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A Facile Preparation of 2,6-Diarylpyrazines

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ABSTRACT: *2,6-Diarylpyrazines were prepared in good yields by a novel method of condensing methoxycarbonylhydrazine with N,N-bis(arylcarbonylmethyl)-p-toluenesulfonamides, unsymmetrical derivatives of which were synthesized by a new (or different) procedure. The structures of these 2,6-diarylpyrazines were established by spectral data and X-ray diffraction analysis.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9:341–345, 1998

INTRODUCTION

Sulfonylureas and heterocyclic sulfonamides have been widely known by their unprecedented levels of herbicidal activity [1,2]. In an attempted search for novel lead compounds, N,N-bis(1,2,3-thiadiazol-5-yl)-arylsulfonamides were targeted in our laboratory. It is known that one of the most convenient methods of preparing 1,2,3-thiadiazoles was developed by Hurd and Mori [3], in which it is necessary to prepare methoxycarbonylhydrazones. Normally, methoxycarbonylhydrazones can be prepared by reacting related ketones with methyl carbazate in the presence of *p*-toluenesulfonic acid (TsOH) [4]. However, the reaction was found to yield the unexpected products 2,6-diarylpyrazines in good yield. This novel preparation of 2,6-diarylpyrazines attracted our attention because of the very low yields (10–30%) of literature preparations of 2,6-diarylpyrazines [5–7] and many applications in the pharmaceutical field of pyrazine derivatives. This prompted us to examine further this novel method.

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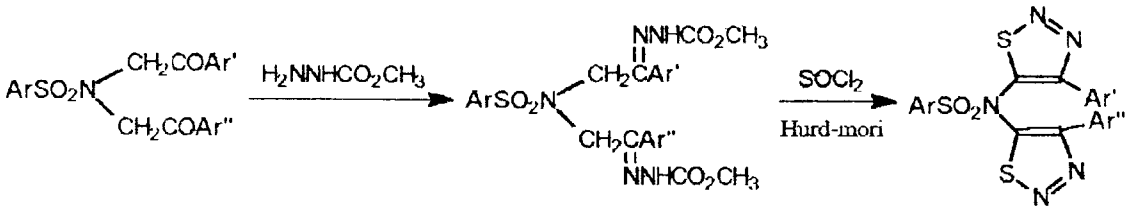
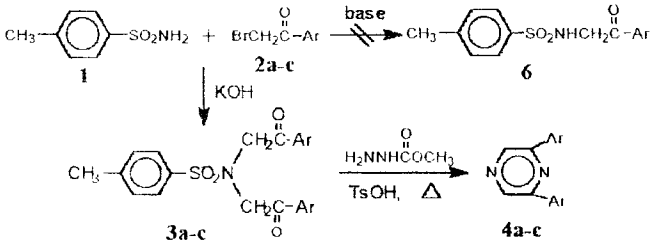
RESULTS AND DISCUSSION

Treatment of the *p*-toluenesulfonamide **1** with two equivalents of α-bromoacetophenones **2a–c** and potassium hydroxide in cold N,N-dimethylformamide gave N,N-bis(arylcarbonylmethyl)-*p*-toluenesulfonamides **3a–c** (Scheme 1). It is interesting that **3a–c** were also obtained when equal equivalents of **1** and **2** were used. The reason for this might be that the nucleophilicity of the nitrogen atom of the intermediate **6** was stronger than that of *p*-toluenesulfonamide **1.** Reactions of compounds **3a–c** with methoxycarbonylhydrazine catalyzed by TsOH in refluxing toluene with azeotropic removal of water afforded the 2,6-diarylpyrazines **3a–c** in good yields. Their structures were confirmed by elemental analysis, ^{1}H-NMR, and MS spectra (see Experimental). The structure of the product **4a** was proven by X-ray crystal analysis (Figure 1, Tables 1–3).

For the reason mentioned earlier, only the 2,6-pyrazines having the same substituents, like **4a–c,** can be synthesized according to Scheme 1. In order to obtain pyrazines that contain two different substituents at the 2- and 6- positions, another approach was developed (Scheme 2). *p*-Toluenesulfonyl chloride **5** was reacted with α-aminoacetophenone [8] to give the N-phenacyl-*p*-toluenesulfonamide **6.** Treatment of **6** with α-bromoacetophenones **7a–b** gave **8a–b.** With **8a–b** in hand, 2,6-pyrazines having different substituents, **9a–b,** were easily obtained. The results of elemental analysis and spectral data of **9a–b** are given in the Experimental section.



SCHEME



a: Ar = C_6H_5; b: Ar = p-ClC_6H_4; c: Ar = p-$CH_3C_6H_4$.

SCHEME 1

In conclusion, the condensation of N,N-bis-(arylcarbonylmethyl)-sulfonamides **3a–c** and **8a–b** with methoxycarbonylhydrazine provides a facile preparation of 2,6-diarylpyrazines. Unfortunately, the detailed mechanism of this new reaction is not quite clear. It will be the subject of our further work.

EXPERIMENTAL

Instruments

Melting points were determined on a micro-melting point apparatus and are uncorrected. IR spectra were recorded with a Shimadzu-IR 435 infrared spectrophotometer. ^{1}H-NMR spectra were determined with a Bruker AC-P200 (200 MHz) spectrometer. Elemental analysis data were obtained from a Yanaco CHN Corder MT-3 apparatus. MS were taken with a VG-7070E spectrometer (70 eV).

N,N-Bis(arylcarbonylmethyl)-p-toluenesulfonamide **3a–c:** *General Procedure*

To a solution composed of each of α-bromoacetophenone **2a–c** (0.03 mol) and N,N-dimethylformamide (10 mL), a mixture of *p*-toluenesulfonamide **1** (0.015 mol), potassium hydroxide (0.03 mol), water (3 mL), and N,N-dimethylformamide (20 mL) was added dropwise at room temperature. After the mixture had been stirred at room temperature for 4 hours, 60 mL of ice water was added to the reaction mixture. The precipitated sulfonamides **3a–c** were collected by filtration and recrystallized from acetone/petroleum ether.

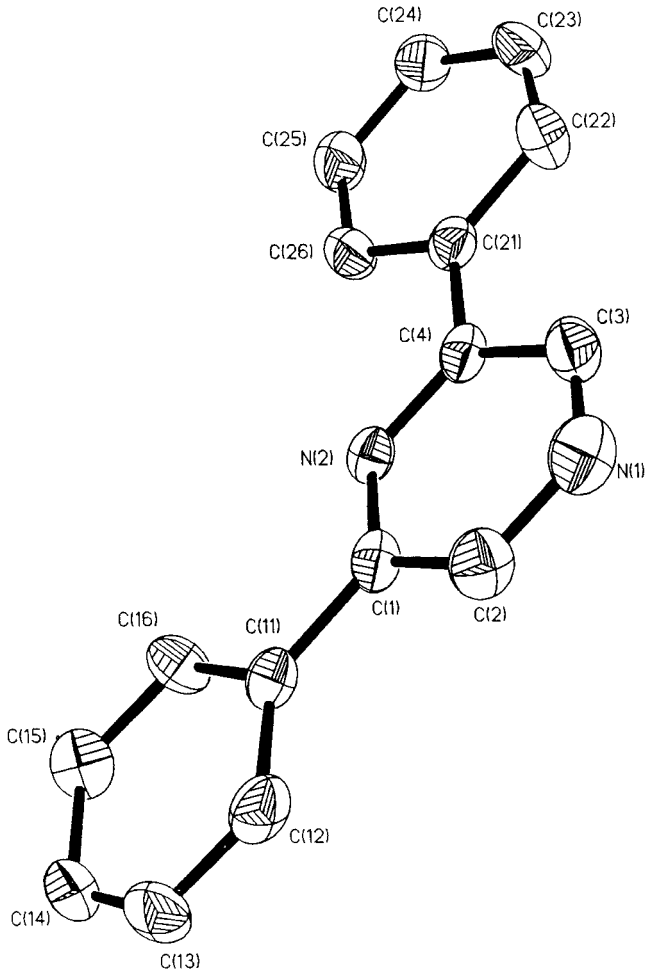


FIGURE 1 Molecular structure of compound **4a** according to X-ray analysis.

3a: Mp 103.8–105.0°C, yield 91%. IR (KBr, cm^{-1}): 3061 w, 1684 s, 1310 m, 1162 m. ^{1}H-NMR ($CDCl_3$): δ 2.52 (s, 3H, CH_3), 5.02 (s, 4H, CH_2), 7.2–8.2 (m, 14H, Ph–H). Anal. calcd for $C_{23}H_{21}NO_4S$: C, 67.79; H, 5.11; N, 3.44. Found: C, 67.49; H, 5.14; N, 3.45.

3b: Mp 164.0–166.0°C, yield 82%. IR (KBr,

TABLE 1 Atomic Coordinates and Thermal Parameters of **4a**

Atom	*x*	*y*	*z*	*Beq* (A^2)
N(1)	0.4275 (2)	0.493 (1)	0.9084 (2)	8.1 (1)
N(2)	0.4295 (2)	0.143 (8)	0.8118 (2)	6.7 (1)
C(1)	0.4719 (2)	0.144 (1)	0.8741 (2)	8.4 (1)
C(2)	0.4713 (3)	0.320 (1)	0.9219 (3)	909 (2)
C(3)	0.3817 (3)	0.495 (1)	0.8461 (3)	10.6 (2)
C(4)	0.3797 (2)	0.314 (1)	0.7956 (3)	8.6 (1)
C(11)	0.5228 (2)	−0.047 (1)	0.8889 (2)	8.2 (1)
C(12)	0.5737 (3)	−0.062 (1)	0.9530 (3)	10.0 (2)
C(13)	0.6201 (3)	−0.244 (1)	0.9649 (3)	10.6 (2)
C(14)	0.6167 (3)	−0.408 (1)	0.9145 (3)	10.5 (2)
C(15)	0.5654 (3)	−0.398 (1)	0.8508 (3)	9.8 (2)
C(16)	0.5189 (3)	−0.217 (1)	0.8386 (3)	9.1 (2)
C(21)	0.3283 (2)	0.308 (1)	0.7266 (3)	8.1 (1)
C(22)	0.2785 (3)	0.480 (1)	0.7044 (3)	9.8 (2)
C(23)	0.2703 (3)	0.462 (1)	0.6395 (4)	11.1 (2)
C(24)	0.2296 (3)	0.277 (1)	0.5946 (3)	9.8 (2)
C(25)	0.2792 (3)	0.104 (1)	0.6162 (3)	10.3 (2)
C(26)	0.3268 (3)	0.117 (1)	0.6816 (3)	9.4 (2)

Isotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: Beq = (4/3) × [a^2 × β(1,1) + b^2 × β(2,2) + c^2 × β(3,3) + ab(cos Γ) × β(1,2) + ac(cos β) × β(1,3) + bc(cos α) × β(2,3)].

Table 2 Bond Lenths (Å) for **4a**

Atom 1	*Atom 2*	*Length*	*Atom 1*	*Atom 2*	*Length*
N(1)	C(2)	1.312(6)	C(12)	C(13)	1.389(6)
N(1)	C(3)	1.322(7)	C(13)	C(14)	1.372(7)
N92)	C(1)	1.323(5)	C(14)	C(15)	1.395(7)
N(2)	C(4)	1.330(5)	C(15)	C(16)	1.387(6)
C(1)	C(2)	1.392(6)	C(21)	C(22)	1.390(6)
C(1)	C(11)	1.487(6)	C(21)	C(26)	1.393(6)
C(3)	C(4)	1.439(6)	C(22)	C(23)	1.380(7)
C(4)	C(21)	1.471(6)	C(23)	C(24)	1.371(7)
C(11)	C(12)	1.399(7)	C(24)	C(25)	1.393(6)
C(11)	C(16)	1.385(6)	C(25)	C(26)	1.386(7)

cm^{-1}): 3042 w, 1693 s, 1340 m, 1175 m. ^{1}H-NMR ($CDCl_3$): δ 2.41 (s, 3H, CH_3), 4.94 (s, 4H, CH_2), 7.26 (d, 2H, J = 8.2 Hz, *p*-MePh–H), 7.72 (d, 2H, *p*-MePh–H), 7.34 (d, 4H, J = 8.6 Hz, *p*-ClPh–H), 7.81 (d, 4H, *p*-ClPh–H). Anal. calcd. for $C_{23}H_{19}Cl_2NO_4S$: C, 57.99; H, 4.02; N, 2.94. Found: C, 57.86; H, 3.96; N, 2.79.

3c: Mp 135.5–137.5°C, yield 76%. IR (KBr, cm^{-1}): 3096 w, 1697 s, 1339 m, 1179 m. ^{1}H-NMR ($CDCl_3$): δ 2.40 (s, 9H, CH_3), 5.04 (s, 4H, CH_2), 7.88–7.32 (m, 12H, Ph–H). Anal. calcd. for $C_{25}H_{25}NO_4S$: C, 68.94; H, 5.78; N, 3.22. Found: C, 69.20; H, 5.75; N, 3.06.

N-Phenacyl-p-toluenesufonamide **6**

α-Aminoacetophenone hydrochloride (4.8 g, 28 mmol) and *p*-toluenesulfonyl chloride (5.3 g, 28 mmol) were mixed with dichloromethane (50 mL) in a flask. Triethylamine (5.7 g, 56 mmol) was added dropwise to the mixture maintained in the ice bath. The mixture was stirred for 1 hour at room temperature, then filtered. The filtrate was washed with cold water (10 × 3 mL), dried over anhydrous sodium sulfate, and filtered. After evaporation of the solvent, the residue was washed with cold ether (8 mL) and recrystallized from petroleum ether/chloroform to yield 7.2 g of white crystals. Mp 118.5–120.0°C, yield 89%. IR (KBr, cm^{-1}): 3256 s, 1685 s, 1342 s, 1156 s. ^{1}H-NMR (acetone-d_6): δ 2.10 (s, 3H, CH_3), 4.29 (s, 2H, CH_2), 7.0–7.8 (m, 9H, Ph–H). Anal. calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.22; N, 4.84. Found: C, 61.80; H, 4.80; N, 4.62.

N,N-Bis(*arylcarbonylmethyl*)*-p-toluenesulfonamide* **8a–b:** *General Procedure*

To a solution of **6** (1.5 g, 5 mmol) and each α-bromoacetophenone **7a–b** (5 mmol) in 15 mL of N,N-dimethylformamide, aqueous potassium hydroxide (potassium hydroxide, 0.28 g, 5 mmol; water, 8 mL) was added with stirring for 50 minutes at room temperature. After having been stirred for 2 hours, the mixture was poured into 40 mL of ice water and allowed to stand overnight. The precipitate was collected by filtration and washed with 8 mL of cold ether. The crude compound was dried in air and recrystallized from absolute ethanol.

8a: Mp 151.5–152.5°C, yield 79%. IR (KBr, cm^{-1}): 1690 s, 1336 m, 1154 m. ^{1}H-NMR ($CDCl_3$): δ 2.43 (s, 3H, CH_3), 5.00 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 7.4–7.9 (m, 13H, Ph–H). Anal. calcd for $C_{23}H_{20}ClNO_4S$: C, 62.51; H, 4.56; N, 3.17. Found: C, 62.59; H, 4.47; N, 2.89.

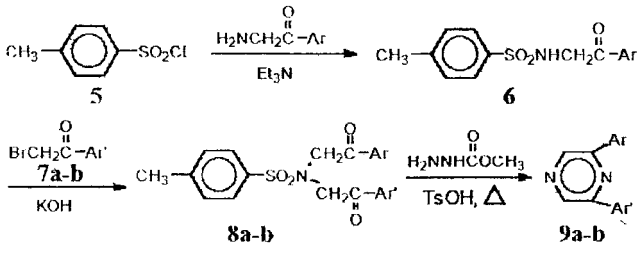
8b: Mp 1330–134.5°C, yield 78%. IR (KBr, cm^{-1}): 1695 s, 1680 s, 1330 s, 1157 s. ^{1}H-NMR ($CDCl_3$): δ 2.42 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.98 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 6.8–8.0 (m, 13H, Ph–H). Anal. calcd for $C_{24}H_{23}NO_5S$: C, 65.89; H, 5.03; N, 3.20. Found: C, 65.68; H, 5.05; N, 2.96.

2,6-Diarylpyrazines **4a–c** *and* **9a–b:** *General Procedure*

A mixture of each sulfonamide **3a–c** and **8a–b** (4 mmol), methoxycarbonylhydrazine (0.008 mol), and a small amount of *p*-toluenesulfonic acid (TsOH) in toluene was heated at reflux with azeotropic removal of water. The reaction was completed after 5 hours.

Table 3 Bond Lengths (deg) for **4a**

Atom 1	*Atom 2*	*Atom 3*	*Angle*	*Atom 1*	*Atom 2*	*Atom 3*	*Angle*
C(2)	N(1)	C(3)	116.8(4)	C(11)	C(12)	C(13)	119.6(5)
C(1)	N(2)	C(4)	119.1(4)	C(12)	C(13)	C(14)	129.7(5)
N(2)	C(1)	C(2)	129.2(4)	C(13)	C(14)	C(15)	129.2(5)
N(2)	C(1)	C(11)	116.6(4)	C(14)	C(15)	C(16)	119.4(5)
C(2)	C(1)	C(11)	123.2(4)	C(11)	C(16)	C(15)	129.9(4)
N(1)	C(2)	C(1)	123.3(4)	C(4)	C(12)	C(22)	123.0(4)
N(1)	C(3)	C(4)	121.6(5)	C(4)	C(21)	C(26)	119.6(4)
N(2)	C(4)	C(3)	119.1(4)	C(22)	C(21)	C(26)	117.4(4)
N(2)	C(4)	C(21)	118.5(5)	C(21)	C(22)	C(23)	120.5(5)
C(3)	C(4)	C(21)	122.4(5)	C(22)	C(23)	C(24)	122.3(5)
C(1)	C(11)	C(12)	121.3(4)	C(23)	C(24)	C(25)	117.7(5)
C(1)	C(11)	C(16)	119.4(4)	C(24)	C(25)	C(26)	120.4(5)
C(12)	C(11)	C(16)	119.4(4)	C(21)	C(26)	C(25)	121.5(5)



Ar = C_6H_5. a: Ar' = p–ClC_6H_4; b: Ar' = p–$CH_3OC_6H_4$.

SCHEME 2

The solvent was removed under reduced pressure, and the products **4a–c** and **9a–b** were separated by column chromatography on silica gel with acetone/petroleum ether (1:5).

4a: Mp 91.0–92.5°C, yield 70%. IR (KBr, cm^{-1}): 3076 w, 1506 w, 1396 m, 1270 m, 1100 m, 1025 m, 766 s, 682 s. ^{1}H-NMR ($CDCl_3$), δ 7.4–8.2 (m, 10H, Ph–H), 8.96 (s, 2H, pyrazine-H). MS: 232 (94), 231 (18), 204 (9), 102 (100), 76 (24). Anal. calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 83.24; H, 5.29; N, 11.59.

4b: Mp 197.0–198.0°C, yield 67%. ^{1}H-NMR ($CDCl_3$): δ 7.44 (d, 4H, J = 8.6 Hz, Ph–H), 8.02 (d, 4H, Ph–H), 8.88 (s, 2H, pyrazine-H). MS: 304 (13), 302 (66), 300 (100), 136 (61). Anal. calcd for $C_{16}H_{10}Cl_2N_2$: C, 63.81; H, 3.35; N, 9.30. Found: C, 63.51; H, 3.52; N, 9.36.

4c: Mp 133.0–133.5°C, yield 67%. ^{1}H-NMR ($CDCl_3$): δ 2.42 (s, 6H, CH_3), 7.31 (d, 4H, J = 8.0, Ph–H), 8.04 (d, 4H, Ph–H), 8.89 (s, 2H, pyrazine-H). Anal. calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.76. Found: C, 82.99; H, 6.23; N, 10.64.

9a: Mp 117.0–1185°C, yield 69%. IR (KBr, cm^{-1}): 3042 w, 1594 m, 1515 m, 1490 m, 1427 s, 1162 s, 1085 s, 825 s, 766 s. ^{1}H-NMR ($CDCl_3$): δ 7.24–8.14 (m, 9H, Ph–H), 8.91 (s, 1H, pyrazine-H), 8.95 (s, 1H, pyrazine-H). Anal. calcd for $C_{16}H_{11}ClN_2$: C, 72.05; H, 4.16; N, 10.05. Found: C, 72.40; H, 4.34; N, 10.55.

9b: Mp 95.0–95.5°C, yield 74%. IR (KBr, cm^{-1}): 3028 w, 1604 m, 1513 s, 1411 m, 1252 s, 828 m, 768 m. ^{1}H-NMR ($CDCl_3$): δ 8.70 (s, 3H, OCH_3), 7.0–8.2 (m, 9H, Ph–H), 8.88 (s, 1H, pyrazine-H), 8.89 (s, 1H, pyrazine-H). Anal. calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.63; H, 5.52; N, 10.57.

X-ray Diffraction Analysis of **4a**

Crystal Data. $C_{16}H_{12}N_2$, monoclinic space group C2/c; a = 23.357(5), b = 5.276(2), c = 21.669(3) Å; β = 114.97(2); D_x = 1.257 Mg m^{-3}; Z = 8. Data collection: crystal size 0.2 × 0.3 × 0.5 mm; Enraf-Nonius CAD4 diffractometer; monochromatized M_0K_α ration; 1893 measured reflections (R = 0.089). Structure solution and refinement: the structure was solved by direct methods and refined by a full-matrix least-squares method; hydrogen atoms were not included at calculated positions. Refinement with 842 reflections [$I \geq 3\sigma(I)$] and 163 parameters converged at R = 0.074, R_w = 0.071 (unit weights); the residual electron density was between 0.22 and −0.18 e $Å^{-3}$. Tables 1, 2, and 3 list atomic coordinates, bond lengths, and angles, respectively.

ACKNOWLEDGMENTS

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REFERENCES

[1] J. V. Hay, *Pestic. Sci., 29,* 1990, 247.
[2] A. Percival, *Pestic. Sci., 31,* 1991, 569.
[3] C. D. Hurd, R. I. Mori, *J. Am. Chem. Soc., 77,* 1955, 5359.
[4] K. Masuda et al., *J. Chem. Soc. Perkin I, (5),* 1981, 1591.
[5] F. Tutin, *J. Chem. Soc., 97,* 1910, 2495.
[6] P. A. Reddy, V. R. Srinivasan, *Indian J. Chem., 18B,* 1979, 482.
[7] T. Suzuki et al., *Jpn. Kokai Tokyo Koho JP, 3/74,* 1991, 370.
[8] G. M. Abdalla, J. W. Sowell, *J. Heterocyclic Chem., 24,* 1987, 297.