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Research Article

Synthesis of deuterated 4, 4′-diaminodiphenylsulfone (Dapsone) and related analogs

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Summary

A general scheme for the synthesis of 4, 4′-diaminodiphenylsulfone-d_5 (Dapsone) from aniline-d_5 is described. The method may have general application and the preparation of the related analogs, 4, 4′-dimethylamino-diphenyl sulfone from aniline-d_5 and 4, 4′-dimethoxydiphenyl sulfone from phenol-d_5, is also described. Copyright © 2002 John Wiley & Sons, Ltd.

Key Words: 4, 4′-diaminophenyl sulfone; Dapsone; deuterated; synthesis

Introduction

4, 4′-Diaminodiphenyl sulfone (Dapsone, **1a**, Figure 1) was originally marketed as an anti-leprosy agent, but has seen a resurgence in use in the last few years as it has become widely used in the treatment of *Pneumocystis carinii* pneumonia in AIDS patients. At therapeutic concentrations, **1a** is metabolized by cytochrome P450 2C9 to a hydroxylamine metabolite (**1d**).[1] Recent work in our laboratory has also

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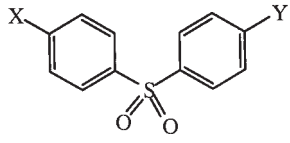

1

a X = Y = NH_2 **e** X = Y = H
b X = Y = $NHCH_3$ **f** X = Y = CH_3
c X = Y = OCH_3 **g** X = NH_2 Y = NO_2
d X = NH_2, Y = NHOH

Figure 1. Structure of Dapsone (1a), analogs prepared (1a–c), and analogs of biochemical interest

demonstrated that **1a** can 'activate' the metabolism of other CYP2C9 substrates such as flurbiprofen and naproxen.[2, 3] Co-incubation of either flurbiprofen or naproxen with **1a** results in a simultaneous increase in V_{max} and decrease in K_m for the metabolism of flurbiprofen or naproxen. In addition, several related compounds including diphenyl sulfone (**1e**) and 4, 4′-dimethyldiphenyl sulfone (**1f**) have the same affect. Interestingly, 4-amino-4′-nitrodiphenyl sulfone (**1g**), a close analog of **1a**, has just the opposite affect and inhibits the metabolism of flurbiprofen.

These findings have led to the hypothesis that both **1a** and another substrate (e.g. flurbiprofen or naproxen) can be present simultaneously in the enzyme active site.[3] This simultaneous binding of **1a** and flurbiprofen to the active site increases the likelihood that binding will be productive due to steric constraints imposed by **1a**, and the active site itself, on flurbiprofen. To test this hypothesis we need to be able to prepare **1a** analogs with the non-exchangeable protons replaced by deuterium. The resulting protio and deuterio compounds **1** are to be used for an isotope edited NMR experiment,[4] the success of which depends on the isotopic purity of **1**.

Results and discussion

Initially, we examined noble metal catalyzed exchange between **1a** and deuterium gas[5] D_2O and various catalysts[6, 7] or DCl.[8] These efforts were met with limited success. Under some of these conditions, partial exchange was observed but we were unable to achieve the high level of

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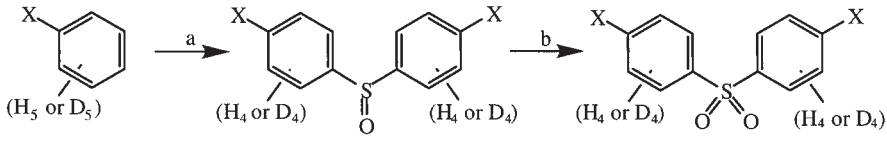

2a X = NHAc
2b X = N(CH$_3$)Ac
2c X = OCH$_3$

3a X = NHAc
3b X = N(CH$_3$)Ac
3c X = OCH$_3$

4a X = NHAc
4b X = N(CH$_3$)Ac
1c X = OCH$_3$

Figure 2. Generalized synthetic scheme used to prepare either protio or deutero Dapsone and analogs (1a–c)

isotopic purity we required. Therefore, we explored an alternative approach based on commercially available deuterated materials such as aniline-d_5.

In the case of **1a**, the synthetic scheme shown in Figure 2 was followed.[9] Thus, aniline or aniline-d_5 was acetylated to protect the amino group (**2a**) and then treated with $SOCl_2$ and $AlCl_3$ in carbon disulfide to give the sulfoxide **3a** which was then oxidized with 30% H_2O_2 in acetic acid to give the sulfone **4a**. Finally, **4a** was deprotected in hydrochloric acid (deuterium chloride for deuterium labeled compounds) to give **1a**. The isotopic purity of each of the intermediates and products were determined by mass spectrometry and this indicated that there was little or no H–D exchange in any of the reactions used to prepare **1a** (1% or less). H–D exchange was possible due to the acidic nature of all of the reaction conditions used to convert aniline (aniline-d_5) to **1a**.

The generality of the scheme used here was examined by preparing two additional analogs of **1a**, the *N*-methylamino derivative **1b** and the methoxy derivative **1c**. Compound **1b** requires the preparation of deuterated *N*-methylaniline **2b**, which can be obtained by methylation of deuterated aniline. Compound **1c** requires the preparation of deuterated anisole **2c**, which can be obtained from methylation of phenol-d_5. These intermediates were successfully coupled to form the sulfoxide (**3b** and **3c**) and oxidized to the corresponding sulfone (**4b** and **1c**).

Compounds **4a** and **4b** were then hydrolyzed to remove the acetyl protecting group and yielded **1a** and **1b**, respectively. Depending on the substrate, some modification of the reaction conditions for the coupling step was required. In particular, due to the greater reactivity of the starting material for **2c**, the amount of $AlCl_3$ used, reaction time and

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temperature had to be significantly decreased. However, other than this problem, the approach presented here provides a general route to these compounds and will aid both metabolic and NMR investigations.

Experimental

Unless otherwise noted, solvents and reagents were used as received (Aldrich Chem. Co.). Acetic anhydride and acetic acid were distilled prior to use. A Varian Gemini 2000, 300 MHz broadband spectrometer was used to measure NMR spectra, IR were measured on a Perkin-Elmer 782 spectrophotometer, UV were measured on a Beckman DU 640 spectrophotometer, and MS on a Micromass ZMD. ^{1}H, ^{2}H NMR and ^{13}C NMR data were recorded. However, multiplicities, coupling constants and chemical shifts are reported for the ^{1}H product only as, in all cases the chemical shift data for the protio and deutero derivatives were identical. All procedures described apply to either unlabeled substrates or to deuterium containing substrates. All reactions were monitored by TLC (silica gel, $MeOH/CH_2Cl_2$).

N-acetylaniline **2a**

Aniline (1 g, 10.8 mmol) or aniline-d_5 was added to acetic anhydride (2.5 ml) and the mixture heated at reflux (30 min). After cooling to room temperature (r.t.), water (3 ml) was added and heated at reflux (10 min), cooled to r.t., diluted with water to precipitate the product which was filtered, washed with water, recrystallized from water and dried to yield **2a** (1.14 g, 85%). mp 112–114°C; IR (KBr) cm^{-1} 3300, 3170, 3090, 1665, 1430, 1320; ^{1}H NMR (dmso-d_6) δ ppm 2.06 (3H, s), 7.10 (1H, t, $J=7.2$ Hz) 7.26 (2H, t, $J=7.2$ Hz) 7.64 (2H, d, $J=7.2$ Hz), 9.929 (1H, bs); ^{13}C NMR (dmso-d_6) δ ppm 24.63, 119.6, 123.6, 129.3, 140.0, 168.9; UV (MeOH) λ_{max} (log ε) 241 (3.80); MS m/z (intensity) 136 (100), 94 (80). **2a-d_5**: mp 114–116°C; MS m/z (intensity) 141 (100), 99 (67); isotopic purity 99%.

4,4′-Di-N-acetylaminodiphenyl sulfoxide **3a**

To a suspension of **2a** (0.59 g, 4.37 mmol) in CS_2 (6 ml) was added $SOCl_2$ (0.24 g, 2.02 mmol), and $AlCl_3$ (1.1 g, 8.24 mmol). After the initial reaction subsided, the mixture was heated at reflux (6 h), cooled

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to r.t. and quenched by the addition of ammonium chloride (10%, 10 ml). The mixture was filtered, the filter cake was then washed with water. The filter cake was then dissolved in THF, filtered, and the filtrate concentrated in vacuo to yield **3a** (480 mg, 70%). mp 281–283°C; IR (KBr) cm^{-1} 3305, 3250, 3160, 3080, 1670, 1515, 1400, 1300, 1280, 1050; ^1H NMR (dmso-d_6) δ ppm 2.04 (6H, s), 7.57 (4H, d, $J = 8.7$ Hz), 7.71 (4H, d, $J = 8.7$ Hz), 10.21 (2H, bs); ^{13}C NMR (dmso-d_6) δ ppm 24.20, 119.3, 125.0, 139.1, 141.6, 168.7; UV (MeOH) λ_{max} (log ε) 271 (3.95), 254 (s) (3.88); MS m/z (intensity) 317 (40), 303 (20), 136 (100). **3a-d_8**: mp 289–291°C; MS m/z (intensity) 325 (19), 139 (100); isotopic purity 99%.

4, 4′-Di-N-acetylaminodiphenyl sulfone **4a**

To a suspension of **3a** (400 mg, 1.27 mmol) in glacial acetic acid (5 ml) was added H_2O_2 (30%, 0.5 ml) and the mixture was allowed to stand for 3 h at r.t., heated at 50°C for 2 h and then at reflux until the mixture was homogenous. The mixture was then cooled to r.t., H_2O_2 (30%, 0.3 ml) added, stored overnight at 4°C and the mixture concentrated *in vacuo* to yield **4a** (294 mg, 70%). mp 275–278°C; IR (KBr) cm^{-1} 3335, 3250, 3100, 1682, 1585, 1525, 1405, 1315, 1294, 1150; ^1H NMR (dmso-d_6) δ ppm 2.06 (6H, s), 7.76 (4H, d, $J = 8.8$ Hz), 7.84 (4H, d, $J = 8.8$ Hz), 10.38 (2H, bs); ^{13}C NMR (dmso-d_6) δ ppm 22.4, 117.1, 126.6, 133.3, 141.8, 167.3; UV (MeOH) λ_{max} (log ε) 283 (4.19), 255 (4.05); MS m/z (intensity) 333 (12), 291 (100), 259 (21), 198 (22), 156 (24), 124 (23). **4a-d_8** mp 280–283°C; MS m/z (intensity) 341 (15), 299 (100); isotopic purity 98%.

4, 4′-Diaminodiphenyl sulfone (Dapsone) **1a**

A suspension of **4a** (200 mg, 0.6 mmol) in 10% HCl (2 ml) or DCl with **4a-d_8**, was heated at reflux (1.5 h), decolorizing carbon added, then heated at reflux an additional 1 h, filtered while still hot and cooled to r.t. Sodium hydroxide (10%) was then added to adjust the pH to 14 and the resulting precipitate isolated by filtration, recrystallized from water/MeOH, and dried *in vacuo* to yield **1a** (120 mg, 80%). mp 174–6°C (lit 175–6°C); IR (KBr) cm^{-1} 3480, 3300, 3275, 1630, 1570, 1275, 1213, 1135; ^1H NMR (dmso-d_6) δ ppm 5.97 (4H, bs), 6.57 (4H, d, $J = 8.4$ Hz), 7.44 (4H, d, $J = 8.4$ Hz); ^{13}C NMR (dmso-d_6) δ ppm 113.5, 128.8, 129.2, 153.4; UV (MeOH) λ_{max} (log ε) 295 (4.67), 260 (4.45); MS m/z

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(intensity) 249 (100), 156 (50), 149 (32). **1a-d_8** mp 196–198°C; MS m/z (intensity) 257 (100), 160 (73); isotopic purity 98%.

N-acetyl-N-methylaniline ***2b***

N-methylaniline (1 g, 9.35 mmol) was treated exactly as described for **2a** to give **2b** (1.24 g, 89%). mp 97–99°C; IR (KBr) cm^{-1} 3050, 2940, 1640, 1600, 1500, 1420, 1385, 1140; ^1H NMR (dmso-d_6) δ ppm 1.75 (3H, s), 3.33 (3H, s), 7.32 (2H, d, $J = 7.8$ Hz), 7.44 (3H, m); ^{13}C NMR (dmso-d_6) δ ppm 22.85, 37.18, 127.7, 128.0, 130.2, 145.0, 169.7; UV (MeOH) λ_{max} (log ε) 228 (3.85); MS m/z (intensity) 150 (100), 108 (5). **2b-d_5** mp 96–98°C; MS m/z (intensity) 155 (100), 113 (6); isotopic purity 99%.

4, 4′-Di-(N-acetyl-N-methylamino)diphenyl sulfoxide **3b**

Compound **2b** (0.65 g, 4.4 mmol) was treated as described for **2a** to yield **3b** (550 mg, 77%). mp 269–271°C; IR (KBr) cm^{-1} 3160, 3080,1672,1515,1405,1310, 1285,1050; ^1H NMR (dmso-d_6) δ ppm 1.75 (6H, s), 2.03 (6H, s), 7.50 (4H, d, $J = 8.7$ Hz), 7.72 (4H, d, $J = 8.7$ Hz), 10.11 (2H, bs); ^{13}C NMR (dmso-d_6) δ ppm 23.00, 38.20, 120.6, 126.5, 141.1, 143.2, 169.5; UV (MeOH) λ_{max} (log ε) 270 (4.00), 254 (s) (3.90); MS m/z (intensity) 345 (30), 330 (25), 149 (100). **3b-d_8** mp 276–278°C; MS m/z (intensity) 353 (35) 338 (20), 153 (100); isotopic purity 99%.

4, 4′-Di-(N-acetyl-N-methylamino)diphenyl sulfone **4b**

A suspension of **3b** (500 mg, 1.45 mmol) was treated as described for **3a** to yield **4b** (390 mg, 75%). mp 265–266°C; IR (KBr) cm^{-1} 3106,1690,1585,1400,1305,1290,1145; ^1H NMR (dmso-d_6) δ ppm 2.05 (6H, s), 7.77 (4H, d, $J = 8.8$ Hz), 7.86 (4H, d, $J = 8.8$ Hz), 10.30 (2H, bs); ^{13}C NMR (dmso-d_6) δ ppm 18.4, 23.3, 118.4, 128.0, 135.1, 142.8, 169.1; UV (MeOH) λ_{max} (log ε) 285 (4.20), 259 (4.15); MS m/z (intensity) 361 (12), 319 (100), 198 (22), 134 (23). **3b-d_8** mp 271–274°C; MS m/z (intensity) 369 (10), 327 (100), 174 (60); isotopic purity 98%.

4, 4′-Diaminomethyldiphenyl sulfone **1b**

A suspension of **4b** (200 mg, 0.55 mmol) as described for **4a** to yield **1b** (115 mg, 75%). mp 162–164°C; IR (KBr) cm^{-1} 3470,3320, 3075,

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1625,1575,1250,1145; ^{1}H NMR (dmso-d_6) δ ppm 3.01 (6H, s), 5.90 (4H, bs), 6.65 (4H, d, $J = 8.4$ Hz), 7.34 (4H, d, $J = 8.4$ Hz); ^{13}C NMR (dmso-d_6) δ ppm 38.02, 114.0, 130.1, 129.9, 151.3; UV (MeOH) λ_{max} (log ε) 295 (4.70), 263 (4.50); MS m/z (intensity) 277 (100), 170 (50), 163 (32). **1b-d_8** mp 190–192°C; MS m/z (intensity) 285 (100), 171 (20); isotopic purity 98%.

4, 4′-Dimethoxydiphenyl sulfoxide **3c**

To a solution of **2c** (1 g, 9.26 mmol) in CS_2 (12 ml) was added $SOCl_2$ (0.55 g, 4.63 mmol) and $AlCl_3$ (1.36 g, 10.2 mmol). The mixture was stirred at r.t. (1 h) and quenched by the addition of ammonium chloride (10%, 30 ml). The reaction mixture was then extracted with CH_2Cl_2 (3 × 30 ml), the combined extracts dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield **3c** as a light yellow oil (0.97 g, 80%). IR (neat) cm^{-1} 2995,2980,2890,1590,1495,1261, 1178,1065,1030; ^{1}H NMR (dmso-d_6) δ ppm 3.80 (6H, s), 7.23 (4H, d, $J = 8.7$ Hz), 7.64 (4H, d, $J = 8.7$ Hz); ^{13}C NMR (dmso-d_6) δ ppm 56.72, 117.8, 133.4, 134.0, 163.5; UV (MeOH) λ_{max} (log ε) 258 (3.82); MS m/z (intensity) 263 (12), 246 (44), 232 (40), 231 (38), 85 (100). **3c-d_8**, light yellow oil; MS m/z (intensity) 271 (10), 254 (35), 240 (47), 111 (100); isotopic purity 98%.

4, 4′-Dimethoxydiphenyl sulfone **1c**

Compound **3c** (0.90 g, 3.7 mmol) was treated as described for **3a** to yield **1c** (0.88 g, 85%) as a viscous oil. IR (KBr) cm^{-1} 3300, 3105,3063, 2980,2845,1595,1500,1255,1145,1020; ^{1}H NMR (dmso-d_6) δ ppm 3.74 (6H, s), 7.04 (4H, d, $J = 8.4$ Hz), 7.77 (4H, d, $J = 8.4$); ^{13}C NMR (dmso-d_6) δ ppm 56.38, 115.5, 129.9, 132.3, 163.5; UV (MeOH) λ_{max} (log ε) 259 (5.01), 234 (5.00); MS m/z (intensity) 279 (100), 171 (6), 87 (3). **1c-d_8**, viscous oil; MS m/z (intensity) 287 (100), 175 (10); isotopic purity 97%.

Conclusions

A method for the preparation of deuterated 4, 4′-diaminodiphenyl sulfone (**1a**, Dapsone) has been devised. The method is based on using commercially available deuterated materials such as aniline-d_5 and

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phenol-d_5 which can be obtained inexpensively (according to the catalog of the Cambridge Isotope Laboratories, Inc., the cost of 1 g of aniline (ring-D_5; 99%) is 45 dollars and 1 g of phenol (ring-D_5; 98%) is 85 dollars). Using the method described, virtually no loss in isotopic purity is observed (1% or less). The method will likely have broader applicability as two additional analogs of **1a**, 4,4′-*N*-methylaminophenyl sulfone and 4,4′-methoxyphenyl sulfone, were readily prepared with only minor changes in the reaction conditions. Finally, the high isotopic purity of **1** will permit the use of this material in isotope edited NMR experiments and may find additional uses in metabolism studies.

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