acid, while recourse to THF as solvent provided ketone 5 in reduced yield (56%) together with a small quantity of sulfide 6 (3%). The observations may be rationalized as illustrated in the scheme.

Whereas intermediate A is formed in ethereal solution,[6] its intervention in the more polar HMPA is electrostatically precluded because of effective dissociation of the carboxylate species from its lithium counterion (see B). Intermediate A gives rise to ketone 5 upon aqueous work-up, or to 6 by a process paralleling that operative during



Haller-Bauer cleavage.[2,7] On this basis, it appeared plausible that the fragmentation of A might be markedly accelerated by increasing the reactivity of its oxyanionic centers. Indeed, treatment of A , formed in ether, with HMPA led to fragmentation and formation of 6 in high yield (87%).

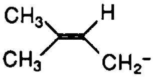
Analogous treatment of the acids 3 yielded the hydrocarbons 7 (E=H). In addition, the



intermediate benzylic carbanion could be captured with other electrophiles to yield functionalized tertiary derivatives directly. Representative examples are compiled in Table I.

Cleavage of acids 8 and 9[7b] under similar conditions yielded a mixture of hydrocarbons 10 and 11. Interestingly, the ratio of 10:11 proved to be highly dependent on the nature of the solvent at the time of aqueous acidic work-up (Figure 1). In both examples, approximately equal amounts of 10 and 11 are formed in ether, while 11 predominates when the environment is more polar. Related trends have been observed during Haller-Bauer

Table I. Formation of 7 from Carboxylic Acids 3.[8]

R	electrophile	E in 7	yield, %[a]
$C_6H_5CH_2$-	$H_3O^+Cl^-$	H	83
	CH_3I	CH_3	54
	CH_3SSCH_3	SCH_3	53
	$(CH_3)_3SiCl$	$Si(CH_3)_3$	68
	$H_3O^+Cl^-$	H	78
	CH_3SSCH_3	SCH_3	63
	$(CH_3)_3SiCl$	$Si(CH_3)_3$	49

[a] Yields determined after isolation by medium pressure liquid chromatography except for the last entry where preparative gas chromatography was used.

cleavage of the corresponding phenyl ketones.[7b] Once again, coordination of lithium ion to the carbanion favors equatorial protonation while a more dissociated ion pair is more conducive to axial proton transfer.

In summary, we have demonstrated that the reaction of carboxylic acids with alkyllithium reagents is highly solvent dependent. *In effect, one can deliberately increase the efficiency of bond fragmentation to generate the derived stabilized carbanion in high yield.* Quenching the intermediate with appropriate electrophiles constitutes an equivalent of the Hunsdiecker reaction[9] and related processes[10] that is more tolerant of the presence of double bonds.

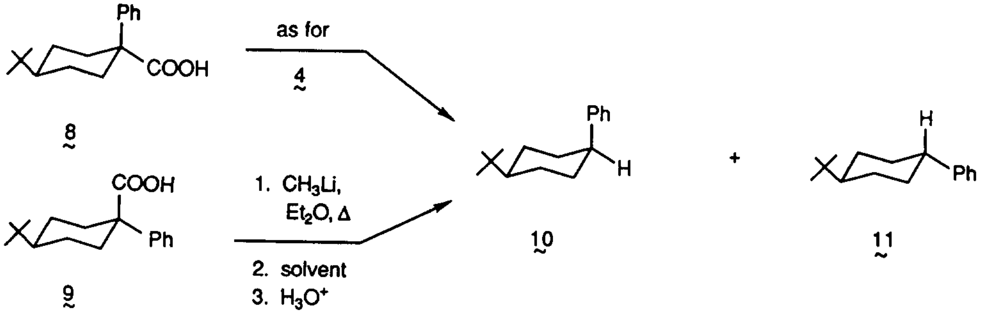
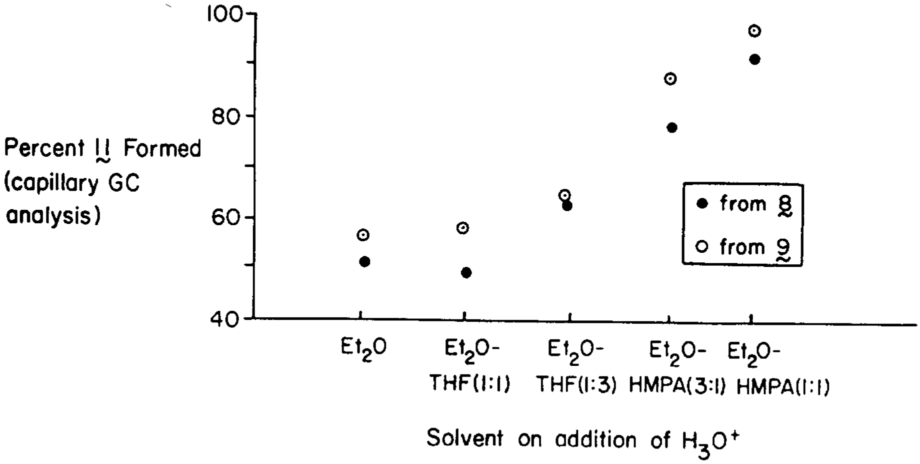


Figure I



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(6) If an α-proton is present, formation of the dianion by deprotonation is, of course, the major pathway.

(7) (a) Paquette, L. A.; Gilday, J. P. submitted for publication. (b) Paquette, L. A.; Ra, C. S. submitted for publication.

(8) Typical procedure: the acid (∿0.5 mmol) was dissolved in ether (6 mL) and cooled to 0 °C, methyllithium (1.5 M in ether, *ca* 5 equiv) was added, and the mixture was stirred at 0 °C to room temperature over 90 min. After recooling to 0 °C, HMPA (1 mL) was added followed by the electrophile (>5 equiv). After aqueous work-up, the product was isolated by MPLC (SiO_2, elution with 0.5-1% ethyl acetate in petroleum ether).

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