



Aza-Diels–Alder reactions and synthetic applications of thio-substituted 1,3-dienes with arylsulfonyl isocyanates

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Abstract

The first aza-Diels–Alder reactions of arylsulfonyl isocyanates with thio-substituted 1,3-dienes via the 3-sulfolene precursors **1** gave the cyclized products **3** with complete control of regio- and chemoselectivity. The cyclized products **3a** and **4** underwent further interesting reactions with nucleophiles and bases to give useful heterocyclic compounds. © 2000 Elsevier Science Ltd. All rights reserved.

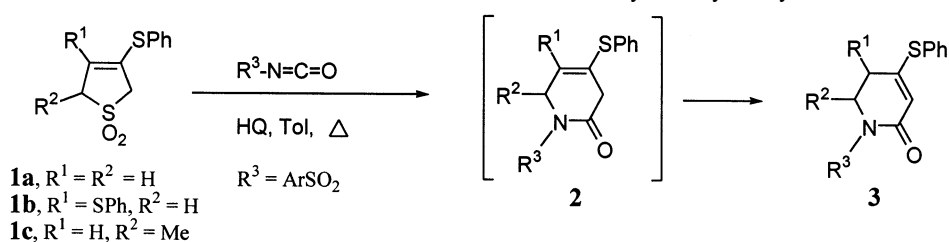
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Reactions of dienes with compounds containing C=N double bonds to give six-membered aza-heterocycles have opened up a wide variety of opportunities for organic synthesis, in particular for the construction of alkaloids and other natural products.¹ In general, the use of strongly electron-deficient imines is a prerequisite. This can sometimes be accomplished by the attachment of an acyl² or a sulfonyl group³ to the nitrogen. Although arylsulfonyl isocyanates have an electron-deficient C=N moiety, their aza-Diels–Alder reactions with dienes were not viable because the [2+2] cycloaddition or electrophilic substitution predominates.⁴ In this paper we describe the first aza-Diels–Alder reactions of arylsulfonyl isocyanates with thio-substituted 1,3-butadienes to give the cyclized products with complete control of regio- and chemoselectivity. The cyclized products could undergo further interesting reactions with nucleophiles and bases.

It is well established that 3-sulfolenes are useful precursors to 1,3-dienes.⁵ We have used this method to synthesize many sulfur-substituted dienes.⁶ Herein we report that thio-substituted 3-sulfolenes **1**⁷ can undergo in situ thermal desulfonylation and subsequent cycloaddition with arylsulfonyl isocyanates to give the cyclized products **2** and **3**. The results are summarized in Table 1.

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Table 1
Aza-Diels–Alder reactions of 3-sulfolenes **1** with arylsulfonyl isocyanates



Entry	1	R ³	Condition ^a	Yield (%)
1 ^{b,c}	1a	Ts (5 equiv.)	110°C, 4.5 h	2a (51), 3a (6)
2 ^b	1a	Ts (3 equiv.)	110°C, 4.5 h	3a (71)
3	1a	Ts (3 equiv.)	110°C, 4.5 h	3a (46)
4 ^{b,d}	1a	Ts (5 equiv.)	110°C, 4.5 h	3a (17)
5	1a	PhSO ₂ (5 equiv.)	110°C, 4 h	3b (30)
6 ^{b,d}	1a	PhSO ₂ (5 equiv.)	110°C, 4.5 h	3b (23)
7 ^b	1a	PhSO ₂ (5 equiv.)	110°C, 4.5 h	3b (50)
8	1a	<i>p</i> -ClPhSO ₂ (5 equiv.)	110°C, 4 h	3c (38)
9 ^{b,c}	1b	Ts (5 equiv.)	130°C, 8 h	2b (21), 3d (34)
10	1b	Ts (3 equiv.)	130°C, 8 h	3d (60)
11	1b	Ts (3 equiv.)	150°C, 5 h	3d (42)
12	1b	Ts (3 equiv.)	130°C, 12 h	3d (55)
13	1b	Ts (5 equiv.)	130°C, 8 h	3d (72)
14	1b	PhSO ₂ (5 equiv.)	130°C, 8 h	3e (73)
15	1b	<i>p</i> -ClPhSO ₂ (5 equiv.)	130°C, 8 h	3f (47)
16	1c	Ts (5 equiv.)	110°C, 4.5 h	3g (62)

^a Unless noted otherwise, a mixture of the 3-sulfolene **1**, the isocyanate and a catalytic amount of hydroquinone (HQ) was heated at 110°C in toluene under nitrogen. If a higher temperature was needed, then a sealed tube was used. After workup the crude product was purified by silica gel column chromatography using hexane/EtOAc/Et₃N as eluent.

^b One equivalent of anhydrous NaHCO₃ was also added.

^c Triethylamine was not included in the eluent of the silica gel chromatography.

^d THF was used as the solvent.

The cycloaddition of thio-substituted 3-sulfolene **1a** with *p*-toulenesulfonyl isocyanate (PTSI) could be carried out in refluxing toluene to give the cyclized product **2a** and a small amount of the double bond-isomerized product **3a** (entry 1). Under this condition the diene was generated in situ from desulfonylation of the 3-sulfolene **1a**. In this reaction one equivalent of sodium bicarbonate was present to remove the sulfur dioxide generated, and a catalytic amount of hydroquinone (HQ) was used to prevent polymerization of the diene. Since the ¹H NMR spectrum of the crude product did not show the presence of **3a**, its formation probably resulted from the isomerization of **2a** during silica gel chromatography. Indeed, when 10% of triethylamine was included in the eluent of chromatography, complete isomerization to product **3a** was achieved (entry 2). If the cycloaddition was carried out in the absence of NaHCO₃, only product **3a** was obtained (entry 3), no trace of **2a** being detected from the ¹H NMR spectrum of the crude product. Apparently, the sulfur dioxide generated from the reaction caused the isomerization of **2a** to **3a**. Thus, both acid and base catalyzed the isomerization of **2** to **3**. The cycloaddition of **1a** also proceeded with other arylsulfonyl isocyanates (entries 5–8).

Polar solvents cannot be used for the cycloaddition because they react with the isocyanates. It was found that toluene was a better solvent than THF (compare entries 2 with 4, and 6 with 7). Furthermore, the addition of sodium bicarbonate increased the yield (compare entries 2 with 3, and 5 with 7). The cycloaddition reactions of the bis(phenylthio)-substituted 3-sulfolene **1b** with arylsulfonyl isocyanates were similar to those of **1a**, but required higher temperatures (entries 9–15). The reaction time and equivalents of arylsulfonyl isocyanates had some effects on the yields of reaction. Under similar conditions, 3-sulfolene **1c**^{5a} reacted with PTSI to give the cyclized product **3g** in 62% yield (entry 16). Although the thio-substituted 1,3-dienes are unsymmetrical, their aza-Diels–Alder reactions with arylsulfonyl isocyanates gave only one regioisomer, which was shown by spectroscopic methods to be the ‘*para*’ adduct (with respect to the nitrogen).⁸ The regiochemistry is consistent with that predicted either by a concerted or stepwise mechanism.^{1d}

Under similar conditions, isoprene (5–10 equiv.) reacted with PTSI to give the cyclized product **3** only in 5–7% yield. Obviously, the thio-substituent enhances the reactivity of the diene toward PTSI. We have also examined similar reactions with many other monosubstituted-dienes such as 2-trimethylsilyloxy-1,3-butadiene, 2-phenylsulfinyl-1,3-butadiene, 2-phenylsulfonyl-1,3-butadiene, or disubstituted dienes derived from **1** ($R^1 = \text{NHAc}$, SOPh , SO_2Ph , $R^2 = \text{H}$), but they all failed to undergo aza-Diels–Alder reactions with PTSI. It appears that the thio-substituent on the diene strikes a balance of reactivity with PTSI: an electron-donating group is needed to increase the reactivity of cycloaddition, but too strong an electron-donating group leads to other reaction pathways.

The cyclized product **3a** contains an interesting structure of an α,β -unsaturated lactam, which also bears a phenylthio leaving group at the β -position. The sulfide group in **3a** could easily be oxidized to the sulfone **4** by mCPBA (2.5 equiv.) in dichloromethane at room temperature in 98% yield. The lactams **3a** and **4** could react with various nucleophiles and bases to give addition, substitution, or elimination products. The results are summarized in Table 2.

Table 2
Reactions of lactams **3a** and **4** with nucleophiles and bases

3a R = SPh 4 R = SO₂Ph 5 6 7				
Entry	3a or 4	Nu [−] /B [−]	Condition	Yield (%)
1	3a	Allyl-MgBr (4 equiv.)	THF, rt, 70 min	5a (91)
2	3a	MeLi (4 equiv.)	THF, rt, 1 h	5b (66)
3	3a	BuLi (4 equiv.)	THF, rt, 1 h	5c (60)
4	3a	LiAlH ₄ (2.5 equiv.)	THF, rt, 5 h	5d (23)
5	3a	MeLi (4 equiv.), CuI (4 equiv.)	THF, −78°C, 3 h	6a (90)
6	3a	BuLi (4 equiv.), CuI (4 equiv.)	THF, −78°C, 3 h	6b (91)
7	4	Allyl-MgBr (4 equiv.)	THF, rt, 1 h	5e (88)
8	4	NaN ₃ (1.1 equiv.)	DMF, 0°C, 0.5 h	6c (76)
9	4	NaCN (1.1 equiv.)	DMF, 0°C, 30 min	6d (93)
10	4	NaCH(CO ₂ Me) ₂ (2 equiv.)	THF, −78°C, 1h; rt, 1 h	6e (63)
11	4	KF (10 equiv.)	DMF, rt, 5 h	7 (89)

The sulfide-substituted lactam **3a** reacted with Grignard reagent, organolithium reagents and hydride reducing agents to give the double addition products **5a–d** (entries 1–4). Decreasing the amount of the nucleophile only resulted in lower yields of **5a–d**. Apparently, the monoaddition intermediate readily undergoes an elimination to form an iminium ion which reacts with a second nucleophile. The lactam **3a** reacted with organocopper reagents to give the substitution products **6a–b** (entries 5–6). Attempted reactions of **3a** with weaker nucleophiles (NaN_3 , NaCN or Et_2NH) led only to recovered starting material. The sulfone-substituted lactam **4** also yielded the double addition product **5e** with Grignard reagent (entry 7), but gave the substitution products **6c–e** with sodium azide, sodium cyanide and dimethyl malonate anion, respectively (entries 8–10). Thus, the phenylsulfonyl group in **4** activates the nucleophilic addition and is also a much better leaving group than the phenylthio group in **3a**. Reactions of **4** with amines or other bases led to the elimination product **7** (entry 11), which should be useful for reacting with various dienes and dienophiles.⁹ Presumably, **7** was formed from **4** via a series of double bond isomerization followed by elimination of the sulfone group.

In summary, we have carried out the first aza-Diels–Alder reactions of arylsulfonyl isocyanates with thio-substituted 1,3-dienes via the 3-sulfolene precursors **1** to give the cyclized products **3** with complete control of regio- and chemoselectivity. The cyclized products **3a** and **4** underwent further interesting reactions with nucleophiles and bases to give useful heterocyclic compounds.

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- The regiochemistry of the cycloaddition was unequivocally determined by spectroscopic methods. For example, ^1H NMR spectral data of **3a**: δ 2.38 (3 H, s), 2.67 (2 H, t, $J=6.3$ Hz), 4.06 (2 H, t, $J=6.3$ Hz), 5.13 (1 H, s), 7.27 (2 H, d, $J=8.2$ Hz), 7.38–7.45 (5 H, m), 7.88 (2 H, d, $J=8.2$ Hz).
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