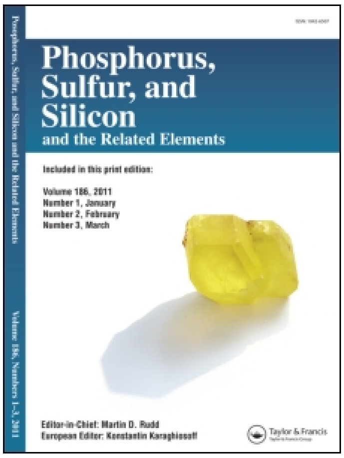
This article was downloaded by:
On: *28 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

REACTION OF α-BENZENESULFONYLPHENYLACETIC ACID WITH ALKYL HALIDES. DECARBOXYLATIVE ALKYLATION VS. DECARBOXYLATIVE PROTONATION

Blanka Wladislaw[a]; Fernando Perna[a]; Regina Maria de Almeida Neves[a]; Liliana Marzorati[a]; Claudio Di Vitta[a]
[a] Instituto de Química da Universidade de São Paulo, São Paulo, Brazil

Online publication date: 16 August 2010

To cite this Article Wladislaw, Blanka , Perna, Fernando , Neves, Regina Maria de Almeida , Marzorati, Liliana and Vitta, Claudio Di(2004) 'REACTION OF α-BENZENESULFONYLPHENYLACETIC ACID WITH ALKYL HALIDES. DECARBOXYLATIVE ALKYLATION VS. DECARBOXYLATIVE PROTONATION', Phosphorus, Sulfur, and Silicon and the Related Elements, 179: 7, 1403 — 1409

To link to this Article: DOI: 10.1080/10426500490463592

URL: http://dx.doi.org/10.1080/10426500490463592

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Phosphorus, Sulfur, and Silicon, 179:1403–1409, 2004
Copyright © Taylor & Francis Inc.
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500490463592

REACTION OF α-BENZENESULFONYLPHENYLACETIC ACID WITH ALKYL HALIDES. DECARBOXYLATIVE ALKYLATION VS. DECARBOXYLATIVE PROTONATION

Blanka Wladislaw, Fernando Perna,
Regina Maria de Almeida Neves, Liliana Marzorati,
and Claudio Di Vitta
Instituto de Química da Universidade de São Paulo,
São Paulo, Brazil

(Received October 29, 2003; accepted November 7, 2003)

Downloaded At: 10:14 28 January 2011

The reaction of α-benzenesulfonylphenylacetic acid with some alkyl halides, using as base NaH in DMSO, leads to decarboxylative protonation to give benzylphenylsulfone. Decarboxylative alkylation occurs only when CO_2 is expelled by flushing with nitrogen. The mechanism of the decarboxylative protonation is investigated.

Keywords: Alkylation; decarboxylation; protonation; sodium hydride

In the course of our investigations on the decarboxylative electrophilic substitution of carboxylic acids containing an activated methylene group, in aprotic media,[1,2] we became interested in the decarboxylative alkylation of α-sulfonyl carboxylic acids.

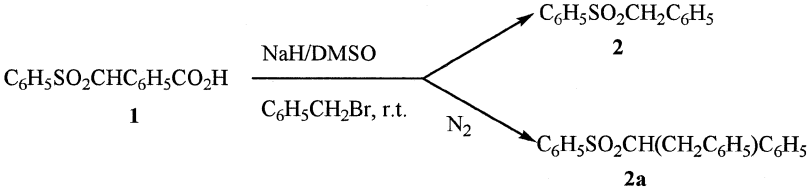
Our studies were initiated by the reaction of α-benzenesulfonylphenylacetic acid, **1**, with NaH in DMSO, followed by reaction with benzyl bromide at room temperature (r.t.). However, surprisingly, instead of the expected decarboxylative alkylation, decarboxylative protonation took place to give benzylphenylsulfone, **2**, as the only reaction product. However, it was observed that, upon flushing the

---

We are grateful to the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) for financial support and to the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for scholarships. We thank Professor F. H. Quina for revising the manuscript.

Address correspondence to Blanka Wladislaw, Instituto de Química, Universidade de São Paulo, Av. Prof. Lineu Prestes, 748-C.P. 26007, São Paulo, S.P., 05513-970, Brazil. E-mail: bwlad@iq.usp.br

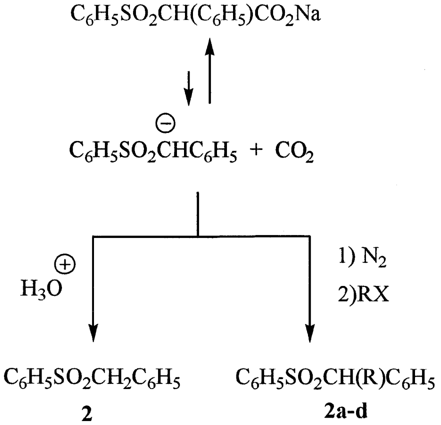
reaction mixture with nitrogen, decarboxylative alkylation does occur, yielding the benzyl substituted sulfone **2a** (Scheme 1).



SCHEME 1

The same reaction, performed using other alkyl halides to obtain the α-alkylsubstituted sulfones **2b–d,** was successful only when nitrogen was flushed through the reaction mixture (Table I).

Assuming an equilibrium between the sodium carboxylate and the sulfonyl carbanion, with the equilibrium constant favouring the carboxylate, sulfone **2** could be formed in the absence of nitrogen by decarboxylative protonation during the work-up. Upon flushing the reaction mixture with nitrogen, this equilibrium would be shifted toward the sulfonyl carbanion, which could then undergo alkylation (Scheme 2).



SCHEME 2

However, this possibility was disproved by the results of comparative experiments in which benzylphenylsulfone, **2**, and benzenesulfonylphenylacetic acid, **1**, were treated with 1 equiv. of NaH in DMSO. Sulfone **2** formed a deep yellow carbanion solution, as demonstrated by the desapearance of the methylene signal in the ^{1}HNMR spectrum.

Downloaded At: 10:14 28 January 2011

TABLE I Reaction of Benzenesulfonylphenylacetic Acid **1** with Some Alkyl Halides,[a] Flushing the Reaction Mixture with Nitrogen

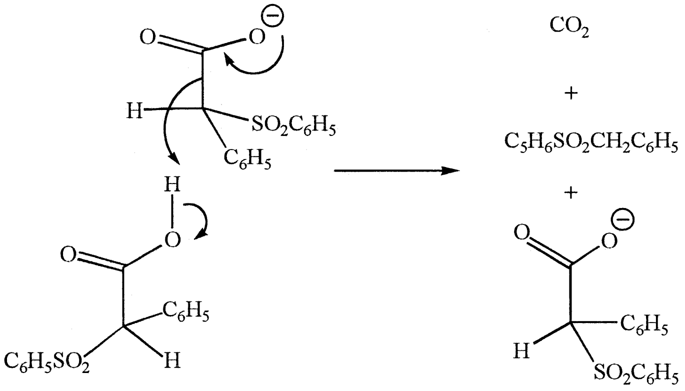
Entry	RX	$C_6H_5SO_2CH(R)C_6H_5$	Yield (%)
1	*p*-CH_3—$C_6H_5CH_2Br$	**2b**	41
2	CH_3I	**2c**	43
3	C_2H_5I	**2d**	41

[a] NaH/DMSO, r.t.

However, in the case of the benzenesulfonylphenylacetic acid, **1**, a colorless solution of sulfone **2** was obtained. The latter was stable in the presence of NaH, affording the corresponding yellow carbanion solution only after flushing with nitrogen. As expected, subsequent treatment with methyl tosylate yielded sulfone **2c** in admixture with benzylphenylsulfone **2** (2:1).

As for the mechanism of formation of benzylphenylsulfone, **2**, from the sulfonyl acid **1**, an unimolecular mechanism in which the carbanion is formed by departure of CO_2 from carboxylate may be excluded. A bimolecular mechanistic description similar to that proposed to explain the retention of chirality in the protonation of S,S-benzenesulfonyl α-phenylpropionic acid[3] seems to be more appropriate (Scheme 3).

Downloaded At: 10:14 28 January 2011



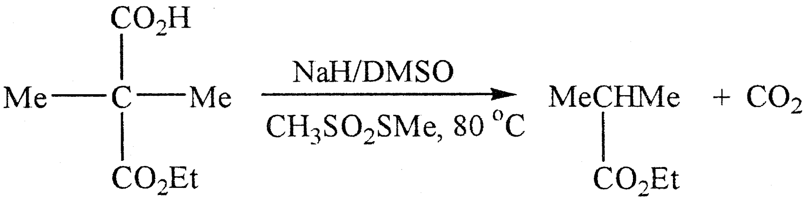
SCHEME 3

In our case, this mechanism proved to be operative as demonstrated by an experiment, in the presence of a catalytic amount of NaH in DMSO in which benzenesulfonylphenylacetic acid, **1**, underwent decomposition, in only a few minutes, to give benzylphenylsulfone, **2**. It is noteworthy that, in the absence of NaH, the decomposition also occurred, but took ca. 50 min.

Downloaded At: 10:14 28 January 2011

The catalytic nature of this decarboxylation conflicts with the lack of formation of the carbanion when sulfonyl acid **1** is treated with one equiv. of NaH. The observed inhibition of carbanion formation could be due to the presence of the evolved CO_2. In fact, in an experiment in which benzylphenylsulfone **2** was added to a suspension of NaH in DMSO, previously saturated with CO_2, the ^{1}HNMR spectrum of the resulting colourless solution showed that no deprotonation took place. Additionally, no methylation occurred upon addition of methyl iodide.

It is interesting to note that this bimolecular mechanism can also explain the decarboxylative protonation, observed previously in this laboratory,[4] in the reaction of α, α'-dimethyl malonate half ester, **3**, in the presence of NaH/DMSO with a sulfenylating agent, to give ester **4** (Eq. 1).



$$\underset{\textbf{3}}{Me-\overset{CO_2H}{\underset{CO_2Et}{C}}-Me} \xrightarrow[CH_3SO_2SMe,\ 80\ ^{\circ}C]{NaH/DMSO} \underset{\textbf{4}}{\underset{CO_2Et}{MeCHMe}} + CO_2 \quad (1)$$

Furthermore, it was verified that the lack of formation of the carbanion in the presence of CO_2 is not limited to benzylphenylsulfone, **2**. Indeed phenylacetonitrile and ethyl phenylacetate, when treated with NaH in DMSO, afforded a violet and a yellow solution, respectively, of the corresponding carbanion, as evidenced by ^{1}HNMR. However, lighter coloured mixtures, containing mainly unreacted starting materials, were formed when CO_2 saturated DMSO was employed.

It was also verified that the lack of reactivity of NaH toward benzylphenylsulfone, **2**, in the presence of CO_2 is not limited to DMSO, which is known to interact with CO_2,[5] but is also observed with other solvents, such as DMF and THF.

The possibility that formation of sodium formate,[6] is responsible for deactivation of NaH was eliminated by showing that a solution of benzylphenylsulfone, **2**, in DMSO, containing sodium formate, did not become yellow upon flushing with nitrogen.

Therefore, it seems reasonable to attribute the lack of reactivity of NaH as deprotonating agent in the presence of CO_2 to deactivation of the hydride surface or to a decrease of its solubility.

In summary, protonative decarboxylation of benzenesulfonylphenylacetic acid, in the presence of NaH in DMSO, occurs via a catalytic bimolecular non-carbanion mechanism. NaH deactivation, in the presence of CO_2, precludes carbanion formation and further alkylation. However, this drawback can be circumvented by flushing the reaction mixture with nitrogen.

EXPERIMENTAL

General

Microanalysis was performed on a Perkin-Elmer 240B Elemental Analyser. m.p.s are uncorrected and were determined on a Kofler hot-stage apparatus.

^{1}HNMR spectra were recorded on a Varian Inova 300 spectrometer with $SiMe_4$ as internal standard. Chemical shifts (δ) are expressed in ppm relative to $SiMe_4$. NMR spectra for samples dissolved in DMSO or DMF were recorded using a sealed capillary tube containing DMSO-d6 for internal lock. Gravity chromatography was performed on Merck Kieselgel 60 (70–230 mesh).

Starting Materials

Benzenesulfonylacetic acid, **1**, was prepared by carbonation of benzylphenylsulfone, **2**, according to a described procedure[7] and was dried by lyophilization; sulfone **2** was prepared by oxidation of the corresponding sulfide.[8]

Reaction of Benzenesulfonylphenylacetic Acid, 1, with Benzyl Bromide Without Nitrogen Flushing

A solution of acid **1** (0.100 g, 0.362 mmol) in 1.0 mL of DMSO was added dropwise via syringe to a suspension of oil-free NaH (0.035 g, 0.792 mmol, 50% in mineral oil) in DMSO (1.0 mL). After stirring for 1 h at r.t., benzyl bromide (0.062 g, 0.362 mmol) was added dropwise via syringe, further stirring for 3 h. The mixture was poured into water, yielding quantitatively sulfone **2**. ^{1}HNMR, $CDCl_3$, $\delta = 4.25$ (s; 2H), 6.84–7.70 (m, 10H).

Decarboxylative Alkylation of Benzenesulfonylphenylacetic Acid, 1

General Procedure

To a suspension of oil-free NaH (0.0550 g, 50% in mineral oil, 1.15 mmol) in 2.0 mL of dry DMSO was added, at r.t., a solution of acid

Downloaded At: 10:14 28 January 2011

1 (1.08 mmol) in 1.0 mL of DMSO, continuously purging the reaction mixture with nitrogen. After 1 h, the alkylating agent (1.14 mmol) was added dropwise via syringe and the solution was stirred at r.t. for an additional period of time (see below) before being poured into 20 mL of saturated aqueous ammoniun chloride solution. When solid, the crude product was filtered or, when oily, extracted with dichloromethane.

1-Methyl-4-[(2-phenyl-2-(phenylsulfonyl)ethyl] benzene, 2b

Using p-methylbenzylbromide and stirring for 5 h, a pale yellow solid was obtained. Recrystallization from ethanol yielded **2b** (41%) as white crystals. m.p. 169–171°C. ^{1}HNMR, $CDCl_3$, $\delta = 2.20$ (s, 3H), 3.35 (dd, 1H, J = 13.8 and 11.6Hz), 3.78 (dd, 1H, J = 13.8 and 3.2 Hz), 4.21 (dd, 1H, J = 11.6 and 3.2Hz), 6.83 (d, 2H, J = 8Hz), 6.91 (d, 2 H, J = 8Hz), 7.03–7.56 (m, 10 H). Calcd. for $C_{21}H_{20}O_2S$: C, 75.0; H, 6.0. Found: C, 74.9; H, 5.9.

Downloaded At: 10:14 28 January 2011

[(1-Phenylethyl)sulfonyl]benzene, 2c

Using methyl iodide and stirring for 1 h, an oil was obtained after the work-up. Crystallization from ethyl ether yielded **2c** as a pale yellow solid (43%). m.p. 108–114°C (Lit.[9] 113°C). ^{1}HNMR, $CDCl_3$, $\delta = 1.77$ (d, 3H, J = 7.2Hz), 4.24 (q, 1H, J = 7.2Hz), 7.09–7.57 (m,10H).

[(1-Phenylpropyl)sulfonyl]benzene, 2d

Using ethyl iodide and stirring for 1 h, a yellow oil was obtained which solidified on standing. After column chromatography using hexane-ethyl acetate (4:1), sulfone **2d** was isolated (41%). m.p. 91–95°C (Lit.[10] 99.5–100°C). ^{1}HNMR, $CDCl_3$, $\delta = 0.87$ (t, 3H, J = 7.4 Hz), 2.07–2.24 (m,1H), 2.43–2.56 (m, 1H), 3.94 (dd, 1H, J = 11.4 and 3.8 Hz), 7.06–7.57 (m, 10 H).

Attempts to Prepare the Benzylphenylsulfonyl Carbanion

From Benzylphenylsulfone 2

A solution of sulfone **2** (0.040 g, 1.7 mmol) in DMSO (0.5 mL) was introduced via syringe into a NMR tube containing oil-free NaH (0.007 g, 60% in mineral oil, 1.8 mmol). Evolution of gas and formation of a yellow colored solution was observed. ^{1}HNMR, DMSO, $\delta = 4{,}50$ (bs, 1H), 6.6–7.8(m, 10H); ^{13}CNMR, DMSO, $\delta = 60$ (bs). Addition of excess methyl iodide to this mixture afforded a colorless solution with a ^{1}HNMR spectrum identical to that of sulfone **2c**.

From Benzenesulfonylphenylacetic Acid, 1

A solution of benzenesulfonylphenylacetic acid, **1** (0.030 g, 1.1 mmol), in 0.5 mL of DMSO was added to a suspension of oil-free NaH (0.003 g, 1.3 mmol) in DMSO. The ^{1}HNMR spectrum of the resulting colorless solution was identical to that obtained for sulfone **2**. Addition of excess methyl iodide did not afford sulfone **2c**, as verified by ^{1}HNMR spectroscopy. Using the same procedure described above, but purging the reaction mixture with nitrogen for 1 h before adding methyl iodide, sulfone **2c** was formed in admixture (2:1) with sulfone **2**, as verified by ^{1}HNMR spectroscopy.

Downloaded At: 10:14 28 January 2011

REFERENCES

[1] B. Wladislaw, L. Marzorati, and C. L. Donnici, *J. Chem. Soc. Perkin Trans. I*, 3167 (1993).

[2] B. Wladislaw, L. Marzorati, C. Di Vitta, and N. F. Claro, *Phosphorus, Sulfur and Silicon*, **161,** 1 (2000).

[3] J .E. Taylor and F. H. Verhoek, *J. Am. Chem. Soc.*, **81,** 4537 (1959).

[4] B. Wladislaw, L. Marzorati, and C. L. Donnici, unpublished results.

[5] P. Raveendran and S. L. Wallen, *J. Am. Chem. Soc.*, **124,** 12590 (2002).

[6] H. Moissan, *Ann. Chim. Phys.*, **6,** 297 (1905).

[7] E. A. Lehto and D. A. Shirley, *J. Org. Chem.*, **22,** 989 (1957).

[8] G. A. Russell and J. M. Pecoraro, *J. Org. Chem.*, **44,** 3990 (1979).

[9] P. Charreau, M. Julia, and J. N. Verpeaux, *J. Organomet. Chem.*, **379,** 201 (1989).

[10] D. J. Pasto and J. L. Miesel, *J. Am. Chem. Soc.*, **85,** 2118 (1963).