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# AZA-DIELS-ALDER REACTIONS OF 2-(PHENYLTHIO)-1,3-BUTADIENE WITH SIMPLE IMINIUM SALTS

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## ABSTRACT

The titled compound 2 was readily prepared by thermal desulfonylation of 3-(phenylthio)-3-sulfolene (1). The aza-Diels-Alder reactions of 2 with some simple iminium salts gave the cyclized products 3-7 in good yield with complete control of regiochemistry.

The piperidine ring is one of the most abundant molecular fragments in both natural and synthetic compounds with various biological activities.<sup>1–4</sup> The aza-Diels-Alder reaction is potentially one of the most versatile and rapid routes to substituted piperidines.<sup>5,6</sup> Disappointingly, most imines fail to participate in these [4+2] cycloadditions. In general, the use of strongly electron-deficient imines seems to be a prerequisite. This can sometimes be accomplished by simple protonation,<sup>7–10</sup> but more general success has been achieved by the attachment of an acyl<sup>11</sup> or a sulfonyl group<sup>12–14</sup> to the nitrogen. When only an alkyl group is attached to the imine nitrogen, the scope of the aza-Diels-Alder reaction

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is considerably reduced; even in the presence of a Lewis acid, intermolecular cycloadditions are possible only with highly reactive dienes.<sup>15–18</sup> Another major difficulty in using the aza-Diels-Alder reaction is the availability of dienes with proper functional groups, which are often quite sensitive to heat, light, and acids.<sup>19</sup>

Sulfur-substituted dienes have widely been used in the Diels-Alder reaction.<sup>20</sup> The sulfur atom not only enhances the reactivity of the diene, but also adds control to the regioselectivity of this reaction and increases the synthetic versatility of the cycloadducts. It is now well-established that 3-sulfolenes are useful precursors to 1,3-dienes.<sup>21,22</sup> We have used this method to synthesize many thio-<sup>23–25</sup> and sulfone-substituted dienes,<sup>26</sup> and have explored some of their synthetic applications.<sup>27–31</sup> However, the sulfur-substituted dienes in the aza-Diels-Alder reaction have little been studied. Only strongly electron-deficient bis(phenylsulfonyl)butadienes were reported to react with aryl imines.<sup>32,33</sup> In this paper, we describe the first reactions of a weakly electron-rich diene, 2-(phenylthio)-1,3-butadiene (2), with some simple iminium salts prepared in situ from alkyl or aryl amine hydrochlorides and aldehydes to give the cyclized products **3–7** with complete regiocontrol.

The literature<sup>34</sup> preparation of diene **2** by desulfonylation of 3-(phenylthio)-3-sulfolene ( $\mathbf{1}$ )<sup>35</sup> proceeded only in 64% yield. We modified this reaction by using sodium bicarbonate to quench the acid generated, and also by adding some hydroquinone (HQ) to prevent the free radical-initiated polymerization of diene  $\mathbf{2}$ .<sup>21–25</sup> The diene  $\mathbf{2}$  can then be prepared in 96% yield (Eq. 1).

After trying various activation methods reported in the literature,  $^{7-16,15-18}$  we found that the best results were obtained by the utilization of iminium salts using the method developed by Grieco and coworkers.<sup>7</sup> The reactions of 2-(phenylthio)-1,3-butadiene (**2**) with the methyliminium salt generated in situ from methylamine hydrochloride and phenylglyoxal gave the cyclized product **3** (Eq. 2). The yields varied significantly with the solvent used (Table 1), with DMF giving the best result, which is similar to that reported for a related cyclization.<sup>10</sup>



Based on the above results, further reactions of 2-(phenylthio)-1,3-butadiene (2) with various iminium salts generated in situ from alkyl or aryl amine hydrochlorides and phenylglyoxal or formaldehyde (35% in H<sub>2</sub>O) were carried out in DMF and gave the cyclized products 3–7 in good yield (Eq. 3). The results are summarized in Table 2.



The reactions of diene 2 with iminium salts derived from methylamine hydrochloride or benzylamine hydrochloride and phenylglyoxal gave the cyclized products 3 and 4 in good yields, whether the diene or the iminium salt was used in excess (compare entries 1–4), but the iminium salts derived from aniline hydrochloride and phenylglyoxal (entry 5) or amine hydrochlorides and formaldehyde (entries 6–7) gave good results only when the diene was used in excess. When the less reactive formaldehyde was used as the substrate (entries 6–7), higher reaction temperature was also needed.

*Table 1.* The Aza-Diels-Alder Reactions of Diene **2** with Methylamine Hydrochloride and Phenylglyoxal in Various Solvents<sup>a</sup>

Entry	Solvent <sup>b</sup>	Yield (%)	
1	DMF		
2	CH <sub>3</sub> CN	57	
3	EtOH (95% aq)	39	
4	CH <sub>2</sub> Cl <sub>2</sub>	31	
5	THF	29	
6	H <sub>2</sub> O	trace	

<sup>a</sup>The diene was used in 1 equiv. and the other two reagents were used in 10 equiv. <sup>b</sup>The reaction was carried out at room temperature, for 24 h.

Entry	<b>R</b> <sub>1</sub>	$R_2$	Condition	Product	Yield (%)
1 <sup>b</sup>	Me (1 eq)	Bz (2 eq)	DMF, rt, 24 h	3	63
$2^{c}$	Me (10 eq)	Bz (10 eq)	DMF, rt, 24 h	3	72
3	Bn (1 eq)	Bz (2 eq)	DMF, rt, 24 h	4	74
4 <sup>c</sup>	Bn (10 eq)	Bz (10 eq)	DMF, rt, 24 h	4	82
5	Ph (1 eq)	Bz (2 eq)	DMF, rt, 24 h	5	95
6	Me (1 eq)	H (2 eq)	DMF, 60°C, 24 h	6	88
7	Bn (1 eq)	H (2 eq)	DMF, $60^{\circ}$ C, 24 h	7	81

*Table 2.* The Aza-Diels-Alder Reactions of Diene 2 with Imines Derived from Amine Hydrochlorides and Aldehydes<sup>a</sup>

<sup>a</sup>The diene was used in 10 equiv. unless noted otherwise.

<sup>b</sup>The diene was used in 6.9 equiv.

<sup>c</sup>The diene was used in 1 equiv.

Although the imino dienophiles are unsymmetrical, the reactions with diene **2** gave only one regioisomer, which was shown by spectroscopic methods to be the "*para*" adduct (with respect to the nitrogen). The regiochemistry is consistent with that predicted either by a concerted or stepwise mechanism.<sup>36</sup>

We have also carried out the reaction of diene 2 with N-benzylidenebenzenesulfonamide ( $R_1 = PhSO_2$ ,  $R_2 = Ph$ ) under thermal or acidic conditions to give the cyclized product in very low yield. Attempted reactions of diene 2 with imines prepared in situ from amides ( $R_1 = Ts$ , Bz) and aldehydes ( $R_2 = Ph$ , H) under aqueous acidic conditions resulted only in the decomposition of the diene.

In summary, we have carried out the aza-Diels-Alder reactions of diene 2 with some simple iminium salts to give the cyclized products 3-7 in good yield. The method is simple and high-yielding, and the product is easy to isolate. Particularly notable is the complete regioselectivity of these reactions. The thio-substituted piperidine derivatives obtained should be quite useful for further synthetic applications.

#### EXPERIMENTAL

Infrared spectra were recorded with an FT-IR spectrometer Analect RFX-65. <sup>1</sup>H and <sup>13</sup>C NMR spectra were measured for samples in CDCl<sub>3</sub> with an FT-NMR spectrometer Bruker AC-300 at 300 and 75 MHz, respectively, with tetramethylsilane as the internal standard. Mass spectra were recorded with a spectrometer JEOL JMS-D-100. High-resolution mass spectra were measured with a mass spectrometer JEOL TMS-HX 110.

#### 2-(PHENYLTHIO)-1,3-BUTADIENE

Melting points were measured with an apparatus Mel-Temp, and were uncorrected. The silica gel used for flash column chromatography was made by Merck (60 H). All reagents were of reagent grade, and DMF was distilled from  $CaH_2$  before use.

#### 2-(Phenylthio)-1,3-butadiene (2)

A mixture of compound 1 (2.26 g, 10 mmol), hydroquinone (20 mg, 0.2 mmol), and NaHCO<sub>3</sub> (840 mg, 10 mmol) was heated in toluene (40 mL) at 110°C for 5 h. The solvent was then removed by rotary evaporation. The residue was purified by flash chromatography using hexane/ethyl acetate (8:1) as eluent to give compound 2 (1.555 g, 96% yield) as a colorless liquid.<sup>34</sup>

# General Procedure for the Aza-Diels-Alder Reactions of 2-(Phenylthio)-1,3-butadiene with Imines Derived from Amine Hydrochlorides and Aldehydes

A mixture of 2-(Phenylthio)-1,3-butadiene (2) with an amine hydrochloride and an aldehyde was stirred in DMF at ambient temperature or  $60^{\circ}$ C for 24 h (see Table 2 for the equivalents of reagents used). The solvent was removed under vacuum. The residue was then purified by flash chromatography using sequentially hexane and hexane/ethyl acetate (8:1) as the eluent, both containing 5–10% (v/v) of triethylamine.

2-Benzoyl-1-methyl-4-(phenylthio)-1,2,3,6-tetrahydropyridine 3

Light yellow liquid; IR (film) 3056, 2924, 2853, 1670, 1630, 1594, 1556, 1475, 1448, 1373, 1268, 720, 691 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  2.39 (3 H, s), 2.35–2.63 (2 H, m), 3.23–3.31 (1 H, m), 3.62–3.69 (1 H, m), 4.15–4.20 (1 H, m), 6.06 (1 H, br s), 7.13–7.31 (5 H, m), 7.40–7.57 (3 H, m), 8.01–8.03 (2 H, m); <sup>13</sup>C NMR  $\delta$  31.3, 41.6, 54.1, 64.5, 126.8, 127.1, 127.8, 128.5, 128.9, 129.0, 130.7, 133.2, 133.7, 135.8, 199.7; FABMS (relative intensity) *m*/*z* 310 (M<sup>+</sup>+H, 35), 308 (34), 306 (37), 204 (100), 202 (90), 148 (78), 105 (52), 91 (38), 69 (48), 57 (48), 55 (67); exact mass calc. for C<sub>19</sub>H<sub>19</sub>NOS *m*/*z* 309.1187, FABHRMS (NBA) *m*/*z* 310.1276 (M<sup>+</sup>+H).

2-Benzoyl-1-benzyl-4-(phenylthio)-1,2,3,6-tetrahydropyridine 4

Light yellow liquid; IR (film) 3058, 2923, 2836, 1683, 1629, 1595, 1580, 1475, 1447, 1439, 1217, 1175, 1024, 739,  $695 \text{ cm}^{-1}$ ; <sup>1</sup>H NMR  $\delta$  2.56

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(2 H, br s), 3.27–3.33 (1 H, m), 3.57–3.63 (1 H, m), 3.63 (1 H, d, J = 13 Hz), 3.84 (1 H, d, J = 13 Hz), 4.38 (1 H, t, J = 5.7 Hz), 6.02 (1 H, br s), 7.12–7.53 (13 H, m), 7.94 (2 H, d, J = 7.2 Hz); <sup>13</sup>C NMR  $\delta$  29.3, 50.2, 57.4, 61.8, 126.6, 127.2, 127.6, 128.2, 128.3, 128.5, 128.8, 129.1, 129.2, 130.5, 132.9, 133.8, 135.8, 138.2, 200.3; FABMS (relative intensity) *m*/*z* 386 (M<sup>+</sup>+H, 25), 384 (25), 280 (97), 278 (59), 224 (31), 105 (37), 91 (100), 77 (16); exact mass calc. for C<sub>25</sub>H<sub>23</sub>NOS *m*/*z* 385.1500, FABHRMS (NBA) *m*/*z* 386.1580 (M<sup>+</sup>+H).

## 2-Benzoyl-1-phenyl-4-(phenylthio)-1,2,3,6-tetrahydropyridine 5

White solid; m.p.  $121^{\circ}-122^{\circ}$ C; IR (film) 3057, 2904, 2837, 1688, 1597, 1579, 1502, 1475, 1446, 1315, 1301, 1210, 1023, 937, 747, 690 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  2.63 (1 H, d, J = 15.9 Hz), 2.88–3.02 (1 H, m), 4.13–4.30 (2 H, m), 5.56–5.59 (1 H, m), 6.19–6.22 (1 H, m), 6.78–6.84 (3 H, m), 7.03–7.51 (10 H, m), 7.86 (2 H, d, J = 7.2 Hz); <sup>13</sup>C NMR  $\delta$  31.1, 47.5, 57.3, 114.0, 118.7, 126.1, 126.6, 128.0, 128.6, 128.8, 128.8, 128.9, 129.3, 130.4, 133.1, 135.3, 148.8, 199.5; FABMS (relative intensity) m/z 372 (M<sup>+</sup>+H, 18), 371 (11), 370 (32), 368 (23), 267 (25), 266 (94), 264 (50), 262 (28), 210 (63), 172 (59), 156 (38), 154 (41), 105 (100), 104 (70), 91 (37), 77 (82), 69 (37), 57 (42), 55 (50); exact mass calc. for C<sub>24</sub>H<sub>21</sub>NOS m/z 371.1344, FABHRMS (NBA) m/z 372.1412 (M<sup>+</sup>+H).

# 1-Methyl-4-(phenylthio)-1,2,3,6-tetrahydropyridine 6

Light yellow liquid; IR (film) 3055, 2937, 2840, 2779, 1599, 1475, 1438, 1200, 742, 691 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  2.27–2.31 (2 H, m), 2.34 (3 H, s), 2.56 (2 H, t, J = 5.7 Hz), 3.01–3.04 (2 H, m), 5.89–5.91 (1 H, m), 7.20–7.36 (5 H, m); <sup>13</sup>C NMR  $\delta$  30.5, 45.3, 52.5, 55.3, 126.7, 128.1, 128.8, 130.2, 131.0, 133.9; FABMS (relative intensity) *m*/*z* 206 (M<sup>+</sup>+H, 64), 205 (19), 204 (94), 203 (77), 202 (100), 163 (32), 124 (51), 110 (56), 109 (25), 96 (93), 94 (43), 92 (46), 60 (58), 58 (57); exact mass calc. for C<sub>12</sub>H<sub>15</sub>NS *m*/*z* 205.0925, FABHRMS (NBA) *m*/*z* 206.0997 (M<sup>+</sup>+H).

# 1-Benzyl-4-(phenylthio)-1,2,3,6-tetrahydropyridine 7

Light yellow liquid; IR (film) 3057, 2920, 2799, 1578, 1475, 1438, 1364, 1023, 738, 690 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  2.23–2.27 (2 H, m), 2.60 (2 H, t, J = 5.7 Hz), 3.05–3.07 (2 H, m), 3.57 (2 H, s), 5.84–5.87 (1 H, m), 7.19–7.35 (8 H, m), 7.46–7.49 (2 H, m); <sup>13</sup>C NMR  $\delta$  30.4, 50.1, 53.5, 62.2, 126.8,

#### 2-(PHENYLTHIO)-1,3-BUTADIENE

127.0, 127.5, 128.1, 128.9, 130.5, 130.7, 131.1, 133.9, 138.0; FABMS (relative intensity) m/z 206 (M<sup>+</sup>+H, 64), 205 (19), 204 (94), 203 (77), 202 (100), 163 (32), 124 (51), 110 (56), 109 (25), 96 (93), 94 (43), 92 (46), 60 (58), 58 (57); exact mass calc. for C<sub>12</sub>H<sub>15</sub>NS m/z 205.0925, FABHRMS (NBA) m/z 206.0997 (M<sup>+</sup>+H).

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#### REFERENCES

- 1. Strunz, G.M.; Findlay, J.A. Pyridine and Piperidine Alkaloids In *The Alkaloids*; Brossi, A., Ed.; Academic New York, **1985**, Vol. *26*, 89.
- Numata, A.; Ibuka, I. Alkaloids from Ants and Other Insects In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987, Vol. 31, 193.
- 3. Rubiralta, M.; Giralt, E.; Diez, E. Piperidine, Structure, Preparation, Reactivity and Synthetic Applications of Piperidine and its Derivatives; Elsevier: Amsterdam, **1991**.
- Daly, J.W.; Garraffo, H.M.; Spande, T.F. In *The Alkaloids*; Cordell, G.A., Ed.; Academic Press: New York, **1993**, Vol. 43, 185.
- 5. Weinreb, S.M. In *Comprehensive Organic Synthesis*; Trost, B.M., Fleming, I., Eds.; Pergamon: Oxford, 1991, Vol. 5, 401–449.
- 6. Boger, D.L.; Weinreb, S.M. Hetero Diels-Alder Methodology in Organic Synthesis; Academic Press: Orlando, 1987.
- 7. Grieco, P.A.; Larsen, S.D. J. Am. Chem. Soc. 1985, 107, 1768.
- Fobare, W.F.; Grieco, P.A.; Larsen, S.D. Tetrahedron Lett. 1986, 27, 1975.
- 9. Waldmann, H. Liebigs Ann. Chem. 1989, 231.
- Bailey, P.D.; Wilson, R.D.; Brown, G.R. Tetrahedron Lett. 1989, 30, 6781.
- 11. Weinreb, S.M. Acc. Chem. Res. 1985, 18, 16.
- 12. Loven, R.P.; Speckamp, W.N.; Zunnebeld, W.A. Tetrahedron 1975, 31, 1717.
- 13. Sisko, J.; Weinreb, S.M. Tetrahedron Lett. 1989, 30, 3037.
- Birkinshaw, T.N.; Tabor, A.B.; Holmes, A.B.; Kaye, P.; Mayne, P.M.; Raithby, P.R. J. Chem. Soc., Chem. Commun. 1988, 1599.
- 15. Danishefsky, S.; Vogel, C. J. Org. Chem. 1986, 51, 3915.

- 16. Pfrengle, W.; Kunz, H. J. Org. Chem. 1989, 54, 4261.
- 17. Midland, M.M.; Koops, R.W. J. Org. Chem. 1992, 57, 1158.
- 18. Waldmann, H.; Braun, M. J. Org. Chem. 1992, 57, 4444.
- Fringuelli, F.; Taticchi, A. Dienes in the Diels-Alder Reaction; Wiley & Sons: New York, 1990.
- 20. Petrzilka, M.; Grayson, J.L. Synthesis 1981, 753.
- 21. Chou, T.S.; Tso, H.H. Org. Prep. Proc. Int. 1989, 21, 257.
- 22. Chou, T.S.; Chou, S.S.P. J. Chin. Chem. Soc. 1992, 39, 625.
- 23. Chou, S.S.P.; Liou, S.Y.; Tsai, C.Y.; Wang, A.J. J. Org. Chem. **1987**, *52*, 4468.
- 24. Chou, S.S.P.; Sun, C.M.; Wey, S.J. Synth. Commun. 1989, 19, 1593.
- 25. Chou, S.S.P.; Sun, D.J.; Tai, H.P. J. Chin. Chem. Soc. 1995, 42, 809.
- 26. Chou, S.S.P.; Tsai, C.Y.; Sun, C.M. J. Chin. Chem. Soc. 1989, 36, 149.
- 27. Chou, S.S.P.; Sun, D.J. J. Chem. Soc., Chem. Commun. 1988, 1176.
- 28. Chou, S.S.P.; Wey, S.J. J. Org. Chem. 1990, 55, 1270.
- 29. Chou, S.S.P.; Yuan, T.M. Synthesis 1991, 171.
- 30. Chou, S.S.P.; Lee, C.S.; Cheng, M.C.; Tai, H.P. J. Org. Chem. **1994**, 59, 2010.
- 31. Chou, S.S.P.; Yu, Y.J. J. Chin. Chem. Soc. 1998, 45, 163.
- 32. Padwa, A.; Harrison, B.; Norman, B.H. Tetrahedron Lett. **1989**, *30*, 3259.
- Padwa, A.; Gareau, Y.; Harrison, B.; Norman, B.H. J. Org. Chem. 1991, 56, 2713.
- 34. Gundermann, K.D.; Holtmann, P. Angew. Chem., Int. Ed. Engl. **1966**, *5*, 668.
- 35. Hopkins, P.B.; Fuchs, P.L. J. Org. Chem. 1987, 52, 244.
- 36. Weinreb, S.M.; Levin, J.I. Heterocycles 1979, 12, 949.
- Lucchini, V.; Prato, M.; Scorrano, G.; Tecilla, P. J. Org. Chem. 1988, 53, 2251.

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