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Synthesis of 2-Acetamido-5,6-dihalophenyl Acetates

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Summary. 2-Acetamido-5,6-dihalophenyl acetates were synthesized as intermediates for the preparation of 6, 7-dihalo-8-quinolinols *via* the *Skraup* procedure.

Keywords. 6-Chloro-2-acetamidophenyl acetate; 6-Bromo-2-acetamidophenyul acetate; 5,6-Dichloro-2-acetamidophenyl acetate; 5,6-Dibromo-2-acetamidophenyl acetate.

Introduction

A recent part of our study on structure *vs*. antifungal activity relationships of 8-quinolinol and its substituted analogues involved preparation of a series dihalo-8-quinolinols [1]. While these could be prepared generally from monohalo-8-quinolinols using suitable blocking agents when needed, 6,7-dihalo derivatives caused extra problems. The more reactive 5-position of 6-halo-8-quinolinol was blocked by sulfonation. On halogenation of 6-halo-8-quinolinol-5-sulfonic acid, the sulfonic acid was replaced in part, leading to a mixture of 6,7-dihalo-8-quinolinol-5-sulfonic acid and a by-product of 5,6,7-trihalo-8-quinolinol [1]. The separation of the two compounds was accomplished by washing the mixture with warm acetone, leaving the sulfonic acid as a residue on the filter. The sulfonic acid was subsequently desulfonated to yield 6,7-dihalo-8-quinolinol. Yields of the desired product were thus diminished [1].

Another route to 6,7-dihalo-8-quinolinols was considered: a *Skraup* ring closure reaction on 2-amino-5,6-dihalophenol. The required intermediates seemed to present difficult synthetic problems, since they contained four contiguous *o*, *p*-directing groups which appeared to present problematic synthetic tasks in adjusting the directive influences of the groups already on the ring as well as steric hindrance. Based on experience with the preparation of 6-halo-8-quinolinols [2] and our work with 6-halo-2-nitro-phenols [3,4,5], facile syntheses of the desired 6,7-dihalo-8-quinolinols were achieved by *Skraup* reactions using acetylated 2-amino-5,6-dihalophenols. Preparation of the 2-acetamido-5,6-dihalophenyl acetates is reported here.

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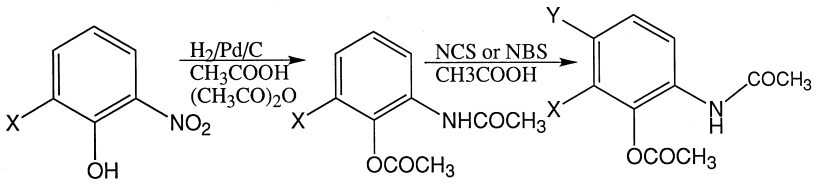

1 2 3

1a, **2a**: X = Cl; **1b**, **2b**: X = Br

3a: X = Cl, Y = Cl; **3b**: X = Br, Y = Br

Scheme 1

Results and Discussion

The synthetic approach to the 2-acetamido-5,6-dihalophenyl acetates is outlined in Scheme 1. Nitration of *o*-halophenols directs the entering nitro group primarily in the *ortho*-position to the phenolic hydroxyl group. Furthermore, the product can be purified by steam distillation which takes advantage of the strong intramolecular hydrogen bonding of the substituted *o*-nitrophenol. Reductive acetylation of the nitro group was done by catalytic hydrogenation in a mixture of acetic acid and acetic anhydride. The resulting 6-halo-2-acetamidophenyl acetate was reacted with N-halosuccinimide (*NXS*) to yield the title compounds. Since no entering group is directed between two others already present in a molecule, the problem of steric hindrance is minimal.

That acetamido is a stronger *o*,*p*-director than the acetoxy group has been established by *Theilacker* in 1938 [6], and we took advantage of this in an earlier synthesis of 6-halo-8-quinolinol [2]. When *o*-aminophenol was heated with acetic anhydride under reflux, a triacetyl deivative was formed which cannot be halogenated with *NXS* in acetic acid. The diacetyl derivative as described by Theilacker [6] is amenable to halogenation [7].

Experimental

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. The purity of samples was established by ^{1}H and ^{13}C NMR spectroscopy at 300 and 75 MHz, respectively, with a Bruker DPX-300 spectrometer using *DMSO*-d_6 as solvent and *TMS* as internal standard. Mass spectra of the new compounds **2a**,**b** and **3a**,**b** were obtained using a Fisons VG7070E double-focusing sector mass spectrometer with a resolution of 3000 (Valley) and perfluorokerosene (Lancaster) as a calibration standard.

2-Acetamido-6-chlorophenyl acetate (**2a**; $C_{10}H_{10}ClNO_3$)

A mixture of **1a** (8.7 g, 0.05 mol) [3], 1.5 g of 10% palladium on characoal, 50 cm^3 of acetic acid, and 50 cm^3 of acetic anhydride were shaken in a *Parr* hydrogenator under three atmospheres of hydrogen until the theoretical amount of hydrogen was consumed. The catalyst was removed by filtration, and the solution was stirred overnight, after which it was poured onto ice and stirred until the residual acetic anhydride was hydrolyzed and complete crystallization of **2a** took place. The product was

recovered by filtration, washed with water, and dried at 50°C. The yield of compound was 8.7 g (76%), m.p.: 124°C. A pure sample recrystallized from ethanol melted at 127°C.

^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 9.58 (s, NH), 7.95 (d, $J_{34} = 7.5$ Hz, H-3), 7.29 (dd, $J_{35} = 1.8$ Hz, $J_{45} = 8.0$ Hz, H-5), 7.24 (t, H-4), 2.36 (s, CH_3CONH), 2.10 (s, CH_3COO) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d^6): 168.77 (C=ONH), 167.88 (C=OO), 137.74 (C-1), 132.95 (C-2), 126.63 (C-4), 126.44 (C-6), 124.54 (C-4), 122.14 (C-3), 23.60 (CH_3CONH), 20.69 (CH_3COO) ppm; *m/z*: calcd. for $C_{10}H_{10}{}^{35}ClNO_3$: 227.03492, found: 227.03438.

2-Acetamido-6-bromophenyl acetate (**2b**; $C_{10}H_{10}BrNO_3$)

Compound **2b** was prepared from **1b** [4] in the same manner as **2a** was obtained from **1a**. A 0.055 mol run yielded 25.3% of product, m.p.: 122–124°C. A pure sample recrystallized from aqueous ethanol melted at 127–128°C.

^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 9.56(s, NH), 7.97 (d, $J_{34} = 8.0$ Hz, H-3), 7.42 (d, H-5), 7.18 (t, $J_{45} = 8.2$ Hz, H-4) 2.38 (s, CH_3COO), 2.10 (s, CH_3CONH) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 169.46 (C=ONH), 168.58 (C=OO), 139.08 (C-1), 133.01 (C-2), 127.56 (C-5), 127.12 (C-4), 122.80 (C-3), 116.37 (C-6), 23.59 (CH_3CONH), 20.90 (CH_3COO) ppm; *m/z*: calcd. for $C_{10}H_{10}{}^{79}BrNO_3$: 270.98440, found: 270.98329.

2-Acetamido-5,6-dichlorophenyl acetate (**3a**; $C_{10}H_9C_{l2}NO_3$)

A mixture of **2a** (13.6 g, 0.06 mol) and *NCS* (8.0 g, 0.06 mol) in 70 cm^3 of acetic acid was stirred at 50°C overnight until a negative starch iodide test was obtained. The solution was poured into 5 volumes of water and stirred for 0.5 h. The product was recovered by filtration, washed with water, and dried at 50°C. The yield of compound was 11.4 g (76.2%), m.p.: 147–150°C. A pure sample crystallized from aqueous ethanol melted at 171–172°C.

^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 9.68 (s, NH), 8.03 (d, H-3), 7.53 (d, $J_{34} = 9.0$ Hz, H-4), 2.40 (s, CH_3COO), 2.12 (s, CH_3CONH) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 168.98 (C=ONH), 167.79 (C=OO), 138.81 (C-1), 131.96 (C-2), 127.05 (C-4), 126.17 (C-5), 125.48 (C-6), 122.26 (C-3), 23.66 (CH_3CONH), 20.75 (CH_3COO) ppm; *m/z*: calcd. for $C_{10}H_9{}^{35}Cl_2NO_3$: 260.99595, found: 260.99586.

2-Acetamido-5,6-dibromophenyl acetate (**3b**; $C_{10}H_9Br_2NO_3$)

Compound **3b** was prepared from **2b** as **3a** from **2a**. A 0.01 mol run yielded 77.2% of product, m.p.: 158–160°C. A pure sample crystallized from aqueous ethanol melted at 177–178°C.

^{1}H NMR (300 MHz, δ, *DMSO*-d^6: 9.64 (s, NH), 7.98 (d, $J_{34} = 8.95$ Hz, H-3), 7.64 (d, H-4), 2.38 (s, CH_3COO), 2.10 (s, CH_3CONH) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6: 168.92 (C=ONH), 167.81 (C=OO), 140.05 (C-1), 132.11 (C-2), 130.24 (C-4), 123.34 (C-5), 119.65 (C-5), 118.25 (C-6), 23.64 (CH_3CONH), 21.00 (CH_3COO); *m/z*: calcd. for $C_{10}H_9{}^{79}Br_2NO_3$: 348.89492, found: 348.89536.

6,7-Dichloro-8-quinolinol

To 24 g sulfuric acid, 10.2 cm^3 H^2O, 12 g sodium *m*-nitrobenzenesulfonate, 11.2 g glycerol, and 10.0 g (0.038 mol) **3a** were added. The mixture was stirred vigorously and heated to reflux slowly. After 3 h the mixture was allowed to cool to 80°C and poured into 1 dm^3 of water. The insoluble material was removed by filtration, the *pH* of the filtrate was adjusted to 7 with NH_4OH, and the solution was steam distilled. A volatile product (0.4 g) melting at 177–178°C was not identified. The residue after steam distillation was recovered and dried at 50°C; yield: 6.33 g (77.5%), m.p: 182–184°C. Upon sublimation, washing with a little acetone, and crystallization from acetonitrile the

product melted at 190–191°C (Ref. [1]: m.p.: 191–192°C). A mixed melting point with an authentic sample showed no depression, and the ^{1}H NMR spectra of both samples were identical.

^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 8.94 (dd, $J_{23} = 4.12$ Hz, $J_{24} = 1.41$ Hz, H-2), 8.36 (dd, H-4), 7.74 (dd, $J_{34} = 8.7$ Hz, H-3), 10.8 (s, OH); ppm; ^{13}C NMR (75 MHz, δ *DMSO*-d_6): 151.3 (C-8), 149.3 (C-2), 137.1 (C-8a), 135.6 (C-4), 130.2 (C-6), 126.9 (C-4a), 123.0 (C-3), 117.5 (C-5), 114.9 (C-7); *m/z*: calcd. for $C_9H_5{}^{35}Cl_2NO$: 212.97482, found: 212.97461.

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