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Mechanism of the pinacol–pinacolone rearrangement of 2,3-di-(3-pyridyl)-2,3-butanediol in sulfuric acid

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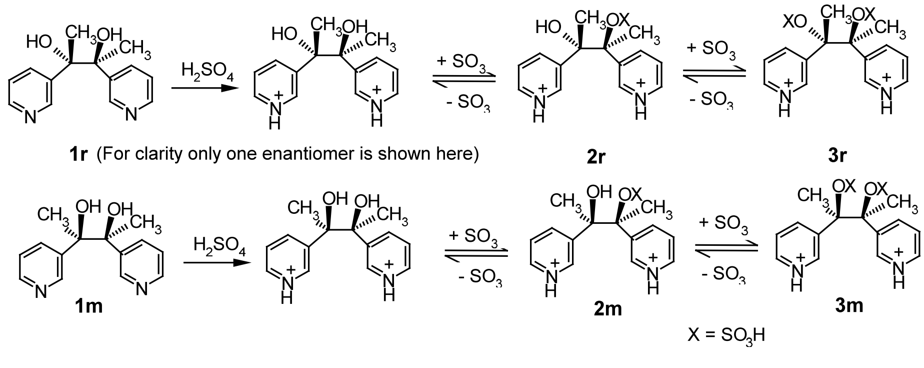
Abstract—The reaction of 2,3-di-(3-pyridyl)-2,3-butanediol (**1**) in H_2SO_4 was studied. It was found that the *meso* and racemic forms give mono- and bis-SO_3 addition products, which rearrange to a ketone (Metopirone®) and two other major by-products. The formation of SO_3 addition products and a marked increase in reaction rates with greater amount of SO_3 suggest an alternate mechanism involving sulfonyloxy leaving groups. © 2002 Elsevier Science Ltd. All rights reserved.

The pinacol rearrangement is a well-known reaction in which a glycol dehydrates and rearranges under acidic conditions to give ketonic products. In the case of symmetrical glycols, the reaction has been extensively studied to compare the migratory aptitudes of different substituents by measuring the relative amounts of pinacolones obtained in the reaction.[1]

The classical acid-catalyzed pinacol rearrangement mechanism proceeds by protonation of a hydroxyl group and subsequent loss of water, which leads to formation of a carbocation. The driving force for a 1,2-shift comes from the formation of a more stable carbocation in which the positive charge can be delocalized on the remaining hydroxyl oxygen.

The 2,3-di-(3-pyridyl) pinacol requires extremely forcing conditions (H_2SO_4/SO_3) to effect the rearrangement.[2] Since the pyridine nitrogens are fully protonated under the strong acid conditions, we wondered if the presence of the two positive charges altered the mechanism to avoid an unlikely intermediate containing a triple cation.

We first isolated pure *meso* (**1m**) and *racemic* (**1r**) forms of the pinacol so that their reactivities could be studied individually.[3] Upon dissolving **1r** in concentrated H_2SO_4, we observed by HPLC the immediate formation of mono-SO_3 addition product (**2r**) and di-SO_3 addition product (**3r**) existing in equilibrium with **1r** (Scheme 1).



Scheme 1.

Keywords: pinacol–pinacolone rearrangement; methyl migration; pyridinyl migration.

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The same equilibrium was observed between **1m**, **2m**, and **3m**.

All the SO_3-addition products could be isolated as their ammonium salts for characterization.[4] Addition of SO_3 at the hydroxyl positions was unambiguously confirmed by ^1H and ^{13}C NMR data.[5] Dissolving **2r** or **3r** in concentrated H_2SO_4 gave essentially the same equilibrium mixture obtained from **1r**. The equilibrium concentrations were established immediately and did not change over time. Adding SO_3 in the form of fuming H_2SO_4 shifted the equilibrium towards **3r** or **3m**, whereas adding water favored **1r** or **1m** (Table 1).

We also studied the rearrangement reactions of **1r** and **1m** using HPLC.[6] We found that in concentrated H_2SO_4 there were three reaction pathways (Scheme 2). In addition to the methyl and pyridinyl rearrangement products (**4** and **5**), we also observed a small amount of product **6** presumably from an elimination pathway, which rapidly underwent a second elimination to give diene **7**. Ketone **4** was extremely stable under the reaction conditions, and did not react further even when subjected to heat or the addition of fuming H_2SO_4. Compounds **5** and **7** were reasonably stable in concentrated H_2SO_4, but after several hours the formation of SO_3-addition products could be observed. Ketone **5** eventually formed **10** which was stable in concentrated H_2SO_4 but would reacted further to give **11** upon the addition of fuming H_2SO_4. Diene **7** appeared to undergo a cycloaddition reaction with SO_3 to form **8** which would then undergo hydrolysis and SO_3 addition to give a single isomer of **9**.[7] We used HPLC measurements to compare the initial rates of formation of **4**, **5**, and **7** (Table 1). We also wondered if interconversion between *racemic* and *meso* forms occurs in concentrated H_2SO_4. Although interconversion did occur, we found that it was relatively slow. After about 25% of **1r** had reacted in concentrated H_2SO_4, the remaining pinacol was a mixture of 95% **1r** and 5% **1m**. The same ratio was observed in 85:15 concentrated H_2SO_4/water at 65°C when measured at the same extent of reaction.

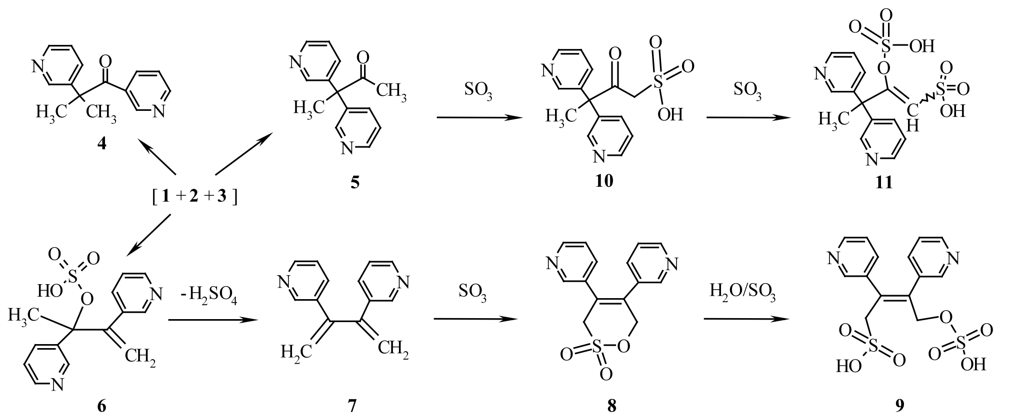
The rearrangement rate dependence on the amount of SO_3 that is present in the reaction mixture, and the

Table 1. Reactions of **1r** and **1m** in H_2SO_4, $H_2SO_4+SO_3$, and $H_2SO_4+\text{water}$

	Solvent composition			Equilibrium ratio at 23°C			Initial rate of formation (%/h)			
Starting material	% Fuming H_2SO_4	% Conc. H_2SO_4	% Water	**1r**	**2r**	**3r**	Rxn. temp. (°C)	**4**	**5**	**7**
1r	–	100	–	55	43	2	23	5.7	0.29	1.4
2r	–	100	–	55	44	1	23	–	–	–
3r	–	100	–	52	46	2	23	–	–	–
1r	50	50	–	5	11	84	23	10.6	0.77	3.5[a]
1r	–	95	5	83	17	0.4	23	0.20	0.0075	0.13
1r	–	90	10	95	5	–	65	2.2	[b]	2.6
1r	–	85	15	99	1	–	65	0.12	[b]	0.23
1r	–	80	20	100	0.2	–	65	0.0048	[b]	0.0095
1r	–	75	25	100	0.1	–	95	0.17	0.010	0.37
				1m	**2m**	**3m**				
1m	–	100	–	50	48	2	23	0.50	0.95	0.76
1m	50	50	–	2	9	89	23	0.90	2.1	2.0[a]
1m	–	95	5	93	7	–	–	–	–	–

[a] Value is based on concentration of **9**, which forms rapidly from **7** under these conditions.

[b] The reaction was discontinued before the concentration of **5** was measurable by HPLC.

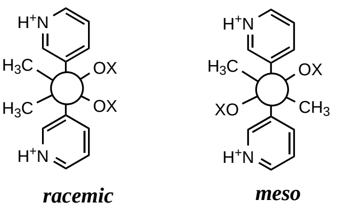


Scheme 2.

presence of substantial amounts of mono- and bis-SO_3 addition products clearly suggests that the major mechanism does not involve carbocation formation as in simple pinacols. The rapid formation of **4** from **1r** (methyl migration) is by far the most facile of all the reactions observed. A possible explanation can be seen in Fig. 1, which shows the conformations in which the two protonated pyridyl groups are anti in order to minimise steric repulsion. In such a conformation, the *racemic* form has a methyl group *anti* to a potential leaving group. This arrangement allows the methyl group to migrate by a concerted mechanism. For the *meso* form, neither the methyl nor the protonated pyridyl group are *anti* to a potential leaving group. This explains the 10 times lower reactivity of **1m**, which would have to adopt a less favored conformation to allow the concerted mechanism to operate. A concerted mechanism would be advantageous because forming a carbocation intermediate would be highly unfavorable in a dipyridyl pinacol, which already contains two positively charged pyridyl nitrogens under the acidic reaction conditions.

Another interesting result is the drastic change in reaction rates when water or SO_3 was added. The reaction rates increased by a factor of about two when switching from concentrated H_2SO_4 to 50:50 concentrated H_2SO_4/fuming H_2SO_4. On the other hand, adding only 5% water to concentrated H_2SO_4 caused the rates to decrease by a factor of about 30. Increasing water from 10 to 20% caused two orders of magnitude further reduction in rate. A change in the ratio of rearrangement to elimination product also occurred (Fig. 2). This suggests that the mechanism may change as the amount of SO_3 increases, and a much more reactive species is formed that can undergo the rearrangement reaction through a more facile concerted mechanism. This change occurs in the range of 5 to 15% of added water, which coincides with the appearance of the monosulfates **2r** and **2m** and disulfates **3r** and **3m**.

Interestingly, under the conditions which give fastest rearrangement (50:50 concentrated H_2SO_4/fuming H_2SO_4) almost all of the pinacol is in the form of a mono- or disulfate and 5% or less is present as 'free' pinacol. We suspect that **2** or **3** may be involved as the reactive species, or formed from an even more reactive species such as an extended sulfonic anhydride[8] containing a further activated leaving group, but which is not stable enough to survive the addition of water during isolation and HPLC analysis.



racemic *meso*

Figure 1.

References

1. Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley-Interscience, 2001; pp. 1396–1398.
2. Bencze, W.; Allen, M. *J. Am. Chem. Soc.* **1959**, *81*, 4015–4018.
3. Pure **1r** and **1m** pinacols were separated from material containing approximately 70% **1r** and 30% **1m** as follows: 150 g of the mixed pinacol was stirred in 100 mL of water and 2 equiv. of conc. HCl was added (~100 mL) to obtain initially a clear solution, which became cloudy. After stirring overnight, the solids were filtered off. Compound **1m** could be obtained from the solids by redissolving the HCl salt in water (150 mL) and EtOH (100 mL), then precipitating the free base by slowly adding 20% NaOH (~55 mL) at 70°C to pH 10, then cooling and filtering. The solids were recrystallized from MeOH to give 28.6 g (19%) of **1m** (>99% pure), mp 252–255°C; ^1H NMR (300 MHz, DMSO) δ 8.64 (2H, bd, $J=1.9$ Hz), 8.40 (2H, dd, $J=4.7$, 1.9 Hz), 7.82 (2H, dt, $J=8.1$, 1.9 Hz), 7.29 (2H, ddd, $J=8.1$, 4.7, 0.6 Hz), 5.31 (2H, s), 1.27 (6H, s); ^{13}C NMR (75.5 MHz, DMSO) δ 149.1, 147.4, 141.9, 135.3, 122.3, 76.1, 25.0. ESI-MS calcd for $C_{14}H_{16}N_2O_2$ 244.12, found $[M+H]^+$ 245.

   Similarly, **1r** could be precipitated from the HCl filtrate by adding EtOH (180 mL) and slowly adding 20% NaOH (~145 mL) at 70°C to pH 10, then cooling and filtering. Recrystallization from EtOH gave 93.5 g (62%) of **1r** (>99% pure), mp 232–235°C; ^1H NMR (300 MHz, DMSO) δ 8.24 (2H, dd, $J=4.7$, 1.9 Hz), 8.21 (2H, bd,

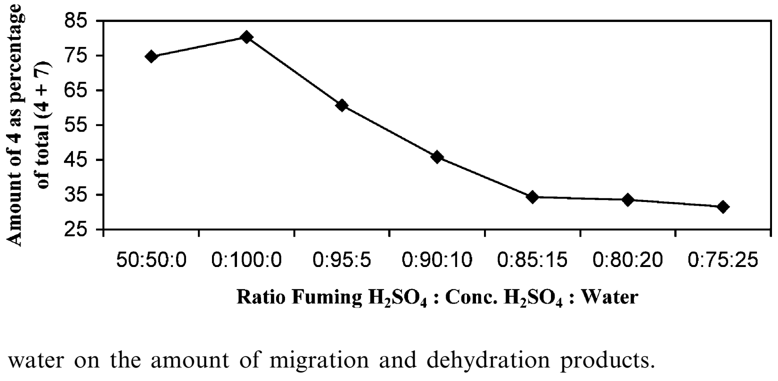
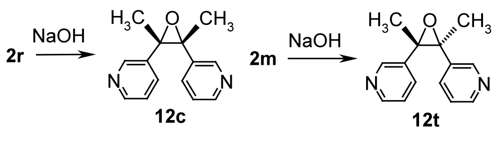


Figure 2. Effect of adding water on the amount of migration and dehydration products.

$J=1.9$ Hz), 7.35 (2H, dt, $J=8.1$, 1.9 Hz), 7.07 (2H, ddd, $J=8.1$, 4.7, 0.6 Hz), 5.42 (2H, s), 1.61 (6H, s); ^{13}C NMR (75.5 MHz, DMSO) δ 148.6, 147.1, 141.5, 134.7, 121.8, 76.1, 24.5. ESI-MS calcd for $C_{14}H_{16}N_2O_2$ 244.12, found [M+H]$^+$ 245.

4. Pure samples of the monosulfates and disulfates were obtained by adding 7.0 g of **1r** or **1m** to a cooled mixture of 50 g of concentrated H_2SO_4 and 50 g of fuming H_2SO_4. The reaction was added to stirred ice water (800 g). The mixture was brought to pH 9–10 with 30% aq. NH_3 ($\sim$150 mL). After evaporation of water, the solids were triturated in EtOH (200 mL) and the ammonium sulfate filtered off. The filtrate was evaporated, and pure samples were isolated using a reversed-phase column (C-18 silica gel, 0–20% MeCN/water). Since only the purest fractions were isolated, yields are not reported. Drying under high vacuum gave glassy solids which appeared by ^{1}H NMR in all cases to be partially hydrated ammonium and inner salt mixtures typically showing an ammonium signal at about 7.1 ppm (t, $J=49$ Hz) and a broad signal at about 3.5–4.5 ppm. These signals are not included in the spectral data below. **2r**: ^{1}H NMR (300 MHz, DMSO) δ 8.29–8.26 (2H, m), 8.11 (2H, d, $J=2.1$ Hz), 7.39–7.31 (2H, m), 7.15–7.11 (2H, m), 5.68 (1H, s), 2.03 (3H, s), 1.66 (3H, s); ^{13}C NMR (75.5 MHz, DMSO) δ 148.1, 147.6, 146.7, 145.7, 141.3, 140.1, 136.9, 135.7, 122.1, 121.9, 84.4, 76.2, 24.6, 18.8. ESI-MS calcd for $C_{14}H_{16}N_2O_5S$: 324.08, found [M+H]$^+$ 325. **2m**: ^{1}H NMR (300 MHz, DMSO) δ 8.69 (1H, d, $J=1.9$ Hz), 8.60 (1H, d, $J=1.7$ Hz), 8.44–8.40 (2H, m), 7.94–7.85 (2H, m), 7.36–7.32 (2H, m), 5.37 (1H, s), 1.60 (3H, s), 1.24 (3H, s); ^{13}C NMR (75.5 MHz, DMSO) δ 148.8, 148.5, 147.0, 146.3, 141.8, 139.9, 137.2, 136.0, 122.6, 122.1, 84.4, 75.9, 25.2, 20.0. ESI-MS calcd for $C_{14}H_{16}N_2O_5S$: 324.08, found [M+H]$^+$ 325. **3r**: ^{1}H NMR (300 MHz, DMSO) δ 8.25 (2H, dd, $J=4.9$, 1.7 Hz), 8.06 (2H, d, $J=1.7$ Hz), 7.25 (2H, dt, $J=7.9$, 1.7 Hz), 7.07 (2H, dd, $J=7.9$, 4.9 Hz), 2.05 (6H, s); ^{13}C NMR (75.5 MHz, DMSO) δ 148.3, 146.2, 139.5, 136.6, 121.7, 83.9, 19.1. ESI-MS calcd for $C_{14}H_{16}N_2O_8S_2$: 404.03, found [M+NH$_4$]$^+$ 422, [M+H]$^+$ 405, [MH–SO$_3$]$^+$ 325. **3m**: ^{1}H NMR (300 MHz, DMSO) δ 8.67 (2H, d, 1.7 Hz), 8.48 (2H, dd, $J=5.1$, 1.7 Hz), 8.02 (2H, dt, $J=7.9$, 1.7 Hz), 7.47 (2H, dd, $J=7.9$, 5.1 Hz), 1.60 (6H, s); ^{13}C NMR (75.5 MHz, DMSO) δ 147.5, 145.2, 140.1, 138.9, 122.8, 83.6, 19.9. ESI-MS calcd for $C_{14}H_{16}N_2O_8S_2$: 404.03, found [M+NH$_4$]$^+$ 422, [M+H]$^+$ 405, [MH–SO$_3$]$^+$ 325.
5. The position of SO_3 addition was indicated by: (a) significant changes in the ^{13}C NMR chemical shifts of the tertiary carbons; (b) the presence of only one hydroxyl signal in the ^{1}H NMR spectra of **2** and the complete absence of hydroxyl signals in **3**, and (c) the reaction of **2r** and **2m** in 0.5 M NaOH which cleanly forms the *cis* and *trans* epoxides while compounds **1** and **3** did not react under NaOH conditions.

   12c: Mp 40–46°C, ^{1}H NMR (300 MHz, DMSO) δ 8.41 (2H, dd, $J=2.3$, 0.8 Hz), 8.27 (2H, dd, $J=4.7$, 1.9 Hz), 7.40 (2H, ddd, $J=7.9$, 2.3, 1.9 Hz), 7.01 (2H, ddd, $J=7.9$, 4.7, 0.8 Hz), 1.85 (6H, s); ^{13}C NMR (75.5 MHz, DMSO) δ 148.1, 147.8, 135.8, 133.6, 122.5, 66.1, 20.8. ESI-MS calcd for $C_{14}H_{14}N_2O$ 226.11, found [M+H]$^+$ 227. **12t**: Mp 107–109°C, ^{1}H NMR (300 MHz, DMSO) δ 8.71 (2H, dd, $J=2.3$, 0.9 Hz), 8.59 (2H, dd, $J=4.7$, 1.7 Hz), 7.66 (2H, ddd, $J=7.9$, 2.3, 1.7 Hz), 7.34 (2H, ddd, $J=7.9$, 4.7, 0.9 Hz), 1.33 (6H, s); ^{13}C NMR (75.5 MHz, DMSO) δ 148.9, 148.0, 136.2, 133.9, 123.2, 66.5, 21.5. ESI-MS calcd for $C_{14}H_{14}N_2O$ 226.11, found [M+H]$^+$ 227.
6. HPLC conditions: Waters Symmetry C-18 column, 4.6× 250 mm; gradient 0% B to 100% B in 11 min, A=95:5 (v/v) 0.1% NH$_4$OAc/MeCN, B=95:5 (v/v) MeCN/H$_2$O; flow rate, 1.2 mL/min; detection, UV 260 nm. Reaction samples were quenched by adding to rapidly stirred ice cold water, then neutralizing with Na_2HPO_4 before injection. Ret. times (min): **1**, 6.0; **2r**, 5.1; **2m**, 5.4 **3r**, 2.9; **3m**, 3.0; **4**, 8.1; **5**, 7.1; **6**, 5.8 and 6.2; **7**, 8.8; **8**, 7.5; **9**, 3.6; **10**, 5.3, **11**, 4.9. To separate **1r** and **1m**, the gradient was changed to 40% B to 100% B in 10 min, A=95:5 (v/v) 0.1% NH$_4$OAc/MeCN, B=90:10 (v/v) 0.05% HOAc/ MeCN. Ret. times (min): **1r**, 4.3; **1m**, 4.6.
7. To obtain samples of compounds **4**–**7** and **9** for characterization, 9.2 g of **1m** was stirred in concentrated H_2SO_4 (100 mL) for 70 h. The reaction was intentionally stopped before completion so that samples of intermediates could be isolated as well as final products. HPLC before workup indicated that about 10% of **1m** and **2m** remained unreacted, and the major products were **4** (20%), **5** (29%), **7** (15%), and **9** (21%) with minor amounts of **6** and **10** (<3%). After quenching on ice and neutralization of acid with 30% NH$_3$, compounds **4**, **5**, and **7** were extracted into toluene and isolated using chromatography (C-18 silica gel, 5–50% MeCN). Compounds **4**, **5** and **7** are known[2] and showed satisfactory spectral analysis. Isolated yields were 1.9 g (22%), 3.2 g (38%), and 1.0 g (13%), respectively. The water-soluble compounds **6** and **9** were chromatographed separately (C-18 silica gel, 0 to 30% MeCN) and samples isolated as ammonium salts. Compound **6** appeared by ^{1}H NMR to exist as major and minor isomers, which could be partially separated by chromatography and were isolated in amounts of only about 50 and 30 mg, respectively. Compound **9** (1.8 g) was isolated from the purest fractions and another estimated 0.4 g was present in impure fractions, giving a total yield of about 14%. Samples of compounds **10** and **11** were prepared separately by the action of H_2SO_4+fuming H_2SO_4 on compound **5** and were isolated by reversed-phase chromatography. Compound **11** appeared by ^{1}H NMR and HPLC to be only one isomer.

   Analytical data. **6**: Major isomer; ^{1}H NMR (300 MHz, D$_2$O) δ 8.29 (2H, brd, $J=4.9$ Hz), 8.18 (2H, bd, $J=1.9$ Hz), 7.76–7.70 (2H, m), 7.38–7.32 (2H, m), 5.11 (2H, s), 2.36 (3H, s). ESI-MS calcd for $C_{14}H_{14}N_2O_4S$: 306.07, found [M+H]$^+$ 307. Minor isomer; ^{1}H NMR (300 MHz, D$_2$O) δ 8.58–8.54 (4H, m), 7.99–792 (2H, m), 7.62–7.55 (2H, m), 4.61 (2H, s), 1.96 (3H, s). ESI-MS calcd for $C_{14}H_{14}N_2O_4S$: 306.07, found [M+H]$^+$ 307. **8** could not be isolated and was identified by HPLC-MS analysis of reaction mixtures; ESI-MS calcd for $C_{14}H_{12}N_2O_3S$: 288.06, found [M+H]$^+$ 289. **9**: ^{1}H NMR (300 MHz, D$_2$O) δ 8.74–8.63 (4H, bm), 8.23 (1H, dt, $J=8.1$, 1.7 Hz), 8.14 (1H, dt, $J=8.1$, 1.7 Hz), 7.78 (1H, dd, $J=8.1$, 5.3 Hz), 7.73 (1H, dd, $J=8.1$, 5.3 Hz), 4.69 (2H, s), 3.97 (2H, s);

^{13}C NMR (75.5 MHz, D_2O) δ 146.8, 146.7, 146.2, 141.5, 140.6, 136.8, 135.9, 135.5, 134.2, 125.5, 125.1, 69.1, 56.6. ESI-MS calcd for $C_{14}H_{14}N_2O_7S_2$: 386.02, found [M+H]$^+$ 387. **10**: ^{1}H NMR (300 MHz, DMSO) δ 8.49 (2H, bdd, J=4.9, 1.5 Hz), 8.36 (2H, bd, J=2.4 Hz), 7.57 (2H, ddd, J=8.1, 2.4, 1.5 Hz), 7.39 (1H, ddd, J=8.1, 4.9, 0.8 Hz), 3.79 (2H, s), 2.10 (3H, s); ^{13}C NMR (75.5 MHz, DMSO) δ 201.9, 149.1, 147.7, 138.9, 136.2, 123.3, 59.7, 59.0, 24.3. ESI-MS calcd for $C_{14}H_{14}N_2O_4S$: 306.07, found [M+H]$^+$ 307. **11**: ^{1}H NMR (300 MHz, D_2O) δ 8.85 (2H, bd, J=5.7 Hz), 8.77 (2H, bd, J=2.1 Hz), 8.50 (2H, ddd, J=8.3, 2.1, 1.3 Hz), 8.11 (2H, bdd, J=8.3, 5.7 Hz), 5.93 (1H, s), 2.39 (3H, s); ^{13}C NMR (75.5 MHz, DMSO) δ 198.2, 147.4, 142.2, 141.7, 140.9, 127.9, 78.3, 60.9, 25.0. ESI-MS calcd for $C_{14}H_{14}N_2O_7S_2$: 386.02, found [M+H]$^+$ 387, [M+NH_4]$^+$, 404.

8. The existence of pyrosulfates in fuming sulfuric acid is known, see: Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed.; Wiley, New York, 1988; pp. 114–115.