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Stereoselective Synthesis of 2,6-Disubstituted Tetrahydropyridines Via Aza-Diels-Alder Reactions

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ABSTRACT

The aza-Diels-Alder reactions of (*E*)-2-(phenylthio)-1,3-pentadiene (**2**) with iminium salts gave the 2,6-disubstituted tetrahydropyridines **3**–**8**. Factors influencing the stereochemistry and reactivity of these reactions were also studied.

Key Words: Aza-Diels-Alder reactions; Tetrahydropyridines; Thio-substituted dienes.

The piperidine ring is one of the most abundant molecular fragments in both natural and synthetic compounds with various biological activities.[1–4]

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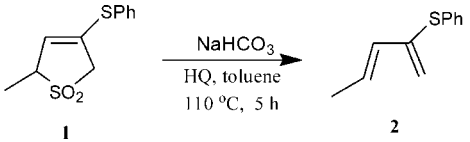
The aza-Diels-Alder reaction is potentially one of the most versatile and rapid routes to substituted piperidines.[5,6] However, most imines fail to participate in these [4 + 2] cycloadditions. In general, a strongly electron-withdrawing group such as an acyl[7] or a sulfonyl group[8–10] attached to the nitrogen or carbon of the imine is needed. When only an alkyl group is attached to the imine nitrogen, the scope of the aza-Diels-Alder reaction is considerably reduced; even in the presence of a Lewis acid, intermolecular cycloadditions are possible only with highly reactive dienes.[11–14]

We have recently reported effective aza-Diels-Alder reactions of thio-substituted dienes with unactivated imines,[15,16] simply by in situ preparation of the iminium salts from amine hydrochlorides and aldehydes.[17–19] In this paper we describe the aza-Diels-Alder reactions of 2-(phenylthio)-1,3-pentadiene (**2**) with iminium salts to achieve the synthesis of 2,6-disubstituted tetrahydropyridines **3**–**8**, and disclose some factors affecting the stereochemistry and reactivity of these reactions.

(*E*)-2-(Phenylthio)-1,3-pentadiene (**2**) was conveniently prepared by desulfonylation of 2-methyl-4-(phenylthio)-3-sulfolene (**1**).[20] We modified the literature procedure[21] by adding some sodium bicarbonate to remove the acid generated, and also by using hydroquinone (HQ) to prevent the free radical-initiated polymerization of diene **2**. The diene **2** was prepared from **1** in 92% yield, and its structure had previously[20] been shown to have the trans configuration (Eq. 1).



1 **2** (1)

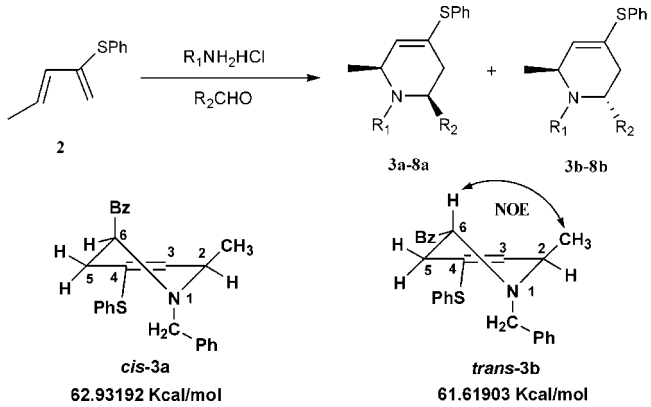
Following our previous method,[15] the diene **2** (1 equiv.) was treated with a mixture of an amine hydrochloride (10 equiv.) and an aldehyde (10 equiv.) in DMF to give the cyclized products **3**–**8** (Eq. 2 and Table 1). It can be seen that the reactivity of the aldehydes (compare entries 1, 5, 8, 9) varies with the substituent R_2 (Bz > CO_2Et > Ph > H), indicating that electron-withdrawing groups enhance the reactivity of the iminium ions. The reactivity of methylamine is greater than that of benzylamine (compare entry 1 with 12, and 5 with 17), probably due to the steric effect. It is also interesting to note that the ratio of the trans/cis products increases with the reaction temperature. The stereochemistry of the products is determined by NOE experiments. For example, the methyl group of **3b** has an NOE enhancement with the H-6, whereas the methyl group of **3a** does not have such an NOE effect. We have also used the PM3 method of the HyperChem package to calculate the relative energies of the most stable conformers of **3a** and **3b**. Indeed,

Table 1. The Aza-Diels-Alder reactions of diene **2** with imines derived from amine hydrochlorides and aldehydes.[a]

Entry	R_1	R_2	Temp	Product	Yield (%)	Cis : Trans
1	Bn	Bz	rt	**3**	60	trans only
2	Bn	Bz	0°C	**3**	60	2 : 7
3[b]	Bn	Bz	−20°C	**3**	52	2 : 5
4	Bn	CO_2Et	90°C	**4**	34	1 : 9
5	Bn	CO_2Et	rt	**4**	33	12 : 5
6	Bn	Ph	90°C	**5**	27	5 : 9
7	Bn	Ph	60°C	**5**	22	4 : 3
8	Bn	Ph	rt	**5**	26	cis only
9	Bn	H	60°C	**6**	14	
10	Me	Bz	90°C	**7**	78	2 : 7
11	Me	Bz	60°C	**7**	88	1 : 2
12	Me	Bz	rt	**7**	76	1 : 3
13	Me	Bz	−10°C	**7**	52	3 : 4
14[b]	Me	Bz	−20°C	**7**	75	1 : 1
15	Me	CO_2Et	90°C	**8**	67	5 : 9
16	Me	CO_2Et	60°C	**8**	72	1 : 1
17	Me	CO_2Et	rt	**8**	58	5 : 2
18	Me	CO_2Et	−10°C	**8**	38	7 : 2

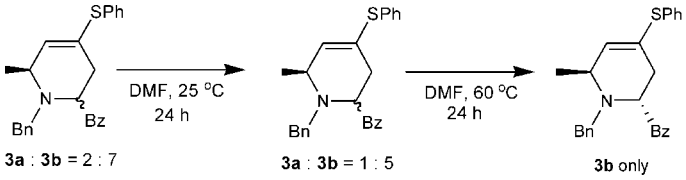
[a]The diene **2** (1 equiv.) was reacted with amine hydrochloride (10 equiv.) and aldehyde (10 equiv.) in DMF at the specified temperature for 24 h.
[b]The reaction time was 5 d.

the *trans*-**3b** is more stable than the *cis*-**3a**, probably because the latter has an axial benzoyl group.



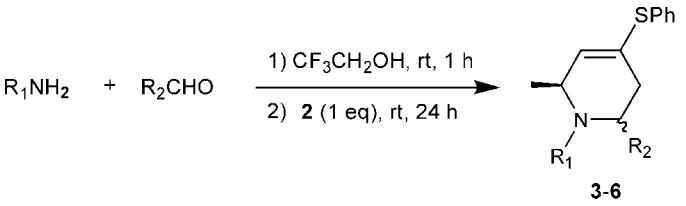
(2)

To show that *trans*-**3b** is thermodynamically more stable than the *cis*-**3a**, a mixture of **3a** and **3b** (2 : 7) was stirred at 60°C for 24 h to give only **3b** (Eq. 3). Thus, the trans products are thermodynamic products, and the cis products are kinetic products. The cis product arises from an endo transition state, which is probably favored by a secondary orbital interaction of the unsaturated R_2 substituent with the diene moiety.



(3)

It was reported that the rate of the aza-Diels-Alder reactions of vinyl ethers with arylimines increases significantly when trifluoroethanol was used as solvent.[22] Thus, we also studied the cycloaddition reactions of diene **2** with imines in trifluoroethanol. An equimolar mixture of an amine and an aldehyde was stirred in trifluoroethanol at room temperature for 1 h. Then another equivalent of the diene **2** was added (Eq. 4, Table 2). It can be seen that the yields of some of these reactions increased significantly (entries 2, 3, and 4), but the other reactions (entries 1, 5, and 6) gave very low yield or no products at all. It can be reasoned that aqueous methylamine (entries 5 and 6) or phenylglyoxal monohydrate (entry 1) is not easily converted to the imine in trifluoroethanol under neutral conditions. It should also be noted that the stereoselectivity of the reaction in CF_3CH_2OH is considerably lower than that in DMF (compare entries 1–3 of Table 2 with entries 1, 5, 8 of Table 1, respectively).



(4)

In summary, we have shown that diene **2**, generated conveniently from 3-sulfolene **1**, can undergo the aza-Diels-Alder reactions with imines derived from aldehydes and amine hydrochlorides in DMF to give the 2,6-disubstituted tetrahydropyridine products **3**–**8**. The reaction temperature has an important effect on the ratio of the cis/trans products: lower reaction temperatures favor the kinetic cis products, whereas higher reaction

Table 2. The Aza-Diels-Alder reactions of diene **2** in trifluoroethanol.

Entry	R_1	R_2	Temp	Product	Yield (%)	Cis : Trans
1	Bn	Bz	rt	**3**	25	1 : 1.1
2	Bn	CO_2Et	rt	**4**	96	1 : 1.4
3[b]	Bn	Ph	rt	**5**	76	1 : 1.7
4	Bn	H	rt	**6**	67	
5	CH_3	Bz	rt	—[a]		
6	CH_3	CO_2Et	rt	—[a]		

[a]Only unreacted diene **2** was recovered.

temperatures favor the thermodynamic trans products. The cis products can be converted to the trans products simply by heating at higher temperatures in DMF. Trifluoroethanol can increase significantly the yields of some of these cyclization reactions, but the stereoselectivity decreases.

EXPERIMENTAL

Infrared spectra were recorded with an FT-IR spectrometer Perkin Elmer-1600. ^1H and ^{13}C NMR spectra were measured for samples in $CDCl_3$ with an FT-NMR spectrometer Bruker AVANCE-300, Bruker DMX-600, Bruker AV-500 or Bruker AV-400, with tetramethylsilane as the internal standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded with a spectrometer JEOL JMS-SX102A. 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-Pentadiene (2)

A mixture of compound **1** (1.34 g, 5.57 mmol), hydroquinone (10 mg, 0.1 mmol), and $NaHCO_3$ (467 mg, 5.56 mmol) was heated in toluene (20 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** (0.90 g, 92% yield) as a colorless liquid.[20]

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

A mixture of 2-(phenylthio)-1,3-pentadiene (**2**, 176 mg, 1.0 mmol), an amine hydrochloride (10.0 mmol), and an aldehyde (10.0 mmol) was stirred in DMF (10 mL) for 24 h (see Table 1 for the reaction temperatures used). The solvent was removed under vacuum. The residue was then purified by flash chromatography using hexane/ethyl acetate (10 : 1) as the eluent, containing 5–10% (v/v) of triethylamine.

***cis*-6-Benzoyl-1-benzyl-2-methyl-4-(phenylthio)-1,2,5,6-tetrahydropyridine 3a.** Light yellow liquid; IR (film) 3064, 2922, 1709, 1680, 1642, 1548, 1535, 1477, 1449, 1265, 1175, 735, 693 cm^{-1}; ^1H NMR δ 1.00 (3 H, d, J = 6.8 Hz), 3.49–3.58 (1 H, m), 3.84 (1 H, d, J = 14.4 Hz), 3.96 (1 H, d, J = 14.4 Hz), 4.38 (1 H, t, J = 5.4 Hz), 5.88–5.89 (1 H, m); ^{13}C NMR δ 20.8, 27.1, 55.6, 57.1, 63.0, 128.3, 128.4, 128.5, 128.98, 129.01, 129.8, 130.0, 131.2, 132.5, 132.8, 132.9, 136.1, 136.4, 138.8, 199.7.

***trans*-6-Benzoyl-1-benzyl-2-methyl-4-(phenylthio)-1,2,5,6-tetrahydropyridine 3b.** Light yellow liquid; IR (film) 3064, 2922, 2854, 1709, 1622, 1556, 1540, 1473, 1455, 1266, 726, 693 cm^{-1}; ^1H NMR δ 1.34 (3 H, d, J = 6.9 Hz), 2.26 (1 H, dd, J = 5.0, 18.0 Hz), 2.72 (1 H, dd, J = 9.0, 18.0 Hz), 3.47 (1 H, d, J = 13.8 Hz), 3.49–3.58 (1 H, m), 3.60 (1 H, d, J = 13.8 Hz), 4.57 (1 H, dd, J = 5.0, 9.0 Hz), 5.98–6.00 (1 H, m), 7.04–7.57 (13 H, m), 8.05 (2 H, d, J = 7.2 Hz); ^{13}C NMR δ 20.5, 26.8, 53.3, 54.5, 58.5, 127.03, 127.05, 128.05, 128.25, 128.4, 128.5, 128.8, 129.11, 129.14, 131.10 (×2), 133.8, 136.1, 139.3, 200.6; MS (relative intensity) m/z 399 (M^+, 36), 398 (26), 294 (88), 105 (31), 91 (100), 77 (24); exact mass calcd for $C_{26}H_{25}NOS$ m/z 399.1657, HRMS m/z 399.1705.

***cis*-Ethyl 1-Benzyl-2-methyl-4-(phenylthio)-1,2,5,6-tetrahydropyridine-6-carboxylate 4a.** Light yellow liquid; IR (film) 3060, 3027, 2979, 2930, 2853, 1731, 1582, 1495, 1475, 1455, 1189, 1026, 743, 697 cm^{-1}; ^1H NMR δ 1.15 (3 H, d, J = 6.8 Hz), 1.22 (3 H, t, J = 7.1 Hz), 2.34 (1 H, ddd, J = 1.6, 5.5, 16.8 Hz), 2.57 (1 H, ddd, J = 1.6, 5.5, 16.8 Hz), 3.45–3.51 (1 H, m), 3.53 (1 H, t, J = 5.5 Hz), 3.94 (1 H, d, J = 14.7 Hz), 3.99 (1 H, d, J = 14.7 Hz), 4.03 (1 H, dq, J = 10.8, 7.1 Hz), 4.08 (1 H, dq, J = 10.8, 7.1 Hz), 5.87 (1 H, t, J = 1.6 Hz), 7.21–7.39 (10 H, m); ^{13}C NMR δ 14.2, 18.3, 31.8, 54.9, 56.1, 59.2, 60.7, 126.9, 127.1, 127.8, 128.2, 128.4, 128.8, 129.0, 131.1, 133.9, 138.8, 173.4; MS (relative intensity) m/z 367 (M^+, 29), 366 (51), 294 (62), 258 (23), 91 (100), 77 (26), 73 (19); exact mass calcd for $C_{22}H_{25}NO_2S$ m/z 367.1606, HRMS m/z 367.1628.

***trans*-Ethyl 1-Benzyl-2-methyl-4-(phenylthio)-1,2,5,6-tetrahydropyridine-6-carboxylate 4b.** Light yellow liquid; IR (film) 3060, 3027, 2975,

2925, 2850, 1923, 1731, 1583, 1475, 1454, 1439, 1369, 1186, 1160, 1025, 870, 828, 741, 697 cm^{-1}; ^1H NMR δ 1.17 (3 H, t, J = 7.1 Hz), 1.23 (3 H, d, J = 6.5 Hz), 2.37 (1 H, ddd, J = 2.5, 5.5, 17.0 Hz), 2.54 (1 H, ddd, J = 2.9, 5.7, 17.0 Hz), 3.58 (1 H, dt, J = 2.5, 5.6 Hz), 3.73 (1 H, d, J = 14.4 Hz), 3.83–3.89 (1 H, m), 3.99 (1 H, d, J = 14.4 Hz), 4.05 (1 H, dq, J = 10.7, 7.1 Hz), 4.15 (1 H, dq, J = 10.7, 7.1 Hz), 5.96 (1 H, br s), 7.20–7.33 (10 H, m); ^{13}C NMR δ 14.3, 20.9, 32.4, 53.6, 54.6, 57.2, 60.3, 126.9, 127.0, 128.38, 128.45, 128.98, 129.04, 130.8, 134.3, 136.3, 139.8, 172.6; MS (relative intensity) m/z 367 (M^+, 29), 366 (51), 294 (62), 258 (23), 91 (100), 77 (26), 73 (19); exact mass calcd for $C_{22}H_{25}NO_2S$ m/z 367.1606, HRMS m/z 367.1628.

***cis*-1-Benzyl-2-methyl-6-phenyl-4-(phenylthio)-1,2,5,6-tetrahydropyridine 5a.** Light yellow liquid; IR (film) 3059, 3027, 2965, 2923, 2851, 1642, 1613, 1582, 1493, 1453, 1440, 1343, 1171, 1075, 1025, 757, 741, 700 cm^{-1}; ^1H NMR δ 1.11 (3 H, d, J = 5.9 Hz), 2.21–2.25 (1 H, m), 2.51–2.56 (1 H, m), 3.43–3.46 (1 H, m), 3.58 (1 H, d, J = 15.2 Hz), 3.78–3.81 (1 H, m), 3.80 (1 H, d, J = 15.2 Hz), 5.82 (1 H, br s), 7.14–7.36 (15 H, m); ^{13}C NMR δ 21.7, 39.5, 55.7, 57.8, 64.7, 125.9, 126.3, 126.9, 127.2, 127.8, 128.2, 128.3, 128.4, 129.0, 131.0, 131.7, 134.6, 140.1, 143.4; MS (relative intensity) m/z 371 (M^+, 16), 370 (32), 294 (48), 262 (16), 185 (20), 91 (31), 77 (100); exact mass calcd for $C_{25}H_{25}NS$ m/z 371.1708, HRMS m/z 371.1688.

***trans*-1-Benzyl-2-methyl-6-phenyl-4-(phenylthio)-1,2,5,6-tetrahydropyridine 5b.** Light yellow liquid; IR (film) 3060, 3027, 2959, 2922, 2850, 1658, 1613, 1582, 1494, 1475, 1453, 1440, 1025, 745, 697 cm^{-1}; ^1H NMR δ 1.27 (3 H, d, J = 6.8 Hz), 2.43 (1 H, dd, J = 4.2, 17.1 Hz), 2.60 (1 H, dd, J = 10.2, 17.1 Hz), 3.36–3.38 (1 H, m), 3.42 (2 H, s), 4.25 (1 H, dd, J = 4.2, 10.2 Hz), 6.03–6.09 (1 H, m), 7.19–7.45 (15 H, m); ^{13}C NMR δ 19.1, 30.7, 51.0, 53.4, 55.5, 126.8, 127.0, 127.7, 128.1, 128.2, 129.1, 129.2, 129.5, 130.7, 133.4, 134.2, 135.0, 140.1, 141.9; MS (relative intensity) m/z 371 (M^+, 16), 370 (32), 294 (48), 262 (16), 185 (20), 91 (31), 77 (100); exact mass calcd for $C_{25}H_{25}NS$ m/z 371.1708, HRMS m/z 371.1688.

1-Benzyl-2-methyl-4-(phenylthio)-1,2,5,6-tetrahydropyridine 6. Colorless liquid; IR (film) 3060, 3028, 2957, 2923, 2802, 1658, 1565, 1483, 1409, 1166, 1072, 1043, 1021, 886, 838, 750, 697 cm^{-1}; ^1H NMR δ 1.23 (3 H, d, J = 6.6 Hz), 2.04–2.27 (2 H, m), 2.38–2.46 (1 H, m), 2.84–2.92 (1 H, m), 3.15–3.21 (1 H, m), 3.42 (1 H, d, J = 13.6 Hz), 3.94 (1 H, d, J = 13.6 Hz), 5.80–5.85 (1 H, m), 7.09–7.38 (10 H, m); ^{13}C NMR δ 19.0, 29.6, 47.3, 55.8, 57.1, 126.81, 126.97, 127.03, 127.13, 128.2, 128.9, 129.0, 131.0, 134.8, 139.0.

***cis*-6-Benzoyl-1,2-dimethyl-4-(phenylthio)-1,2,5,6-tetrahydropyridine 7a.** Light yellow liquid; ^1H NMR δ 1.28 (3 H, d, J = 6.5 Hz), 2.16–2.22 (1 H, m),

2.24 (3 H, s), 2.66–2.72 (1 H, m), 3.16–3.18 (1 H, m), 4.03 (1 H, dd, J = 3.9, 10.8 Hz), 5.86 (1 H, br s), 7.14–7.54 (8 H, m), 8.16 (2 H, d, J = 7.5 Hz);

trans-6-Benzoyl-1,2-dimethyl-4-(phenylthio)-1,2,5,6-tetrahydropyridine 7b. Light yellow liquid; ^{1}H NMR δ 1.35 (3 H, d, J = 7.0 Hz), 2.33 (3 H, s), 2.38 (1 H, dd, J = 5.2, 17.9 Hz), 2.63 (1 H, dd, J = 7.1, 17.9 Hz), 3.63–3.65 (1 H, m), 4.53 (1 H, dd, J = 5.2, 7.1 Hz), 6.01–6.02 (1 H, m), 7.14–7.54 (8 H, m), 8.01 (2 H, d, J = 7.5 Hz). The following spectra were obtained from a mixture (1 : 3) of **7a** and **7b**: ^{13}C NMR δ 19.78, 19.98, 27.53, 32.23, 38.36, 38.52, 57.41, 58.99, 60.15, 68.47, 126.87, 127.13, 127.45, 128.53, 128.71, 129.01, 129.06, 129.13. 129.26, 130.78, 131.04, 133.14, 133.40, 133.57, 133.88, 133.92, 134.13, 134.34, 135.61, 136.07, 199.55, 199.87 (some characteristic absorptions for **7a**: 19.98, 32.23, 38.52, 58.99, 68.46, 199.55; **7b**: 19.78, 27.53, 38.36, 57.41, 60.15, 199.87); MS (relative intensity) m/z 323 (M^+, 20), 322 (23), 218 (100), 214 (14), 105 (60), 77 (22); exact mass calcd for $C_{20}H_{21}NOS$ m/z 323.1344, HRMS m/z 323.1321.

***cis*-Ethyl 1,2-dimethyl-4-(phenylthio)-1,2,5,6-tetrahydropyridine-6-carboxylate 8a.** Colorless liquid; IR (film) 2975, 2923, 1738, 1475, 1440, 1258, 1201, 1160, 1033, 742, 691 cm^{-1}; ^{1}H NMR δ 1.26 (3 H, t, J = 7.4 Hz), 1.29 (3 H, d, J = 7.0 Hz), 2.29 (1 H, dd, J = 17.0, 3.9 Hz), 2.37 (3 H, s), 2.59 (1 H, dd, J = 17.0, 10.5 Hz), 3.00–3.15 (1 H, m), 3.31–3.33 (1 H, dd, J = 3.9, 10.5 Hz), 4.16–4.24 (2 H, m), 5.75 (1 H, br s), 7.23–7.36 (5 H, m); ^{13}C NMR δ 14.4, 19.4, 32.6, 38.3, 58.9, 61.0, 65.1, 127.3, 128.5, 129.2, 131.2, 133.3, 135.1, 171.9; MS (relative intensity) m/z 291 (M^+, 5), 290 (72), 218 (100), 182 (11), 109 (83), 73 (45); exact mass calcd. for $C_{16}H_{21}NO_2S$ m/z 291.1293, HRMS m/z 291.1316.

***trans*-Ethyl 1,2-dimethyl-4-(phenylthio)-1,2,5,6-tetrahydropyridine-6-carboxylate 8b.** Colorless liquid; IR (film) 2977, 2928, 2810, 1731, 1582, 1475, 1440, 1184, 1156, 1031, 743, 692 cm^{-1}; ^{1}H NMR δ 1.20 (3 H, t, J = 6.8 Hz), 1.22 (3 H, t, J = 7.4 Hz), 2.41 (1 H, ddd, J = 17.2, 6.4, 3.2 Hz), 2.53 (3 H, s), 2.67 (1 H, ddd, J = 17.2, 3.2, 2.4 Hz), 3.64 (1 H, dd, J = 3.2, 6.4 Hz), 3.66 (1 H, dq, J = 2.4, 6.8 Hz), 4.10 (1 H, dq, J = 10.8, 7.2 Hz), 4.16 (1 H, dq, J = 10.8, 7.2 Hz), 5.94 (1 H, t, J = 2.4 Hz), 7.19–7.33 (5 H, m); ^{13}C NMR δ 14.3, 19.7, 32.3, 39.8, 54.7, 60.4, 61.3, 126.4, 126.9, 129.0, 130.7, 134.2, 136.0, 172.0; MS (relative intensity) m/z 291 (M^+, 5), 290 (72), 218 (100), 182 (11), 109 (83), 73 (45); exact mass calcd. for $C_{16}H_{21}NO_2S$ m/z 291.1293, HRMS m/z 291.1316.

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