Synthesis of a Novel Bismesoionic Phenylsydnonyl-Münchnone System as an *in-situ* Intermediate Intended for the Preparation of Phenylsydnonyl-Heterocycles

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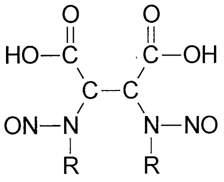
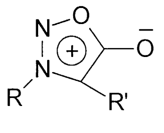
The title bismesoionic system was generated *in-situ* by the treatment of N-(3-phenylsydnonyl-4-carbonyl)-N-substituted amino acid with acid anhydride. The sydnonyl münchnone reacted with DMAD and gave phenylsydnonyl-pyrrole.

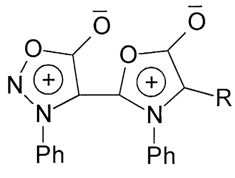
Mesoionic compounds have been extensively studied because of their unique structures, their reactions with unsaturated compounds leading to the formation of different heterocyclic rings, and their pharmaceutical properties.[1] Although a large number of compounds with mono-mesoionic nucleus are known, derivatives containing two positively charged mesoionic nuclei of direct connection are not common. Samples of such bismesoionic system are only found in sydnones, which are synthesized either by cyclodehydration of N,N'-aryl/alkyl-N,N'-dinitroso-α,α'-diamino butanedioic acid (**I**),[2] or by the direct coupling of two appropriately substituted sydnone rings (**II**, R'= PdCl;[3a] HgCl;[3a] Br[3bc]). The bismesoionic system with direct connection between two different mesoionic nuclei is practically unknown. For this reason and the various biological activities of 3-arylsydnonyl heterocycles frequently reported,[4-10] we therefore synthesized the 3-phenylsydnone-münchnone bismesoionic system (**III**) which can be used as a key intermediate in the formation of various sydnonyl-heterocyles via 1,3-dipolar cycloaddition of the active münchnone ring.



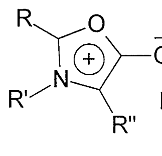
I



II

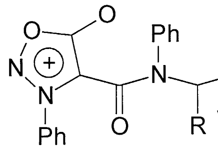


III

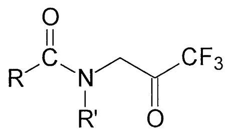


IV

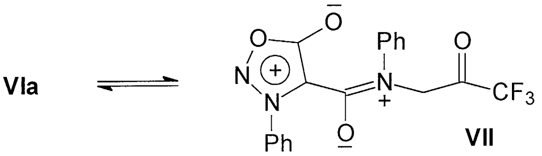
N-phenylglycine and N-phenylalanine have been prepared by coupling aniline with sodium bromoacetate and sodium 2-bromopropionate respectively. The N-(3-phenylsydnonyl-4-carbonyl)-N-phenylgylcine (**Va**)[11] was prepared by the treatment of the readily available phenylsydnone acid chloride (**II**, R=Ph; R'=COCl)[12] with N-phenylglycine, and N-(3-phenylsydnonyl-4-carbonyl)-N-phenylalanine (**Vb**)[13] was similarly obtained from N-phenylalanine. According to the general method in münchnone synthesis,[14] treating **Va** with trifluoroacetic anhydride (TFAA) yielded the anticipated bismesoionic system 2-(3-phenyl-sydnonyl)-3-phenyl-4-trifluoroacetyl-1,3-oxazol-5-one (**III**, R= $COCF_3$), and **Vb** gave the 2-(3-phenylsydnonyl)-3-phenyl-4-methyl-1,3-oxazol-5-one (**III**, R=CH_3). ^{1}H NMR spectra of the *in-situ* products indicated the presence of **III** (R=$COCF_3$; CH_3). **III** (R=$COCF_3$) in TFAA/**d**-acetone solvent mixture showed two aromatic ring proton signals at δ 7.40 and 7.60 ppm at a ratio of 1 : 1; and **III** (R=CH_3) in TFAA/$CDCl_3$ revealed the two aromatic ring protons at δ 7.3-7.8 ppm (two peaks overlapped) and CH_3 protons at δ 2.18 ppm. ^{13}C NMR spectra of **III** (R=$COCF_3$) and **III** (R=CH_3) also supported the structures. The ^{13}C NMR spectrum of **III** (R=$COCF_3$) in TFAA/$CDCl_3$ showed six types of CH carbons, three from each of the two benzene rings, at δ 123.57, 125.86, 129.36, 130.72. 131.37, and 133.98 ppm. There were nine quaternary carbons. Three of them were carbonyl carbons, the sydnone carbonyl carbon at δ 162.27 ppm (carbonyl carbon of 3-phenylsydnone is at δ 168.8 ppm, in deuterated DMSO), the münchnone carbonyl carbon at δ 158.22 ppm, and the carbonyl carbon of the $COCF_3$ at δ 167.30 ppm as a quartet. The other six were at δ 93.07, 98.13, 132.59, 133.19, 141.72, and 116.00 ppm. 116.00 ppm was the CF_3 carbon of the $COCF_3$ group, a quartet overlapped with TFA and TFAA. The ^{13}C NMR of **III** (R = CH_3) in TFAA/$CDCl_3$ showed one CH_3 carbon at δ 8.08 ppm, six CH carbons at δ 134.22, 132.92, 130.63, 130.53, 126.56, and 124.59 ppm, seven quaternary carbons at δ 93.52, 124.83, 130.03, 133.41, 135.23, 151.76, 159.94 ppm. All spectra were in good accordance to the structures of the two sydnone-münchnone compounds. However, isolations of münchnones were not successful, N-(3-phenylsydnonyl-4-carbonyl)-N-trifluoroacetomethyl aniline (**VIa**)[15] was the only product obtained from the reaction of **Va** with TFAA, and no identifiable product was able to be isolated from the reaction of **Vb**. **VIa** was a product formed after hydrolysis of **III** (R=$COCF_3$) by air moisture and followed by subsequent decarboxylation. This transformation of münchnone was first observed and reported in 1979, in which **VIb** was obtained[16] from **IV** (R=EtS; R'=Me; R"=$COCF_3$).



Va R=H
b R=Me

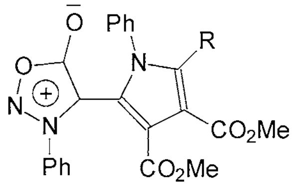


VIa R=3-phenylsydnonyl
R'=Ph
b R=EtS; R'=Me



VIa **VII**

In the ^{1}H NMR spectrum of **VIa**, two types of methylene proton were observed as singlets at δ 4.21 and δ 5.08 ppm, and the proton ratio was 0.7 : 1.3, using 10 aromatic protons as reference. After the addition of D_2O, the signal at 5.08 ppm disappeared, while the signal at 4.21 ppm increased to 2 protons compared with 10 benzene protons. No deuterium exchange was detected. This indicated the existence of tautomerism between **VIa** and **VII**. In the presence of D_2O, formation of D bonds with nitrogen and oxygen occurred in **VIa**, while only with oxygen in **VII**. Thus, it caused a larger decrease in entropy in the case of **VIa**, which became an important factor for its existence as the only tautomer in the presence of D_2O.



VIIIa R=H
b R=Me

By gently refluxing a mixture of **V** in acetic anhydride in the presence of dimethylacetylene dicarboxylate (DMAD), the sydnonyl-pyrrole was formed in good yield, *via* the sydnonyl-münchnone intermediate generated *in-situ*. Thus, **Va** yielded the 3,4-dimethoxycarbonyl-1-phenyl-2-(3-phenylsydnonyl) pyrrole (**VIIIa**)[17] through the cycloaddition reaction of 2-(3-phenylsydnonyl)-3-phenyl-1,3-oxazol-5-one (**III**, R=H) with DMAD, and **Vb** in the same manner gave 5-methyl-3,4-dimethoxycarbonyl-1-phenyl-2-(3-phenylsydnonyl) pyrrole (**VIIIb**)[18] *via* 2-(3-phenylsydnonyl)-3-phenyl-4-methyl-1,3-oxazol-5-one (**III**, R=Me). Reactions with weak diplarophiles such as maleic anhydride, dimethyl maleate, were unsuccessful.

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11 **Va** : mp = 186-187 °C (yield = 60%). ^{1}H NMR (400 MHz, acetone-d_6): δ 4.57 (s, br, 2H); 7.28-7.36 (m, 5H); 7.65-7.80 (m, 5H). IR (cm^{-1}) : 3350-2900 (br); 1759; 1725; 1647; 1596; 1588; 1494; 1474; 1456; 1442. MS (ESI): (m+1)/z 340.1057 (calcd 340.0934).

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13 **Vb** : mp = 165-166 °C (yield = 54%). ^{1}H NMR (400 MHz, acetone-d_6): δ 1.39 (d, 3H; J=7.2 Hz); 4.82 (s, br, 1H); 7.36 (s, 5H); 7.60-7.68 (m, 5H). IR (cm^{-1}) : 3500-3000 (br); 1746; 1734; 1689; 1643; 1594; 1492; 1473; 1453; 1439. MS (ESI): (m+1)/z 354.1132 (calcd 354.1091).

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15 **VIa**, mp = 103-104 °C (yield = 91%). ^{1}H NMR (400 MHz, acetone-d_6): δ 4.21 (s, 0.7H); 5.08 (s, 1.3H); 7.20-7.95 (m, 10H). IR (cm^{-1}) : 3308 (br); 3065; 1758; 1605; 1592; 1494; 1479; 1463; 1453; 1430; 1410. MS (ESI): (m+1)/z 392.0845 (calcd 392.0859).

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17 **VIIIa** : mp = 138-139 °C (yield = 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 1H); 3.83 (s, 3H); 3.84 (s, 3H); 6.97-7.50 (m, 10H). IR (cm^{-1}) : 3137; 2952; 1767; 1733; 1720; 1594; 1529; 1493; 1468; 1456. MS (ESI): (m+1)/z 420.1279 (calcd 420.1197).

18 **VIIIb** : mp = 118-119 °C (yield = 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 3H); 3.79 (s, 3H); 3.85 (s, 3H); 7.20-7.57 (m, 10H). IR (cm^{-1}) : 3065; 3015; 2941; 1747; 1720; 1712; 1495; 1463; 1439; 1418. MS (ESI): (m+1)/z 434.1424 (calcd 434.1352).