Uses of Sydnones for Heterocyclic Syntheses

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N-(4-Bromo-3-chlorophenyl)sydnone is prepared and subjected to chlorination and bromination. 1,3-Dipolar addition of these sydnones with dimethyl acetylenedicarboxylate produces the substituted pyrazoles which could serve as intermediates.

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On prépare la *N*-(bromo-4 chloro-3 phényl) sydnone et on la soumet à des réactions de chloruration et de bromuration. Les réactions d'addition dipolaire-1,3 de ces sydnones avec l'acétylènedicarboxylate de méthyle conduisent à des pyrazoles substituées qui peuvent servir d'intermédiaire. [Traduit par le journal]

Sydnones unsubstituted at the 4-position undergo electrophilic substitution reactions (1). However, in view of the difficulties experienced in the synthesis of 4-halosydnones (2) an attempt was made to introduce a halogen atom at the *N*-arylglycine ethyl ester stage in the synthesis of sydnones and it resulted in the halogen entering the phenyl group rather than the side chain; this was proved by the elemental analysis and spectral data (Fig. 1) of the compound. *N*-(*m*-Chlorophenyl)glycine ethyl ester was taken as the starting material in the first instance, since there is a report that the chloro substituent in any position of the sydnone molecule enhances its biological activity (3). 3-Phenylsydnones undergo 1,3-dipolar addition with dimethyl acetylenedicarboxylate to produce the 3,4-disubstituted pyrazoles. 5-Halopyrazoles could easily be prepared by reaction of 4-halosydnones with dimethyl acetylenedicarboxylate. It is known that 1-phenylpyrazoles do not undergo halogenation in the 5-position easily (4, 5). The electrophilic attack may be initiated at the 4-position of the pyrazole ring or at the *para* position of the phenyl ring. This has been clearly interpreted by Lynch and co-workers (6) (Fig. 2).

The required *N*-(*m*-chlorophenyl)glycine ethyl ester was prepared from *m*-chloroaniline and

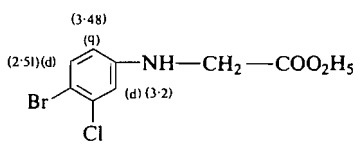

FIG. 1. Coupling constants for *N*-(4-bromo-3-chlorophenyl)glycine ethyl ester.

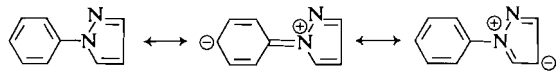

FIG. 2. Electrophilic attack on 1-phenylpyrazoles.

ethyl chloroacetate. The glycine ethyl ester was brominated in chloroform to yield *N*-(4-bromo-3-chlorophenyl)glycine ethyl ester. This was further hydrolyzed with 10% alkali and the resulting glycine subjected to nitrosation in alcoholic medium. The nitrosoglycine was heated with acetic anhydride to yield the sydnone. The sydnone was brominated in acetic acid medium to yield the 4-bromosydnone. Chlorination was effected with *N*-chlorosuccinimide to give 4-chlorosydnone. The sydnone and the 4-substituted sydnones were treated with dimethyl acetylenedicarboxylate in xylene to produce pyrazoles.

The i.r. spectrum of the sydnone carbonyl group is at 1750–1780 cm^{-1} (7). A band at *ca.* 3100 cm^{-1} is due to the sydnone C—H (7), whereas this is absent in the 4-halosydnones (8). The spectrum of pyrazoles shows absorptions at 1750 and 1740 cm^{-1} (CO_2CH_3).

Experimental

N-(m-Chlorophenyl)glycine Ethyl Ester

A mixture of ethyl chloroacetate (62.0 g), *m*-chloroaniline (64.0 g), ethanol (50 ml), and sodium acetate (60.0 g) was refluxed at 125° for 5 h in an oil bath. Water (200 ml) was then added and the precipitated ester collected and washed; recrystallized from ethanol, m.p. 105°; yield, 80.0 g.

Anal. Calcd. for $C_{10}H_{12}NO_2Cl$: C, 56.20; H, 5.62. Found: C, 55.80; H, 5.32.

N-(4-Bromo-3-chlorophenyl)glycine Ethyl Ester

N-(*m*-Chlorophenyl)glycine ethyl ester (40.0 g) was suspended in a mixture of chloroform (400 ml) and ether (200 ml), containing sodium bicarbonate (40.0 g). Bromine (5.4 ml) was added dropwise and the solution was stirred for 2 h at room temperature. The solution was filtered and the filtrate evaporated under reduced pressure. The resulting solid crystallized from petroleum ether, m.p. 85°; yield, 48.0 g.

Anal. Calcd. for $C_{10}H_{11}BrClNO_2$: C, 41.10; H, 3.76. Found: C, 40.8; H, 3.40.

Infrared (KBr) 1750 cm^{-1} (C=O); 3340 cm^{-1} (NH); n.m.r. ($CDCl_3$): 8.68 (3H, t, J_{CH_2,CH_3} = 7.5 Hz, CH_3 of $COOCH_2CH_3$), 6.08 (2H, d, $J_{CH_2,NH}$ = 6.0 Hz, CH_2 flanked between NH and ($COOCH_2CH_3$), 5.67 (2H, q, $J_{CH_2CH_3}$ = 7.5 Hz, CH_2 of ($COOCH_2CH_3$), 3.48 (1H, q, J_{ortho} = 8.0 Hz and J_{meta} = 2.5 Hz), 3.2 (1H, d, J_{meta} = 2.5 Hz), 2.51 (1H, d, J_{ortho} = 8.0 Hz).

N-(4-Bromo-3-chlorophenyl)glycine

N-(4-Bromo-3-chlorophenyl)glycine ethyl ester (40.0 g) was hydrolyzed with sodium hydroxide solution (10%, 95 ml) and ethanol (10 ml). The solution was refluxed for 1 h, then cooled and acidified. The glycine was filtered and crystallized from ethanol, m.p. 150°; yield, 30.0 g.

Anal. Calcd. for $C_8H_7BrClNO_2$: C, 36.29; H, 2.64. Found: C, 35.90; H, 3.14.

N-(4-Bromo-3-chlorophenyl)-N-nitrosoglycine

N-(4-Bromo-3-chlorophenyl)glycine (25.0 g) was suspended in a mixture of alcohol (100 ml) and water (250 ml). Sodium nitrite (8.0 g) in water (25 ml) was added at 0–5° with stirring. After 2 h of stirring the solution was acidified and the *N*-nitroso acid collected and crystallized from benzene, m.p. 125°; yield, 20.0 g.

Anal. Calcd. for $C_8H_6BrClN_2O_3$: C, 32.71; H, 2.04. Found: C, 32.34; H, 2.12.

N-(4-Bromo-3-chlorophenyl)sydnone

The above *N*-nitroso acid (20.0 g) was heated with acetic anhydride (100 ml) on a water bath for 2 h. Then it was poured into water and the solid filtered and crystallized from benzene – petroleum ether, m.p. 138°; yield, 12.5 g.

Anal. Calcd. for $C_8H_4BrClN_2O_2$: C, 34.85; H, 1.45. Found: C, 34.40; H, 1.3.

4-Bromo-N-(4-bromo-3-chlorophenyl)sydnone

N-(4-Bromo-3-chlorophenyl)sydnone (5.0 g) was dissolved in acetic acid (50 ml) containing sodium acetate (15.0 g) and cooled in ice. Bromine (1.1 ml) in acetic acid (5 ml) was added dropwise and the solution stirred for 2 h. Then it was diluted with water and the precipitated bromosydnone was crystallized from ethanol, m.p. 146°; yield, 4.0 g.

Anal. Calcd. for $C_8H_3Br_2ClN_2O_2$: C, 27.08; H, 0.84. Found: C, 26.69; H, 0.65.

4-Chloro-N-(4-bromo-3-chlorophenyl)sydnone

A solution of *N*-(4-bromo-3-chlorophenyl)sydnone (2.5 g) and *N*-chlorosuccinimide (1.6 g) in wet methanol (100 ml) was stirred for 5 min at room temperature. Evaporation of methanol furnished a slurry which was poured into water and extracted with chloroform. Evaporation of the chloroform extracts gave a residue which was crystallized from ethanol, m.p. 132°; yield, 1.8 g.

Anal. Calcd. for $C_8H_3BrCl_2N_2O_2$: C, 30.96; H, 0.96. Found: C, 31.20; H, 0.74.

Dimethyl 1-(4-Bromo-3-chloro)phenylpyrazole-3,4-dicarboxylate

N-(4-Bromo-3-chlorophenyl)sydnone (1.0 g) was dissolved in xylene (50.0 ml) and dimethyl acetylenedicarboxylate (1.0 ml) was added. The solution was refluxed until the evolution of carbon dioxide ceased. The solvent was removed under reduced pressure and the residue crystallized from petroleum ether, m.p. 142°; yield 1.2 g.

Anal. Calcd. for $C_{13}H_{10}BrClN_2O_4$: C, 41.77; H, 2.67. Found: C, 41.90; H, 3.40.

Dimethyl 1-(4-Bromo-3-chloro)phenyl-5-bromopyrazole-3,4-dicarboxylate

4-Bromo-*N*-(4-bromo-3-chlorophenyl)sydnone (1.0 g) was dissolved in dry xylene (50.0 ml) and dimethyl acetylenedicarboxylate (1.0 ml) added. On working up as in the earlier case, the compound obtained was crystallized from petroleum ether, m.p. 116°; yield, 0.9 g.

Anal. Calcd. for $C_{13}H_9Br_2ClN_2O_4$: C, 34.47; H, 1.98. Found: C, 34.07; H, 1.68.

Dimethyl 1-(4-Bromo-3-chloro)phenyl-5-chloropyrazole-3,4-dicarboxylate

4-Chloro-*N*-(4-bromo-3-chlorophenyl)sydnone (1.0 g) was dissolved in dry xylene (50.0 ml) and dimethyl acetylenedicarboxylate (1.0 ml) added. On working up as in the earlier case, the compound crystallized from petroleum ether, m.p. 104°; yield, 0.8 g.

Anal. Calcd. for $C_{13}H_9BrCl_2N_2O_4$: C, 38.23; H, 2.20. Found: C, 37.68; H, 1.88.

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