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OXIDATIVE COUPLING OF CARBOXYLIC ACID DIANIONS[#]

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Abstract: The conditions, scope, and stereochemical consequences of a versatile approach to succinic acid derivatives are described.

Controlled generation of carbon-carbon bonds forms the core of organic synthesis (1). Oxidative coupling of electron-rich intermediates is a powerful, but underutilized, methodology for achieving such transformations. Known examples include the Glaser-Eglinton reaction (2), the joining of phenolic substrates during alkaloid synthesis (3), the Kolbe electrolysis (4), and a variety of enolate (5) and carbanion (6) dimerizations.

Several investigators (7-11) have exploited the ability of ester enolates to undergo oxidative coupling. Unfortunately, formation of self-condensation by-products constitutes a significant complication (9,12). Because side reactions between a carboxylic acid dianion (13) and a carboxylate salt are disfavored electrostatically, an alternative to ester enolate coupling employing carboxylic acid dianions seemed an intriguing possibility.

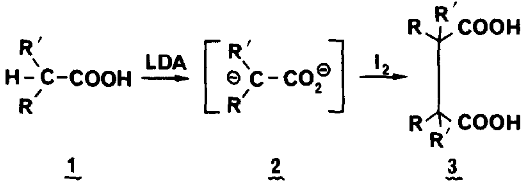
Treatment of phenylacetic acid with 2.0 equivalents of n-BuLi followed by stirring for several hours produces the corresponding dianion in 90% yield (14), as estimated by trapping with benzyl chloride. Reaction of the dianion with 0.5 equivalents of I_2 gives 1,2-diphenylsuccinic acid in 90% yield (Procedure A (22): TABLE I).

Preparation of the dianion of hexanoic acid with n-BuLi is unsatisfactory (15). But, 2.0 equivalents of LDA do afford a 90% yield of the dianion, as judged by trapping with benzyl chloride. Surprisingly, the reaction of the LDA-generated dianion with 0.5 equivalents of I_2 gives only 60% of the diacid and 40% of recovered starting material . Our approach to improved yields of diacid coupling product has evolved from the work of Ashby (16), who reports isolation of solid lithioenolates prior to their reaction with electrophiles. By a straightforward operation (Procedure B (22)), the dianion salt can be obtained as an off-white powder. Resuspension in fresh THF followed by the addition of 0.5 equivalents of I_2 produces (in 100% mass balance) 82% of the 1,2-diacid, 9% of 2-iodohexanoic acid, and 9% hexanoic acid. Apparently, the diisopropylamine formed by protonation of the LDA interferes with the coupling reaction. By this same technique (Procedure B (22): TABLE I), other symmetrically substituted succinic acid derivatives are readily prepared.

Variation in the stoichiometric ratio of I_2 to dianion is of interest. If one equivalent of I_2 is added to hexanoic acid dianion, 62% of 2-iodohexanoic acid is obtained. Similar treatment of cyclopentanecarboxylic acid dianion produces 48% of the corresponding iodide. Preliminary experiments suggest that inverse addition (17) of the dianion to 2^+ equivalents of I_2 in THF at -78° is even more promising. Thus, by inverse addition, 3-phenylpropionic acid dianion yields 70% of 2-iodo-3-phenylpropionic acid, whereas addition of I_2 to the same dianion leads almost exclusively to coupling product.

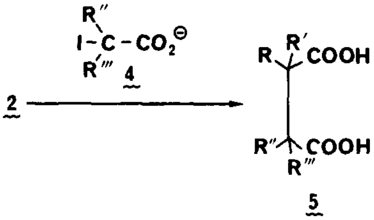
[#] Dedicated to Prof. Milton Orchin on the occasion of his 70th birthday.

TABLE I



	1 R,R′	**3** R,R′	Yield (%)	Proced. (22)
a	ϕ, H	ϕ, H	90	A
b	4-CH_3O-ϕ, H	4-CH_3O-ϕ, H	70	A
c	n-Bu, H	n-Bu, H	82	B
d	ϕCH_2, H	ϕCH_2, H	77	B
e	ϕ, CH_3	ϕ, CH_3	78	B
f	$(CH_2)_4$	$(CH_2)_4$	58	B
g	CH_3, CH_3	CH_3, CH_3	60	B

TABLE II



	2 R,R′	**4** R″,R‴	**5** R,R′	R″,R‴	Yield (%)
a	ϕ, H	n-Bu, H	ϕ, H	n-Bu, H	69
b	ϕ, H	H,H	ϕ, H	H,H	71
c	ϕ, H	$(CH_2)_4$	ϕ, H	$(CH_2)_4$	38

The reaction of 2-iodocarboxylate salts with carboxylic acid dianions is a versatile approach to unsymmetrically substituted succinic acid derivatives. Confirming the work of Petragnani (18), we note that this transformation is moderately successful even with tertiary 2-iodocarboxylates (TABLE II).

Phenylacetic acid is a convenient substrate (19) to explore the stereochemistry of dianion coupling. NMR analysis of the diethyl ester of the 1,2-diphenylsuccinic acid product indicates an 11:1 dl:meso isomer ratio. Conversely, coupling of ethyl phenylacetate enolate (using the published procedures of Rathke (8) or of Brocksom (9)) gives a 1:5 dl:meso product ratio. Similarly, the coupling of 3-phenylpropionic acid dianion **2d** yields 2,3-dibenzylsuccinic acid **3d**, whose melting point, after recrystallization (169-171°), suggests that the product is largely dl (lit. mps (20) for dl = 172°C; for meso = 203°C).

Hauser has reported (7) a 1:2 dl:meso ratio in an ester enolate coupling. He also discovered that nitrile α-anions couple in favor of the dl product. Yoshida noted (21) highly selective dl coupling for a thioamide α-anion.

A hypothetical model **6**, consistent with the observed stereochemistry in the coupling of carboxylic acid dianions, invokes a lithium ion bridge between the two carboxylates (23) and maximum separation of large eclipsed substituents.

The overall carbon skeleton and the dl stereochemistry of the 2,3-dibenzylsuccinic acid **3d** are representative of many lignans (24). This large group of natural products contains members which possess significant biological activity. Thus, application of our methodology to the synthesis of lignan targets such as enterolactone **7** (25) is in progress.

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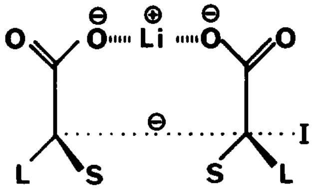

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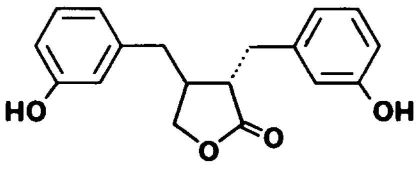

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22. Yields refer to chromatographed material possessing satisfactory analytical and spectroscopic properties. In our hands, simple phenylacetic acids give more satisfactory coupling with Procedure A (but note result with **1e**). The optimal times required for dianion formation and for addition of I_2 are somewhat substrate dependent.

    Procedure A: Dropwise addition of 2.0 equivalents of n-BuLi to the carboxylic acid in THF at -78°C is followed by stirring for four hours at R.T. The solution is recooled to -65°C and 0.5 equivalents of I_2 in THF is added over one minute. The mixture is allowed to stir overnight at R.T. After volatiles are removed, the residue is taken up in $CHCl_3$, acidified with HCl, and the organic layer is washed with H_2O, sat'd $NaHSO_3$ solution, and sat'd brine. After drying, filtration, and evaporation, the crude product is purified by flash chromatography using a combination of Et_2O, $CHCl_3$, and CH_3OH to elute the diacid.

    Procedure B: Using commercially available Schlenk apparatus and an argon atmosphere, 2.0 equivalents of LDA is generated at 0°C. The base solution is then cooled to -78°C, the carboxylic acid in THF is added, and the resulting mixture allowed to warm to R.T. over four hours. The THF and i-Pr_2NH are then removed at 0°C by application of a high vacuum. Fresh THF is added followed by another vacuum treatment. The resulting solid is suspended in THF, cooled to -65°C, and a solution of 0.5 equivalents of I_2 in THF is added over one minute. After stirring at R.T. overnight, work-up and purification are as in Procedure A.

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