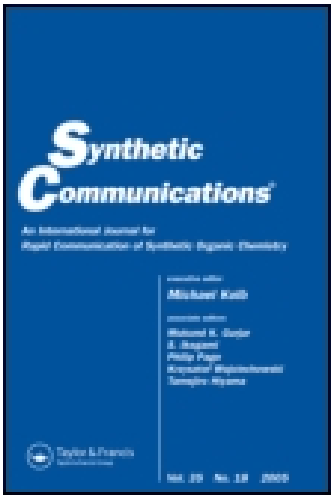


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Condition-Directable Reaction: Regio- and Stereoselective Elimination of 2,3-Dibromo-2-methylpropyl Phenyl Sulfone via Base-solvent Selection

Xiaojin Li [a]
[a] Laboratory of Immunogenetics, National Institute of Allergy and Infectious Diseases , National Institutes of Health , Rockville, Maryland, USA
Published online: 19 Aug 2006.

To cite this article: Xiaojin Li (2006) Condition-Directable Reaction: Regio- and Stereoselective Elimination of 2,3-Dibromo-2-methylpropyl Phenyl Sulfone via Base-solvent Selection, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 36:3, 393-399, DOI: 10.1080/00397910500377552

To link to this article: http://dx.doi.org/10.1080/00397910500377552

Synthetic Communications®, 36: 393–399, 2006

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500377552

Condition-Directable Reaction: Regio- and Stereoselective Elimination of 2,3-Dibromo-2-methylpropyl Phenyl Sulfone via Base-solvent Selection

Xiaojin Li
Laboratory of Immunogenetics, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, Maryland, USA

Abstract: Diversity-oriented organic synthesis is an important approach for combinatorial chemistry and drug discovery. An example of this approach is selective elimination of 2,3-dibromo-2-methylpropyl phenyl sulfone **5** to potentially useful vinyl sulfones **6*E*/*Z*** and vinyl bromides **7*E*/*Z***, which is achieved by choosing reaction conditions.

Keywords: Diversity-oriented, reaction condition-directable, regio- and stereoselective, elimination, vinyl sulfones, vinyl bromides, dibromo, phenyl sulfone

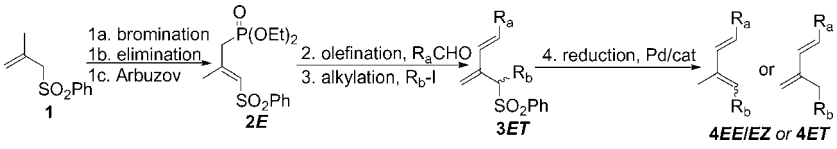
INTRODUCTION

Regio- and stereoselective synthesis has been a main area of interest in organic synthesis, and many efforts have focused on asymmetric catalyses[1] and chiral auxiliaries.[2] However, substrate- and condition-directable reactions have received far less attention.[3] Herein is reported an example of regio- and

Received in the USA July 12, 2005

This work was done during my graduate research under the guidance of Philip L. Fuchs in the Department of Chemistry at Purdue University, West Lafayette, Indiana, USA.

Address correspondence to Xiaojin Li, LIG, NIAID, National Institutes of Health, 12441 Parklawn Dr., Twinbrook II, Rockville, MD 20852, USA. E-mail: lixi@niaid.nih.gov



Scheme 1.

stereoselective synthesis of vinyl sulfones **6*E*/*Z*** and vinyl bromides **7*E*/*Z*** (Table 1) by appropriate selection of bases and solvents.

Vinyl sulfones,[4] allylic sulfones,[5] and vinyl bromides[6] have been found to be useful intermediates in organic synthesis. However, their regio- and stereoselective synthesis has not been well documented.[5a,7] In conjunction with development of target-oriented conjunctive reagents, we recently reported phosphonate sulfone **2*E*** as a conjunctive reagent for synthesis of 1,3-dienes **4*EE*/*EZ*/*ET*** via a common intermediate **3*ET*** in three operations (Scheme 1).[5c] (Note: The notion of ***T*** in ***ET*** or elsewhere in the article stands for a terminal carbon–carbon double bond in a compound to distinguish it from the nonterminal double bonds ***E*** and ***Z***. The notion was first used in Ref. 5c.) Reagent **2*E*** was synthesized by a bromination–elimination of methallyl phenyl sulfone **1**[8] via the corresponding dibromo phenyl sufone **5** (Table 1), followed by the Arbuzov reaction of the resulting bromo vinyl sulfone **6*E*** (Table 1, Scheme 1). Initial synthesis of **6*E*** suffered from selectivity problems, and the factors involved in chemoselectivity and stereospecificity in the elimination step were not straightforward. More extensive studies were carried out to fully explore and better understand the formation of vinyl sulfones **6*E*/*Z*** and vinyl bromides **7*E*/*Z*** in the dehydrobromination of **5**.

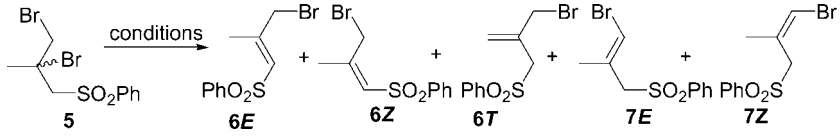
RESULTS AND DISCUSSIONS

Initially, dehydrobromination was carried out using triethylamine (TEA) in CCl_4, and the elimination gave vinyl sulfones **6*E*/*Z*** in 84% yield with an unexpected **6*E*/*Z*** ratio of 1.0/1.7 (Table 1, entry 1). With a solvent change from CCl_4 to $CHCl_3$, the reaction even more strongly favored formation of vinyl sulfone **6*Z*** (**6*E*/*Z***: 1/3.7) (Table 1, entries 1, 2). With DABCO in CCl_4, the elimination gave *Z*-dominated vinyl sulfones **6*E*/*Z*** with a ratio of 1/10.5, and in chloroform, an even higher selectivity for **6*Z*** (**6*E*/*Z***: 1/14.1) was observed (Table 1, entries 3, 4). It should be noted that when more than 0.5 equivalent of DABCO was used, the reaction produced a significant amount of amine–vinyl sulfone adduct salts (detected by ^{1}H NMR), most likely from nucleophilic attack of DABCO's N-atom on the allylic bromide moiety of vinyl sulfones **6*E*/*Z***. When one or more equivalents of DABCO were used, no bromo vinyl sulfones **6** survived. The same phenomenon was

observed, but to a different extent, in cases where DBU or pyridine was used as the base (Table 1, entries 5, 6).

Interestingly, when weaker amine bases were used, the reaction selectivity for **6*E*/*Z*** was reversed (Table 1, entries 6–14). With 2,6-lutidine in $CHCl_3$, vinyl sulfones **6*E*/*Z*** were afforded in 55% yield in a ratio of 11.1/1 (Table 1, entry 7). With 2,4,6-collidine, an even higher *E*-selectivity and high yield of vinyl sulfones **6*E*/*Z*** resulted (Table 1, entries 8–14). The stereoselectivity was solvent dependent: the less polar the solvent, the better the selectivity observed for vinyl sulfone **6*E***. The best selectivity (***E*/*Z***: 21.0/1) and nearly quantitative yield of the desired **6*E*** were achieved when non polar carbon tetrachloride was used as the solvent (Table 1, entry 8).

Table 1. Selective elimination of dibromo phenyl sulfone **5**



Entry	Conditions[a]	Product ratio[b] (**6*E*/6*Z*/6*T*/7*E*/7*Z***)	Yield (%)[c]
1	TEA (1.5 eq), CCl_4, rt, 2 h	1/1.7/—/—/—	84
2	TEA (1.5 eq), $CHCl_3$, rt, 4 h	1/3.7/—/—/—	71
3	DABCO (0.5 eq), CCl_4, rt, 13 h	1/10.5/—/—/—	68
4	DABCO (0.5 eq), $CHCl_3$, rt, 1 d	1/14.1/—/—/—	70
5	DBU (0.7 eq), $CHCl_3$, rt, 12 h	1.2/1/—/—/—	91
6	Pyridine (1.0 eq), $CHCl_3$, rt, 2 d	1.3/1/—/—/—	34
7	2,6-Lutidine (2.0 eq), $CHCl_3$, rt, 2 d	11.1/1/—/—/—	55
8	2,4,6-Collidine (2.0 eq), CCl_4, rt, 2 d	21.0/1/—/—/—	99
9	2,4,6-Collidine (2.0 eq), $CHCl_3$, rt, 2 d	11.4/1/—/—/—	99
10	2,4,6-Collidine, $CHCl_3$ (1.5 eq), rt, 2 d	11.8/1/—/—/—	82
11	2,4,6-Collidine (2.0 eq), CH_2Cl_2, rt, 2 d	13.5/1/—/—/—	98
12	2,4,6-Collidine (2.0 eq), toluene, rt, 2 d	18.7/1/—/—/—	74
13	2,4,6-Collidine (2.0 eq), ether, rt, 2 d	16.5/1/—/—/—	80
14	2,4,6-Collidine (2.0 eq), THF, rt, 2 d	14.0/1/—/—/—	89
15	K_2CO_3 (2.0 eq), CH_2Cl_2, reflux, 1 d	2.1/1/—/—/—	65
16	LiOH (2.0 eq), H_2O/t-BuOH (10/1), rt, 20 h,	0.1/—/—/1/3.1	83
17	KOH (1.0 eq), EtOH, 10 h, rt; KOH (0.5 eq) more, rt, 2 h	—/—/1/13.2/—	80

[a]The reaction was stopped when no further progress was observed over 2 h (monitored by TLC or ^{1}H NMR) or after two days.

[b]The ratios were determined by HPLC, except in the case of entry 16, where ^{1}H NMR was used. The stereochemistry was determined from "γ-gauche effect," and the configuration of **7*E*** was confirmed by NOE.[5c]

[c]The yields were combined yields and calculated based on limiting reagents used.

With weak inorganic base K_2CO_3 in methylene chloride under reflux, the elimination gave **6*E*/*Z*** in 65% yield with ratio of 2.1/1 (Table 1, entry 15). Interestingly, with LiOH in water, **6*E*** was observed as a minor product and the vinyl bromides **7*E*/*Z*** predominated (**6*E*/7*E*/7*Z***: 0.1/1/3.1). The yield in this case was 83% favoring the **7*Z*** stereoisomer (Table 1, entry 16). With stronger inorganic base KOH in ethanol, the elimination gave bromo phenyl sulfones **7*E*/6*T*** in 80% yield with high **7*E*** selectivity (13.2/1) (Table 1, entry 17).

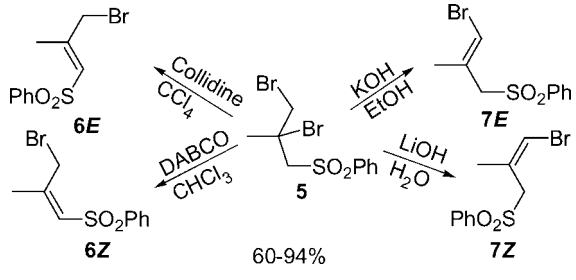
The study demonstrated that the selective elimination of dibromo phenyl sulfone **5** depends on the nature of bases and the characteristics of solvents used in the reaction. For the region- and stereoselective formation of vinyl sulfones **6*E*/*Z*** (using amine bases), the 3-bromo and phenyl sulfone groups of **5** might be involved by neighboring group participation. For the formation of vinyl bromides **7*E*/*Z*** (using inorganic bases in a protic solvent), it is likely that the vinyl bromides (or **6*T***) would arise from elimination of dibromide **5** followed by base-catalyzed isomerization of **6*E*/*Z***, and the stereoselectivity would be stereoelectronically and sterically governed by its reaction transition state. However, detailed mechanistic aspects and the scope of this selective elimination must be examined in the future.

In summary, the potentially useful vinyl sulfones and vinyl bromides were selectively prepared from a common precursor by appropriate selection of reaction conditions without requiring the use of a catalyst or mediator (Scheme 2). The report provides an example of diversity-oriented organic synthesis.

TYPICAL EXPERIMENTAL PROCEDURES

2,3-Dibromo-2-methylpropyl Phenyl Sulfone (5)[5c]

A solution of bromine (2.6 ml, 51.52 mmoL) in carbon tetrachloride (25.5 mL) was added to a solution of sulfone **1**[8] (10.00 g, 50.95 mmol) in carbon tetrachloride (51.0 mL) via a dropping funnel at 0°C. The mixture was stirred at this temperature for 30 min and then stirred at room temperature overnight



Scheme 2.

(the reaction was actually completed in 4 h). Removal of the solvent afforded dibromo phenyl sufone **5** (18.14 g, colorless oil) in quantitative yield (chloroform and ether are also suitable solvents for the reaction). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, $J = 7.5$ Hz, 2 H), 7.62 (m, 3 H), 4.12 (s, 2 H), 3.94 (d, $J = 14.4$ Hz, 1 H), 3.78 (d, $J = 14.7$ Hz, 1 H), 2.15 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 134.1, 129.4, 127.9, 65.1, 58.2, 43.1, 30.1.

General Procedure for Elimination of 2,3-Dibromo-2-methylpropyl Phenyl Sulfone (5)

The elimination of **5** was performed on 0.15-mmol scale, and a representative procedure (Table 1) is described. 2,4,6-Collidine (39 μL, 0.30 mmol) was added to a solution of dibromide **5** (53.4 mg, 0.15 mmol) in CCl_4 (0.3 mL) at 0°C. After stirring at room temperature for 2 days, the mixture was acidified with 5% HCl, and the organic layer was separated. The aqueous layer was extracted with methylene chloride (3 × 0.3 mL). The combined organic layers were washed with water and brine and dried over Na_2SO_4. After the solvents were removed, the residue was purified by silica-gel column chromatography (25% ethyl acetate in hexanes) to give ***6E/Z*** (40.8 mg, 99% with ratio 21/1) as a colorless oil.

2-(Bromomethyl)-2-propenyl Phenyl Sulfone (***6T***)[5c]

6T was separated by preparative TLC (25% ethyl acetate in hexanes) (Table 1, entry 17). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, $J = 7.5$ Hz, 2 H), 7.56 (m, 3 H), 5.42 (s, 1 H), 4.94 (s, 1 H), 4.08 (s, 2 H), 3.92 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 133.9, 133.7, 129.1, 128.2, 124.5, 59.6, 35.1.

(1*E*)-3-Bromo-2-methyl-1-propenyl Phenyl Sulfone (***6E***)[5c]

6E was separated by preparative LC (5% ethyl acetate in hexane at rate of 20 mL/min) (Table 1, entry 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, $J = 7.2$ Hz, 2 H), 7.56 (m, 3 H), 6.45 (s, 1 H), 3.85 (s, 2 H), 2.26 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 141.2, 133.5, 129.5, 129.3, 127.3, 36.4, 16.4.

(1*Z*)-3-Bromo-2-methyl-1-propenyl Phenyl Sulfone (***6Z***)[5c]

6Z was separated by preparative LC (5% ethyl acetate in hexane at 20 mL/min) (Table 1, entry 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, $J = 7.2$ Hz, 2 H), 7.57 (m, 3 H), 6.17 (s, 1 H), 4.55 (s, 2 H), 2.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 140.8, 133.6, 129.3, 128.5, 127.5, 27.1, 23.5.

(2*E*)-3-Bromo-2-methyl-2-propenyl Phenyl Sulfone (**7*E***)[5c]

KOH (8.4 mg, 0.15 mmol) was added to a solution of dibromo phenyl sulfone **5** (53.4 mg, 0.15 mmol) in EtOH (0.6 mL) at room temperature. After stirring at this temperature for 10 h, KOH (4.2 mg, 0.075 mmol) was added to the mixture. After stirring for 2 h more at room temperature, water (0.6 mL) was added. The aqueous layer was extracted with methylene chloride (3 × 0.6 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. After the solvents were removed, the crude light yellow solid was recrystallized from chloroform in hexanes to afford a mixture of **7*E*/6*T*** (33.0 mg, 80%) with ratio of 13.2/1 (Table 1, entry 17). **7*E*** was obtained by further recrystallization, and the stereochemistry was confirmed by NOE. White solid mp: 116–117°; NMR (300 MHz, $CDCl_3$) δ 7.80, $J = 7.5$ Hz, 2 H), 7.57 (m, 3 H), 5.90 (s, 1 H), 3.78 (s, 2 H), 1.85 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 133.9, 129.8, 129.1, 128.3, 111.6, 63.9, 19.8; IR (neat) cm^{-1} sp^2 C–H (3080, 3060, 3045), sp^3 C–H (2994, 2944), CH_2 (1450), CH_3 (1380.), C=C (1621), arom. (1575–1440, 737, 693), SO_2 (1302, 1295, 1155), C–Br (535). NOE: between 1-Hs and 3-H (1.5%), between 1-Hs and 2-Me (1.1%); HRMS (CI, NH_3) calcd. for $C_{13}H_{28}O_3Si$ $[M + H]^+$: 274.9741; found 274.9745.

(2*Z*)-3-Bromo-2-methyl-2-propenyl Phenyl Sulfone (**7*Z***).

The procedure for **7*E*** was followed, and **7*Z*** was isolated by preparative TLC (25% ethyl acetate in hexanes) (Table 1, entry 16). White solids mp: 80–81°; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, $J = 7.2$ Hz, 2 H), 7.45 (m, 3 H), 6.15 (s, 1 H), 4.04 (s, 2 H), 2.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 133.9, 130.3, 129.1, 128.6, 109.7, 61.1, 22.5; IR (KBr) cm^{-1} sp^2 C–H (3080), sp^3 C–H (2967, 2913, 2854), CH_2 (1445), CH_3 (1379), C=C (1623), arom. (1581–1443, 730, 711), SO_2 (1309, 1297, 1142), C–Br (528); HRMS (CI, NH_3) calcd. for $C_{13}H_{28}O_3Si$ $[M + H]^+$: 274.9743; found 274.9746.

ACKNOWLEDGMENT

I am grateful to Philip L. Fuchs for his guidance during this research and encouraging me to write this manuscript, John F. Hansen for his valuable suggestions for the preparation of this manuscript, and Douglas Lantrip for his support, especially his analytical support.

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