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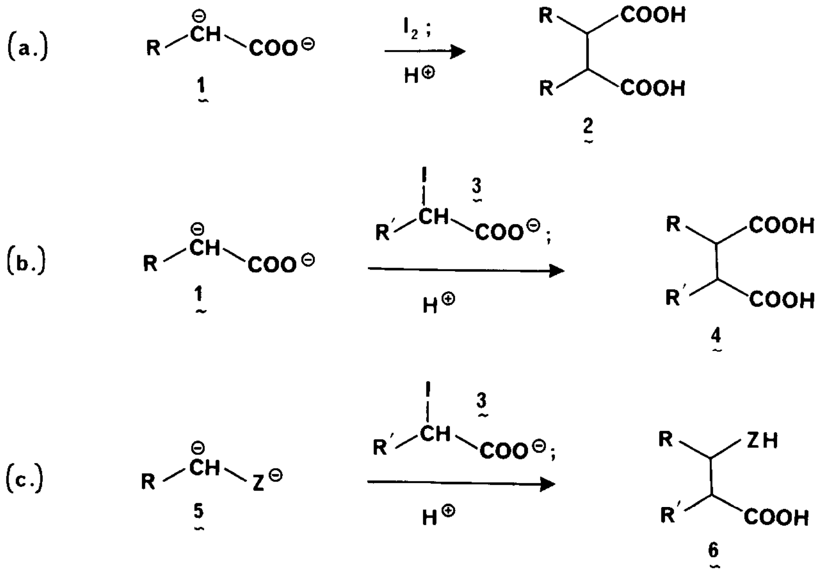
OXIDATIVE COUPLING. III. THE DUCO REACTION

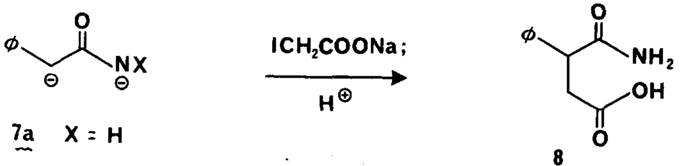
J. L. Belletire*, E. G. Spletzer
Department of Chemistry
University of Cincinnati
Cincinnati, Ohio 45221

Abstract: Acylsulfonamide dianions function as efficient synthetic intermediates and are especially suitable for Doubly Unsymmetrical Carbanion Oxidation.

Our initial examination (1) of carboxylic acid dianion oxidative coupling focused on two specific transformations: (a.) homo-coupling, wherein identical dianions join one another (e.g. **1** + **1** → **2**), and (b.) hetero-coupling, wherein one carboxylic acid dianion reacts with the 2-halocarboxylate derivative of a different acid (e.g. **1** + **3** → **4**). Although considerable flexibility in the choice of possible side chains (R,R') is implicit in the formation of **2** and **4**, a third possibility (c.), in which the precursors to the coupling reaction not only contain different side chains but also different functional groups, will greatly expand this chemistry. Since, formally, this latter transformation is equivalent to the oxidative coupling of two different dianions (2), the term DUCO (for Doubly Unsymmetrical Carbanion Oxidation) seems appropriate.



Our investigation began with a model study of the reaction between amide dianion derivatives **7** (3) and sodium iodoacetate. Besides very polar material having physical characteristics consistent with those expected of **8**, several difficultly separable by-products are also present. Assuming that the high basicity (4) of **7** is somehow facilitating alternative reaction pathways, dianion **9**, a system considerably less basic (4) than **7**, was next examined. Smooth reaction occurs to produce **10** (5) in 81% yield.



7a X = H

7b X = $SiMe_3$

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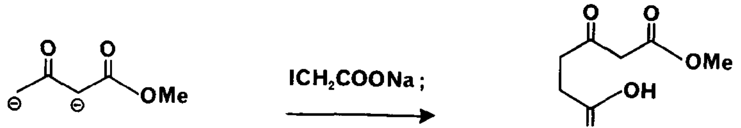

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Thus, an analog of **7** in which X is a strongly electron withdrawing group should stabilize the dianion system and thereby promote smooth coupling. A sulfone moiety is an obvious candidate for X. Indeed, known pK_a values for acylsulfonamides (6) are comparable to those of carboxylic acids.

A convenient, general approach to the preparation of acylsulfonamides, which constitutes a variant on published (7) procedures, employs sequential addition of 1.0 equivalent each of benzenesulfonamide and the appropriate acid chloride to a carefully (!) prepared suspension of 2.0 equivalents of KH in THF. After prolonged (30-72 hrs.) stirring at RT, removal of solvent, and a base/acid extraction, beautifully crystalline **11** results in 65-90% isolated yield. Recrystallization from alcoholic solvents or EtOAc-ligroine affords analytically pure material.

Generation of the acylsulfonamide dianion **12** is readily accomplished by slow addition (*ca.* 20 minutes) of 2.0 equivalents of n-BuLi to a precooled (-78°C) THF solution of **11** in THF followed by stirring a further 30 minutes at -78°C and 2.5 hrs. at 0°C. Given our previous difficulties regarding the use of LDA to prepare dianion coupling precursors (1), clean formation of **12** with n-BuLi is of considerable significance.

Acylsulfonamide dianions are highly reactive. Thus, reaction of **12a** at -50°C with CH_3I or benzyl chloride produces **13a** (80%) and **13b** (84%), respectively. Dianion **12a** adds smoothly in a Michael-type reaction (8) to both isopropyl crotonate and ethyl cinnamate thereby producing the corresponding adducts **13c** and **13d** in unoptimized yields above 50% (5). Homo-coupling of **12a** and **12b** also proceeds well (0.5 equivalents of I_2; THF; -55°C: isolated yields: **14a** = 88%; **14b** = 83%).

$RCH_2CONHSO_2\phi$

11a R = φ

11b R = ϕCH_2

11c R = $CH_3(CH_2)_5$

$R\overset{\ominus}{C}HCO\overset{\ominus}{N}SO_2\phi$

12a R = φ

12b R = ϕCH_2

12c R = $CH_3(CH_2)_5$

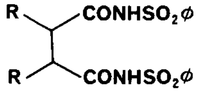
$\phi CHR'CONHSO_2\phi$

13a R' = CH_3

13b R' = $CH_2\phi$

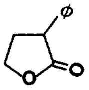
13c R' = $CH(CH_3)CH_2COOCH(CH_3)_2$

13d R' = $CH(\phi)CH_2COOCH_2CH_3$



14a R = φ

14b R = ϕCH_2



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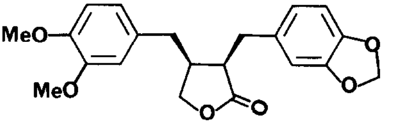
The DUCO reaction itself is exemplified by facile reaction of a variety of acylsulfonamide dianions **12** with sodium iodoacetate and with sodium 2-iodohexanoate (TABLE). After acidification, workup, and removal of solvent, the resulting acylsulfonamide-acid derivatives **16** (5) are obtained in spectroscopically pure form either by trituration of the crude solid or by chromatography on SiO_2 using $Et_2O/CHCl_3$ mixtures as the eluant. Routine recrystallization provides analytically pure (9) material.

TABLE

entry	**12** $RCHCONSO_2Ph$	**15** R"CHICOONa	**16** $RCH(CONHSO_2Ph)$-CHR"(COOH)	
	R	R"	yield	m.p. °C
1	Ph	H	96	182-184
2	$PhCH_2$	H	91	114-116
3	$CH_3(CH_2)_5$	H	86	134-135
4	Ph	$CH_3(CH_2)_3$	75	82-91(10)
5	$PhCH_2$	$CH_3(CH_2)_3$	76	62-84(10)

To enhance the general utility of the DUCO reaction, the products **16** must be easily transformed into more traditional functionality. Illustrative of just such an interconversion, we note that when a solution of **16** (R = Ph; R" = H) is stirred with 1.5 equivalents of $BH_3 \cdot SMe_2$ in THF for 18 hrs., acidified, and partitioned between ether and water, butyrolactone **17** (5) can be isolated in high yield (75% after flash chromatography; oil; λ_{max} (CHCl$_3$) = 1773 cm^{-1}; M$^+$ 162.0680 (calc'd. 162.0681)).

Employment of the DUCO reaction in the successful preparation of butyrolactone **17** suggests obvious application of this methodology to the synthesis of unsymmetrical lignans such as **18** (11) and **19** (12).



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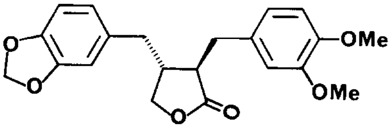

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References and Notes

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3. Reaction of both **7a** and **7b** with more typical electrophiles (e.g. iodomethane and benzyl chloride) led to excellent isolated yields (~90%) of the corresponding C-alkylated products.
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9. (a) **16** (R = Ph; R" = H): Combustion analysis: C; Th, 57.65; Fd, 57.70. H; Th, 4.53: Fd, 4.55. N; Th, 4.20: Fd, 4.16.

   (b) **16** (R = PhCH$_2$; R" = H): Combustion Analysis: C; Th, 58.78; Fd, 58.79. H; Th, 4.93; Fd, 5.04. N; Th, 4.03; Fd, 3.90.
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