Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 303–309

TETRAHEDRON

Efficient synthesis of *N*-acylarenesulfenamides by acylation of arenesulfenamides

Ming Bao,[a] Masao Shimizu,[a,*] Shigeru Shimada[a] and Masato Tanaka[a,b]

[a]*National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba Central 5, 1-1-1 Higashi, Tsukuba, Ibaraki 305-8565, Japan*

[b]*Chemical Resources Laboratory, Tokyo Institute of Technology, 4259 Nagatsuda, Midori-ku, Yokohama 226-8503, Japan*

Received 3 September 2002; accepted 25 November 2002

Abstract—Acylation of arenesulfenamides proceeds efficiently by using either perfluorocarboxylic anhydrides or acid chlorides in the presence of pyridine as a base at low temperatures to give *N*-acylarenesulfenamides. Some *N*-alkylcarbonyl derivatives exist with imidic acid tautomers in an aprotic solvent.

1. Introduction

N-Acylarenesulfenamides are not only versatile intermediates in the synthesis of a variety of sulfur compounds,[1] but also important compounds in view of their biological activities. For example, *N*-benzoyl-4-chlorobenzenesulfenamide has been claimed to be potentially useful as a plant growth regulator.[2] *N*-Acylarenesulfenamides are usually synthesized by the reaction of sulfenyl chlorides with amides,[3] although it was described in a previous review that the sulfenamides resemble amines rather than amides and that their acetyl and benzoyl derivatives easily formed by conventional methods.[4] Generation of sulfenyl chloride, however, requires chlorination of disulfides or thiols with hazardous, poisonous and corrosive chlorine gas, the use of which does not meet the recent requirement in contemporary organic synthesis for reagents of little or no risk.[5] To the best of our knowledge, only two examples of acylation of arenesulfenamides for alternative synthesis of *N*-acylarenesulfenamides have been reported; treatment of arenesulfenamides at room temperature with acetic anhydride (coupled with anhydrous sodium acetate) for a long reaction time forms *N*-acetylarenesulfenamides, but the yield is not satisfactory.[6] The use of acid chlorides does not appear to afford desired *N*-acylarenesulfenamide.[7] Could other acylating reagents be used to achieve acylation of arenesulfenamides? Is it really impossible to prepare *N*-acylarenesulfenamides with acid chlorides? This paper will answer these questions.

2. Results and discussion

Attempted acylation of 2-methoxycarbonylbenzenesulfenamide (**1a**) using carboxylic acid in combination with 1,3-dicyclohexylcarbodiimide[8] or *N*-acylimidazole,[9] both known as excellent reagents for acylation of amines, failed to afford desired products and the starting material **1a** was recovered. The use of $(CH_3CH_2CO)_2O$ or $(PhCO)_2O$ did not work either. However, when $(CF_3CO)_2O$ was used as a strong acylation reagent in the presence of pyridine at room temperature, the acylation did proceed to give *N*-trifluoroacetyl-2-methoxycarbonylbenzenesulfenamide (**2a**) in 46% yield (Scheme 1, Eq. (1)). Lowering the reaction temperature to 0°C increased the yield of **2a** to 73%.

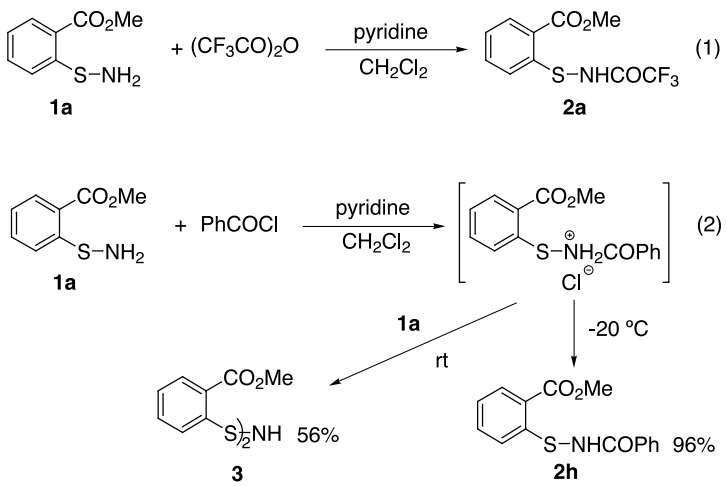
A similar attempt to use benzoyl chloride in place of $(CF_3CO)_2O$ in the acylation reaction of **1a** at room temperature failed to provide desired *N*-benzoyl-2-methoxycarbonylbenzenesulfenamide (**2h**). The product obtained in practice was a disulfenylamine (**3**; 56%), the formation of which is, as described in the literatures,[7] due presumably to the rapid reaction of intermediary *N*-benzoyl-2-methoxycarbonylbenenesulfenamide hydrochloride with **1a**.[2c] However, the foregoing experiments with $(CF_3CO)_2O$ suggests that the reaction temperature plays an important role to determine the reaction course. Indeed, the reaction of **1a** with benzoyl chloride, when effected at 0°C, worked much better to form the desired product **2h** in 78% yield along with only 20% of **3**. At −20°C formation of the latter was totally suppressed to furnish **2h** in 96% yield (Scheme 1, Eq. (2)).

Both of these new acylation procedures have proved to be applicable to a wide range of arenesulfenamides. The results obtained under the standard conditions (0.5 mmol of

Keywords: acylation; sulfenamides; amides; acid chlorides; imidic acids.

* Corresponding author. Tel.: +81-298-61-4575; fax: +81-298-61-4487; e-mail: m.shimizu@aist.go.jp

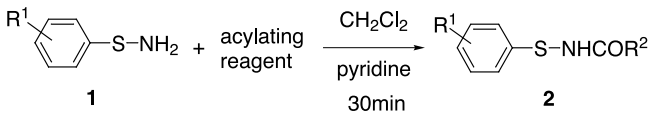
0040–4020/03/$ - see front matter
PII: S0040-4020(02)01554-5



Scheme 1. Acylation reaction of **1a** with trifluoroacetic anhydride and benzoyl chloride.

arenesulfenamide **1**, 0.6 mmol of perfluorocarboxylic anhydride or acid chloride and 1.5 equiv. of pyridine in 6 mL CH_2Cl_2 at 0°C or −20°C for 30 min) are summarized in Table 1. When 2-bromobenzenesulfenamide (**1b**) was employed in the acylation with $(CF_3CO)_2O$, *N*-trifluoroacetyl-2-bromobenzenesulfenamide (**2b**) was obtained in 80% yield (entry 2). Several other arenesulfenamides, such as 4-nitrobenzenesulfenamide (**1c**), 4-methylbenzenesulfenamide (**1d**), and benzenesulfenamide (**1e**), also underwent the acylation with $(CF_3CO)_2O$, and *N*-trifluoroacetyl-4-nitrobenzenesulfenamide (**2c**), *N*-trifluoroacetyl-4-methylbenzenesulfenamide (**2d**), and *N*-trifluoroacetylbenzenesulfenamide (**2e**) were obtained in 82, 63 and 78% yields, respectively (entries 3–5). When the acylation of **1e** with $(CF_3CO)_2O$ was carried out at lower temperature such as −20°C, **2e** was obtained in almost the same yield as the acylation was performed at 0°C (entry 6). This result indicated that acylation of **1** with $(CF_3CO)_2O$ did not need proceeding at lower than 0°C to afford **2** in good yields. $(CF_3CF_2CO)_2O$ used as acylating reagent instead of $(CF_3CO)_2O$ also worked efficiently in the reaction of **1a** and **1c**, and *N*-pentafluoropropionyl-2-methoxycarbonylbenzenesulfenamide (**2f**) and *N*-pentafluoropropionyl-4-nitrobenzenesulfenamide (**2g**) were obtained in good yields (90 and 85%, respectively, entries 7 and 8).

Table 1. Acylation of arenesulfenamides with perfluorocarboxylic anhydrides or acid chlorides



Entry	1	R^1	Acylating reagent	Temperature (°C)	2	Yield[a] (%)
1	**1a**	2-CO_2Me	$(CF_3CO)_2O$	0	**2a**	73
2	**1b**	2-Br	$(CF_3CO)_2O$	0	**2b**	80
3	**1c**	4-NO_2	$(CF_3CO)_2O$	0	**2c**	82
4	**1d**	4-Me	$(CF_3CO)_2O$	0	**2d**	63
5	**1e**	H	$(CF_3CO)_2O$	0	**2e**	78
6	**1e**	H	$(CF_3CO)_2O$	−20	**2e**	76
7	**1a**	2-CO_2Me	$(CF_3CF_2CO)_2O$	0	**2f**	90
8	**1c**	4-NO_2	$(CF_3CF_2CO)_2O$	0	**2g**	85
9	**1a**	2-CO_2Me	PhCOCl	−20	**2h**	96
10	**1c**	4-NO_2	PhCOCl	−20	**2i**	81
11	**1d**	4-Me	PhCOCl	−20	**2j**	67
12	**1e**	H	PhCOCl	−20	**2k**	69
13	**1f**	4-Cl	PhCOCl	−20	**2l**	85

[a] Isolated yield.

The acylations of **1c**–**f** with benzoyl chloride at −20°C furnished *N*-benzoylarenesulfenamides (**2h**–**l**) also in good yields (entries 9–13). Especially, *N*-benzoyl-4-chlorobenzenesulfenamide (**2l**), which was claimed to be a plant growth regulator,[2] was synthesized in 85% yield (entry 13). It is interesting that some of parent arenesulfenamides, in particular those that do not have a strongly electron-withdrawing substituent on the aromatic ring, are thermally rather unstable. Thus, **1b**, **1d**, and **1e** deteriorate over a few hours at room temperature to generate disulfenylamines. However, the corresponding *N*-acylarenesulfenamides **2b**, **2d**, **2e**, **2j**, and **2k** are stable crystalline materials, which retain the structural integrity even after several months at room temperature.

When acetyl chloride was used in acylation of **1a**, an acetylated product was obtained, and X-ray crystal structure determination of the product clearly shows that the structure is *N*-acetyl-2-methoxycarbonylbenzenesulfenamide (**4a**) (Fig. 1).[10] However, the ^{1}H NMR spectrum of **4a** in $CDCl_3$ at room temperature showed mixtures of amide (**4a**) and imidic acid (**5a**) forms, which could be deduced from the tautomerism in *N*-(acetylaminothio)phthalimide reported in the literature.[11] The ratio of **4a** to **5a** increased with the addition of protic solvent, CD_3OD, to the solution of **4a** in $CDCl_3$. Only the amide structure was finally observed when the ^{1}H NMR spectrum of **4a** was measured in CD_3OD.

The structures of two tautomers, **4** and **5**, in $CDCl_3$ were assigned from the following data. When **4a** was treated with iodomethane in the presence of sodium hydride, *N*-methylated product **6a** was only obtained, which was assigned by *N*-methyl peaks in ^{1}H and ^{13}C NMR spectra (Scheme 2, Eq. (3)). Preparation of methyl *N*-sulfenylacetimidate (**8**) was succeeded by the reaction of sulfenyl chloride (**7**) with methyl acetimidate hydrochloride in the presence of triethylamine (Scheme 2, Eq. (4)). ^{1}H NMR spectra of **6** and **8** in $CDCl_3$ showed that the absorption of

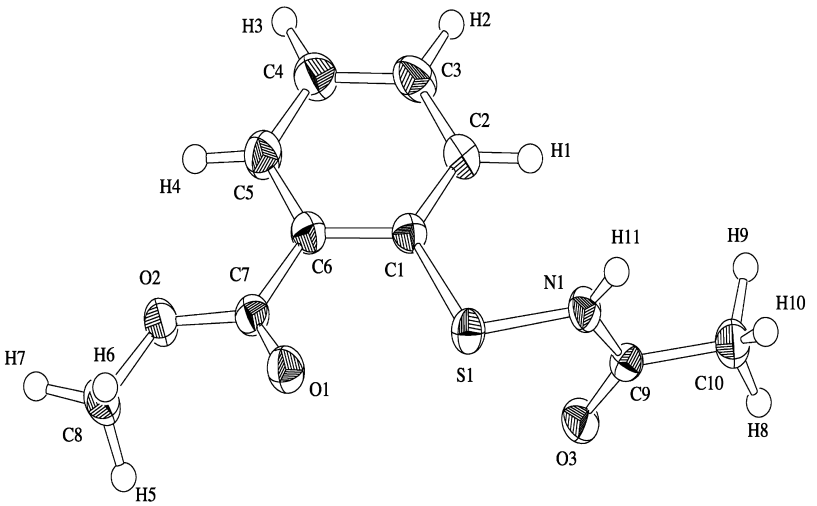
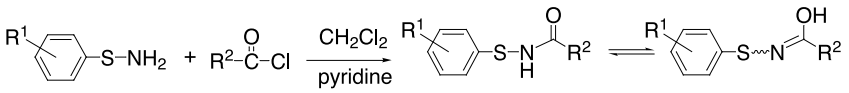


Figure 1. Crystal structure of **4a**.

Table 2. Acylation of **1** with aliphatic acid chlorides



1 **4** **5**

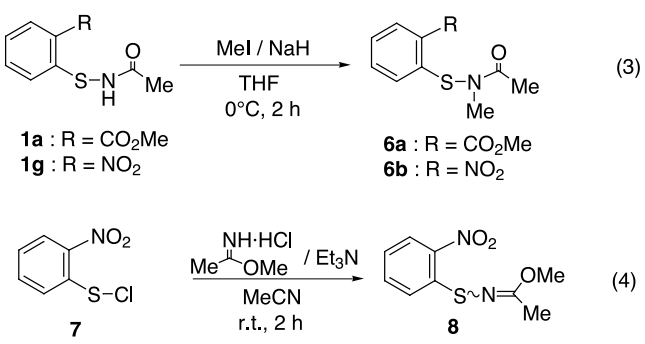
Entry	**1**	R^1	R^2	Yield[a] (%)	Products in $CDCl_3$	Ratio[b] of **4** to **5**
1	**1a**	2-CO_2Me	Me	94	**4a**, **5a**	43:57
2	**1d**	4-Me	Me	65	**4b**, **5b**	45:55
3	**1e**	H	Me	72	**4c**, **5c**	39:61
4	**1f**	4-Cl	Me	82	**4d**, **5d**	37:63
5	**1g**	2-NO_2	Me	78	**4e**, **5e**	57:43
6	**1a**	2-CO_2Me	Et	98	**4f**, **5f**	50:50
7	**1a**	2-CO_2Me	*i*-Pr	85	**4g**, **5g**	71:29
8	**1a**	2-CO_2Me	$PhCH_2$	74	**4h**, **5h**	74:26

[a] Isolated yield.
[b] Calculated with ^{1}H NMR spectra.

methyl groups of an acetyl group and an imidate group appeared at around δ_H 2.3 and 2.2, respectively; methyl groups in acetyl groups appeared in downer field than those in imidate groups. According to these observations, the ratios of **4** to **5** in $CDCl_3$ were determined (Table 2).

3. Conclusion

In summary, perfluorocarboxylic anhydrides are efficient reagents to achieve the acylation of arenesulfenamide at 0°C. Acid chlorides also can be used as efficient acylating reagent, but the reaction temperature plays a key role; at room temperature undesired disulfenylamines are formed, whereas at a low reaction temperature such as −20°C the desired *N*-acylarenesulfenamides are obtained in high yields. These methods offer convenient and safe routes to synthesize *N*-acylarenesulfenamides. *N*-Alkylcarbonyl-arenesulfenamides tautomerized to the imidic acid isomer in an aprotic solvent. Further investigations towards mechanism of tautomerization are currently underway.



Scheme 2. Synthesis of *N*-methyl-*N*-sulfenylacetamides **6** and methyl *N*-sulfenylacetimidate **8**.

4. Experimental

4.1. General

Melting points were determined on a Mettler FP90 microscopic plate and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained with a JEOL LA-500 spectrometer, and chemical shifts are reported in parts per million relative to internal tetramethylsilane and $CDCl_3$ (77 ppm), respectively. IR spectra were recorded on a JASCO FTIR-5300 spectrophotometer. Sulfenamides **1** were prepared by the method described in a previous paper.[5a]

4.2. General procedure for the acylation of arenesulfenamides with perfluorocarboxylic anhydrides

To a mixture of **1** (0.5 mmol) and pyridine (0.75 mmol, 59.3 mg) in CH_2Cl_2 (6 mL) at 0°C was added perfluorocarboxylic anhydride (0.6 mmol). The mixture was stirred for 30 min and then the solvent was removed under a reduced pressure. The crude product was purified with silica gel column chromatography (eluent: CH_2Cl_2).

4.2.1. *N*-Trifluoroacetyl-2-methoxycarbonylbenzenesulfenamide (2a). Colorless crystal with mp 127–128°C (from CH_2Cl_2–hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.96 (3H, s), 7.17 (1H, dd, J=8.6, 0.6 Hz), 7.27 (1H, td, J=7.6, 0.6 Hz), 7.50 (1H, br s), 7.54 (1H, ddd, J=8.6, 7.6, 1.2 Hz), 8.04 (1H, dd, J=7.6, 1.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.8, 115.7 (q, J_{CF}=287.4 Hz, CF_3), 121.5, 124.5, 125.5, 131.3, 133.6, 142.4, 159.2 (q, J_{CF}=37.0 Hz, C=O), 167.4; IR (KBr) 3223, 3090, 2959, 1713, 1696, 1468, 1441, 1319, 1206, 1163, 747 cm^{-1}; HRMS calcd for $C_{10}H_8F_3NO_3S$: 279.0177. Found 279.0141.

4.2.2. *N*-Trifluoroacetyl-2-bromobenzenesulfenamide (2b). Colorless crystal with mp 89–90°C (from CH_2Cl_2–hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13–7.16 (2H, m), 7.33 (1H, ddd, J=8.6, 7.3, 1.2 Hz), 7.54 (1H, dd, J=8.6, 1.2 Hz), 7.56 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 115.5 (q, J_{CF}=288.4 Hz, CF_3), 119.9, 126.3, 128.3, 128.8, 133.2, 136.1, 159.0 (q, J_{CF}=38.1 Hz, C=O); IR (KBr) 3225, 1723, 1468, 1447, 1211, 1167, 1150, 741 cm^{-1}; HRMS calcd for $C_8H_5BrF_3NOS$: 298.9227, 300.9207. Found 298.9210, 300.9216.

4.2.3. *N*-Trifluoroacetyl-4-nitrobenzenesulfenamide (2c). Colorless crystal with mp 111–113°C (from CH_2Cl_2–hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (2H, dt, J=9.2, 2.5 Hz), 7.74 (1H, br s), 8.22 (2H, dt, J=9.2, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 115.4 (q, J_{CF}=288.4 Hz, CF_3), 124.4, 124.6, 144.8, 146.8, 159.0 (q, J_{CF}=39.1 Hz, C=O); IR (KBr) 3274, 1726, 1580, 1522, 1458, 1341, 1211, 1169, 1132 cm^{-1}; HRMS calcd for $C_8H_5F_3N_2O_3S$: 265.9973. Found 265.9953.

4.2.4. *N*-Trifluoroacetyl-4-methylbenzenesulfenamide (2d). Colorless crystal with mp 84–86°C (from CH_2Cl_2–hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (3H, s), 7.18 (2H, d, J=8.0 Hz), 7.43 (2H, d, J=8.0 Hz), 7.53 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 115.6 (q, J_{CF}=287.4 Hz, CF_3), 130.2, 130.9, 131.9, 140.1, 159.1 (q, J_{CF}=38.1 Hz, C=O); IR (KBr) 3289, 3239, 2926, 1725, 1468, 1321, 1163, 804 cm^{-1}; HRMS calcd for $C_9H_8F_3NOS$: 235.0279. Found 235.0291.

4.2.5. *N*-Trifluoroacetylbenzenesulfenamide (2e). Colorless crystal with mp 70–72°C (from CH_2Cl_2–hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.39 (3H, m), 7.43–7.46 (2H, m), 7.53 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 115.6 (q, J_{CF}=287.4 Hz, CF_3), 129.0, 129.1, 129.5, 135.5, 159.1 (q, J_{CF}=37.1 Hz, C=O); IR (KBr) 3245, 1717, 1441, 1321, 1186, 740, 689 cm^{-1}; HRMS calcd for $C_8H_6F_3NOS$: 221.0122. Found 221.0145.

4.2.6. *N*-Pentafluoropropionyl-2-methoxycarbonylbenzenesulfenamide (2f). Colorless crystal with mp 117–118°C (from CH_2Cl_2–hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.96 (3H, s), 7.14 (1H, dd, J=8.2, 0.6 Hz), 7.26 (1H, ddd, J=8.0, 7.3, 0.6 Hz), 7.53 (1H, ddd, J=8.2, 7.3, 1.5 Hz), 7.55 (1H, br s), 8.04 (1H, dd, J=8.0, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.8, 107.1 (tq, J_{CF}=266.8, 39.3 Hz, CF_2), 117.7 (qt, J_{CF}=285.4, 34.0 Hz, CF_3), 121.5, 124.5, 125.5, 131.8, 133.6, 142.4, 159.8 (t, J_{CF}=26.8 Hz, C=O), 167.4; IR (KBr) 3252, 1707, 1443, 1319, 1213, 1148, 1032, 747 cm^{-1}; HRMS calcd for $C_{11}H_8F_5NO_3S$: 329.0145. Found 329.0094.

4.2.7. *N*-Pentafluoropropionyl-4-nitrobenzenesulfenamide (2g). Colorless crystal with mp 88–89°C (from CH_2Cl_2–hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (2H, dt, J=9.2, 2.5 Hz), 7.67 (1H, br s), 8.24 (2H, dt, J=9.2, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 107.0 (tq, J_{CF}=266.8, 40.3 Hz, CF_2), 117.5 (qt, J_{CF}=285.4, 34.0 Hz, CF_3), 124.4, 124.6, 144.7, 146.8, 159.8 (t, J_{CF}=26.8 Hz, C=O); IR (KBr) 3260, 1721, 1512, 1451, 1346, 1208, 1181, 1157, 1030, 855 cm^{-1}; HRMS calcd for $C_9H_5F_5N_2O_3S$: 315.9941. Found 315.9930.

4.3. General procedure for the acylation of arenesulfenamides with acid chlorides

To a mixture of **1a** (0.5 mmol, 91.5 mg) and pyridine (0.75 mmol, 59.3 mg) in CH_2Cl_2 (6 mL) at −20°C was added acid chloride (0.6 mmol). The mixture was stirred for 30 min and then the solvent was removed under a reduced pressure. The crude product was purified with silica gel column chromatography (eluent: CH_2Cl_2/ethyl acetate=10:1 or 20:1).

4.3.1. *N*-Benzoyl-2-methoxycarbonylbenzenesulfenamide (2h). Colorless crystal with mp 156–158°C (from ethyl acetate–hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.92 (3H, s), 7.16 (1H, t, J=7.6 Hz), 7.30 (1H, d, J=7.9 Hz), 7.41–7.45 (3H, m), 7.54 (1H, d, J=7.9 Hz), 7.56 (1H, br s), 7.91 (2H, d, J=7.7 Hz), 7.99 (1H, d, J=7.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.4, 122.1, 124.2, 124.6, 127.7, 128.8, 131.1, 132.4, 133.1, 144.9, 167.1, 169.0; IR (KBr) 3264, 3063, 2951, 1701, 1663, 1453, 1433, 1312, 1256, 1105, 745, 693 cm^{-1}; Anal. calcd for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.87. Found: C, 62.68; H, 4.27; N, 4.76.

4.3.2. *N*-Benzoyl-4-nitrobenzenesulfenamide (2i). Colorless crystal with mp 157–158°C (from ethyl acetate–hexane, lit.,[3a] 157–158°C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (2H, dt, J=9.1, 2.4 Hz), 7.48 (2H, ddd, J=8.2, 7.6, 1.5 Hz), 7.61 (1H, tt, J=7.6, 1.2 Hz), 7.73 (1H, br s), 7.90 (2H, dd, J=8.2, 1.2 Hz), 8.10 (2H, dt, J=9.1, 2.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 122.8, 124.2, 127.8, 129.0, 132.3, 133.1, 145.9, 148.3, 168.7; IR (KBr) 3191, 1659, 1580, 1512, 1339, 1269, 837, 694 cm^{-1}.

4.3.3. *N*-Benzoyl-2-methylbenzenesulfenamide (2j). Colorless crystal with mp 131.5–133°C (from ethyl acetate–hexane, lit.,[3b] 123–124°C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.29 (3H, s), 7.08 (2H, d, J=7.3 Hz), 7.28 (2H, d, J=7.6 Hz), 7.39 (2H, t, J=7.6 Hz), 7.51 (1H, t, J=7.6 Hz), 7.69 (1H, br s), 7.82 (2H, d, J=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 127.3, 127.6, 128.7, 129.8,

132.3, 133.4, 135.0, 137.5, 169.2; IR (KBr) 3302, 1667, 1495, 1418, 1263, 806, 691, 639, 502 cm^{-1}.

4.3.4. *N*-Benzoylbenzenesulfenamide (2k). Colorless crystal with mp 116.5–117°C (from ethyl acetate–hexane; lit.,[1a] 122–124°C); ^1H NMR (500 MHz, $CDCl_3$) δ 7.14–7.17 (1H, m), 7.23–7.26 (4H, m), 7.34–7.37 (2H, m), 7.48–7.51 (1H, m), 7.84 (2H, d, J=7.3 Hz), 7.89 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 125.4, 126.7, 127.7, 128.6, 128.9, 132.3, 133.1, 138.6, 169.3; IR (KBr) 3285, 1665, 1420, 1262, 741, 691 cm^{-1}.

4.3.5. *N*-Benzoyl-4-chlorobenzenesulfenamide (2l). Colorless crystal with mp 143–143°C (from CH_2Cl_2–hexane, lit.,[3b] 143–144); ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (4H, s), 7.45 (2H, dd, J=8.0, 7.5 Hz), 7.56 (1H, tt, J=7.5, 1.2 Hz), 7.60 (1H, br s), 7.85 (2H, d, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 127.3, 127.6, 128.8, 129.2, 132.6, 132.9, 133.1, 137.0, 169.0; IR (KBr) 3291, 1669, 1451, 1420, 1263, 1096, 816, 691 cm^{-1}.

4.3.6. *N*-Acetyl-2-methoxycarbonylbenzenesulfenamide (4a). Colorless crystal with mp 129–130°C (from ethyl acetate–hexane); ^1H NMR (500 MHz, CD_3OD) δ 2.21 (3H, s), 3.91 (3H, s), 7.22 (1H, td, J=7.6, 1.0 Hz), 7.28 (1H, dd, J=8.3, 1.0 Hz), 7.54 (1H, ddd, J=8.3, 7.6, 1.2 Hz), 8.02 (1H, dd, J=7.6, 1.2 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 23.0, 52.8, 123.1, 125.3, 125.5, 132.1, 134.2, 146.5, 168.3, 175.8; IR (KBr) 3264, 2957, 1703, 1667, 1439, 1314, 1290, 1242, 1148, 747 cm^{-1}; Anal. calcd for $C_{10}H_{11}NO_3S$: C, 53.32; H, 4.92; N, 6.22. Found: C, 53.44; H, 4.65; N, 6.11.

Mixture of **4a** *and* **5a**. Compound **4a**: ^1H NMR (500 MHz, $CDCl_3$) δ 2.28 (3H, s), 3.93 (3H, s), 6.75 (1H, br s), 7.19 (1H, t, J=7.3 Hz), 7.24–7.28 (1H, m), 7.49 (1H, t, J=7.7 Hz), 8.01 (1H, d, J=7.7 Hz). Compound **5a**: ^1H NMR (500 MHz, $CDCl_3$) δ 2.16 (3H, s), 3.96 (3H, s), 6.39 (1H, br s), 7.24–7.28 (1H, m), 7.41 (1H, d, J=8.3 Hz), 7.58 (1H, t, J=8.3 Hz), 8.07 (1H, d, J=7.4 Hz).

4.3.7. *N*-Acetyl-4-methylbenzenesulfenamide (4b). Colorless crystal with mp 105.5–106.5°C (from ethyl acetate–hexane, lit.,[1b] 102–105°C); ^1H NMR (500 MHz, CD_3OD) δ 2.20 (3H, s), 2.20 (3H, s), 7.04 (2H, d, J=8.5 Hz), 7.07 (2H, d, J=8.5 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 21.0, 22.8, 127.1, 130.7, 136.7, 138.1, 175.5; IR (KBr) 3712, 1680, 1458, 1246, 802, 590 cm^{-1}.

Mixture of **4b** *and* **5b**. Compound **4b**: ^1H NMR (500 MHz, $CDCl_3$) δ 2.22 (3H, s), 2.34 (3H, s), 6.49 (1H, br s), 7.12–7.14 (2H, m), 7.18 (2H, d, J=7.9 Hz). Compound **5b**: ^1H NMR (500 MHz, $CDCl_3$) δ 2.15 (3H, s), 2.32 (3H, s), 6.78 (1H, br s), 7.12–7.14 (2H, m), 7.26 (2H, d, J=8.2 Hz).

4.3.8. *N*-Acetylbenzenesulfenamide (4c). Colorless crystal with mp 103.5–104.5°C (from ethyl acetate–hexane, lit.,[12] 102.5–104°C); ^1H NMR (500 MHz, CD_3OD) δ 2.09 (3H, s), 7.07 (1H, t, J=7.3 Hz), 7.11 (2H, dd, J=7.3, 1.2 Hz), 7.20 (2H, t, J=7.3 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 22.8, 125.6, 127.5, 130.0, 140.3, 175.5; IR (KBr) 3243, 1672, 1454, 1246, 741, 594 cm^{-1}.

Mixture of **4c** *and* **5c**. Compound **4c**: ^1H NMR (500 MHz, $CDCl_3$) δ 2.21 (3H, s), 6.76 (1H, b rs), and aromatic protons. Compound **5a**: ^1H NMR (500 MHz, $CDCl_3$) δ 2.16 (3H, s), and aromatic protons.

4.3.9. *N*-Acetyl-4-chlorobenzenesulfenamide (4d). Colorless crystal with mp 115–117°C (from CH_2Cl_2–hexane); ^1H NMR (500 MHz, CD_3OD) δ 2.14 (3H, s), 7.20 (2H, dt, J=8.6, 2.1 Hz), 7.31 (2H, dt, J=8.6, 2.1 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 22.8, 127.1, 130.1, 133.2, 139.3, 175.4; IR (KBr) 3241, 1671, 1453, 1248, 1092, 1011, 814 cm^{-1}; Anal. calcd for C_8H_8ClNOS: C, 47.64; H, 4.00; N, 6.95. Found: C, 47.80; H, 3.71; N, 6.90.

Mixture of **4d** *and* **5d**. Compound **4d**: ^1H NMR (500 MHz, $CDCl_3$) δ 2.20 (3H, s), 6.63 (1H, br s), 7.14 (2H, d, J=8.4 Hz), 7.34 (2H, d, J=8.4 Hz). Compound **5d**: ^1H NMR (500 MHz, $CDCl_3$) δ 2.18 (3H, s), 7.02 (1H, br s), 7.20 (2H, d, J=8.4 Hz), 7.27 (2H, d, J=8.4 Hz).

4.3.10. *N*-Acetyl-2-nitrobenzenesulfenamide (4e). Yellow crystal with mp 175–176.5°C (from ethyl acetate, lit.,[13] 179–180°C); ^1H NMR (500 MHz, CD_3OD) δ 2.15 (3H, s), 7.29 (1H, t, J=8.3 Hz), 7.36 (1H, d, J=8.3 Hz), 7.62 (1H, t, J=8.3 Hz), 8.22 (1H, d, J=8.3 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 23.0, 125.0, 126.8, 126.8, 135.6, 142.4, 144.2, 175.6; IR (KBr) 3221, 1667, 1505, 1435, 1339, 1248, 1107, 735 cm^{-1}.

Mixture of **4e** *and* **5e**. Compound **4e**: ^1H NMR (500 MHz, $CDCl_3$) δ 2.32 (3H, s), 6.69 (1H, br s), 7.32–7.37 (m, 1H), 7.63 (1H, t, J=7.6 Hz), 8.31 (1H, d, J=7.6 Hz). Compound **5e**: ^1H NMR (500 MHz, $CDCl_3$) δ 2.18 (3H, s), 6.39 (1H, br s), 7.41 (1H, t, J=7.6 Hz), 7.55 (1H, d, J=7.6 Hz), 7.73 (1H, t, J=7.6 Hz), 8.37 (1H, d, J=7.6 Hz).

4.3.11. *N*-Propionyl-2-methoxycarbonylbenzenesulfenamide (4f). Colorless crystal with mp 138–139°C (from ethyl acetate–hexane); ^1H NMR (500 MHz, CD_3OD) δ 1.21 (3H, t, J=7.6 Hz), 2.50 (2H, q, J=7.7 Hz), 3.90 (3H, s), 7.21 (1H, td, J=7.8, 1.2 Hz), 7.26 (1H, d, J=7.8 Hz), 7.53 (1H, td, J=7.8, 1.5 Hz), 8.01 (1H, dd, J=7.8, 1.2 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 10.2, 30.4, 52.8, 123.0, 125.3, 125.5, 132.1, 134.1, 146.7, 168.3, 179.4; IR (KBr) 3239, 2986, 2949, 2882, 1705, 1676, 1439, 1300, 1277, 1258, 1190, 756 cm^{-1}; Anal. calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85. Found: C, 55.42; H, 5.23; N, 5.77.

Mixture of **4f** *and* **5f**. Compound **4f**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.09 (3H, t, J=7.3 Hz), 2.50 (2H, q, J=7.3 Hz), 3.93 (3H, s), 6.75 (1H, br s), 7.18 (1H, t, J=7.0 Hz), 7.22–7.26 (1H, m), 7.47 (1H, d, J=7.3 Hz), 8.00 (1H, d, J=7.3 Hz). Compound **5f**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (3H, t, J=7.3 Hz), 2.50 (2H, q, J=7.3 Hz), 3.96 (3H, s), 6.37 (1H, br s), 7.22–7.26 (1H, m), 7.40 (1H, d, J=7.9 Hz), 7.57 (1H, t, J=7.6 Hz), 8.06 (1H, d, J=7.6 Hz).

4.3.12. *N*-Isobutyryl-2-methoxycarbonylbenzenesulfenamide (4g). Colorless crystal with mp 148–149°C (from ethyl acetate–hexane). ^1H NMR (500 MHz, CD_3OD) δ 1.24 (6H, d, J=7.0 Hz), 2.76 (1H, sept, J=7.0 Hz), 3.92 (3H, s), 7.21 (1H, t, J=7.3 Hz), 7.25 (1H, d, J=8.2 Hz), 7.52 (1H, ddd, J=8.2, 7.3, 1.2 Hz), 8.02 (1H, dd, J=8.0, 1.2 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 19.9, 36.7, 52.7, 122.7, 125.0, 125.3,

132.0, 133.9, 146.4, 168.1, 182.2; IR (KBr): 3210, 1701, 1674, 1435, 1101, 750 cm^{-1}; Anal. calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 57.07; H, 5.85; N, 5.40.

Mixture of **4g** *and* **5g**. Compound **4g**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.28 (6H, d, J=7.0 Hz), 2.67 (1H, sept, J=7.0 Hz), 3.92 (3H, s), 6.74 (1H, br s), 8.00 (1H, d, J=7.6 Hz), and aromatic protons. Compound **5g**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (6H, d, J=6.1 Hz), 3.18 (1H, brs), 3.96 (3H, s), 6.23 (1H, br s), 8.06 (1H, d, J=7.6 Hz), and aromatic protons.

4.3.13. *N*-Phenylacetyl-2-methoxycarbonylbenzenesulfenamide (4h). Colorless crystal with mp 144.5–145°C (from ethyl acetate–hexane). ^1H NMR (500 MHz, CD_3OD) δ 3.76 (2H, s), 3.89 (3H, s), 7.02 (1H, dd, J=8.2, 0.9 Hz), 7.01–7.03 (1H, m), 7.28–7.39 (6H, m), 7.97 (1H, dd, J=7.9, 1.2 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 44.3, 52.8, 123.0, 125.2, 125.5, 128.3, 129.7, 130.3, 132.1, 134.0, 136.2, 146.5, 168.3, 176.4; IR (KBr): 3196, 1703, 1661, 1435, 1107, 741 cm^{-1}; Anal. calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.95; H, 4.92; N, 4.56.

Mixture of **4h** *and* **5h**. Compound **4h**: ^1H NMR (500 MHz, $CDCl_3$) δ 3.83 (2H, s), 3.90 (3H, s), 6.53 (1H, br s), 7.97 (1H, d, J=7.9 Hz), and aromatic protons. Compound **5h**: ^1H NMR (500 MHz, $CDCl_3$) δ 3.85 (2H, s), 3.98 (3H, s), 6.34 (1H, br s), 8.05 (1H, d, J=7.3 Hz), and aromatic protons.

4.4. General procedure for the methylation of 4

To a solution of **4** (0.7 mmol) in THF (20 mL) was added sodium hydride (1.5 mmol) at 0°C. Iodomethane (1.5 mmol, 213 mg) in THF (5 mL) was added to the solution. The mixture was stirred for 2 h and was quenched with water. Products were extracted with dichloromethane, and the organic layer was washed with water and dried over magnesium sulfate. The solvent was removed under a reduced pressure, and the crude product was purified with silica gel column chromatography (eluent: CH_2Cl_2/acetone/methanol=100:5:1).

4.4.1. *N*-Acetyl-*N*-methyl-2-methoxycarbonylbenzenesulfenamide (6a). Yield 48%; colorless crystal with mp 106–107°C (from hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 2.29 (3H, s), 3.29 (3H, s), 3.96 (3H, s), 7.07 (1H, dd, J=8.2, 0.9 Hz), 7.27 (1H, ddd, J=7.9, 7.3, 0.9 Hz), 7.58 (1H, ddd, J=8.2, 7.3, 1.5 Hz), 8.10 (1H, dd, J=7.9, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 38.9, 52.5, 121.1, 123.9, 125.0, 131.7, 133.7, 144.5, 167.0, 176.8; IR (KBr) 1705, 1669, 1279, 745 cm^{-1}; Anal. calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85. Found: C, 55.22; H, 5.38; N, 5.85.

4.4.2. *N*-Acetyl-*N*-methyl-2-nitrobenzenesulfenamide (6b). Yield 74%; yellow crystal with mp 117.5–118.5°C (from ethyl acetate–hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 2.31 (3H, s), 3.31 (3H, s), 7.19 (1H, d, J=8.2 Hz), 7.42 (1H, t, J=8.2 Hz), 7.72 (1H, td, J=8.2, 1.2 Hz), 8.39 (1H, dd, J=8.2, 1.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 38.8, 122.7, 126.1, 126.5, 135.1, 140.5, 142.6, 176.2; IR (KBr) 1678, 1510, 1337, 1304, 1102, 968, 920, 737 cm^{-1}; Anal. calcd for $C_9H_{10}N_2O_3S$: C, 47.78; H, 4.45; N, 12.38. Found: C, 47.84; H, 4.19; N, 12.30.

4.5. Synthesis of methyl *N*-sulfenylacetimidate 8

To a solution of 2-nitrobenzenesulfenyl chloride (**7**, 189.5 mg, 1.0 mmol) in acetonitrile (20 mL) was added methyl acetimidate hydrochloride (131.5 mg, 1.2 mmol) and triethylamine (303 mg, 3.0 mmol) at room temperature. The mixture was stirred for 2 h and the solvent was removed under a reduced pressure. The crude product was purified with silica gel column chromatography (eluent: CH_2Cl_2/hexane=2:1).

4.5.1. Methyl *N*-(2-nitrobenzenesulfenyl)acetimidate (8). Yield 48%; yellow crystal with mp 103–103.5°C (from hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 2.24 (3H, s), 3.87 (3H, s), 7.26 (1H, ddd, J=8.5, 7.0, 1.2 Hz), 7.66 (1H, ddd, J=8.5, 7.0, 1.2 Hz), 8.32 (2H, dt, J=8.5, 1.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.5, 53.6, 124.1, 125.4, 125.5, 133.9, 141.7, 142.0, 163.2; IR (KBr) 1644, 1591, 1499, 1273, 1042, 893, 733 cm^{-1}; Anal. calcd for $C_9H_{10}N_2O_3S$: C, 47.78; H, 4.45; N, 12.38. Found: C, 48.00; H, 4.22; N, 12.09.

References

1. (a) Miura, Y.; Katsura, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn* **1978**, *51*, 3004–3007. (b) Harpp, D. N.; Mullins, D. F.; Steliou, K.; Triassi, I. *J. Org. Chem.* **1979**, *44*, 4196–4197. (c) Koval', I. V.; Oleinik, T. G.; Kremlev, M. M. *Zh. Org. Khim.* **1980**, *16*, 633–636, *J. Org. Chem. USSR (Engl. Transl.)* **1980**, *16*, 553; *Chem. Abstr.* **1980**, *93*, 71232h. (d) Miura, Y.; Shibata, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn* **1986**, *59*, 3291–3292.
2. (a) Pel'kis, N. P.; Karabanov, Y. V.; Borisenko, V. P.; Levchenko, E. S. *Fiziol. Akt. Veshch.* **1984**, *16*, 47–49, *Chem. Abstr.* **1985**, *103*, 18314k. (b) Craine, L.; Raban, M. *Chem. Rev.* **1989**, *89*, 689–712.
3. For references on synthesis of *N*-acylarenesulfenamides with sulfenyl chlorides, see: (a) Goerdeler, J.; Doerk, K. *Chem. Ber.* **1962**, *95*, 389–393. (b) Dubinina, T. N.; Levchenko, E. S.; Zabolotnaya, T. G. *Zh. Org. Khim.* **1982**, *18*, 162–168, *J. Org. Chem. USSR (Engl. Transl.)* **1982**, *18*, 143–148; *Chem. Abstr.* **1982**, *96*, 162244s. (c) See: Ref. 1.
4. Kharasch, N.; Potempa, S. J.; Wehrmeister, H. L. *Chem. Rev.* **1946**, *39*, 269–332.
5. Recently, we have synthesized many arenesulfenamides with a chlorine-free procedure: (a) Shimizu, M.; Kikumoto, H.; Konakahara, T.; Gama, Y.; Shibuya, I. *Heterocycles* **1999**, *51*, 3005–3012. (b) Shimizu, M.; Takagi, T.; Shibakami, M.; Gama, Y.; Shibuya, I. *Heterocycles* **2000**, *53*, 2803–2808. (c) Shimizu, M.; Sugano, Y.; Konakahara, T.; Gama, Y.; Shibuya, I. *Tetrahedron* **2002**, *58*, 3779–3783.
6. (a) Zincke, Th.; Röse, H. *Ann.* **1914**, *406*, 103–126. (b) Carr, E. L.; Smith, Jr. G. E. P.; Alliger, G. *J. Org. Chem.* **1949**, *14*, 921–934.
7. (a) Ignatov, V. A.; Akchurina, R. A.; Volkov, I. V.; Pirogov, P. A. *Zh. Obshch. Khim.* **1977**, *47*, 1096–1103, *J. Gen. Chem. USSR (Engl. Transl.)* **1977**, *47*, 1004–1010. (b) See: Refs. 2(b) and 6(b).
8. (a) Bonner, W. A.; McNamee, P. I. *J. Org. Chem.* **1961**, *26*, 2554–2555. (b) Guo, J.; Wu, J.; Siuzdak, G.; Finn, M. G. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1755–1758. (c)

Johnson, II., D. C.; Widlanski, T. S. *Tetrahedron Lett.* **2001**, *42*, 3677–3679.

9. (a) Iwataki, I. *Bull. Chem. Soc. Jpn* **1972**, *45*, 3572–3579. (b) Kamijo, T.; Yamamoto, R.; Harada, H.; Iizuka, K. *Chem. Pharm. Bull.* **1982**, *30*, 4242–4244. (c) Calmes, M.; Daunis, J.; Jacquier, R.; Verducci, J. *Tetrahedron* **1987**, *43*, 2285–2292. (d) Suwinski, J.; Walczak, K. *Pol. J. Chem.* **1994**, *68*, 675–681, *Chem. Abstr.* **1994**, *121*, 255714v. (e) Myers, T. G.; Thummel, K. E.; Kalhorn, T. F.; Nelson, S. D. *J. Med. Chem.* **1994**, *37*, 860–867.
10. X-Ray crystallographic analysis was carried out on a Rigaku AFC7R diffractometer using a rotating anode with graphite monochromated Mo Kα radiation (λ=0.7107 Å). Crystal data for **4a**: $C_{10}H_{11}NO_3S$, M=225.26, monoclinic, space group $P2_1/a$, a=8.791(2), b=8.188(2), c=14.896(1) Å, α=90°, β=92.122(8)°, γ=90°, V=1071.5(2) Å^3, T=173.2 K, Z=4, D_c=1.396 g cm^{-3}, μ=0.288 mm^{-1}, goodness of fit=1.433, $R1$ [$I>2\sigma(I)$]=0.0283, $wR2$=0.1045 (all data). Selected bond distances (Å) and angles (°) are shown as follows: S(1)–N(1) 1.695(1), S(1)–C(1) 1.784(1), O(3)–C(9) 1.226(1), N(1)–C(9) 1.360(2), N(1)–S(1)–C(1) 101.00(5), S(1)–N(1)–C(9) 122.00(8), O(3)–C(9)–N(1) 122.0(1), N(1)–C(9)–C(10) 115.43(10). Atomic coordinates, other bond lengths, and other angles and the other important parameters have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication, CCDC No. 186164. Copies of this information can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1233-336033 or e-mail: deposit@ccdc.cam.ac.uk).
11. Bryce, M. R.; Taylor, P. C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3225–3235.
12. Gordon, E. M.; Pluščec, J. *J. Org. Chem.* **1979**, *44*, 1218–1221.
13. Sayo, H.; Mori, K.; Michida, T. *Chem. Pharm. Bull.* **1979**, *27*, 351–356.