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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.

Keywords: aza-Diels–Alder reactions; 1,3-dienes; arylsulfonyl isocyanate.

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 acyl[2] or a sulfonyl group[3] 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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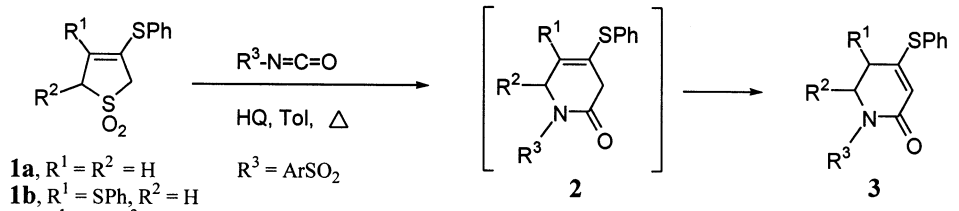
Table 1
Aza-Diels–Alder reactions of 3-sulfolenes **1** with arylsulfonyl isocyanates



1a, $R^1 = R^2 = H$
1b, $R^1 = SPh$, $R^2 = H$
1c, $R^1 = H$, $R^2 = Me$

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**	*p*-$ClPhSO_2$ (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**	*p*-$ClPhSO_2$ (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/Et_3N as eluent.

[b] One equivalent of anhydrous $NaHCO_3$ was also added.

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

[d] THF was used as the solvent.

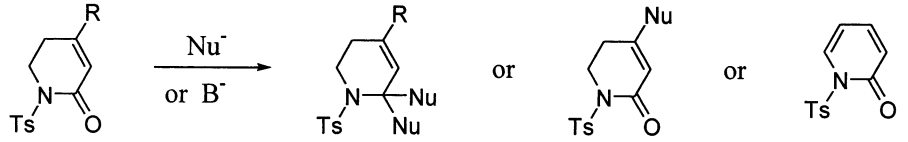
The cycloaddition of thio-substituted 3-sulfolene **1a** with *p*-toulenesulfonyl isocyanate (PTSI) could be carried out in refluxing toluene to give the cyclized product **2a** and a small amount of the double bond-isomerized product **3a** (entry 1). Under this condition the diene was generated in 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 $NaHCO_3$, 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 isocyantes 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 = NHAc, SOPh, SO_2Ph, R^2 = 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 = SO_2Ph

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**	$NaCH(CO_2Me)_2$ (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.

Acknowledgements

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8. The regiochemistry of the cycloaddition was unequivocally determined by spectroscopic methods. For example, ^{1}H 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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