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Stereoselective Olefination and Regiospecific Vicinal Difunctionalization of Imines with α-(Benzothiazol-2-ylsulfonyl) Carbonyl Compounds

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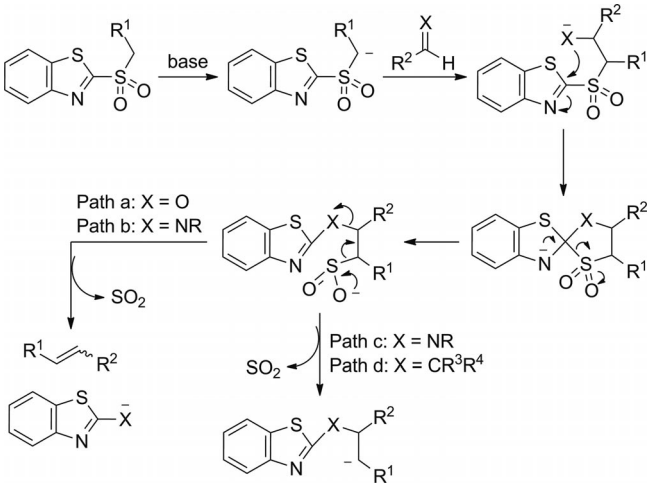
Depending on their structures, imines are able to undergo either olefination or vicinal difunctionalization with various α-(benzothiazol-2-ylsulfonyl) carbonyl compounds in the absence of external bases. The olefination reaction of aromatic imines with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds proceeds smoothly in tetrahydrofuran at 70 °C to give structurally diverse α,β-unsaturated esters, amides, and ketones in good to excellent yields and with extremely high (*E*) selectivity. In contrast, the carbon–nitrogen double bonds of cyclic imines and the carbon–carbon double bonds of α,β-unsaturated imines are subjected to regiospecific vicinal difunctionalization with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds under the same reaction conditions to give a variety of benzothiazole derivatives in good to excellent yields. It is noteworthy that the benzothiazole moiety is present in a number of antitumor agents and bioluminescent molecules. In addition, plausible reaction pathways have been proposed to account for these transformations, and these are substantially supported by ESI-MS analysis of the reaction mixtures.

Introduction

Benzothiazol-2-yl sulfones are readily accessible and frequently employed in the modified Julia reaction for transforming aldehydes into alkenes with generally high levels of stereoselectivity.[1] In recent years, the olefination of aldehydes with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds has emerged as a powerful method for the preparation of electron-deficient alkenes,[2,3] which are not only present in many natural products of biologically significance,[4] but also serve as useful electrophilic species in a broad range of chemical transformations such as Michael addition, cycloaddition, and cross-coupling reactions.[5] According to the generally accepted mechanism for the modified Julia reaction, stoichiometric amounts of bases are needed to deprotonate benzothiazol-2-yl sulfones, including α-(benzothiazol-2-ylsulfonyl) carbonyl compounds, and the resulting sulfonyl-stabilized carbanions undergo addition to C=O bonds followed by the Smiles rearrangement and β-elimination of the heterocyclic moiety to yield alkenes through extrusion of sulfur dioxide (Scheme 1, Path a).[1]



Scheme 1. Reactions of C=X bonds with benzothiazol-2-yl sulfones.

The mechanism for the modified Julia reaction allowed us to envision three new reactions of sulfonyl-stabilized carbanions (or equivalents) with imines rather than aldehydes through similar reaction pathways under appropriate conditions: (1) olefination of imines to give alkenes (Scheme 1, Path b);[6] (2) vicinal difunctionalization of imines to give 2-(alkylamino)benzothiazoles (Scheme 1, Path c); and (3) vicinal difunctionalization of the carbon–carbon double bonds of α,β-unsaturated imines to give 2-alkylbenzothiazoles (Scheme 1, Path d). Whereas the first reaction was anticipated to provide an alternative stereoselective synthesis of electron-deficient alkenes, the latter two

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could yield structurally diverse benzothiazole derivatives. It is noteworthy that the benzothiazole moiety is present in a number of antitumor agents and bioluminescent molecules (Figure 1).[7,8] Although a Mannich addition was recently reported to occur between *N*-Boc-protected imines and α-sulfonyl carbonyl compounds in the presence of a thiourea[9] or a base,[10,11] we believed that our proposed reaction pathways could be realized by tuning the electronic and steric properties of the substituents on the imine nitrogen atoms. In the course of exploring the synthetic utilities of carbon–nitrogen bond cleavage,[12] we found that a variety of imines could react with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds through either stereoselective olefination or regiospecific vicinal difunctionalization under base-free conditions. Herein, we report our results.

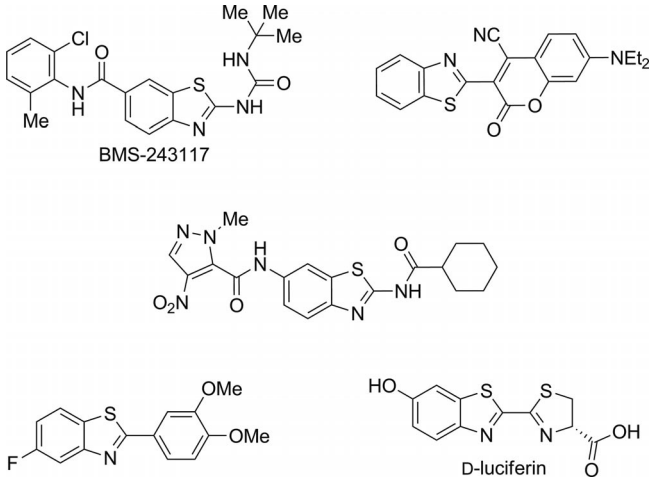
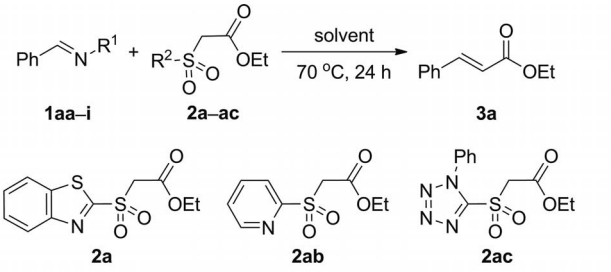


Figure 1. Some biologically important benzothiazole derivatives.

Results and Discussion

We initiated our investigation by employing Schiff base imines as carbon electrophiles to react with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds. To our surprise, in the absence of external bases, the model reaction of *N*-benzylideneaniline (**1aa**) with ethyl α-(benzothiazol-2-ylsulfonyl)acetate (**2a**) proceeded smoothly in a number of organic solvents at 70 °C (Table 1, Entries 1–11).[13,14] Tetrahydrofuran was identified as the solvent of choice; in this solvent the reaction gave α,β-unsaturated ester **3a** in 87% yield and with a selectivity of (*E*)/(*Z*) > 99:1 (Table 1, Entry 5). A slightly enhanced yield (88%) was obtained from the reaction with *N*-benzylidene-*p*-methoxyaniline (**1ab**; Table 1, Entry 12). Nevertheless, replacement of the phenyl group on the imine nitrogen atom in substrate **1aa** with either a bulky aryl group or an alkyl group led to either a much lower yield or no alkene product at all (Table 1, Entries 13–18). Interestingly, no reaction was observed with *N*-benzylidene-*p*-toluenesulfonamide (**1ai**), which is more electrophilic but less basic than Schiff base imine **1ab** (Table 1, Entry 19). Moreover, the imine olefination was significantly affected by the heteroarylsulfonyl group in the carbon nucleophile. Almost no reaction was observed when the benzothiazol-2-ylsulfonyl group in substrate **2a** was replaced by a pyridin-2-ylsulfonyl group or by a 1-phenyl-1*H*-tetrazol-5-ylsulfonyl group (Table 1, Entries 20 and 21).[15]

Table 1. Optimization of reaction conditions.[a]



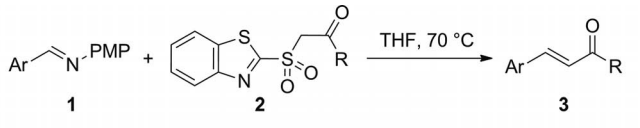
Entry	Imine, R^1	Sulfone	Solvent	Yield [%][b]	(*E*)/(*Z*)[c]
1	**1aa**, Ph	**2a**	toluene	72	>99:1
2	**1aa**, Ph	**2a**	$CHCl_3$	58	>99:1
3	**1aa**, Ph	**2a**	DCE	33	99:1
4	**1aa**, Ph	**2a**	EtOAc	31	>99:1
5	**1aa**, Ph	**2a**	THF	87	>99:1
6	**1aa**, Ph	**2a**	dioxane	trace	
7	**1aa**, Ph	**2a**	DMF	50	99:1
8	**1aa**, Ph	**2a**	DMSO	41	99:1
9	**1aa**, Ph	**2a**	$MeNO_2$	65	99:1
10	**1aa**, Ph	**2a**	MeCN	79	>99:1
11	**1aa**, Ph	**2a**	EtOH	40	>99:1
12	**1ab**, PMP	**2a**	THF	**88**	**>99:1**
13	**1ac**, 2-$MeOC_6H_4$	**2a**	THF	45	99:1
14	**1ad**, 2-HOC_6H_4	**2a**	THF	30	97:3
15	**1ae**, 1-naphthyl	**2a**	THF	0	
16	**1af**, *n*-butyl	**2a**	THF	62	99:1
17	**1ag**, Cy	**2a**	THF	21	98:2
18	**1ah**, $CHPh_2$	**2a**	THF	0	
19	**1ai**, Ts	**2a**	THF	0	
20	**1ab**, PMP	**2ab**	THF	0	
21	**1ab**, PMP	**2ac**	THF	trace	

[a] Reagents and conditions: imine (0.30 mmol), sulfone (0.36 mmol), solvent (1.0 mL), 70 °C (oil bath), 24 h. *p*-Methoxyphenyl (PMP), *p*-tolylsulfonyl (Ts), cyclohexyl (Cy), 1,2-dichloroethane (DCE), tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO). [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis.

A broad range of aromatic and heteroaromatic *N*-(*p*-methoxyphenyl)imines smoothly underwent olefination with alkyl α-(benzothiazol-2-ylsulfonyl)acetates to give structurally diverse α,β-unsaturated esters in good to excellent yields and with excellent (*E*) selectivity (Table 2, Entries 1–12). It is noteworthy that both electron-withdrawing and electron-donating groups were successfully introduced into the alkene products by employing imines bearing such groups on the aromatic rings. To our delight, the imine olefination reaction worked well with α-(benzothiazol-2-ylsulfonyl)acetamides having a wide variety of substituents on the amide nitrogen atoms, and a range of α,β-unsaturated

amides were obtained in good to excellent yields and with selectivities of (*E*)/(*Z*) > 99:1 (Table 2, Entries 13–21). Moreover, α-(benzothiazol-2-ylsulfonyl) ketones served as suitable substrates for the highly (*E*)-selective synthesis of the corresponding α,β-unsaturated ketones (Table 2, Entries 22–24).[16,17]

Table 2. Olefination of aromatic imines with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds.[a]

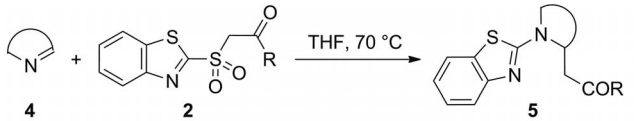


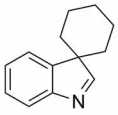
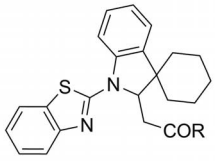
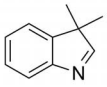
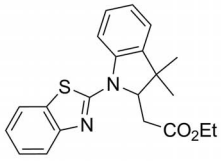
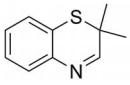
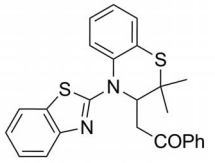
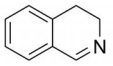
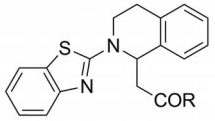
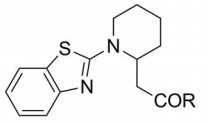
Entry	1, Ar	2, R	3	*t* [h]	Yield [%][b]	(*E*)/(*Z*)[c]
1	**1ab**, Ph	**2a**, OEt	**3a**	24	88	>99:1
2	**1b**, PMP	**2a**, OEt	**3b**	24	84	>99:1
3	**1c**, 4-ClC_6H_4	**2a**, OEt	**3c**	24	85	>99:1
4	**1d**, 4-NCC_6H_4	**2a**, OEt	**3d**	24	92	99:1
5[d]	**1e**, 4-$O_2NC_6H_4$	**2a**, OEt	**3e**	14	76	97:3
6	**1f**, 4-$MeSO_2C_6H_4$	**2a**, OEt	**3f**	40	99	>99:1
7	**1g**, 2-$MeOC_6H_4$	**2a**, OEt	**3g**	48	75	>99:1
8	**1h**, 2,4-$Cl_2C_6H_3$	**2a**, OEt	**3h**	48	90	>99:1
9	**1i**, 2-pyridinyl	**2a**, OEt	**3i**	24	77	>99:1
10	**1j**, 3-pyridinyl	**2a**, OEt	**3j**	40	87	>99:1
11	**1ab**, Ph	**2b**, OCH_2Ph	**3k**	24	84	>99:1
12	**1ab**, Ph	**2c**, $OCMe_3$	**3l**	36	77	>99:1
13	**1ab**, Ph	**2d**, NH_2	**3m**	36	90	>99:1
14	**1ab**, Ph	**2e**, NHPh	**3n**	24	90	>99:1
15	**1ab**, Ph	**2f**, NHMe	**3o**	24	88	>99:1
16	**1ab**, Ph	**2g**, $NH(CH_2Ph)$	**3p**	24	89	>99:1
17	**1ab**, Ph	**2h**, NHCy	**3q**	24	89	>99:1
18	**1ab**, Ph	**2i**, 1-morpholinyl	**3r**	36	86	>99:1
19[e]	**1ab**, Ph	**2j**, 1-piperidinyl	**3s**	12	87	>99:1
20[e]	**1ab**, Ph	**2k**, 1-azapanyl	**3t**	12	86	>99:1
21	**1ab**, Ph	**2l**, NMe(OMe)	**3u**	24	74	>99:1
22	**1ab**, Ph	**2m**, Ph	**3v**	24	84	>99:1
23	**1ab**, Ph	**2n**, Me	**3w**	12	57	>99:1
24	**1ab**, Ph	**2o**, CMe_3	**3x**	24	90	>99:1

[a] Reagents and conditions: imine **1** (0.30 mmol), sulfone **2** (0.36 mmol), THF (1.0 mL), 70 °C (oil bath), 12–48 h. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopic analysis. [d] The reaction was conducted at 120 °C in a sealed tube. [e] The reaction was conducted at 140 °C in a sealed tube.

In sharp contrast, the carbon–nitrogen double bonds of cyclic imines were subjected to vicinal difunctionalization with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds under the same reaction conditions (Table 3). No alkene intermediate was detected by ^1H NMR spectroscopic analysis of the reaction mixture of imine **4a** and sulfone **2a** (Table 1, Entry 1). The derivatives of 3*H*-indole, 2*H*-benzo[*b*][1,4]-thiazine, 3,4-dihydroisoquinoline, and 2,3,4,5-tetrahydropyridine were found to react well with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds to give the corresponding functionalized 2-(alkylamino)benzothiazoles in good to excellent yields. In addition, the structure of product **5f** was confirmed by single-crystal X-ray analysis (Figure 2).[18]

Table 3. Vicinal difunctionalization of cyclic imines with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds.[a]



Entry	Imine	2	Product	*t* [h]	Yield [%][b]
					
1	**4a**	**2a**	**5a**, R = OEt	20	84
2	**4a**	**2i**	**5b**, R = 1-morpholinyl	20	90
3	**4a**	**2m**	**5c**, R = Ph	20	97
					
4	**4b**	**2a**	**5d**	9	90
					
5	**4c**	**2m**	**5e**	30	79
					
6	**4d**	**2k**	**5f**, R = 1-azapanyl	40	83
7	**4d**	**2m**	**5g**, R = Ph	30	94
					
8[c]	**4e**	**2d**	**5h**, R = NH_2	32	73
9[c]	**4e**	**2h**	**5i**, R = NHCy	32	79
10[c]	**4e**	**2o**	**5j**, R = CMe_3	15	96

[a] Reagents and conditions: imine **4** (0.30 mmol), sulfone **2** (0.36 mmol), THF (1.0 mL), 70 °C (oil bath), 9–40 h. [b] Isolated yield. [c] A solution of imine **4e** in ethanol (1.2 M) was used.

Treatment of α,β-unsaturated imines with sulfone **2a** in tetrahydrofuran at 70 °C did not result in the formation of α,β,γ,δ-unsaturated esters. Instead, the carbon–carbon double bonds of α,β-unsaturated imines underwent regiospecific vicinal difunctionalization to give 2-(2-aminoalkenyl)benzothiazoles in good yields and with exclusive (*Z*) selectivity (Table 4). Owing to hydrogen bonding between the enamine N–H bond and the benzothiazole nitrogen atom, such products are sufficiently stable to enable purifi-

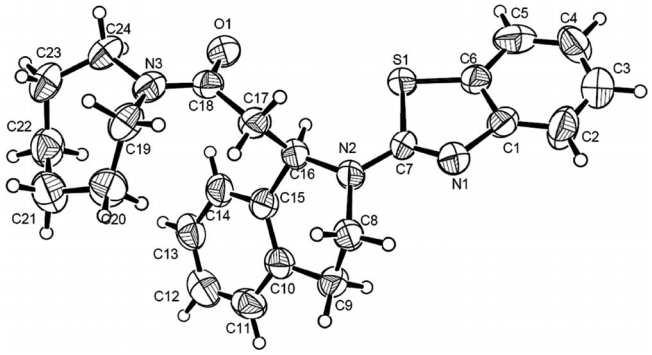
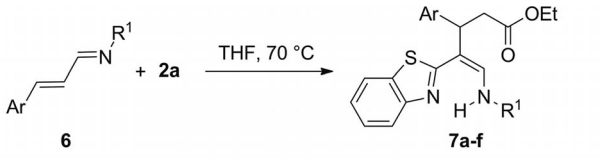


Figure 2. X-ray crystal structure of compound **5f**.[18]

cation by chromatography on silica gel. The structure of product **7a** was confirmed by single-crystal X-ray analysis (Figure 3).[18]

Table 4. Vicinal difunctionalization of α,β-unsaturated imines with sulfone **2a**.[a]



Entry	6	Ar	R^1	Product	Yield [%][b]
1	**6a**	Ph	PMP	**7a**	70
2	**6b**	PMP	PMP	**7b**	72
3	**6c**	4-BrC_6H_4	PMP	**7c**	73
4	**6d**	2-$MeOC_6H_4$	PMP	**7d**	75
5	**6e**	2-$O_2NC_6H_4$	PMP	**7e**	87
6	**6f**	Ph	Cy	**7f**	63

[a] Reagents and conditions: imine **6** (0.30 mmol), sulfone **2a** (0.36 mmol), THF (1.0 mL), 70 °C (oil bath), 24 h. [b] Isolated yield.

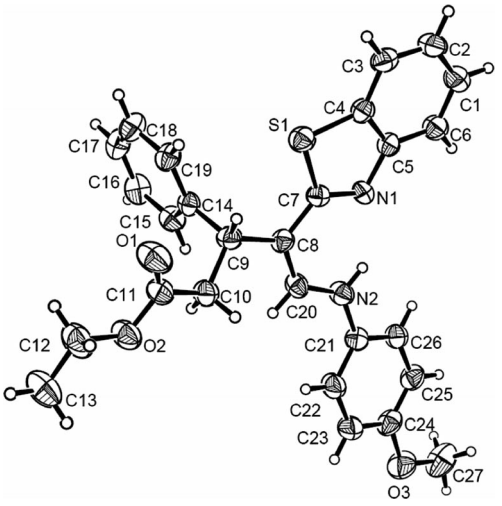
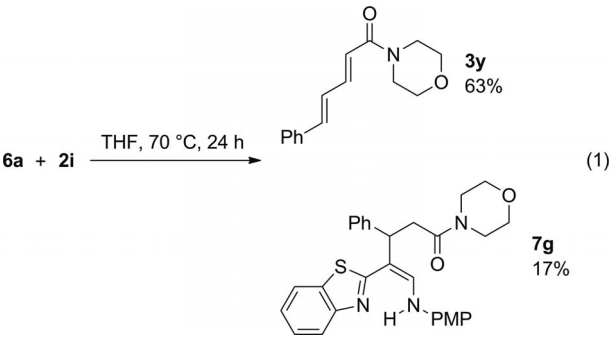
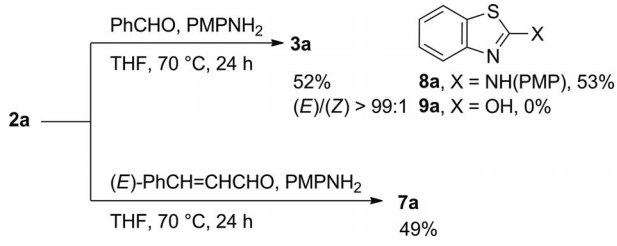


Figure 3. X-ray crystal structure of compound **7a**.[18]

A competition was observed between imine olefination and alkene vicinal difunctionalization in the reaction of α,β-unsaturated imines with α-(benzothiazol-2-ylsulfonyl)-acetamides, which gave a mixture of α,β,γ,δ-unsaturated amides and 2-(2-aminoalkenyl)benzothiazoles. For example, the reaction of imine **6a** with sulfone **2i** proceeded in tetrahydrofuran at 70 °C to give α,β,γ,δ-unsaturated amide **3y** in 63% yield [(*E*)/(*Z*) > 99:1] together with 2-(2-aminoalkenyl)benzothiazole **7g** in 17% yield [Equation (1)]. In contrast, complex mixtures were obtained from the reaction of α,β-unsaturated imines with α-(benzothiazol-2-ylsulfonyl) ketones under the same reaction conditions.



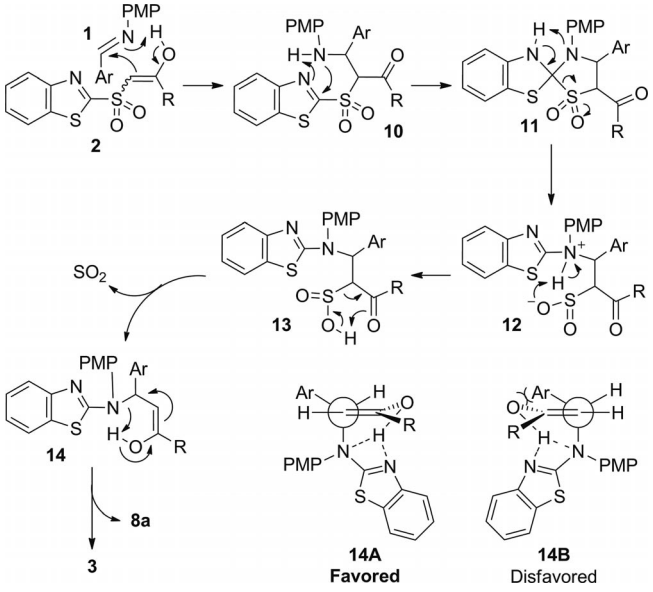
Because Schiff base imines are generally prepared by dehydrative condensation of aldehydes with primary amines,[19] we examined the reaction of sulfone **2a** with an aldehyde and *p*-methoxyaniline, wherein the corresponding Schiff base imine could be generated in situ (Scheme 2). The reaction with benzaldehyde gave α,β-unsaturated ester **3a** in 52% yield, which is much lower than that for the olefination reaction with imine **1ab** (88%, Table 2, Entry 1). Meanwhile, 2-[(*p*-methoxyphenyl)amino]benzothiazole (**8a**) was obtained as a byproduct in a similar yield (53%). The absence of 2-hydroxybenzothiazole (**9a**) (as a byproduct) suggests that the modified Julia reaction did not occur between benzaldehyde and sulfone **2a** in the presence of *p*-methoxyaniline. Instead, imine **1ab** was generated in situ from benzaldehyde and *p*-methoxyaniline and, subsequently, underwent olefination with sulfone **2a**. Similarly, cinnamaldehyde reacted with sulfone **2a** and *p*-methoxyaniline to afford 2-(2-aminoalkenyl)benzothiazole **7a** in 49% yield, which is significantly lower than that obtained for the vicinal difunctionalization of the corresponding imine (70%; Table 4, Entry 1).



Scheme 2. Reactions of sulfone **2a** with aldehydes in the presence of *p*-methoxyaniline.

According to our experimental observations and the mechanistic studies on the modified Julia reaction,[1] we propose the following reaction pathway for the olefination of aromatic imines with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds (Scheme 3). Initial Mannich addition of α-

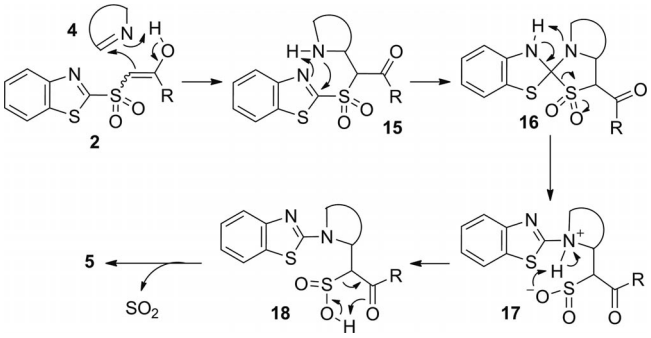
(benzothiazol-2-yl)sulfonyl carbonyl compound **2** (enol form) to aromatic imine **1** gives adduct **10**,[9] which undergoes the Smiles rearrangement through spirocycle **11** to give inner salt **12**.[1] Proton transfer followed by extrusion of sulfur dioxide results in the formation of β-amino carbonyl compound **14**,[20] which prefers to eliminate the amino group through reactive conformation **14A** to give α,β-unsaturated carbonyl compound **3** with (*E*) configuration.[21,22] ESI-MS (positive mode) analysis of the reaction mixture of imine **1** (**1ab**; Ar = Ph) and sulfone **2** (**2m**; R = Ph) substantially supports the formation of imine/sulfone adduct **10** (**11**, **12**, and/or **13**)[23] and intermediate **14** during the olefination reaction.[24]



Scheme 3. Proposed reaction pathway for the olefination of aromatic imines with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds.

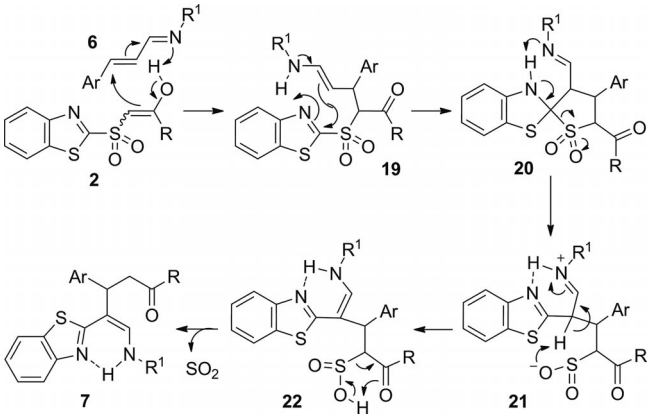
Likewise, vicinal difunctionalization of cyclic imines with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds is proposed to proceed successively through Mannich addition, Smiles rearrangement, proton transfer, and the extrusion of sulfur dioxide (Scheme 4). Cleavage of the carbon–nitrogen bond of product **5** does not take place to yield an alkene, probably due to the stable heterocycle moiety originated from cyclic imine **4**.

A similar reaction pathway is proposed for the vicinal difunctionalization of α,β-unsaturated imines with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds (Scheme 5). Initial Michael addition of sulfone **2** to α,β-unsaturated imine **6** gives enamine **19**, which undergoes the Smiles rearrangement through spirocycle **20** to give inner salt **21**. Owing to the hydrogen bond between the iminium N–H bond and the benzothiazole nitrogen atom, proton transfer in inner salt **21** results in the formation of intermediate **22** with an enamine moiety of (*Z*) configuration. Extrusion of sulfur dioxide from intermediate **22** gives product **7**. Again, ESI-MS (positive mode) analysis of the reaction mixture of imine **6** (**6a**; Ar = Ph, R^1 = PMP) and sulfone **2**



Scheme 4. Proposed reaction pathway for the vicinal difunctionalization of cyclic imines with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds.

(**2a**; R = OEt) substantially supports the formation of imine/sulfone adduct **19** (**20**, **21**, and/or **22**)[23] during the alkene vicinal difunctionalization reaction.[25]



Scheme 5. Proposed reaction pathway for the vicinal difunctionalization of α,β-unsaturated imines with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds.

Conclusions

We have developed three new reactions of imines with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds through stereoselective olefination and regiospecific vicinal difunctionalization under base-free conditions. The olefination reaction of aromatic imines with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds proceeds smoothly in tetrahydrofuran at 70 °C to give structurally diverse α,β-unsaturated esters, amides, and ketones in good to excellent yields and with extremely high (*E*) selectivity. In contrast, the carbon–nitrogen double bonds of cyclic imines and the carbon–carbon double bonds of α,β-unsaturated imines are subjected to regiospecific vicinal difunctionalization with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds under the same reaction conditions to give a variety of benzothiazole derivatives in good to excellent yields. Plausible reaction pathways have been proposed to account for these transformations, and these are substantially supported by ESI-MS analysis of the reaction mixtures.

Experimental Section

General Procedure for the Olefination of Aromatic Imines with α-(Benzothiazol-2-ylsulfonyl) Carbonyl Compounds: Table 2. To a solution of aromatic imine **1** (0.30 mmol) in dry tetrahydrofuran (1.0 mL) under nitrogen, was added α-(benzothiazol-2-ylsulfonyl) carbonyl compound **2** (0.36 mmol). The mixture was stirred at 70 °C for the period specified in Table 2, cooled to room temperature, and purified either by column chromatography on silica gel or by preparative thin layer chromatography (TLC), eluting or developing with petroleum ether/ethyl acetate (10:1 to 3:1), to give compound **3**.

General Procedure for the Vicinal Difunctionalization of Cyclic Imines with α-(Benzothiazol-2-ylsulfonyl) Carbonyl Compounds: Table 3. To a solution of cyclic imine **4** (0.36 mmol) in dry tetrahydrofuran (1.0 mL) under nitrogen, was added α-(benzothiazol-2-yl)sulfonyl carbonyl compound **2** (0.30 mmol). The mixture was stirred at 70 °C for the period specified in Table 3, cooled to room temperature, and purified either by column chromatography on silica gel or by preparative TLC, eluting or developing with petroleum ether/ethyl acetate (20:1 to 3:1), to give compound **5**.

General Procedure for the Vicinal Difunctionalization of α,β-Unsaturated Imines with Sulfone 2a: Table 4. To a solution of α,β-unsaturated imine **6** (0.30 mmol) in dry tetrahydrofuran (1.0 mL) under nitrogen, was added sulfone **2a** (103 mg, 0.36 mmol). The mixture was stirred at 70 °C for 24 h, cooled to room temperature, and purified by column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (50:1 to 10:1) and triethylamine (1% v/v), to give compound **7**.

Supporting Information (see footnote on the first page of this article): General information, experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra for products.

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[16] When compared to the modified Julia reaction with α-(benzothiazol-2-ylsulfonyl) carbonyl compounds,[2] the imine olefination reaction not only saves stoichiometric amounts of bases, but also significantly expands the scope for the synthesis of electron-deficient alkenes in a highly stereoselective manner.
[17] No reaction was observed with the corresponding aliphatic sulfones under the same conditions.
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[24] HRMS (ESI) for intermediate **10** (**10a**; Ar = R = Ph): calcd. for $C_{29}H_{25}N_2O_4S_2$ $[M + H]^+$ 529.12503; found 529.12439. HRMS (ESI) for intermediate **14** (**14a**; Ar = R = Ph): calcd. for $C_{29}H_{25}N_2O_2S$ $[M + H]^+$ 465.16313; found 465.16296.
[25] HRMS (ESI) for intermediate **19** (**19a**; Ar = Ph, R^1 = PMP, R = OEt): calcd. for $C_{27}H_{27}N_2O_5S_2$ $[M + H]^+$ 523.13559; found 523.13522.

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