Synthesis of Arylethyl (*E*)-Styrylsulfones and Arylsulfones by One-Pot DIBAL-H/NaH-Mediated Reaction of β-Ketosulfones

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Abstract: A facile one-pot synthetic route for preparing a series of arylethyl (*E*)-styrylsulfones or arylethyl arylsulfones is developed. The efficient one-pot DIBAL-H/NaH-mediated route includes reduction of α-benzyl-β-arylketosulfones and retroaldol/aldol or retroaldol reaction of the resulting intermediate. The DIBAL-H/NaH-mediated reaction mechanism has been discussed.

Key words: aldol reaction, aluminum, condensation, sulfones, tandem reaction

β-Ketosulfone constitutes a diverse structural class associated with important synthetic and medicinal applications.[1,2] The skeleton is a versatile intermediate as it is a useful precursor for functional-group transformations (e.g., vinyl, β-hydroxy, or β-halosulfones).[3] Amongst these sulfonyl derivatives, substituted aryl sulfones are increasingly drawing interest due to their potential biological activities. Furthermore, benzyl styryl sulfones (e.g., ON013105, ON013100, ON01910.Na), belongs to the class of non-ATP competitive molecules and it is under evaluation as an anticancer agent.[4] The antimigraine medicine eletriptan (Relpax) possesses the arylethyl sulfonyl substituent (Figure 1).[5] Generally, sulfones are prepared by a variety of methods. Thiol or sulfide building blocks are typically employed, and the desired oxidation state is subsequently achieved via redox chemistry.[6,7] In recent years, many efforts have been expanded on developing a transition-metal- or metal-free-catalyzed cross-coupling reaction of substituted sulfinates (or sulfonyl halides) with substituted halides, especially for preparing unsymmetrical diaryl sulfones.[8–10]

Herein, we describe a tandem reduction–retroaldol–aldol or reduction–retroaldol reaction of α-substituted β-ketosulfones under mild reaction conditions, affording arylethyl (*E*)-styrylsulfones **5** and arylsulfones **6** in good yields. To achieve the best reaction conditions, the one-pot reaction of α-benzyl-α-benzoylsulfone **3a** (X = Me) and **4a** (X = Tol) was selected as the model reaction using DIBAL-H (1.0 M in hexane, 1.0 equiv) as a reductant in THF at room temperature, followed by the sequential addition of excess NaH (60% in oil) as the base. The reaction process was traced by TLC until the reactant was consumed. As shown in Scheme 1, compounds **3a** or **4a** were prepared with excellent yields via monobenzylation of β-ketosulfone **1a** or **2a** with benzyl bromide in the presence of K_2CO_3 in boiling acetone for eight hours. Treatment of α-bromo acetophenone with $MeSO_2Na$ or $TolSO_2Na$ afforded the starting material **1a** or **2a** in quantitative yield under refluxing cosolvent of 1,4-dioxane conditions.

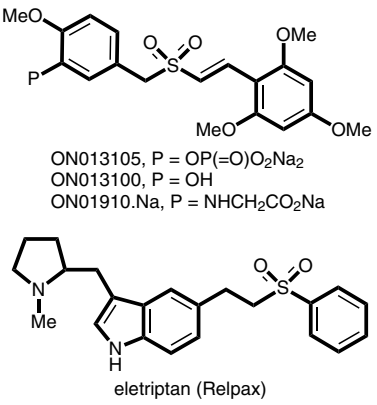
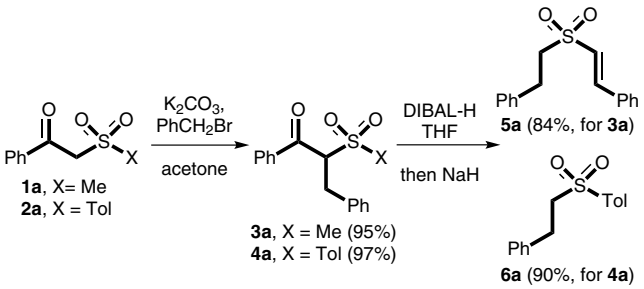


Figure 1 Representative biologically active sulfones



Scheme 1 Synthetic route of compounds **5a** and **6a**

As shown in Table 1, entries 1–4, we found that three equivalents of base, room temperature, and eight hours of reaction time should be the optimal one-pot conditions for increasing the yields of **5a** or **6a**. With the results in hand, four aluminum- or boron-containing reductants and three bases were investigated at room or reflux temperature in the absence of a Lewis acid or transition-metal catalyst. Two products, **5a** and **6a**, were obtained in moderate yields when $LiAlH(O\textit{t}\text{-Bu})_3$/NaH, L-Selectride/NaH, or $LiBHEt_3$/NaH were employed under the above reaction conditions (Table 1, entries 5–7). For a one-pot reaction of compound **3a** with KO*t*-Bu or DBU, Table 1, entries 8 and 9 show that a nearly 1:1 product ratio of an unknown mixture and **5a** were observed. For the formation of **6a**,

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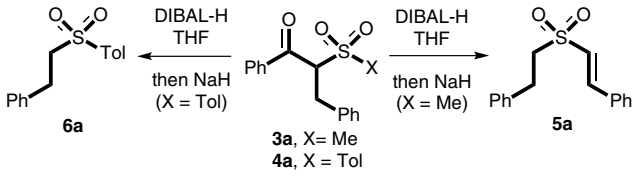
Table 1 Optimization of Reaction Conditions[a]

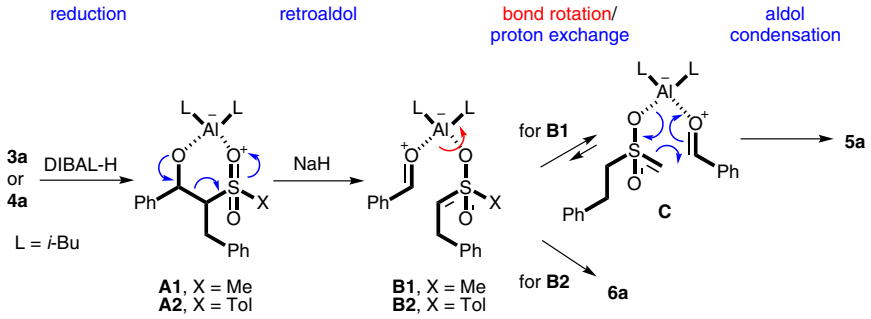


Entry	Reductant (equiv)[b]	Base (equiv)	Temp (°C)	Time (h)	Yield of **5a** (%)[c]	Yield of **6a** (%)[c]
1	DIBAL-H (1)	NaH (3)	25	8	84	90
2	DIBAL-H (1)	NaH (6)	25	8	80	88
3	DIBAL-H (1)	NaH (3)	67	8	79	80
4	DIBAL-H (1)	NaH (3)	25	20	83	83
5	$LiAlH(Ot\text{-}Bu)_3$ (1)	NaH (3)	25	8	80	80
6	L-Selectride (1)	NaH (3)	25	8	73	77
7	$LiBEt_3$ (1)	NaH (3)	25	8	74	82
8	DIBAL-H (1)	KO*t*-Bu (3)	25	8	37[d]	78
9	DIBAL-H (1)	DBU (3)	67	8	45[d]	76
10	DIBAL-H (3)	NaH (3)	25	8	–[e]	85

[a] The one-pot reaction was run on a 0.5 mmol scale with starting materials **3a** or **4a** in THF (10 mL).
[b] 1.0 M of reductant solution was used.
[c] The product was >95% pure as determined by ^{1}H NMR analysis.
[d] An unknown mixture (for entry 8, 40%; entry 9, 38%) was isolated.
[e] Phenylethyl methylsulfone was isolated.

KO*t*-Bu or DBU did not cause byproducts. When three equivalents of DIBAL-H were employed, phenylethyl methylsulfone was isolated at a 76% yield instead of the desired product **5a** (Table 1, entry 10). No influence on the formation of product **6a** was observed for the addition of excess amounts of DIBAL-H. According to the above phenomenon, we envision that DIBAL-H and NaH make up the optimal combination controlling the formation of **5a** and **6a**. The structure of **5a** was determined by single-crystal X-ray crystallography.[11,12]

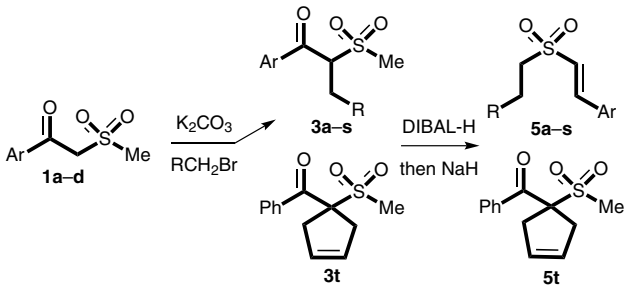
For the possible DIBAL-H/NaH-mediated reaction mechanism, the formation of intermediate **A** was first proposed via the DIBAL-H-mediated reduction of β-ketosulfone **3a** (X = Me) or **4a** (X = Tol), as shown in Scheme 2. With the involvement of NaH, the retroaldol reaction of intermediates **A1** and **A2** caused intermediates **B1** and **B2** with the aluminum-chelated complex of sulfone and benzaldehyde. After the chelated Al–O bond rotation and intramolecular proton exchange (or intermolecular deprotonation), the occurrence of the carbanion equilibrium between intermediates **B1** and **C** should be preferred to be formed. Furthermore, in situ intramolecular aldol condensation of the primary carbanion of intermediate **C** with benzaldehyde motif, followed by the removal of aluminum complex, produced a sole phenylethyl (*E*)-styrylsulfone **5a** via the proposed six-membered ring of intermediate **C**. Because there was no proton exchange of intermediate **B2**, phenylethyl tosylsulfone **6a** was formed from intermediate **B**. For the formation of product **5a**, one equivalent of DIBAL-H was a key factor in the presence



Scheme 2 Possible reaction mechanism

of the base. Excess amounts of DIBAL-H promoted the rapid overreduction (conversion from benzaldehyde into benzyl alcohol) such that intermediate **C** could not react with the resulting benzaldehyde to yield the desired **5a**. Therefore, the equivalent of DIBAL-H was not apparently important for the generation of **6a**.

Table 2 Synthesis of Skeletons **3** and **5**[a–c]



Entry	**1** Ar	**3** R	Yield of **3** (%)	Yield of **5** (%)
1	**1a** Ph	**3a** Ph	95	**5a** 84
2	**1a** Ph	**3b** 2,6-$F_2C_6H_3$	90	**5b** 70
3	**1a** Ph	**3c** 3,5-$(MeO)_2C_6H_3$	92	**5c** 78
4	**1a** Ph	**3d** (*E*)-styrene	94	**5d** 83
5	**1a** Ph	**3e** C_7H_{15}	86	**5e** 70
6	**1a** Ph	**3f** 2-pyridine	82	**5f** 60
7	**1a** Ph	**3g** 1-naphthalene	90	**5g** 80
8	**1a** Ph	**3h** 4-PhC_6H_4	92	**5h** 76
9	**1a** Ph	**3i** 4-$O_2NC_6H_4$	88	**5i** 72
10	**1a** Ph	**3j** 9-anthracene	85	**5j** 73
11	**1b**, 4-PhC_6H_4	**3k** Ph	92	**5k** 78
12	**1b**, 4-PhC_6H_4	**3l** 3,5-$(MeO)_2C_6H_3$	90	**5l** 74
13	**1b** 4-PhC_6H_4	**3m** 2,6-$F_2C_6H_3$	84	**5m** 68
14	**1c** 4-$MeOC_6H_4$	**3n** Ph	94	**5n** 80
15	**1c** 4-$MeOC_6H_4$	**3o** 3,5-$(MeO)_2C_6H_3$	88	**5o** 83
16	**1c** 4-$MeOC_6H_4$	**3p** 2,6-$F_2C_6H_3$	81	**5p** 77
17	**1d** 4-MeC_6H_4	**3q** Ph	93	**5q** 83
18	**1d** 4-MeC_6H_4	**3r** 3,5-$(MeO)_2C_6H_3$	86	**5r** 78
19	**1d** 4-MeC_6H_4	**3s** 2,6-$F_2C_6H_3$	82	**5s** 74
20	–	**3t** cyclopentenyl		**5t** 80

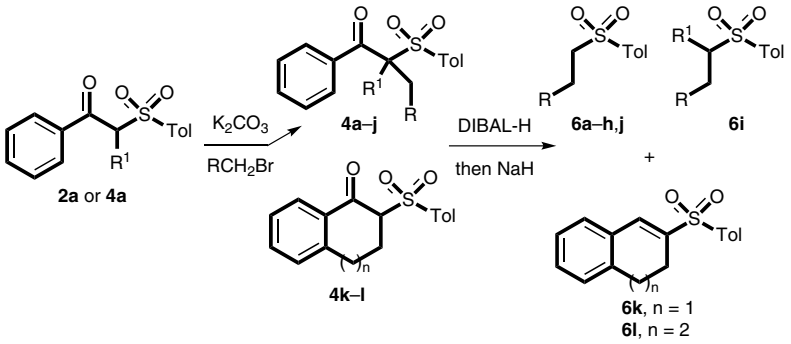
[a] The reaction was run on a 1.0 mmol scale with **1a**–**d**, K_2CO_3 (2.9 equiv), and bromides (1.05 equiv) in acetone (10 mL) at reflux.
[b] The one-pot reaction was run on a 0.5 mmol scale with **3a**–**t**, DIBAL-H (1.0 equiv), and NaH (3.0 equiv) in THF (10 mL) at r.t.
[c] The product was >95% pure as determined by ^{1}H NMR analysis.

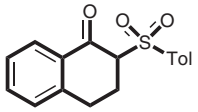
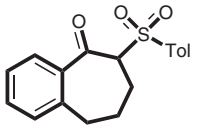
As shown in Table 2, 3a–t were efficiently constructed in good yields (80–95%) by the monoalkylation of β-ketosulfones **1a**–**d** and **3t** with different bromides. Different substituents (R, Ar), with diversified aromatic or aliphatic groups, were well-performed. For a DIBAL-H/NaH-mediated reaction, products **5a**–**t** were isolated at 60–84% yields. Table 2, entry 6 shows that **5f**, with the 2-pyridinyl group, was only separated at a 60% yield. A reasonable reason could be that DIBAL-H chelated the nitrogen atom of the 2-pyridinyl group to decrease the isolated yield of **5f**. For the 2,6-difluorobenzyl group, the given yield of **5b** was lower (68%, Table 2, entry 13) due to the effect of steric hindrance. Table 2, entry 20 shows that 80% of **5t** with the cyclopentenyl group was isolated.

According to the above experimental procedure, synthesis of phenylethyl tosylsulfones **6** was further examined (Table 3). Treatment of **2a** or **4a** with bromides afforded **4a**–**j** in the presence of K_2CO_3 at 80–97% yields. Next, the yields of **6a**–**j** were achieved in the range of 72–87% by the one-pot reaction. For Table 3, entry 6, lower yields of **6f** with the 2-pyridinyl group were also observed. After benzylation of 2**a** and cinnamylation of the resulting **4a**, **4i** with the disubstituted group was generated (Table 3, entry 9). By a one-pot reaction of **4i**, 82% of **6i** with the α,α′-bisalkylated group was easily synthesized. Furthermore, β-ketosulfones **4k**–**l** were chosen as the materials to examine the one-pot reaction. Cyclic vinyl sulfones **6k**–**l** were accomplished at 73% and 70% yields via the intramolecular aldol reaction and dehydration. Under the $CDCl_3$ solution, compound **4k** was easily converted into 2-sulfonylnaphthalene at room temperature within one day. The structure of **6k** was determined by single-crystal X-ray crystallography.[11]

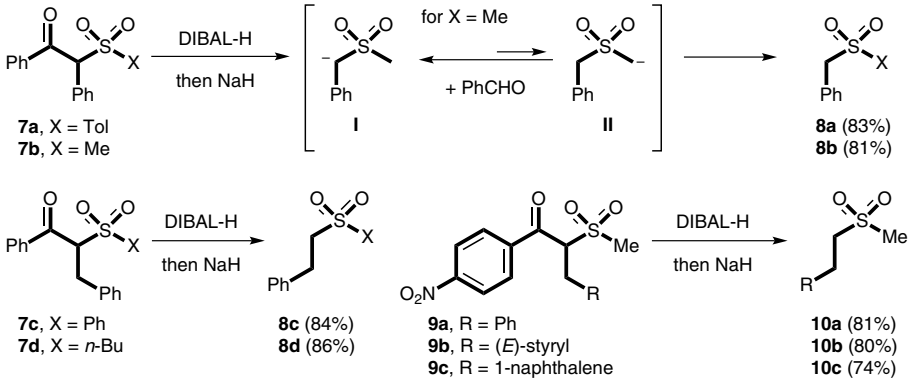
To extend this one-pot protocol, **7a**,**b** were chosen as the starting materials (Scheme 3). Changing the α-substituent of skeleton **3** or **4** to a phenyl group, the formation of benzyl sulfones **8a**,**b** was found at 83% and 81% yields. But attempts to prepare the skeleton of benzyl styryl sulfones failed, and no side arm of an (*E*)-styryl group was determined on the skeleton of **8b**. The possible reason could be that the secondary delocalized carbanion **I** was more stable than primary carbanion **II** such that sequential aldol condensation of intermediate **II** with benzaldehyde did not occur. In another way, by changing the X group of skeleton **3** or **4** to a phenyl or *n*-butyl group, the formation of phenylethyl sulfones **8c**,**d** was found at 84% and 86% yields. The results are similar to a one-pot reaction of compounds **7a**,**b**. After replacing the X group from toluene with benzene group of **7c**, **8c** still yielded (84%). For conversion from **7d** into **8d**, proton exchange equilibrium between intermediates **B1** and **C** (X = *n*-Bu) should not be generated based on the same secondary carbanions. Direct protonation of the initial formed intermediate **B1** should be preferred to proceed. These examples demonstrate that the above one-pot plausible reaction mechanism is a reasonable pathway via the highly regiospecificity. On the basis of the established protocol, a reaction of skeleton **9** (Ar = 4-nitrophenyl) with the combination of DIBAL-H/NaH produced skeleton **10**. The 4-nitrophenyl electron-withdrawing group should inhibit the formation of inter-

Table 3 Synthesis of Skeletons **4** and **6**[a–c]

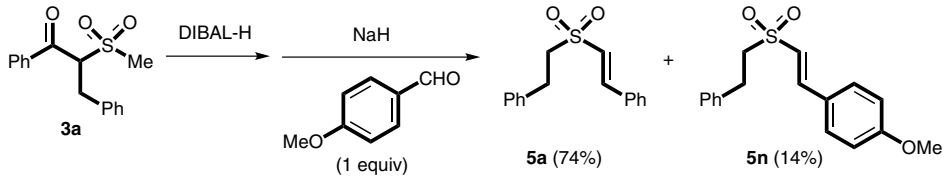


Entry	**2** or **4a** R^1	**4** R	Yield of **4** (%)	Yield of **6** (%)
1	**2a** H	**4a** Ph	97	**6a** 84
2	**2a** H	**4b** 2,6-$F_2C_6H_3$	82	**6b** 87
3	**2a** H	**4c** 3,5-$(MeO)_2C_6H_3$	90	**6c** 84
4	**2a** H	**4d** (*E*)-styrene	88	**6d** 82
5	**2a** H	**4e** C_7H_{15}	86	**6e** 80
6	**2a** H	**4f** 2-pyridine	80	**6f** 72
7	**2a** H	**4g** 1-naphthalene	88	**6g** 81
8	**2a** H	**4h** $CH{=}CH_2$	93	**6h** 86
9	**4a** Bn	**4i** (*E*)-cinnamyl	80	**6i** 82
10	**2a** H	**4j** 9-anthracene	83	**6j** 78
11	–	 **4k**		**6k** 73
12	–	 **4l**		**6l** 70

[a] The reaction was run on a 1.0 mmol scale with **2a** or **4a**, K_2CO_3 (2.9 equiv), and bromides (1.05 equiv) in acetone (10 mL) at reflux.
[b] The one-pot reaction was run on a 0.5 mmol scale with **4a**–**l**, DIBAL-H (1.0 equiv) and NaH (3.0 equiv) in THF (10 mL) at r.t.
[c] The product was >95% pure as determined by ^{1}H NMR analysis.



Scheme 3 Synthesis of compounds **8a–d** and **10a–c**



Scheme 4 Control experiment

mediate **B**, and the expected styryl motif was not involved in skeleton **10**.

To gather more information, a control experiment was set up under standard conditions. Competition reactions between in situ generated benzaldehyde and the addition of one equivalent of 4-methoxybenzaldehyde were carried out following the above protocol (Scheme 4). The ratio of products **5a** (74%) and **5n** (14%) could be obtained as nearly as 5:1 as determined by the separated products. Based on this, we believe that the exchange rate of aryl aldehyde controls this product ratio. This means that an intramolecular benzaldehyde exchange is easier than intermolecular involvement of 4-methoxybenzaldehyde for the aluminum-chelated intermediate **B1**. In summary, we have successfully described the one-pot DIBAL-H/NaH-mediated synthesis of β-ketosulfones **3** or **4** for preparing a series of substituted arylethyl (*E*)-styrylsulfones **5** or arylsulfones **6**. The facile synthetic route begins with simple starting materials and reagents and provides a potential methodology for chemical biology research.

Acknowledgment

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(11) CCDC 979312 (**5a**), 982010 (**5r**), and 979313 (**6k**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk].

(12) **Representative Procedure for the Synthesis of Skeleton 5**DIBAL-H (1.0 M in hexane, 0.5 mL, 0.5 mmol) was added to a solution of substituted β-ketosulfones **3** (0.5 mmol) in THF (10 mL) at r.t. The reaction mixture was stirred at r.t. for 10 min. NaH (60% in oil, 60 mg, 1.5 mmol) was added to the stirred solution at r.t. The reaction mixture was stirred at r.t. for 8 h. NH_4Cl aq (15%, 1 mL) was added to the reaction mixture, and the solvent was concentrated. The residue was diluted with H_2O (10 mL), and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford the crude product. Purification on silica gel (hexanes–EtOAc = 10:1 to 6:1) afforded skeleton **5**.Compound **5a**: yield 84% (114 mg); colorless solid; mp 63–65 °C (recrystallized from hexanes and EtOAc). ESI-HRMS: *m/z* calcd for $C_{16}H_{17}O_2S$ [$M^+ + 1$]: 273.0949; found: 273.0952. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 15.6 Hz, 1 H), 7.48–7.39 (m, 5 H), 7.33–7.21 (m, 5 H), 6.72 (d, *J* = 15.2 Hz, 1 H), 3.39–3.35 (m, 2 H), 3.18–3.14 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.97, 137.52, 132.12, 131.36, 129.08 (2×), 128.85 (2×), 128.55 (2×), 128.40 (2×), 126.95, 124.68, 56.50, 28.78. Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.56; H, 5.92. Found: C, 70.75; H, 6.30. Single-crystal X-ray crystallography: crystal of compound **5a** was grown by slow diffusion of EtOAc into a solution of compound **5a** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the orthorhombic crystal system, space group *Pna*21, *a* = 26.9302(15) Å, *b* = 9.6456(5) Å, *c* = 5.2760(5) Å, *V* = 1372.01(17) Å^3, *Z* = 4, δ_{calcd} = 1.318 g cm^{-3}, *F*(000) = 576, 2*θ* range 1.511–25.057°, *R* indices (all data) *R*1 = 0.0419, *wR*2 = 0.1113.

