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N-(Arylsulphonyl)tetrahydropyridinium Salts: Intermediates for Multi-ring Heterocycles. Part 1. Synthesis of Hexahydropyrido[1,2-*b*][1,2,4]-benzothiadiazine Dioxides[1]

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N-(Arylsulphonyl)tetrahydropyridinium salts were obtained regiospecifically and in high yield by smooth triflate-assisted decarbonylation of the corresponding *N*-(arylsulphonyl)piperidine-2-carboxylic acid chlorides at room temperature. These synthons were converted into the nitroamines, which reductively cyclocondensed to give the new 9-substituted tricyclic azacycles, hexahydropyrido[1,2-*b*][1,2,4]benzothiadiazine 6,6-dioxides.

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The use of iminium ions as intermediates in the synthesis of polycyclic heterocycles either *via* nucleophilic additions,[2] [3 + 2],[3,4] [4 + 2],[5] or 1,3-dipolar cycloadditions,[6] or *via* intramolecular trapping of the iminium ions by electron-rich aromatic nuclei[7] continue to attract conspicuous attention. Earlier we reported[8] the use of silver trifluoromethanesulphonate (silver triflate)[9] as a reagent for the generation of *N*-(arylsulphonyl)pyrrolinium salts at room temperature. We also demonstrated the usefulness of the iminium salts in the synthesis of a variety of novel tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2,4]benzothiadiazine 5,5-dioxides.[10] In connection with our continuing interest in the triflate-assisted decarbonylation reactions of cyclic amino acid chlorides, it seemed appropriate, therefore, to explore the generation of the six-membered analogues: *N*-(arylsulphonyl)tetrahydropyridinium salts. These compounds should be powerful synthons for the preparation of several well known functionalised piperidine alkaloids. We now record their utility in the construction of multi-ring heterocycles such as the new hexahydropyrido[1,2-*b*][1,2,4]benzothiadiazines (**21**)–(**25**).

The therapeutic utility of the 1,2,4-benzothiadiazine dioxides as potent diuretics,[11] hypotensives,[11] anticonvulsants,[12] and tranquilising agents has been widely recognised. In fact, 1,2,4-benzothiadiazines with the 3,4-double bond saturated are well known to be considerably more active than their unsaturated analogues.[13] This therefore gives promise for the new compounds reported here. Despite their potential clinical success, there has been no report on the synthesis of the hexahydropyrido[1,2,4]benzothiadiazines. Apart from a patent by Griot[12] on the synthesis and biological activities of some related seven-membered analogues, azepino[1,2,-*b*][1,2,4]-benzothiadiazine dioxides, no report of the title compounds has appeared in the literature.

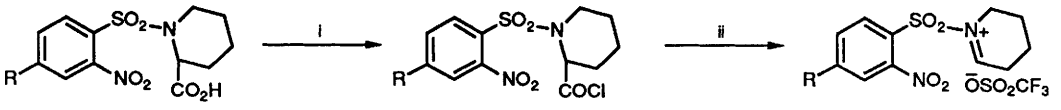
In continuation of our studies in developing the use of the readily generated endocyclic iminium ions as synthons in the regiospecific synthesis of *N*-heterocycles, we decided to extend the reaction to the preparation of the unknown hexahydropyrido[1,2,4]benzothiadiazine dioxides using our readily occurring nucleophilic amino addition to the corresponding readily generated *N*-(arylsulphonyl)tetrahydropyridinium ion, followed by a nucleophilic-electrophilic *exo-tet* cyclocondensation process.

The starting acid chlorides were prepared by condensation of the appropriately substituted 2-nitrobenzenesulphonyl chloride with piperidine-2-carboxylic acid and cold treatment of the resulting new acid adducts (**1**)–(**5**) with thionyl chloride or oxalyl dichloride (Scheme 1).

The decarbonylation reaction of the resulting *N*-(arylsulphonyl)piperidine-2-carboxylic acid chlorides (**6**)–(**10**) on reaction with silver trifluoromethanesulphonate (1.1 mol equiv.) in dichloromethane solution proceeded at room temperature with copious evolution of carbon monoxide. It provided the desired iminium salts (**11**)–(**15**) in excellent yield. As previously suggested[8–10] for the reactions of the *N*-(substituted)pyrrolidine acid chlorides, we also suggest that the decarbonylation of these six-membered analogues proceeds in a parallel manner to the route proposed by Effenberger and Epple[14] for non-aromatic acyl chlorides and therefore proceeds *via* a mixed anhydride[15] intermediate as in Scheme 2.

On quenching with either anhydrous ethylamine or ammonia, the iminium salts were then smoothly converted into the nitroamines (**16**)–(**20**). Interestingly, relatively high and even quantitative yields of the nitroamines were obtained in this instance. No nucleophilic attack at the SO_2 moiety as previously reported by us[8] for the *N*-(arylsulphonyl)pyrolidinium salts was observed.

The mass spectra of the nitroamines consistently gave weak molecular ions but abundant $M - 16$ or $M - 44$ peaks due to loss of NH_2 or NHEt. Thus cleavage at the α-carbon was the major fragmentation process. After this cleavage, it then became difficult to discern clear trends in the fragmentation pattern of the compounds, except for abundant 2-nitrobenzenesulphonyl ions.



(**1**) – (**5**) (**6**) – (**10**) (**11**) – (**15**)

(**1**) R = H (**4**) R = Me
(**2**) R = OMe (**5**) R = CF_3
(**3**) R = OEt

(**6**) R = H (**9**) R = Me
(**7**) R = OMe (**10**) R = CF_3
(**8**) R = OEt

(**11**) R = H (**14**) R = Me
(**12**) R = OMe (**15**) R = CF_3
(**13**) R = OEt

Scheme 1. *Reagents and conditions:* i, $SOCl_2$ or $(COCl)_2$; ii, CF_3SO_3Ag–CH_2Cl_2, room temperature.

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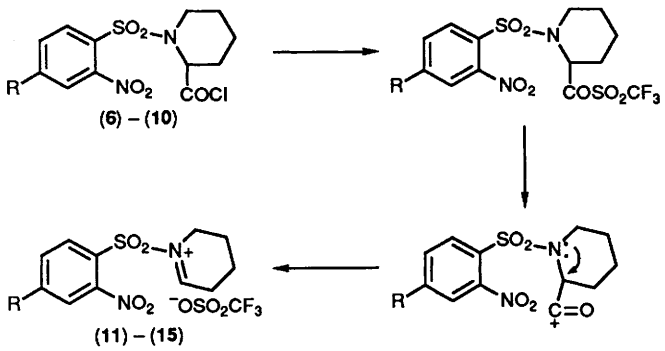


Scheme 2. Mechanism of reaction, of the acid chlorides (**6**)–(**10**) to give the salts (**11**)–(**15**).

The appropriately substituted nitroamines were then subjected to catalytic hydrogen-transfer reductive conditions[16] to give the correspondong diamines quantitatively as oils. These diamines on reflux in acetic or trifluoroacetic acid (TFA) gave the respective 9-substituted hexahydropyrido[1,2-*b*][1,2,4]-benzothiadiazines 6,6-dioxide in >80% yield (Scheme 3). Alternatively, the nitroamines were heated with iron dust in acetic acid as reported earlier by us,[8] to obtain the aforementioned cyclocondensation products. No *N*-ethyl compounds were isolated from the cyclocondensation of compound (**19**).[17]

The use of the *N*-(arylsulphonyl)tetrahydropyridinium salts in the construction of other multi-ring *N*-azacycles, for example as heterodienophile synthons for the synthesis of indolizidine or quinolizidine skeletons, is under active investigation.

Experimental

For general experimental details, see ref. 10. The nitrobenzenesulphonyl chlorides were either obtained commercially or were prepared by chlorine oxidation of the corresponding disulphides.

N-(4-*Substituted*-2-*nitrophenylsulphonyl*)*piperidine*-2-*carboxylic Acids* (**1**)–(**5**).—The appropriate arenesulphonyl chloride (5 mmol) was dissolved in tetrahydrofuran (10 cm^3). A solution of piperidine-2-carboxylic acid (5.1 mmol) in ethanolic potassium carbonate (10 cm^3) was added dropwise and then the mixture was refluxed for 1 h. The mixture was brought to pH 4 with dil. HCl. Solvents were evaporated off and the residue was taken up in dichloromethane. The organic layer was dried and evaporated. The following acids were thus prepared:

N-(2-*Nitrophenylsulphonyl*)*piperidine*-2-*carboxylic acid* (**1**) was obtained as off-white needles after recrystallisation ($CHCl_3$–light petroleum) (80%) m.p. 158–159 °C (Found: C, 47.0; H, 4.6; N, 8.25. $C_{12}H_{14}N_2O_6S$ requires C, 46.27; H, 4.87; N, 8.53%); ν_{max} 1 710 (CO_2H), 1 520 (NO_2), 1 350, and 1 100 cm^{-1} (SO_2N); $\delta(CDCl_3)$ 1.6 (4 H, m), 2.2 (2 H, m), 3.7 (2 H, t), 4.8 (1 H, m, base proton), 7.5 (1 H, br, collapses with D_2O), 7.7 (2 H), and 8.1 (2 H, ArH); *m*/*z* 269 (100%, $M^+ - 45$), 186, 128, and 83.

N-(4-*Methoxy*-2-*nitrophenylsulphonyl*)*piperidine*-2-*carboxylic acid* (**2**) was obtained as prisms from ethanol (82%), m.p. 138–139 °C (Found: C, 45.1; H, 4.55, N, 8.0. $C_{13}H_{16}N_2O_7S$ requires C, 45.34; H, 4.65; N, 8.13%); ν_{max} 1 725 (CO_2H), 1 540, 1 350, 1 250, and 1 120 cm^{-1}; $\delta(CDCl_3)$ 1.64 (4 H, m), 3.41 (2 H, m), 3.65 (2 H, m), 3.94 (3 H, s), 4.7 (1 H), 7.18 (2 H, d), and 8.0 (1 H, d, ArH); *m*/*z* 299 (100%, $M^+ - 45$).

N-(4-*Ethoxy*-2-*nitrophenylsulphonyl*)*piperidine*-2-*carboxylic acid* (**3**) was recrystallised from ethanol to give light-brown prisms (73%), m.p. 140–141 °C (Found: C, 46.8; H, 5.0; N, 7.7. $C_{14}H_{18}O_7S$ requires C, 46.92; H, 5.02; N, 7.82%); ν_{max} 1 720, 1 600, 1 535 (NO_2), 1 360, 1 170 (SO_2N), 1 235, and 1 045 cm^{-1}; $\delta(CDCl_3)$ 1.42 (4 H, m), 1.78 (2 H, m), 3.5 (2 H, dd), 4.2 (2 H, q), 4.6 (2 H, m), 4.7 (1 H, base proton, NCH), 7.17 (2 H, m), and 8.0 (1 H, d, *J* 9.53 Hz); *m*/*z* 358 (M^+), 313 (100%, $M^+ - 45$), 280, and 230 (68.7%).

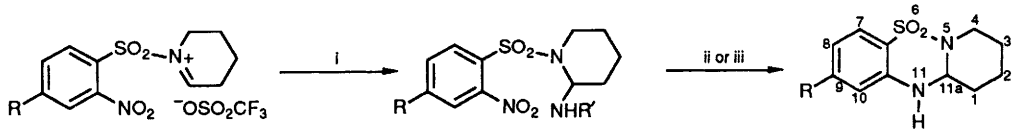
N-(4-*Methyl*-2-*nitrophenylsulphonyl*)*piperidine*-2-*carboxylic acid* (**4**) was obtained as beige microcrystals (69%), m.p. 169–170 °C (Found: C, 46.3; H, 4.7; N, 8.81. $C_{13}H_{16}N_2O_6S$ requires C, 45.85; H, 4.45; N, 8.91%); ν_{max} 1 700, 1 610, 1 550, 1 360, and 1 180 cm^{-1}; $\delta(CDCl_3)$ 1.39 (4 H, m), 1.48 (2 H, m), 2.49 (3 H, s), 3.60 (2 H, dd), 4.54 (1 H, br, exchangeable with D_2O), 4.71 (1 H, d, *J* 4.9 Hz), 7.47 (2 H, d, *J* 10.36 Hz), and 7.95 (1 H, d, *J* 7.96 Hz); *m*/*z* 328 (M^+), 283 (100%, $M^+ - 45$), and 200 (44.9%).

N-(2-*Nitro*-4-*trifluoromethylphenylsulphonyl*)*piperidine*-2-*carboxylic acid* (**5**) was obtained as red needles from light petroleum (97%), m.p. 80–81 °C (Found: C, 40.5; H, 3.3; N, 7.1. $C_{13}H_{13}F_3N_2O_6S$ requires C, 40.83; H, 3.40; N, 7.33%); ν_{max} 1 710, 1 590, 1 520, 1 350, and 1 110 cm^{-1}; $\delta(CDCl_3)$ 4.4 (4 H, m), 2.1 (2 H, m), 3.6 (2 H, t), 4.7 (1 H, q), 7.8 (2 H), and 8.4 (1 H, ArH); *m*/*z* 337 (100%, $M^+ - 45$), 254, 207, 188, 161, and 83.

N-(4-*Substituted*-2-*nitrophenylsulphonyl*)*piperidine*-2-*acid Chlorides* (**6**)–(**10**).—The acid adducts (**1**)–(**5**) (10 mmol) were each treated with an excess of purified thionyl chloride or oxalyl dichloride in refluxing benzene to give the corresponding acid chlorides as off-white, fuming oils or waxy solids, ν_{max} 1 795 (COCl), 1 350, and 1 150 cm^{-1}.

2-*Amino*-N-(4-*substituted*-2-*nitrophenylsulphonyl*)*piperidines* (**16**)–(**20**).—Recrystallised silver triflate (10 mmol) was added to dry dichloromethane (50 cm^3) solutions of each of the acid chlorides (**6**)–(**10**). An immediate and vigorous effervescence ensued. The mixture was further stirred at room temperature for 1.5 h. Cooled, anhydrous ethylamine or conc. ammonia (as appropriate) was slowly injected into the mixture, which was then set aside for 2 h. Filtration of the mixture was followed by appropriate work-up as described for each compound below:

2-*Amino*-N-(2-*Nitrophenylsulphonyl*)*piperidine* (**16**) was obtained as yellow plates after flash chromatography of the filtrate (78%), m.p. 108–111 °C (Found: C, 46.7; H, 5.0; N, 14.3. $C_{11}H_{15}N_3O_4S$ requires C, 46.31; H, 5.26; N, 14.74%); ν_{max} 3 400, 3 300 (NH str), 1 600, 1 540, 1 370, and 1 150 cm^{-1}



(**11**) R = H
(**12**) R = OMe
(**13**) R = OEt
(**14**) R = Me
(**15**) R = CF_3

(**16**) R = H, R′ = H
(**17**) R = OMe, R′ = H
(**18**) R = OEt, R′ = H
(**19**) R = Me, R′ = Et
(**20**) R = CF_3, R′ = H

(**21**) R = H
(**22**) R = OMe
(**23**) R = OEt
(**24**) R = Me
(**25**) R = CF_3

Scheme 3. *Reagents:* i, anhydrous $EtNH_2$ or conc. NH_3; ii, cyclohexene, Pd/C, EtOH; iii, TFA or CH_3CO_2H/Fe.

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(SO_2N); δ($CDCl_3$) 1.5 (4 H, m), 1.8 (2 H, m), 3.4 (2 H, m), 4.6 (1 H, NCHN), 5.6 (2 H, br, collapsed with D_2O), 7.8 (3 H, m, ArH), and 8.1 (1 H); *m/z* 269 (100%, $M^+ - 16$), 186, 123, and 84.

2-Amino-*N*-(4-methoxy-2-nitrophenylsulphonyl)piperidine (**17**) was obtained as a brown solid after MPLC of the filtrate (light petroleum–chloroform) in 76% yield, m.p. 140–141 °C; ν_{max} 3 410, 3 320 (NH), 1 600, 1 540, 1 370, 1 170 (SO_2), and 1 050 cm^{-1}; δ($CDCl_3$) 1.45 (4 H, m), 1.80 (2 H, m), 3.3 (2 H, m), 3.7 (1 H, q, base proton), 3.9 (3 H, s, OMe), 4.3 (2 H, NH, collapsed with D_2O), 7.18 (2 H, m, ArH), and 7.9 (1 H, ArH); *m/z* 299 (100%, $M^+ - 16$), 216 (70.2), 152 (38.9), and 83.

2-Amino-*N*-(4-ethoxy-2-nitrophenylsulphonyl)piperidine (**18**) was obtained as light-brown microcrystals after chromatography of the filtrate in 73% yield, m.p. 120–121 °C; ν_{max} 3 450, 3 310 (NH), 1 650, 1 535, 1 368, 1 170, and 1 170, and 1 060 cm^{-1} (OCHR); δ($CDCl_3$) 1.2 (3 H, t), 1.5–2.0 (6 H, m), 3.0 (4 H, m, NH_2 and NCH_2), 4.1 (2 H, q), 5.6 (1 H, t, NCHN), 7.2 (2 H, m, ArH), and 7.9 (1 H, ArH); *m/z* 313 (100%, $M^+ - 16$), 230 (78), 166 (42), and 83.

2-Ethylamino-*N*-(4-methyl-2-nitrophenylsulphonyl)piperidine (**19**) was obtained in 80% yield as light-yellow prisms after MPLC (light petroleum–chloroform), m.p. 144–145 °C; ν_{max} 3 380 (NH), 1 600, 1 540, 1 360, 1 340, and 1 165 cm^{-1}; δ[$(CD_3)_2CO$] 0.8–1.4 (6 H, m), 1.7 (3 H, t), 2.2 (3 H, s), 2.6 (2 H, m), 3.2 (2 H, m), 4.8 (1 H, m), 5.2 (1 H, NH), 7.3–7.6 (2 H, ArH), and 7.8 (1 H, ArH); *m/z* 327, 5.02% M^+), 283 (100, $M^+ - NHCH_2CH_3$), 200 (81), 136 (46), and 83.

2-*Amino*-N-(2-*nitro*-4-*trifluoromethylphenylsulphonyl*)*piperidine* (**20**) was obtained as brown microcrystals after chromatography (80%), m.p. 88–89 °C (Found: C, 40.5; H, 3.8; N, 11.6, $C_{12}H_{14}F_3N_3O_4S$ requires C, 40.79, H, 3.96; N, 11.89%); ν_{max} 3 343br (NH), 1 613, 1 568, 1 524, 1 323, 1 125, and 1 084 cm^{-1}; δ[$(CD_3)_2CO$] 0.6–1.1 (6 H, m), 2.6 (2 H, m), 4.2 (1 H, m), 4.8 (1 H, NH, collapsed with D_2O), 5.3 (1 H, NH, exchangeable with D_2O), 6.8 (1 H, ArH), and 7.2 and 7.7 (2 H, ArH); *m/z* 337 (100%, $M^+ - 16$), 254, 240, 185, and 83.

Reductive Cyclisation of the Nitroamines.—To each of the nitroamines (**16**)–(**20**) (5 mmol) was added glacial acetic acid (40 cm^3). Diethyl ether-washed finely divided iron filings (2.0 g) were slowly added. The mixture was refluxed for 8–12 h before being poured on ice. The mixture was filtered and the filtrate was extracted several times with hot dichloromethane. The combined organic extract was successively washed with aq. 5% $NaHCO_3$ and brine, then dried. Evaporation of solvents gave the desired products. Alternatively, the nitroamines underwent selective hydrogen-transfer reductions as reported earlier.[16] The following compounds were thus prepared:

1,2,3,4,11,11a-*Hexahydropyrido*[1,2-b][1,2,4]*benzothiadiazine* 6,6-*dioxide* (**21**) was obtained as an off-white solid after recrystallisation ($CHCl_3$–MeOH) (70%), m.p. 140 °C (decomp.) (Found: C, 55.2; H, 5.7; N, 12.0; S, 13.1. $C_{11}H_{14}N_2O_2S$ requires C, 55.46; H, 5.88; N, 11.76; S, 13.44%); *m/z* 238 (100%, M^+), 211 (45), 182 (64), 173 (86, $M^+ - SO_2H$), 146 (8.28, $M^+ - SO_2H - HCN$), and 93 (81); ν_{max} 3 337, 1 650, 1 570, 1 360, and 1 160 cm^{-1} (SO_2N); δ($CDCl_3$) 1.2 (4 H, m), 2.1 (2 H, m), 3.3 (2 H, m, CH_2N), 5.1 (1 H, t, NCHN), 7.1 (3 H, m, ArH), 8.2 (1 H, dd, *J* 9.3 Hz, ArH), and 9.1 (1 H, br s, NH).

1,2,3,4,11,11a-*Hexahydro*-9-*methoxypyrido*[1,2-b][1,2,4]-*benzothiadiazine* 6,6-*dioxide* (**22**) was obtained as white plates after recrystallisation ($CHCl_3$–MeOH) (69%), m.p. 146–147 °C; *m/z* M^+, 267.988 (Found: C, 53.7; H, 5.7; N, 10.45; S, 11.7. $C_{12}H_{16}N_2O_3S$ requires C, 53.73; H, 5.97; N, 10.45; S, 11.94%); ν_{max}(KBr) 3 400 (NH), 1 620, 1 330, 1 160, 1 025, and 750 cm^{-1}; δ[$(CD_3)_2SO$] 1.0–1.9 (6 H, m), 3.2 (3 H, s), 3.8–4.0 (3 H, m), 6.6 (2 H, m, ArH), 7.5 (1 H, dd, ArH), and 9.2 (1 H, br, NH).

9-*Ethoxy*-1,2,3,4,11,11a-*hexahydropyrido*[1,2-b][1,2,4]*benzothiadiazine* 6,6-*dioxide* (**23**) was obtained as light-brown microcrystals (68%) after MPLC with light petroleum–chloroform, m.p. 150–151 °C (Found: C, 55.2; H, 6.4; N, 9.9; S, 11.2. $C_{13}H_{18}N_2O_3S$ requires C, 55.31; H, 6.38; N, 9.92; S, 11.35%); *m/z* 282 (100%, M^+), 255 (47, $M^+ - HCN$), 217 (86, $M^+ - SO_2H$), and 190 (8.2, $M - SO_2H - HCN$); δ[$(CD_3)_2CO$] 1.42 (4 H, m), 1.78 (3 H, m), 3.5 (2 H, dd), 4.2 (2 H, q), 4.6 (2 H, m), 4.7 (1 H, t, NCHN), 7.12 (2 H, m, ArH), 8.0 (1 H, d, *J* 9.53 Hz, ArH), and 9.1 (1 H, NH).

1,2,3,4,11,11a-*Hexahydro*-9-*methylpyrido*[1,2-b][1,2,4]-*benzothiadiazine* 6,6-*dioxide* (**24**) was obtained as beige crystals after recrystallisation of the residue obtained on evaporation ($CHCl_3$–MeOH) (78%), m.p. 171–172 °C (Found: C, 57.0; H, 6.4; N, 11.2; S, 12.9. $C_{12}H_{16}N_2O_2S$ requires C, 57.14; H, 6.35; N, 11.11; S, 12.69%); *m/z* 252 (100%, M^+), 225 (41, $M^+ - HCN$), 199 (16.8), 187 (81, $M^+ - SO_2H$), 169 (4.2), and 160 (9.6, $M^+ - SO_2H - HCN$); ν_{max} 3 368, 1 680, 1 607, 1 317, and 1 151 cm^{-1}; δ($CDCl_3$) 1.1–1.8 (6 H, m), 2.7 (3 H, s, Me), 3.27 (1 H, br), 4.6 (1 H, t), 6.6 (2 H, m, ArH), 7.6 (1 H, dd, ArH), and 9.5 (1 H, NH).

1,2,3,4,11,11a-*Hexahydro*-9-*trifluoromethylpyrido*[1,2-b]-[1,2,4]*benzothiadiazine* 6,6-*dioxide* (**25**) was obtained as light-brown needles after recrystallisation ($CHCl_3$–MeOH) (78%), m.p. 120–121 °C (Found: C, 47.3; H, 4.55; N, 9.5; S, 10.6. $C_{12}H_{13}F_3N_2O_2S$ requires C, 47.06; H, 4.25; N, 9.15; S, 10.46%), *m/z* 306 (100%, M^+), 279 (33), 250 (23), 241 (37), 223 (22), 214 (16, $M^+ - SO_2H - HCN$); ν_{max}(KBr) 3 350, 1 600, 1 350, and 1 145 cm^{-1}; δ[$(CD_3)_2SO$] 0.6–1.1 (6 H, m), 2.6 (2 H, m), 4.8 (1 H, t), 6.8 (1 H, ArH), 7.1 (1 H, ArH), 7.4 (1 H, ArH), and 9.3 (1 H, NH).

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