Steric effects on the sydnones reactivity. New sydnones and pyrazoles

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Abstract
The sydnones 7a,b and 8a-c gave the corresponding pyrazoles 9a-e by 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate (DMAD). The highly sterically hindered 3-(4,6-dibromo-2-methylphenyl)-4-iodosydnone (8d) failed to react with DMAD on heating in boiling xylene. The iodination of sterically hindered sydnone 7b required more drastic reaction conditions than the sydnone 7a.

Keywords: Sydnones, pyrazoles, steric effect, 1,3-dipolar cycloaddition

Introduction
Among the mesoionic compounds sydnones 2 are the best studied and thoroughly known.1-5 Sydnones can readily prepared by cyclodehydration of N-substituted-N-nitroso-aminoacids 1 with reagents such as acetic anhydride. The resulting compounds contain a mesoionic aromatic system which can be depicted with polar resonance structures. Sydnones undergo smooth cycloaddition with acetylenes to give pyrazoles 4 in high yield.6-9 The reaction involves a 1,3-dipolar cycloaddition of the sydnones, behaving like a cyclic azomethine imine, to the corresponding acetylene followed by carbon dioxide evolution and aromatization (Scheme 1).
The present work describes the synthesis of new halogenated sydnones and their cycloaddition reaction to form pyrazoles. The halogen atoms are present in the benzene and/or heterocycle ring. The influence of steric effects on reactivity of sydnones is also discussed.

**Results and Discussion**

The starting material, \(N\)-(2-methylphenyl)glycine (5), was obtained by a method described for \(N\)-(2-ethylphenyl)glycine.\(^{10}\) Monobromination of 5 with bromine/acetic acid gave \(N\)-(4-bromo-2-methylphenyl)glycine (6a) which was identical with the compound described in literature.\(^{11}\) When two equivalents of bromine were used \(N\)-(4,6-dibromo-2-methylphenyl)glycine (6b) was obtained (Scheme 2). The 4-unsubstituted sydnones 7a and 7b were prepared in good yields by known procedure\(^{1-6}\) from the corresponding \(N\)-arylglycines 6a and 6b (Scheme 2). The chemical shift of the 4-H proton of sydnones 7a and 7b in DMSO-\(d_6\) appears as being unusually high (\(\delta = 7.47\) and 7.51 ppm) as compared to those measured in other solvent as CDCl\(_3\) (\(\delta = 6.48\) ppm). A plausible explanation is the formation of hydrogen bonds between DMSO and 4-CH group. This is supported by a \(^{13}\)C-NMR study of sydnones which confirm the tendency of 4-CH group to form hydrogen bonds.\(^{12}\)

The chlorination and bromination of the sydnone 7a were performed with chlorine- and bromine-acetic acid to give 4-chlorosydnone 8a, respectively 4-bromosydnone 8b in good yields (Scheme 2).

Recently\(^{13}\) we obtained good results in the direct iodination of sydnone ring by using the reagent iodine monochloride/acetic acid. By using this method the sydnones 7a and 7b could be iodinated with this reagent in the presence of an equivalent of sodium acetate added to neutralize the hydrochloride acid formed in the reaction. Two new 4-iodosydnones 8c and 8d were obtained by this method.

The iodination of the sydnone 7b required large excess of iodine monochloride and a reaction time of 10 hrs., whereas the iodination of the sydnone 7a was complete in 1 hr. with only a slightly excess of iodination reagent. This was explained by steric hindering at the electrophilic center, C-4 in the sydnone ring.

The \(^{13}\)C-NMR spectra of 4-iodosydnones showed a strong negative increment at C-4 (\(\Delta\delta = 44.4\), respectively 44.9 ppm). A shielding effect of 3-aryl group on C-4 was also apparent, provided that the aromatic ring was not strongly deviated from coplanarity by ortho substituents. A weak influence on polarization of the carbonyl group could also be observed with bromine and chlorine as 4-substituents. The transformation of sydnones 7a,b and 8a-c into halogenated pyrazoles 9a-e was performed by 1,3-dipolar cycloaddition reaction with DMAD.
Scheme 2

The 4-chloro- and 4-bromosydrones were found by Dickopp\textsuperscript{14} to be unstable in non-polar solvents such that the corresponding pyrazoles were obtained in ethylene glycol upon reaction with excess DMAD. In our hands, 4-halogenosydrones 8\textsuperscript{a} and 8\textsuperscript{b} proved to be quite stable in xylene at reflux temperature and their reaction with a small excess of DMAD (1.2 molar ratio) led to the corresponding 5-halogenopyrazoles in yield of over 80%. In addition, 1-(4-Bromo-2-methylphenyl)-3,4-dicarboethoxy-5-iodopyrazole (9\textsuperscript{f}) was obtained by 1,3-dipolar cycloaddition between 4-iodosydnone 8\textsuperscript{c} and diethyl acetylenedicarboxylate. By this method, six new pyrazoles 9\textsuperscript{a-f} were obtained.
The $^{13}$C-NMR spectra of 5-iodopyrazoles $9e$ and $9f$ showed about the same negative increments ($\Delta \delta = 45.6$ and 45.8 ppm) for the signal of C-5 as in the case of the corresponding 4-iodosydnones $8c$ and $8d$. For the 4-iodopyrazoles$^{15}$ negative increments of $\Delta \delta = 41.5$-42.2 were measured.

The highly hindered 3-(4,6-dibromo-2-methylphenyl)-4-iodosydnone ($8d$) failed to react with DMAD (Scheme 2) or diethyl acetylenedicarboxylate for three days in boiling xylene. This finding could be explained by steric hinderance. The $ortho$ substituents at benzene ring and the bulky iodine atom at C-4 in the sydnone ring does not allow the formation of the transition state the between sydnone $8d$ and acetylenic dipolarophiles.

**Experimental Section**

**General Procedures.** $^1$H- and $^{13}$C-NMR spectra were recorded with a Varian Gemini instrument at 300 and 75 MHz, chemical shifts being expressed in $\delta$ values relative to TMS as internal standard. All mps were taken with a micro-Boetius apparatus and are uncorrected.

$N$-(4-Bromo-2-methylphenyl)glycine ($6a$). A solution of 11.2 g (70 mmol) of bromine in 10 mL of glacial acetic acid was dropped under stirring to a suspension of 11.5 g (70 mmol) of $N$-(2-chlorophenyl)glycine ($5$)$^{10}$ in 40 mL of glacial acetic acid. Stirring was continued for 30 min. The reaction mixture was poured into water and the precipitate was filtered by suction. Yield 83%; mp 139-142 °C (Lit.$^{11}$ yield 82%; mp 142-145 °C); $^1$H-NMR (CDCl$_3$+TFA) $\delta$ 7.54 (d, 1H, 2.2, 3'-H); 7.49 (dd, 1H, 8.5, 2.2, 5'-H); 7.31 (d, 1H, 8.5, 6'-H); 4.29 (s, 2H, CH$_2$); 2.45 (s, 3H, CH$_3$); $^{13}$C-NMR (CDCl$_3$+TFA) $\delta$ 168.9 (CO); 135.6 (3'-C); 132.8 (1'-C); 131.7 (2'-C); 131.5 (5'-C); 124.8 (4'-C); 124.0 (6'-C); 51.5 (CH$_2$); 16.2 (CH$_3$).

**General procedure for sydnones $7a$ and $7b$**

To a solution of 2 g NaOH in 30 mL of water were added 20 mmol N-arylglycine $6a,b$ and 1.4 g (21 mmol) of NaNO$_2$. In the cooled solution 10 mL of HCl were dropped under stirring, the temperature maintained under 5 °C. The nitroso derivatives which separated as oils were extracted twice with CH$_2$Cl$_2$. The organic layer was dried on CaCl$_2$ and then the solvent was evaporated off. The residue was treated with 30 mL of acetic anhydride and 2 mL of pyridine and evaporated under reduced pressure on the water bath. The crude products $7a$ and $7b$ were recrystallized from ethanol as colorless crystals.

**3-(4-Bromo-2-methylphenyl)sydnone ($7a$).**$^{16}$ $^1$H-NMR (CDCl$_3$) $\delta$ 7.62 (d, 1H, 2.2, 3'-H); 7.57 (dd, 1H, 8.4, 2.2, 5'-H); 7.32 (d, 1H, 8.4, 6'-H); 6.47 (s, 1H, 4-H); 2.33 (s, 3H, CH$_3$); $^1$H-NMR (DMSO-d$_6$) $\delta$ 7.80 (d, 1H, 2.1, 3'-H); 7.68 (dd, 1H, 8.5, 2.1, 5'-H); 7.60 (d, 1H, 8.5, 6'-H); 7.47 (s, 1H, 4-H); 2.25 (s, 3H, CH$_3$); $^{13}$C-NMR (CDCl$_3$) $\delta$ 168.6 (CO); 135.3 (3'-C); 135.0 (1'-C); 133.0 (2'-C); 130.7 (5'-C); 126.8 (4'-C); 126.5 (6'-C); 96.9 (4-C); 17.1 (CH$_3$).
3-(4,6-Dibromo-2-methylphenyl)sydnone (7b). Yield 77%; mp 189-190°C; $^1$H-NMR (CDCl$_3$) δ 7.81 (d, 1H, 2.1, 5'-H); 7.57 (d, 1H, 2.1, 3'-H); 6.48 (s, 1H, 4-H); 2.29 (s, 3H, CH$_3$); $^1$H-NMR (DMSO-d$_6$) δ 8.05 (d, 1H, 2.1, 5'-H); 7.84 (d, 1H, 2.1, 3'-H); 7.51 (s, 1H, 4-H); 2.21 (s, 3H, CH$_3$); $^{13}$C-NMR (CDCl$_3$) δ 166.6 (CO); 138.3 (1'-C); 135.3 and 134.1 (3'-C and 5'-C); 132.5 (2'-C); 126.8 (4'-C); 120.4 (6'-C); 97.3 (4-C); 17.2 (CH$_3$). Anal. Calcd for C$_9$H$_6$Br$_2$N$_2$O$_2$: C, 32.36; H, 1.81; Br, 47.84; N, 8.38. Found: C, 32.61; H, 2.11; Br, 48.18; N, 8.67.

3-(4-Bromo-2-methylphenyl)-4-chlorosydnone (8a). To a suspension of 2.5 g (10 mmol) sydnone 7a and 1 g dry sodium acetate in 15 mL glacial acetic acid was added dropwise with stirring and cooling 0.71 g (10 mmol) of chlorine dissolved in 15 mL glacial acetic acid. After 20 min. the reaction mixture was poured into water and the precipitate filtered by suction. Yield 75%; mp 131-3°C; $^1$H-NMR (CDCl$_3$) δ 7.67 (d, 1H, 2.2, 3'-H); 7.61 (dd, 1H, 8.4, 2.2, 5'-H); 7.31 (d, 1H, 8.4, 6'-H); 2.27 (s, 3H, CH$_3$); $^{13}$C-NMR (CDCl$_3$) δ 163.4 (CO); 136.1 (1'-C); 134.9 (3'-C); 133.3 (2'-C); 130.8 (5'-C); 127.4 (6'-C); 127.1 (4'-C); 99.6 (4-C); 16.7 (CH$_3$). Anal. Calcd for C$_9$H$_6$BrClN$_2$O$_2$: N, 9.67. Found: N, 9.91.

4-Bromo-3-(4-bromo-2-methylphenyl)sydnone (8b). The method used was the same as that described above but with bromine in place of chlorine. Yield 77%; mp 142-4°C; $^1$H-NMR (CDCl$_3$) δ 7.85 (d, 1H, 2.3, 3'-H); 7.74 (dd, 1H, 8.2, 2.3, 5'-H); 7.64 (d, 1H, 8.5, 6'-H); 2.18 (s, 3H, CH$_3$); $^{13}$C-NMR (DMSO-d$_6$) δ 165.5 (CO); 136.9 (1'-C); 134.7 (3'-C); 132.2 (2'-C); 131.0 (5'-C); 128.9 (6'-C); 126.5 (4'-C); 87.6 (4-C); 16.3 (CH$_3$). Anal. Calcd for C$_9$H$_6$Br$_2$N$_2$O$_2$: C, 32.36; H, 1.81; Br, 47.84; N, 8.38. Found: C, 32.64; H, 2.15; Br, 48.19; N, 8.67.

3-(4-Bromo-2-methylphenyl)-4-iodosydnone (8c). A solution of 22 mmol (1.1 mL) of iodine monochloride in 10 mL of glacial acetic acid was added dropwise to a stirred mixture of 5.1 g (20 mmol) of sydnone 7a and 2.2 g (25 mmol) of dry sodium acetate and of 20 ml glacial acetic acid. Stirring was continued for 1 hr at 50°C, after which the 4-iodosydnone was precipitated by the addition of water. The product was filtered off and thoroughly washed with water. Yield 82%; mp 197-8°C (from ethanol); $^1$H-NMR (CDCl$_3$) δ 7.65 (d, 1H, 2.2, 3'-H); 7.61 (dd, 1H, 8.4, 2.2, 5'-H); 7.21 (d, 1H, 8.4, 6'-H); 2.21 (s, 3H, CH$_3$); $^{13}$C-NMR (CDCl$_3$) δ 168.4 (CO); 136.3 (1'-C); 134.8 (3'-C); 133.3 (2'-C); 130.8 (5'-C); 127.6 (6'-C); 126.9 (4'-C); 52.3 (4-C); 16.9 (CH$_3$). Anal. Calcd for C$_9$H$_6$BrI$_2$N$_2$O$_2$: N, 7.35. Found: N, 7.62.

3-(4,6-Dibromo-2-methylphenyl)-4-iodosydnone (8d). The method used was the same as that described above but with an excess of iodine monochloride (4 molar ratio) and stirring for 10 hrs at 55-60°C. Yield 80%; mp 237-239°C (from AcOH); $^1$H-NMR (CDCl$_3$) δ 7.83 (d, 1H, 2.2, 5'-H); 7.59 (d, 1H, 2.2, 3'-H); 2.20 (s, 3H, CH$_3$); $^{13}$C-NMR (CDCl$_3$) δ 168.4 (CO); 138.7 (1'-C); 134.2 and 133.6 (3'-C and 5'-C); 132.5 (2'-C); 127.3 (4'-C); 121.2 (6'-C); 52.4 (4-C); 17.6 (CH$_3$). Anal. Calcd for C$_9$H$_5$BrI$_2$N$_2$O$_2$: N, 6.09. Found: N, 6.39.

General procedure for pyrazoles 9a-e
A mixture of 10 mmol sydnone (7a,b and 8a-c) and 1.55 g (12 mmol) of DMAD was refluxed in 30 mL xylene for 8 hrs. After removal of the solvent in vacuo, the pyrazoles 9a-e were crystallized from ethanol as colourless crystals.
1-(4-Bromo-2-methylphenyl)-3,4-dicarbomethoxypyrazole (9a). Yield 83%; mp 93-95 °C; \(^1\)H-NMR (CDCl\(_3\)) δ 8.06 (s, 1H, 5-H); 7.50 (d, 1H, 2.1, 3'-H); 7.45 (d, 1H, 8.4, 2.1, 5'-H); 7.22 (d, 1H, 8.4, 6'-H); 3.98 and 3.88 (2s, 6H, OCH\(_3\)); 2.23 (s, 3H, CH\(_3\)); \(^{13}\)C-NMR (CDCl\(_3\)) δ 161.9 and 161.8 (2CO); 144.4 (3-C); 137.5 (1'-C); 136.0 (2'-C); 135.6 (5-C); 134.3 (3'-C); 130.0 (5'-C); 127.7 (6'-C); 123.7 (4'-C); 115.9 (4-C); 52.8 and 52.1 (OCH\(_3\)) 17.8 (CH\(_3\)). Anal. Calcd for C\(_{14}\)H\(_{13}\)BrN\(_2\)O\(_4\): C, 47.59; H, 3.68; Br, 22.66; N, 7.93. Found: C, 47.90; H, 3.97; Br, 22.97; N, 8.24.

1-(4-Bromo-2-methylphenyl)-3,4-dicarbomethoxypyrazole-5-chloropyrazole (9b). Yield 81%; mp 123-4 °C; \(^1\)H-NMR (CDCl\(_3\)) δ 7.54 (d, 1H, 2.2, 3'-H); 7.48 (dd, 1H, 8.4, 2.2, 5'-H); 7.15 (d, 1H, 8.4, 6'-H); 3.96 and 3.93 (2s, 6H, OCH\(_3\)); 2.09 (s, 3H, CH\(_3\)); \(^{13}\)C-NMR (CDCl\(_3\)) δ 161.3 (2CO); 144.3 (3-C); 138.2 (1'-C); 134.9 (2'-C); 134.1 (3'-C); 132.6 (5-C); 130.1 (5'-C); 129.3 (6'-C); 124.8 (4'-C); 112.6 (4-C); 52.8 and 52.5 (OCH\(_3\)) 17.2 (CH\(_3\)). Anal. Calcd for C\(_{14}\)H\(_{12}\)BrClN\(_2\)O\(_4\): N, 7.23. Found: N, 7.50.

5-Bromo-1-(4-bromo-2-methylphenyl)-3,4-dicarbomethoxypyrazole (9c). Yield 88%; mp 128-130 °C; \(^1\)H-NMR (CDCl\(_3\)) δ 7.54 (d, 1H, 2.1, 3'-H); 7.48 (dd, 1H, 8.4, 2.1, 5'-H); 7.14 (d, 1H, 8.4, 6'-H); 3.96 and 3.93 (2s, 6H, OCH\(_3\)); 2.07 (s, 3H, CH\(_3\)); \(^{13}\)C-NMR (CDCl\(_3\)) δ 161.5 and 161.1 (2CO); 144.7 (3-C); 138.2 (1'-C); 135.8 (2'-C); 133.9 (3'-C); 129.9 (5'-C); 129.3 (6'-C); 124.6 (4'-C); 119.4 (4-C); 115.7 (5-C); 52.7 and 52.3 (OCH\(_3\)) 17.1 (CH\(_3\)). Anal. Calcd for C\(_{14}\)H\(_{12}\)Br\(_2\)N\(_2\)O\(_4\): C, 38.92; H, 2.79; Br, 36.99; N, 6.48. Found: C, 39.21; H, 3.04; Br, 37.33; N, 6.79.

1-(4-Bromo-2-methylphenyl)-3,4-dicarboethoxy-5-iodopyrazole (9d). Yield 79%; mp 107-8 °C; \(^1\)H-NMR (CDCl\(_3\)) δ 7.53 (d, 1H, 2.1, 3'-H); 7.48 (dd, 1H, 8.4, 2.1, 5'-H); 7.11 (d, 1H, 8.4, 6'-H); 3.95 and 3.93 (2s, 6H, OCH\(_3\)); 2.03 (s, 3H, CH\(_3\)); \(^{13}\)C-NMR (CDCl\(_3\)) δ 162.1 and 161.3 (2CO); 145.5 (3-C); 138.4 (1'-C); 137.5 (2'-C); 134.0 (3'-C); 130.0 (5'-C); 129.7 (6'-C); 124.7 (4'-C); 121.0 (4-C); 90.8 (5-C); 52.8 and 52.4 (OCH\(_3\)) 17.4 (CH\(_3\)). Anal. Calcd for C\(_{14}\)H\(_{12}\)BrIN\(_2\)O\(_4\): N, 5.85. Found: N, 6.11.

1-(4,6-Dibromo-2-methylphenyl)-3,4-dicarbomethoxypyrazole (9e). Yield 92%; mp 153-4 °C; \(^1\)H-NMR (CDCl\(_3\)) δ 7.97 (s, 1H, 5-H); 7.67 (d, 1H, 2.2, 3'-H); 7.42 (d, 1H, 2.1, 3'-H); 3.94 and 3.85 (2s, 6H, OCH\(_3\)); 2.06 (s, 3H, CH\(_3\)); \(^{13}\)C-NMR (CDCl\(_3\)) δ 161.6 and 161.5 (2CO); 144.5 (3-C); 139.9 (1'-C); 136.7 (2'-C); 136.4 (5-C); 133.2 (5'-C); 123.9 (3'-C); 124.4 (4'-C); 122.6 (6'-C); 115.9 (4-C); 52.6 and 52.0 (OCH\(_3\)) 17.8 (CH\(_3\)). Anal. Calcd for C\(_{14}\)H\(_{12}\)Br\(_2\)N\(_2\)O\(_4\): C, 39.21; H, 3.04; Br, 37.33; N, 6.77.

1-(4-Bromo-2-methylphenyl)-3,4-dicarboethoxy-5-iodopyrazole (9f). The method used was the same described for 9d but with diethyl acetylenedicarboxylate in place of DMAD. Yield 82%; mp 86-8 °C (from ethanol); \(^1\)H-NMR (CDCl\(_3\)) δ 7.49 (d, 1H, 2.2, 3'-H); 7.42 (d, 1H, 2.1, 3'-H); 3.94 and 3.85 (2s, 6H, OCH\(_3\)); 2.06 (s, 3H, CH\(_3\)); \(^{13}\)C-NMR (CDCl\(_3\)) δ 161.6 and 161.0 (2CO); 145.8 (3-C); 138.3 (1'-C); 137.4 (2'-C); 133.8 (3'-C); 129.8 and 129.7 (6'-C and 5'-C); 124.5 (4'-C); 120.7 (4-C); 90.3 (5-C); 61.8 and 61.4 (OCH\(_3\)); 17.3 (CH\(_3\)); 14.0 and 13.9 (CH\(_2\)CH\(_3\)). Anal. Calcd for C\(_{16}\)H\(_{16}\)BrIN\(_2\)O\(_4\): C, 5.52. Found: C, 5.80.
References and Notes