NEW HALOGENATED SYDNONES AND THEIR CYCLOADDITION TO FORM PYRAZOLES

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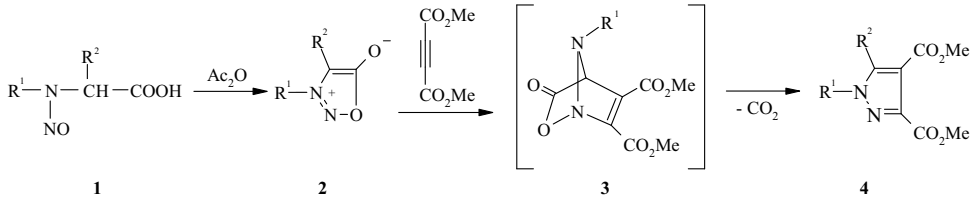
New halogenated pyrazoles **9b-d** were obtained by 1,3-dipolar cycloaddition reaction of several halogenated sydnones **8b-d** with dimethyl acetylenedicarboxylate. The hydrogen bonds formation between 4-H proton of sydnones **8a,b** was put in evidence by ^{1}H-NMR The structure of new compounds was assigned by elemental analysis, ^{1}H- and ^{13}C-NMR spectra.

Introduction

Among the mesoionic compounds syndromes 2 are the best studied and thoroughly known [1÷5]. Sydnones can readily prepared by cyclodehydration of N-substituted-N-nitrozo-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).



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.

Experimental

All melting points were recorded with a Boetius microapparatus and are uncorrected. NMR spectra were recorded with a Varian Gemini 300 instrument, the chemical shifts being expressed in δ values relative to TMS as internal standard.

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N-(4-Bromo-2-chlorophenyl)glycine **(6b)**

A solution of 4.8 g (30 mmol) of bromine in 15 ml of glacial acetic acid was dropped under stirring to a suspension of 7.9 g (30 mmol) of N-(2-chlorophenyl)glycine (**5**) [10] in 25 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. Mp 149÷151°C (Lit. [11] 156÷157 °C); yield 87%.

^{1}H-NMR ($CDCl_3$+TFA, δ_{ppm}, J_{Hz}): 4.52 (s, 2H, CH_2); 7.64 (dd, 1H, 8.6, 2.1, H-5'); 7.79 (d, 1H, 8.6, H-6'); 7.80 (d, 1H, 2.1, H-3').

^{13}C-NMR ($CDCl_3$+TFA, δ_{ppm}): 51.1 (CH_2); 126.2 (C-4'); 126.5 (C-6'); 128.7 (C-2'); 129.8 (C-1'); 132.6 (C-5'); 134.3 (C-3'); 169.7 (CO).

Sydnones 8a,b – General procedure

To a solution of 2 g NaOH in 30 ml of water were added 20 mmol N-arylglycine **6a,b** and 1.66 g (21 mmol) of $NaNO_2$. In the cooled solution 10 ml of HCl were dropped under stiring, the temperature maintened under 5 °C. The nitroso derivatives **7a,b**, which separated as oils, were extracted twice with CH_2Cl_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 **8a,b** were recrystallized from ethanol.

3-(2-Chlorophenyl)sydnone **(8a) Mp 84-85°C (Lit.[12] 82÷84°C)**

^{1}H-NMR ($CDCl_3$, δ_{ppm}): 6.65 (s, 1H, H-4); 7.60 (m, 4H, Ar-H).

^{1}H-NMR (DMSO-d_6, δ_{ppm}, J_{Hz}): 7.64 (s, 1H, H-4); 7.68 (td, 1H, 7.8, 1.7, H-5'); 7.79 (td, 1H, 7.8, 1.7, H-4'); 7.87 (dd, 1H, 7.8, 1.6, H-3'); 7.96 (d, 1H, 7.8, 1.6, H-6').

^{13}C-NMR (CDCl, δ_{ppm}): 97.9 (C-4); 127.1 (C-6'); 128.3 (C-2'); 129.1 (C-5'); 131.4 (C-3'); 132.8 (C-1'); 133.4 (C-4'); 168.0 (CO).

^{13}C-NMR (DMSO-d_6, δ_{ppm}): 99.9 (C-4); 128.9 (C-6'); 129.0 (C-2'); 129.6 (C-5'); 131.8 (C-3'); 132.9 (C-1'); 134.8 (C-4'); 169.0 (CO).

3-(4-Bromo-2-chlorophenyl)sydnone **(8b) Mp 112-113°C (EtOH); yield 68%.**

^{1}H-NMR ($CDCl_3$, δ_{ppm}, J_{Hz}): 6.64 (s, 1H, H-4); 7.50 (d, 1H, 8.5, H-6'); 7.68 (dd, 1H, 8.5, 2.0, H-5'); 7.83 (d, 1H, 2.0, H-3').

^{1}H-NMR (DMSO-d_6, δ_{ppm}): 7.68 (s, 1H, H-4).

^{13}C-NMR ($CDCl_3$, δ_{ppm}): 97.8 (C-4); 127.2 (C-4'); 128.6 (C-6'); 130.1 (C-2'); 131.4 (C-1'); 131.7 (C-5'); 134.1 (C-3'); 168.3 (CO).

Anal. Calcd. for $C_8H_4BrClN_2O_2$: N, 10.17; Found: N, 10.39 .

4-Iodosydnones 8c,d – General procedure

A solution of 22 mmol (1.1 ml) of iodine monochloride in 10 ml of glacial acetic acid was added dropwise to stirred mixture of 20 mmol of sydnone **8a,b** and 2.2 g of (25 mmol) dry sodium acetate and of 15 ml glacial acetic acid. Stirring was continued for 2 hrs. at

55÷60 °C, after which the 4-iodosydnone was precipitated by the addition of water. The product was filtered off and thoroughly washed with water.

3-(2-Chlorophenyl)-4-iodosydnone **(8c) Mp 156-158°C (EtOH); yield 82%.**

^{1}H-NMR ($CDCl_3$, δ_{ppm}): 7.50 (m, H-3'); 7.60 (m, H-5'); 7.71 (m, H,-4', H-6').

^{13}C-NMR ($CDCl_3$, δ_{ppm}): 53.1 (C-4); 127.9 (C-6'); 128.3 (C-5'); 130.6 (C-2'); 131.2 (C-1'); 132.8 (C-1'); 133.8 (C-4'); 168.4 (CO).

Anal. Calcd. for $C_8H_4ClIN_2O_2$: N, 8.69; Found: N, 8.82.

3-(4-Bromo-2-chlorophenyl)-4-iodosydnone **(8d) Mp 178-180°C (EtOH); yield 83%.**

^{1}H-NMR ($CDCl_3$, δ_{ppm}, J_{Hz}): 7.38 (d, 1H, 8.5, H-6'); 7.73 (dd, 1H, 8.5, 2.0, H-5'); 7.88 (d, 1H, 2.0, H-3').

^{13}C-NMR ($CDCl_3$, δ_{ppm}): 53.2 (C-4); 127.7 (C-4'); 128.9 (C-6'); 130.2 (C-2'); 131.7 (C-1'); 131.8 (C-5'); 134.0 (C-3'); 168.2 (CO).

Anal. Calcd. for $C_8H_3BrClIN_2O_2$: N, 6.98; Found: N, 7.26.

Pyrazoles 9b-d – General procedure

A mixture of 10 mmol of the sydnones **8b-d** and 1.7 g (12 mmol) of DMAD was refluxed in 30 ml toluene (4hrs. for **8b**) or 30 ml xylene (8hrs. for **8c,d**). After removal of the solvent in vacuo, the pyrazoles were recrystallized from ethanol.

1-(4-Bromo-2-chlorophenyl)-3,4-dicarbomethoxypyrazole **(9b) Mp 105-106°C (EtOH); yield 91%.**

^{1}H-NMR ($CDCl_3$, δ_{ppm}, J_{Hz}): 3.89 and 3.99 (2s, 6H, OCH_3); 7.50 (d, 1H, 8.5, H-6'); 7.56 (dd, 1H, 8.5, 1.9, H-5'); 7.73 (d, 1H, 1.9, H-3'); 8.32 (s, 1H, H-5).

^{13}C-NMR ($CDCl_3$, δ_{ppm}): 52.1 and 52.8 (OCH_3); 116.0 (C-4); 123.6 (C-4'); 128.9 (C-6'); 129.5 (C-2'); 131.2 (C-5'); 133.3 (C-3'); 135.7 (C-1'); 136.2 (C-5); 144.7 (C-3); 161.6 and 161.7 (CO).

Anal. Calcd. for $C_{13}H_{10}BrClN_2O_4$: N, 7.50; Found: N, 7.79.

3,4-Dicarbomethoxy-1-(2-chlorophenyl)-5-iodopyrazole **(9c) Mp 93-94°C (EtOH); yield 78%.**

^{1}H-NMR ($CDCl_3$, δ_{ppm}, J_{Hz}): 3.92 and 3.94 (2s, 6H, OCH_3); 7.39 (dd, 1H, 7.6, 2.2 H-6'); 7.43 (td, 1H, 7.6, 1.7, H-5'); 7.50 (td, 1H, 7.6, 2.2, H-4'); 7.57 (dd, 1H, 7.6, 1.7, H-3').

^{13}C-NMR ($CDCl_3$, δ_{ppm}): 52.3 and 52.7 (OCH_3); 91.4 (C-5); 121.0 (C-4); 127.6 (C-5'); 129.9 (C-6'); 130.3 (C-4'); 131.9 (C-3'); 132.8 (C-2'); 137.0 (C-1'); 145.4 (C-3); 161.2 and 162.0 (CO).

Anal. Calcd. for $C_{13}H_{10}ClIN_2O_4$: N, 6.67; Found: N, 6.90.

1-(4-Bromo-2-chlorophenyl)-3,4-dicarbomethoxy-5-iodopyrazole **(9d) Mp 92-93°C (EtOH); yield 87%.**

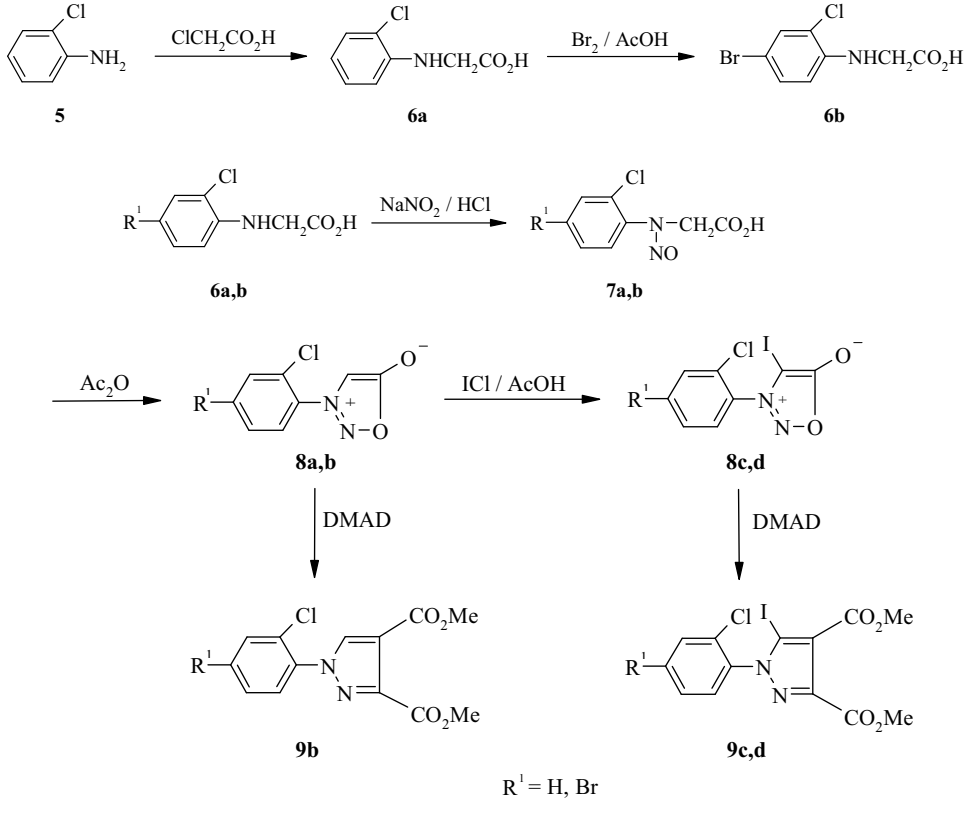
^{1}H-NMR ($CDCl_3$, δ_{ppm}, J_{Hz}): 3.94 and 3.96 (2s, 6H, OCH_3); 7.29 (d, 1H, 8.5, H-6'); 7.60 (dd, 1H, 8.5, 1.9, H-5'); 7.76 (d, 1H, 1.9, H-3').

^{13}C-NMR ($CDCl_3$, δ_{ppm}): 52.3 and 52.8 (OCH_3); 91.4 (C-5); 121.2 (C-4); 125.3 (C-4'); 130.9 and 131.0 (C-5', C-6'); 133.1 (C-3'); 134.0 (C-2'); 136.0 (C-1'); 145.7 (C-3); 161.1 and 161.9 (CO).

Anal. Calcd. for $C_{13}H_9BrClIN_2O_4$: N, 5.61; Found: N, 5.90.

Results and Discussion

The sydnones **8a,b** were obtained from 2-chloroaniline according to Scheme 2. We prepared N-(4-bromo-2-chlorophenyl)glycine (**6b**) by bromination of **6a**. This represents a new method for preparation of **6b**. 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 **8a,b** 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. The products were obtained in a highly pure state and in yields of over 80%. Two new 4-iodosydnones **8c,d** were obtained by this method.



Scheme 2.

The chemical shift of the 4-H proton of sydnones **8a,b** in DMSO-d_6 appears as being unusually high (δ = 7.64 and 7.68 ppm) as compared to those measured in other solvent as

$CDCl_3$ (δ = 6.65 and 6.64 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 [14].

The ^{13}C-NMR spectra of 4-iodosydnones showed a strong negative increment at C-4 (Δδ =44.7). A shielding effect of 3-aryl group on C-4 was also apparent, provided that the aromatic ring was not strongly deviated by coplanarity by orto substituents.

The transformation of sydnones **8b-d** into halogenated 1-arylpyrazoles was performed by 1,3-dipolar cycloaddition reactions with dimethyl acetylenedicarboxylate (DMAD). The cycloaddition reaction of 4-iodosydnones **8c,d** required a higher boiling solvent (xylene) and a long period of time (8hrs.) than 4-unsubstituted sydnone **8b** (toluene, 4hrs.). The difference of reactivity is explained by steric effect of bulky 4-iodo substituent on the formation of intermediate cycloadduct of type **3**.

By this method three new halogenated pyrazoles **9b-d** were obtained. The ^{13}C-NMR spectra of 5-iodopyrazoles showed about the same negative increments (Δδ = 44.8) for signal of C-5 as in the case of corresponding 4-iodosydnones (Δδ = 44.7).

For 4-iodopyrazoles [15] negative increments of Δδ were measured.

All new halogenated compounds **8b-d** and **9b-d** were fully characterized by elemental analysis, ^{1}H-, ^{13}C- and NMR experiments, namely APT, HETCOR and HH-COSY.

Conclusion

Polihalogenated pyrazoles **9b-d** were obtained by 1,3-dipolar cycloaddition between 4-unsubstituted **8b** and 4-iodosydnones **8c,d** with dimethyl acetylenedicarboxylate.

The ^{1}H-NMR spectra in DMSO-d_6 of sydnones **8a,b** put in evidence the formation of the hydrogen bonds between 4-H atom of the sydnone ring and DMSO.

The structure of the new compounds **8b-d** and **9b-d** was assigned by elemental analysis and ^{1}H- and ^{13}C-NMR spectra.

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