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DIRECT CARBOXAMIDATION OF SYDNONES WITH CHLOROSULFONYL ISOCYANATE

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ABSTRACT: Various 4-carboxamido sydnones **2** can be prepared in good yield by reaction of the corresponding 3-substituted sydnones (*cf.* **1**) with chlorosulfonyl isocyanate at room temperature.

Sydnones, *cf.* **1**, undergo a variety of transformations including electrophilic aromatic substitution (at the 4-position, if unsubstituted),[1] cleavage with HCl to form hydrazines[2] or heterocycles[3] and 1,3-dipolar cycloadditions to form pyrazoles or related species.[4] Perhaps the greatest interest in these mesoionic compounds, however, stems from their biological activity; *inter alia* they have shown efficacy as antibacterial,[5] antitumour,[6] and antihypertensive[7] agents.

Recently, in this vein, we required 4-carboxamido-3-arylsydnones (*cf.* **2**) as precursors to analogues of pyrazofurin, an antiviral pyrazole carboxamide.[8] Surprisingly, even though brominations, nitrations and similar processes can be effected readily,[1] no satisfactory, direct route to **2** exists. Previously, such species (*i.e.* **2**) have been prepared in modest yield by abstraction of the sydnone ring proton (in **1**) with BuLi,[9] treatment with CO_2, conversion to the acyl chloride and subsequent reaction with ammonia[10] and by treatment of 4-

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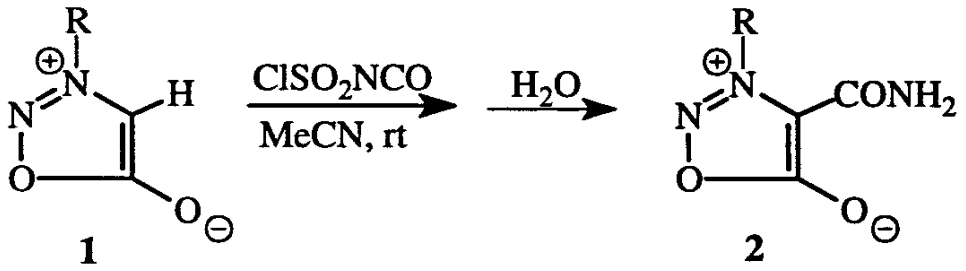
acylsydnones with hydrazoic acid.[11] Both of these methods suffer from considerable disadvantages; in the former, multiple steps lead to a low overall yield and substantial time investment while, in the latter, the use of potentially explosive hydrazoic acid is problematic. We required a direct, preferably one-step, process and we were attracted to reports of amidation of activated heterocycles with chlorosulfonyl isocyanate.[12] Since the sydnone ring is activated towards electrophilic aromatic substitution, this approach seemed viable and, indeed, treatment of various 3-substituted sydnones **1** with chlorosulfonyl isocyanate in acetonitrile at room temperature followed by an aqueous work-up gave moderate to excellent yields of the corresponding 4-carboxamido sydnones **2**.

The reaction is successful in the presence of a variety of functional groups including alkyl (in **1d** and **1e**), arylalkyl (in **1h**), alkoxy (in **1b**), halo (in **1c**), ester (in **1f**) and nitro (in **1g**) moieties. In general, the reaction apparently was unaffected by the nature or position of the substituent, however, when the strongly electron-withdrawing nitro group was present at the *ortho*-position (in **1g**), complete conversion to **2** required a considerable excess of chlorosulfonyl isocyanate and product yields over 55% were not realized.

The identities of the 4-carboxamido sydnones **2** followed from their spectral data, satisfactory microanalysis figures or comparison with authentic samples (for **2a**). For the new compounds (*viz.* **2b-h**) their IR spectra showed the absence of the signature sydnone C-H stretch at ~3150cm^{-1} and the presence of the carboxamido C=O stretch at ~1670 cm^{-1} and NH stretch at ~3400cm^{-1} and ~3100-3300cm^{-1}; indicating that amidation had occurred. In their ^{1}H-NMR spectra, the absence of the sydnone ring proton (usually ~6.5-7 δ) was apparent and the NH_2 group showed 2 signals at ~7.9 δ and 7.2 δ. In their ^{13}C-NMR spectra the amide carbonyl signal appeared at ~156 ppm and, for the 3-aryl examples, a shift of the sydnone C-4 signal to ~103 ppm (from ~95 ppm in **1**) was observed.

No obvious trend in product yield was apparent in the effects of electron-donating or electron-withdrawing groups on the aryl ring, although especially low yields were obtained with the strongly electron withdrawing nitro group.

Overall, we have shown that 4-carboxamido sydnones can be prepared in good to excellent yield using chlorosulfonyl isocyanate. The advantages to this



1 2

Table. Reaction of 3-substituted sydnones with $ClSO_2NCO$

Product	R	Yield [%]	m.p.[°C]
2 a	Ph	79	229-230[a]
b	3-$MeOC_6H_4$	81	175-6
c	4-ClC_6H_4	79	173-5
d	2,3-$Me_2C_6H_3$	72	164-5
e	3,4-$Me_2C_6H_3$	68.5	182-4
f	2-MeO_2C	78	178-9
g	2-NO_2	55	186-8
h	$PhCH_2$	69	158-9

[a]lit.[10] mp 227°C

method over those previously employed are the one-step nature of the process and the resultant higher yields. We plan to study this approach further in order to assess its scope and limitations.

EXPERIMENTAL

Preparation of 4-Carboxamido-3-Substituted Sydnones (2); General Procedure.

To a stirred solution of the sydnone **1** (0.75 mmol) in acetonitrile (3 mL / 100 mg) at 0°C was added chlorosulfonyl isocyanate (0.425 g, 3.00 mmol)

dropwise. After 10 min, the mixture was allowed to warm to room temperature, stirred for a further 1.5 h and poured carefully over ice (*ca.* 15 mL). In a few cases a precipitate was obtained which was collected by filtration, otherwise, the water / acetonitrile was removed *in vacuo* or under a stream of air. The resultant solid was recrystallized from hot ethanol to yield the pure carboxamide **2.**

Preparation of 4-Carboxamido-3-phenylsydnone (2a).

Using 3-phenylsydnone **1a** (0.1215 g) in the general procedure gave the title compound **2a** as colourless needles, 0.122 g (79%); m.p. 229-30°C (lit. m.p.[10] 227°C); IR (KBr) ν 3385, 3149 (NH str.), 1757 (sydnone C=O str.), 1679 (amide C=O str.) cm^{-1} (lit.[11] 3375, 3140, 1750, 1674 cm^{-1}).

Preparation of 4-Carboxamido-3-(3-methoxyphenyl)sydnone (2b).

Using 3-(3-methoxyphenyl)sydnone[13] (0.144 g) in the general procedure gave the title compound **2b** as colourless needles, 0.143 g (81%); m.p. 175-6°C; IR (KBr) ν 3432, 3319 (NH str.), 1774 (sydnone C=O str.), 1686 (amide C=O str.), 1604, 1465, 1257 cm^{-1}; ^{1}H-NMR δ (DMSO-d_6) 3.81 (s, 3H), 7.13 (s, 1H), 7.23-7.57 (m, 4H), 7.80 (s, 1H); ^{13}C-NMR (DMSO-d_6) 55.7 (O<u>C</u>H$_3$), 102.8 (sydnone <u>C</u>-CONH$_2$), 111.6, 117.5, 117.6, 129.9 (aromatic CH's), 135.7, 159.2 (aromatic C's), 156.0 (amide C=O), 166.4 (sydnone C=O) ppm; analysis: calculated for $C_{10}H_9N_3O_4$: C, 51.09; H, 3.83; N, 17.87. Found: C, 51.18; H, 3.88; N, 17.85.

Preparation of 4-Carboxamido-3-(4-chlorophenyl)sydnone (2c)

Using 3-(4-chlorophenyl)sydnone[14] (0.1475 g) in the general procedure gave the title compound **2c** as colourless needles, 0.142 g (79%); m.p. 173-5°C; IR (KBr) ν 3408, 3205 (NH str.), 1752 (sydnone C=O str.), 1671 (amide C=O str.), 832 cm^{-1}; ^{1}H-NMR δ (DMSO-d_6) 7.14 (s, 1H), 7.69-7.81 (dd, 4H), 7.87 (s, 1H); ^{13}C-NMR (DMSO-d_6) 102.9 (sydnone <u>C</u>-CONH$_2$), 127.5, 129.0 (aromatic CH's), 133.4, 136.6 (aromatic C's), 156.0 (amide C=O), 166.1 (sydnone C=O) ppm; analysis: calculated for $C_9H_6ClN_3O_3$: C, 45.09; H, 2.51; N, 17.54. Found: C, 45.20; H, 2.46; N, 17.31.

Preparation of 4-Carboxamido-3-(2,3-dimethylphenyl)sydnone (2d)

Using 3-(2,3-dimethylphenyl)sydnone[15] (0.1425 g) in the general procedure gave the title compound **2d** as colourless needles, 0.126 g (72%); m.p. 164-5°C; IR (KBr) ν 3398, 3131 (NH str.), 1759 (sydnone C=O str.), 1685 (amide C=O str.), 1476, 1242, 787 cm^{-1}; ^{1}H-NMR δ (DMSO-d_6) 2.01 (s, 3H), 2.34 (s, 3H), 7.09 (s, 1H), 7.27-7.48 (m, 3H), 7.80 (s, 1H); ^{13}C-NMR (DMSO-d_6) 13.4 (CH_3), 19.5 (CH_3), 103.4 (sydnone C-$CONH_2$), 123.7, 126.0, 132.7 (aromatic CH's), 132.2, 134.6, 138.1 (aromatic C's), 155.9 (amide C=O), 166.2 (sydnone C=O) ppm; analysis: calculated for $C_{11}H_{11}N_3O_3$: C, 56.68; H, 4.72; N, 18.02. Found: C, 56.49; H, 4.69; N, 17.88.

Preparation of 4-Carboxamido-3-(3,4-dimethylphenyl)sydnone (2e)

Using 3-(3,4-dimethylphenyl)sydnone[15] (0.1425 g) in the general procedure gave the title compound **2e** as colourless needles, 0.12 g (68.5%); m.p. 182-4°C; IR (KBr) ν 3400, 3163 (NH str.), 1769 (sydnone C=O str.), 1690 (amide C=O str.), 1462, 1238, 1062, 692 cm^{-1}; ^{1}H-NMR δ (DMSO-d_6) 2.29 (s, 3H), 2.32 (s, 3H), 7.14 (s, 1H), 7.41 (m, 3H), 7.80 (s, 1H); ^{13}C-NMR (DMSO-d_6) 19.2 (2 CH_3), 102.5 (sydnone C-$CONH_2$), 122.7, 125.8, 129.7 (aromatic CH's), 132.4, 137.3, 140.8 (aromatic C's), 156.1 (amide C=O), 166.5 (sydnone C=O) ppm; analysis: calculated for $C_{11}H_{11}N_3O_3$: C, 56.68; H, 4.72; N, 18.02. Found: C, 56.57; H, 4.71; N, 17.99.

Preparation of 4-Carboxamido-3-(2-methoxycarbonylphenyl)-sydnone (2f)

Using 3-(2-methoxycarbonylphenyl)sydnone[16] (0.165 g) in the general procedure gave the title compound **2f** as colourless crystals, 0.154 g (78%); m.p. 178-9°C; IR (KBr) ν 3434, 3414, 3265 (NH str.), 1758 (sydnone C=O str.), 1723 (ester C=O str.), 1686 (amide C=O str.), 1601, 1502 cm^{-1}; ^{1}H-NMR δ (DMSO-d_6) 3.75 (s, 3H), 7.07 (s, 1H), 7.66 (m, 4H), 8.15 (m, 1H); ^{13}C-NMR (DMSO-d_6) 52.7 (CO_2CH_3), 103.6 (sydnone C-$CONH_2$), 125.9, 127.8, 130.9, 132.4, 133.8, 134.1 (aromatic C's and CH's), 156.2 (amide C=O), 163.2 (ester C=O), 165.9 (sydnone C=O) ppm; analysis: calculated for

$C_{11}H_9N_3O_5$: C, 50.20; H, 3.45; N, 15.96. Found: C, 50.26; H, 3.39; N, 15.87.

Preparation of 4-Carboxamido-3-(2-nitrophenyl)sydnone (2g)

Using 3-(2-nitrophenyl)sydnone[16] (0.1553 g) in the general procedure (but using 8 equivalents of chlorosulfonyl isocyanate added in 2 portions, 60 min apart) afforded the title compound **2g** as light yellow crystals, 0.103 g (55%); m.p. 186-8°C; IR (KBr) ν 3419, 3137 (NH str.), 1753 (sydnone C=O str.), 1677 (amide C=O str.), 794 cm^{-1}; ^{1}H-NMR δ (DMSO-d_6) 7.13 (s, 1H), 7.96-8.06 (m, 4H), 8.46 (d, 1H); ^{13}C-NMR (DMSO-d_6) 103.0 (sydnone C-$CONH_2$), 125.8, 129.0, 133.8, 155.5 (aromatic CH's), 127.8, 143.0 (aromatic C's), 156.2 (amide C=O), 165.3 (sydnone C=O) ppm; analysis: calculated for $C_9H_6N_4O_5$: C, 43.23; H, 2.40; N, 22.40. Found: C, 43.34; H, 2.61; N, 22.21.

Preparation of 4-Carboxamido-3-(2-benzyl)sydnone (2h)

Using 3-(2-benzyl)sydnone[14] (0.132 g) in the general procedure afforded the title compound **2h** as colourless crystals, 0.113 g (69%); m.p. 158-59°C; IR (KBr) ν 3417, 3308 (NH str), 1752 (sydnone C=O str.), 1656 (amide C=O str.), 1499 cm^{-1}; ^{1}H-NMR δ (DMSO-d_6) 6.08 (s, 2H), 7.07 (s, 1H), 7.36-7.51 (m, 5H), 7.78 (s, 1H); ^{13}C-NMR (DMSO-d_6) 54.9 (CH_2), 98.4 (sydnone C-$CONH_2$), 127.3, 127.4, 127.7 (aromatic CH's), 130.5 (aromatic C), 155.9 (amide C=O), 165.0 (sydnone C=O) ppm; analysis: calculated for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 19.17. Found: C, 55.00; H, 4.02; N, 18.95.

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