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"REMOTE" DIANIONS—I. UTILITY OF 4-PHENYLSULFONYLBUTANOIC ACID IN THE MILD CONVERSION OF ALDEHYDES AND KETONES TO LACTONES.[†]

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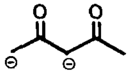
Abstract: Ketones and aldehydes are converted to lactones in high yield by stepwise treatment with the dianion of 4-phenylsulfonylbutanoic acid and trifluoroacetic anhydride.

The utility of dianions in which at least one of the anions resides at carbon is well established.[1] Typical examples of these reagent-based dianions are the β-dicarbonyl (1) or α-carboxylate (2) type where the anionic sites are separated by one atom (functional group).



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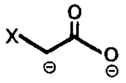

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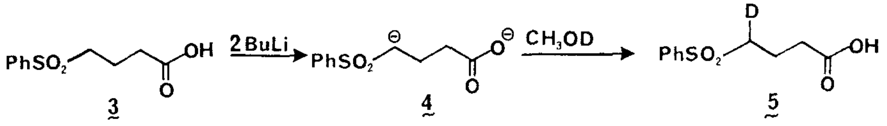
Thus, we wished to examine monocarbon-based dianions with at least one intervening ("remote") methylene unit for potential synthetic application.

Prompted by the report of Iwai et al.[2] that 3-sulfur functionalized propanoic acid dianions may be generated and added to carbonyl compounds, albeit in low yield, we sought to examine the bis-deprotonation of the homologue, 4-phenylsulfonylbutanoic acid[3] (4-PSBA; 3).[4]

When 4-PSBA was treated with 200 mol% of n-butyllithium in tetrahydrofuran at -78 °C (Eqn. 1) a yellow solution resulted which was presumed to be dianion 4. This was demonstrated , in part, by quenching the mixture with methanol-d. Standard workup and subsequent NMR analysis was consistent with structure 5, deuterium incorporation at C-4 being >95%.

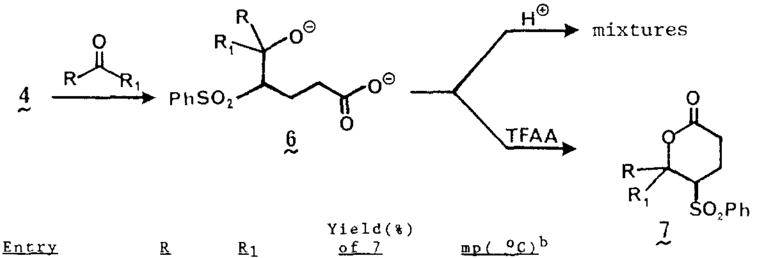
[†] Dedicated to the memory of Prof. James Wilt



(1)

In consort with the previous investigators of the propanoic series[2], 200 mol% of lithium diisopropylamide did not effect as high a conversion to dianion.[5]

The initial application of the 4-PSBA dianion was directed towards carbonyl addition with the expectation that the resultant alkoxide-carboxylate would lactonize readily upon acidification. However, a noted feature of α-sulfonyl carbanions is that they tend to be somewhat unreactive due to steric hindrance (comparable to neopentyl).[4] This concern was partially removed when the dianion of 4-PSBA was found to add readily to a variety of aldehydes and ketones at -78 °C (Scheme I)! Unfortunately, acidification of the reaction mixture did not effect complete cyclization and mixtures were obtained. Presumably, our initial concern of steric hindrance was surfacing in the cyclization step where the alkoxide is clearly congested. To circumvent this problem, the dianion (6) was quenched with trifluoroacetic anhydride[6] and high conversion to 4-phenylsulfonyl lactones were obtained.



Scheme I

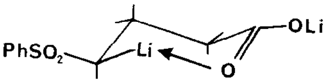
Entry	R	R₁	Yield(%) of 7	mp(°C)[b]
a	n-Bu	H	77[a]	101
b	Ph	H	84[a]	114-115
c	PhCH=CH	H	72[a]	128-129
d	$C_{11}H_{23}$	H	71[a]	85
e	Me	Me	75	138-139
f	Et	Et	89	139
g	-$(CH_2)_5$-		66	176
h	Ph	Me	62[a]	142-144

a) mixture of isomers
b) single isomer crystallized from $CHCl_3/Et_2O$

It is noteworthy that a variety of carbonyl compounds are readily attacked by the dianion of 4-PSBA and converted to pentanolides under mild conditions. This is exemplified by entry (7g), conversion of cyclohexanone to 1-oxaspiro-[5.5]undeca-2-one and entry (7c), regiospecific 1,2 addition to afford the

5-cinnamylpentanolide in 66 and 71% yield, respectively, after purification. All 4-phenylsulfonyl lactones were stable, crystalline materials.[7]

The chemical behavior of the reagent deserves comment. 4-PSBA is an extremely stable, non-hygroscopic crystal (mp=89-90 °C) of apparently long shelf life. The dianion is easily generated and stable in solution between -78 °C and room temperature. That this somewhat hindered α-sulfonyl carbanion added readily to carbonyl compounds may be indicative of intramolecular chelation (8) which possibly facilitates approach by the electrophile. This concept may be supported, in part, by the dianion solubility in THF.[5] Although this particular chelate has not been established, dipole stabilized carbanions have been implicated elsewhere.[8]



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We are currently examining the versatility and stereochemical consequences of this reaction as well as transformations of the 4-phenylsulfonyl lactones directed towards natural product synthesis.9

General procedure for the conversion of aldehydes and ketones to pentanolides: 4-Phenylsulfonylbutanoic acid (912 mg, 4 mmol) was dissolved in 80 mL anhydrous THF and chilled to -78 °C. n-Butyllithium (1.55 M in hexanes, 8 mmol, 5.16 mL)[10] was added dropwise and the mixture stirred for 0.5 hour. After the carbonyl compound (4 mmol) was added either neat or in a 3 mL solution of THF, the mixture generally quenched of color. The dry ice bath was exchanged for a 0 °C ice bath and the solution stirred for 0.5 hour. Trifluoroacetic anhydride (8 mmol, 1.68 g, 1.13 mL) was added and the reaction monitored by thin layer chromatography (the cyclization requiring 0.25 - 0.5 hour to complete).

The 0 °C solution was poured into 75 mL of saturated sodium carbonate and diluted with 50 mL ethyl ether. The aqueous layer was washed twice with 50 mL portions of ethyl ether. The organic layers were washed successively with 50 mL portions of saturated sodium carbonate, water and brine. The crude product(s) (yields of crude were 80 -90%) were flash chromatographed[11] with ethyl ether/petroleum ether mixtures. All compounds were recrystallized from chloroform-ethyl ether mixtures prior to analysis.

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3. We have prepared 4-PSBA in 60% overall yield from commercially available ethyl-4-bromobutyrate by the following sequence: i. NaI, acetone, reflux, 3 hr.; ii. benzenesulfinic acid, sodium salt (120 mol %), ethanol, reflux, 6 hr.; iii. LiOH (250 mol %), water/ethanol (9:1), RT, 1.5 hr. Neutralize and recrystallize solid from chloform-carbon tetrachloride. Further details of the synthesis forthcoming. See also: a. Hammam,A-E,G. J.Chem.Eng.Data (1979) **24** 379.; b. Kukalenko,S.S. Zh.Org.Khim. (1970) **6** 680.

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5. Other base combinations (NaH, LDA; NaH, BuLi; KH, LDA; KH, BuLi; etc) were also less successful. Concentrations of dianion greater than 0.05 M generally precipitated the dianion.

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10. In some cases, higher yields of lactones may be obtained by using 225 mol % of dianion.

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