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Tetrabutylammonium iodide catalyzed allylic sulfonylation of Baylis–Hillman acetates with sulfonylhydrazides in water†

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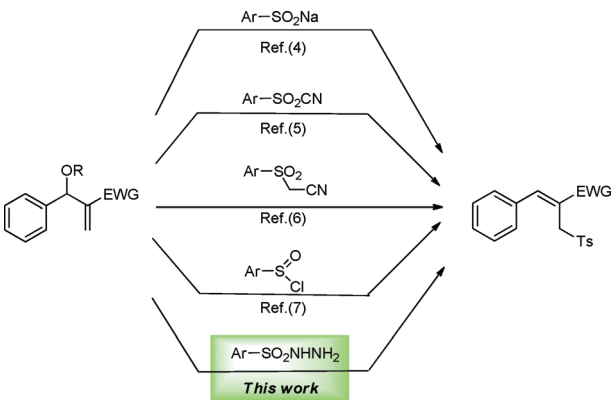
A tetrabutylammonium iodide catalyzed method for the synthesis of allyl aryl sulfone derivatives with Baylis–Hillman acetates and sulfonylhydrazides using *tert*-butyl hydroperoxide as an oxidation agent in water has been developed. In this process, the group eliminated from the sulfonyl precursor is molecular nitrogen.

Introduction

In recent years the tetrabutylammonium iodide (TBAI)/*tert*-butyl hydroperoxide (TBHP) catalyzed system has become a significant field of interest.[1] The simple operation, nontoxic and easy to handle reagents, and products free of heavy metal impurities make it a versatile alternative for transition-metal catalysts in numerous important organic transformations such as C–O, C–N and C–C bond formations. However, TBAI catalyzed C–S bond formation has not been considered of high value.[1n]

The allyl aryl sulfone derivatives are important intermediates in organic synthesis[2] and have been found to exhibit important biological activities.[3] Traditionally, they can be prepared by the reaction of Baylis–Hillman adducts with sulfonyl precursors such as sulfinates,[4] arenesulfonyl cyanides,[5] *p*-toluenesulfonylmethyl isocyanide[6] and sulfinyl chlorides[7] (Scheme 1). Generally, these reactions occurred in ionic liquid or organic solvents with the elimination of undesirable byproducts from sulfonyl precursors. Thus, there is still a need for facile and environmentally benign methods to afford allyl aryl sulfone derivatives.

Recently, our group has developed a novel TBAI catalyzed protocol for the direct allylic sulfonylation of α-methyl styrene derivatives using sulfonylhydrazides as a sulfonyl precursor.[1n] To the best of our knowledge, this is the first example of a TBAI–TBHP system catalyzed C–S bond formation reaction. As a logical extension of this catalytic method, and encouraged by our previous work on the transformation of Baylis–Hillman adducts,[8] we herein report a TBAI–TBHP system catalyzed allylic sulfonylation of Baylis–Hillman acetates with sulfonylhydrazides in water. A process that includes C–S bond formation and C–O bond cleavage affords substituted allyl aryl sulfones (Scheme 1).



Scheme 1 Synthesis of substituted allyl sulfones.

Results and discussion

At the beginning of our study, we chose Baylis–Hillman acetates **1a** and $TsNHNH_2$ (**2a**) as model substrates for this sulfonylation using the standard reaction conditions established by our previous work (1.2 equiv. of $TsNHNH_2$, 2 equiv. of TBHP, and 20 mol% of TBAI in MeCN at 80 °C).[1n] The desired allylic sulfone **3aa** was obtained in 23% yield (Table 1, entry 1). A similar result was obtained when EtOAc was used as the solvent (Table 1, entry 2). To our delight, the yield increased to 66% when the reaction occurred in water. Moreover, the reaction could finish within 0.5 h (Table 1, entry 3). No effect in yield was observed with higher amounts of $TsNHNH_2$ and TBHP (Table 1, entry 4).

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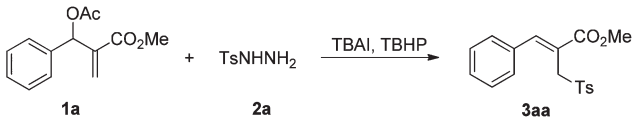
†Electronic supplementary information (ESI) available: Spectra for compounds **3**. See DOI: 10.1039/c3ob27329f

Table 1 Optimization of reaction conditions[a]



Entry	1a/2a	TBHP (eq.)	Solvent	Time (h)	Yield[b] (%)
1	1 : 1.2	2	MeCN	10	23
2	1 : 1.2	2	EtOAc	10	21
3	1 : 1.2	2	H_2O	0.5	66
4	1 : 1.5	3	H_2O	0.5	64

[a] Reaction conditions: 0.5 mmol of Baylis–Hillman acetates (**1a**), $TsNHNH_2$ (**2a**), 20 mol% TBAI, TBHP (70% aqueous solution) in 3.0 mL of solvent. [b] Isolated yield.

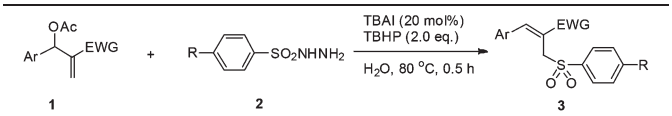
With the optimized reaction conditions, the scope of this transformation was then examined by using various Baylis–Hillman acetates and sulfonylhydrazides (Table 2). Treatment of $TsNHNH_2$ (**2a**) with a series of Baylis–Hillman acetates derived from benzaldehyde derivatives and acrylic esters (**1a–1k**) furnished the corresponding products (**3aa–3ka**) in 44–78% yields. Generally, electron-rich Baylis–Hillman acetates showed better reactivity and gave higher yields than electron-deficient ones. Baylis–Hillman acetates derived from acrylonitrile or cinnamaldehyde were well tolerated and the desired sulfones **3la**, **3ma** and **3lb** were provided in 65%, 52% and 69% yields, respectively. Heteroaryl species such as thiophenyl underwent the desired reaction to give the corresponding product **3na** in 72% yield. Phenyl and *p*-bromophenyl substituted sulfonylhydrazides were also suitable partners with Baylis–Hillman acetates to access the corresponding sulfones (**3ab**, **3gb**, **3hb**, **3lb** and **3ac**, **3fc**) in moderate yields. Unfortunately, alkyl-substituted Baylis–Hillman acetates failed to give the desired products which might be due to the difficulty in the elimination of acetoxy radicals. The stereochemistry in all cases was similar to that reported in the literature.[4–6]

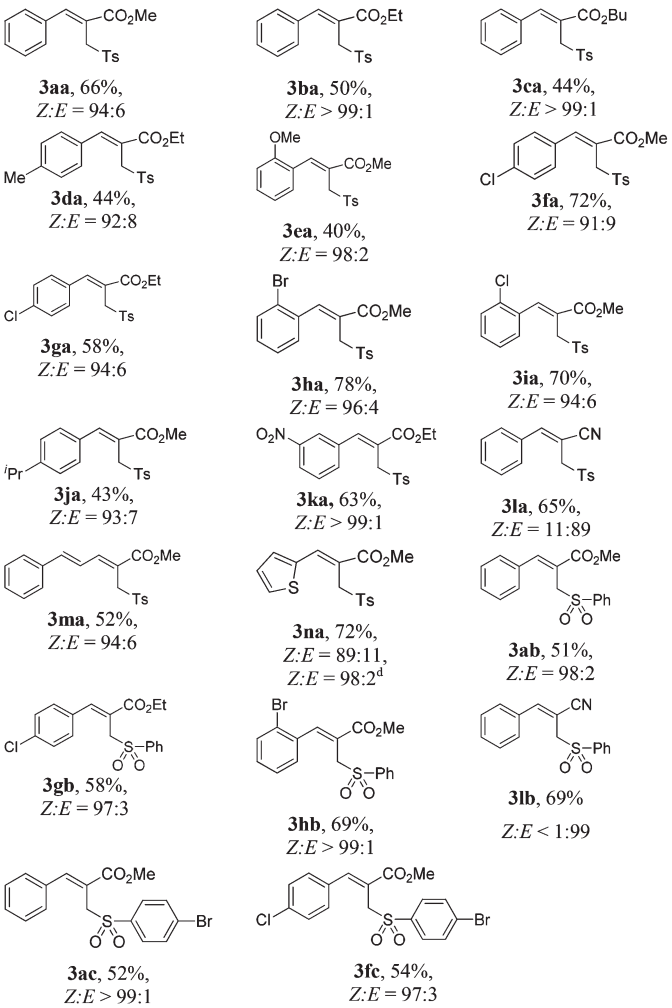
The proposed mechanism is similar to that of our previous study of TBAI catalyzed allylic sulfonylation of α-methyl styrene derivatives with sulfonylhydrazides.[1n] As shown in Scheme 2, initially, sulfonyl radicals were generated *via* TBAI–TBHP system catalyzed hydrogen abstraction of sulfonylhydrazides with the elimination of molecular nitrogen.[9] The addition of resultant sulfonyl radicals to the double bond of Baylis–Hillman acetates and subsequent β-acetoxy radicals elimination[10] afforded sulfones **3**. Hydrogen elimination did not happen in this process, perhaps due to the relatively higher C–H bond energy.

Conclusion

In summary, an environmentally friendly entry to allyl aryl sulfones starting from Baylis–Hillman acetates and sulfonylhydrazides has been developed. The protocol involves TBAI–TBHP system catalyzed C–S bond formation and C–O bond cleavage. This new protocol is distinguished by (1) using readily available sulfonylhydrazides as a sulfonyl precursor, (2) the group eliminated from the sulfonyl precursor is molecular nitrogen, (3) using water as a solvent, and (4) short reaction time. Currently, radical reactions based on the TBAI–TBHP system catalyzed radical species generation from hydrazine compounds are under investigation in our laboratory.

Table 2 Scope of the reaction[a,b,c]



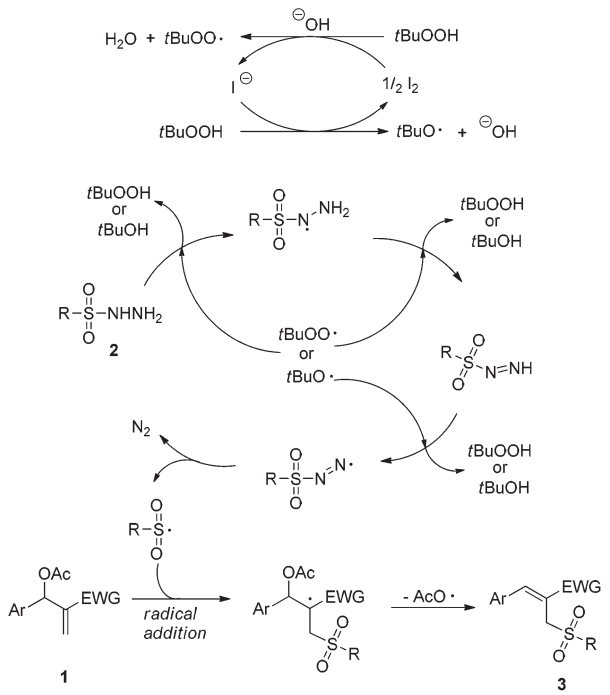


[a] Reaction conditions: 0.5 mmol of Baylis–Hillman acetates (**1**), 0.6 mmol of sulfonylhydrazides (**2**), 20 mol% TBAI, 1 mmol of TBHP (70% aqueous solution) in 3.0 mL of H_2O at 80 °C for 0.5 h. [b] Isolated yield. [c] Ratio of isomers was determined by ^1H NMR spectroscopy of the isolated product. [d] After crystallization.

Experimental section

General methods

All reagents and solvents were purchased from commercial suppliers and used without purification. The ^1H NMR and ^{13}C



Scheme 2 Proposed preliminary mechanisms.

NMR spectra were recorded at 25 °C in $CDCl_3$ at 500 and 125 MHz, respectively, with TMS as the internal standard. Chemical shifts (δ) are expressed in ppm and coupling constants J are given in Hz. High resolution mass spectra (HRMS) were obtained on a TOF MS instrument with an ESI source. Baylis–Hillman acetates were prepared by the reported procedure.[11]

General procedure for the synthesis of allyl aryl sulfone derivatives 3. To a flask containing the Baylis–Hillman acetates **1** (0.5 mmol), sulfonylhydrazides **2** (0.6 mmol), and tetrabutylammonium iodide (0.1 mmol) in H_2O (3 mL), TBHP (70% aqueous solution) (1.0 mmol) was added. The suspension was stirred at 80 °C for 0.5 h. The mixture was then extracted with AcOEt (4 × 10 mL) and the extract was washed with brine, dried (anh. Na_2SO_4), and concentrated. The residual was treated with silica gel chromatography (ethyl acetate–petroleum ether) to give allyl aryl sulfones **3**. The characterization data for known compounds (**3aa**,[5] **3fa**,[4a] **3ga**,[4b] **3ha**,[5] **3ka**,[4b] **3la**,[4a] **3ma**,[5] **3na**,[4b] **3ab**,[5] **3hb**,[5] **3lb**[5]) are provided in the ESI.†

*(Z)-Ethyl 3-phenyl-2-(tosylmethyl)acrylate (**3ba**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.49–7.42 (m, 2H), 7.38–7.33 (m, 3H), 7.25 (d, J = 8.0 Hz, 2H), 4.48 (s, 2H), 4.07 (q, J = 7.1 Hz, 2H), 2.41 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 145.8, 144.7, 136.4, 133.8, 129.6, 129.5, 129.2, 128.7, 128.5, 121.5, 61.5, 55.1, 21.6, 14.1. HRMS (ESI) calcd for $C_{19}H_{21}O_4S$ $(M + H)^+$: 345.1161; found: 245.1150.

*(Z)-Butyl 3-phenyl-2-(tosylmethyl)acrylate (**3ca**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.49–7.42 (m, 2H), 7.37–7.32 (m, 3H), 7.25 (d, J = 8.0 Hz, 2H), 4.48 (s, 2H), 4.02 (t, J = 6.8 Hz, 2H), 2.41 (s, 3H), 1.65–1.52 (m, 2H), 1.42–1.37 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 145.7, 144.7, 136.4, 133.8, 129.6, 129.5, 129.2, 128.7, 128.5, 121.5, 65.4, 55.1, 30.5, 21.6, 19.2, 13.7. HRMS (ESI) calcd for $C_{21}H_{25}O_4S$ $(M + H)^+$: 373.1474; found: 373.1462.

*(Z)-Ethyl 3-(p-tolyl)-2-(tosylmethyl)acrylate (**3da**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 4.49 (s, 2H), 4.04 (q, J = 7.1 Hz, 2H), 2.42 (s, 3H), 2.37 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 146.0, 144.6, 140.1, 136.6, 131.0, 129.6, 129.4, 129.4, 128.6, 120.3, 61.4, 55.3, 21.6, 21.4, 14.1. HRMS (ESI) calcd for $C_{20}H_{23}O_4S$ $(M + H)^+$: 359.1317; found: 359.1304.

*(Z)-Methyl 3-(2-methoxyphenyl)-2-(tosylmethyl)acrylate (**3ea**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.58 (dd, J = 7.6, 0.9 Hz, 1H), 7.37–7.30 (m, 1H), 7.24 (d, J = 8.0 Hz, 2H), 6.95 (t, J = 7.4 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 4.44 (s, 2H), 3.79 (s, 3H), 3.63 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 157.3, 144.4, 142.2, 136.5, 131.1, 129.8, 129.5, 128.5, 122.7, 121.0, 120.6, 110.5, 55.5, 55.4, 52.2, 21.6. HRMS (ESI) calcd for $C_{19}H_{21}O_5S$ $(M + H)^+$: 361.1110; found: 361.1099.

*(Z)-Methyl 3-(2-chlorophenyl)-2-(tosylmethyl)acrylate (**3ia**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.65–7.60 (m, 1H), 7.40–7.24 (m, 5H), 4.37 (s, 2H), 3.65 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 144.7, 142.8, 136.3, 134.1, 132.3, 130.5, 130.0, 129.7, 129.7, 128.4, 127.0, 123.3, 55.0, 52.5, 21.6. HRMS (ESI) calcd for $C_{18}H_{18}ClO_4S$ $(M + H)^+$: 365.0614; found: 365.0603.

*(Z)-Methyl 3-(4-isopropylphenyl)-2-(tosylmethyl)acrylate (**3ja**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.73 (dd, J = 8.4, 1.7 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 7.28–7.24 (m, 4H), 4.52 (s, 2H), 3.60 (s, 3H), 2.95–2.89 (m, 1H), 2.43 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 151.0, 146.3, 144.6, 136.4, 131.2, 129.6, 128.6, 126.8, 120.0, 55.3, 52.3, 34.0, 23.8, 21.6. HRMS (ESI) calcd for $C_{21}H_{25}O_4S$ $(M + H)^+$: 373.1474; found: 373.1462.

*(Z)-Ethyl 3-(4-chlorophenyl)-2-((phenylsulfonyl)methyl)acrylate (**3gb**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.86 (d, J = 7.4 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.53–7.43 (m, 4H), 7.35 (d, J = 8.5 Hz, 2H), 4.45 (s, 2H), 4.04 (q, J = 7.1 Hz, 2H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 144.5, 139.3, 135.7, 133.8, 132.1, 130.5, 129.0, 129.0, 128.4, 121.7, 61.6, 55.0, 14.0. HRMS (ESI) calcd for $C_{18}H_{18}ClO_4S$ $(M + H)^+$: 365.0614; found: 365.0602.

*(Z)-Methyl 2-(((4-bromophenyl)sulfonyl)methyl)-3-phenyl acrylate (**3ac**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.69–7.62 (m, 2H), 7.61–7.55 (m, 2H), 7.43–7.36 (m, 5H), 4.52 (s, 2H), 3.68 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 146.4, 138.1, 133.5, 132.3, 130.1, 129.7, 129.2, 129.0, 128.8, 120.8, 54.9, 52.5. HRMS (ESI) calcd for $C_{17}H_{16}BrO_4S$ $(M + H)^+$: 394.9953; found: 394.9939.

*(Z)-Methyl 2-(((4-bromophenyl)sulfonyl)methyl)-3-(4-chlorophenyl)acrylate (**3fc**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.71–7.65 (m, 2H), 7.65–7.60 (m, 2H), 7.45–7.35 (m, 4H), 4.46

(s, 2H), 3.65 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 145.1, 138.1, 136.1, 132.3, 131.9, 130.4, 130.1, 129.4, 129.1, 121.2, 55.0, 52.6. HRMS (ESI) calcd for $C_{17}H_{15}BrClO_4S$ $(M + H)^+$: 428.9563; found: 428.9550.

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