Chemistry of Heterocyclic Compounds, Vol. 40, No. 6, 2004

OXIDATIVE RECYCLIZATION OF 4,6,7-TRICHLORO-5-HYDROXY-2-(2-PYRIMIDYL-AMINO)-2,3-DIHYDROBENZO[*b*]FURAN

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When 4,6,7-trichloro-5-hydroxy-2-(2-pyrimidylamino)- 2,3-dihydrobenzo[b]furan reacted with phenyliodoso diacetate, an unexpected oxidative recyclization was observed to give 3-(3,5,6-trichloro-1,4-benzoquinon-2-yl)imidazo[1,2-a]pyrimidine. 2-[N-2-(3,5,6-Trichloro-1,4-benzoquinon-2-yl)ethenyl-amino]pyrimidine is the intermediate product in the conversion.

Keywords: 4,6,7-trichloro-5-hydroxy-2-(2-pyrimidylamino)-2,3-dihydrobenzo[*b*]furan, 3-(3,5,6-trichloro-1,4-benzoquinon-2-yl)imidazo[1,2-*a*]pyrimidine, phenyliodoso diacetate.

The structural units of imidazo[1,2-*a*]pyridine, imidazo[1,2-*a*]pyrazine, and imidazo[1,2-*a*]pyrimidine are encountered in many pharmacologically active substances, such as antagonists of benzodiazepine and bradykinin receptors, inhibitors of gastric acid secretion, anti-inflammatories, cytoprotective agents, antibacterials, antifungal agents, cardiostimulators, etc. (see [1,2] and literature cited therein). The classical method for the synthesis of imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrazines, and imidazo[1,2-*a*]pyrimidines is the condensation of α-halo ketones with the corresponding 2-aminoazines [3-5]. A one step synthesis of imidazo[1,2-*a*]azines via a three component condensation of a 2-aminoazine, an aldehyde, and an isonitrile has been described [1,2] recently.

In this paper the design of the ring of trichloro-1,4-benzoquinolyl-substituted imidazo[1,2-*a*]pyrimidine in an unexpected oxidative recyclization reaction of 4,6,7-trichloro-5-hydroxy-2-(2-pyrimidylamino)-2,3-dihydrobenzo[*b*]furan (**1**) is proposed. We have shown recently [6] that the benzo[*b*]furan **1** is formed in the reaction of 4,6,7-trichloro-2,5-dihydroxy-2,3-dihydrobenzo[*b*]furan with 2-aminopyrimidine.

When the benzo[*b*]furan **1** reacts with phenyliodoso diacetate in DMSO solution at 20°C oxidation scission of the dihydrobenzofuran ring occurs with the formation of the intermediate 2-[N-2-(3,5,6-trichloro-1,4-benzoquinon-2-yl)ethenylamino]pyrimidine (**2**), which then itself undergoes original oxidative cyclization to give 3-(3,5,6-trichloro-1,4-benzoquinon-2-yl)imidazo[1,2-*a*]pyrimidine (**3**). The benzoquinone **3** is easily reduced to 3-(3,4,6-trichloro-2,5-dihydroxyphenyl)imidazo[1,2-*a*]pyrimidine (**4**), so that the ^{1}H NMR spectrum (in DMSO-d_6) of compound **3** corresponds to the structure of the hydroquinone **4**.

Reduction of **3** to **4** was carried out by boiling in ethanol. Acylation of compound **4** with acetyl anhydride in pyridine in the presence of 4-dimethylaminopyridine (DMAP) [7] gave 3-(5-acetoxy-3,4,6-trichloro-2-hydroxyphenyl)imidazo[1,2-*a*]pyrimidine (**5**). The phenolic hydroxy group in position 2 is not acylated under these conditions, possibly because of an intramolecular hydrogen bond between the OH group and the nitrogen atom of the heterocycle.

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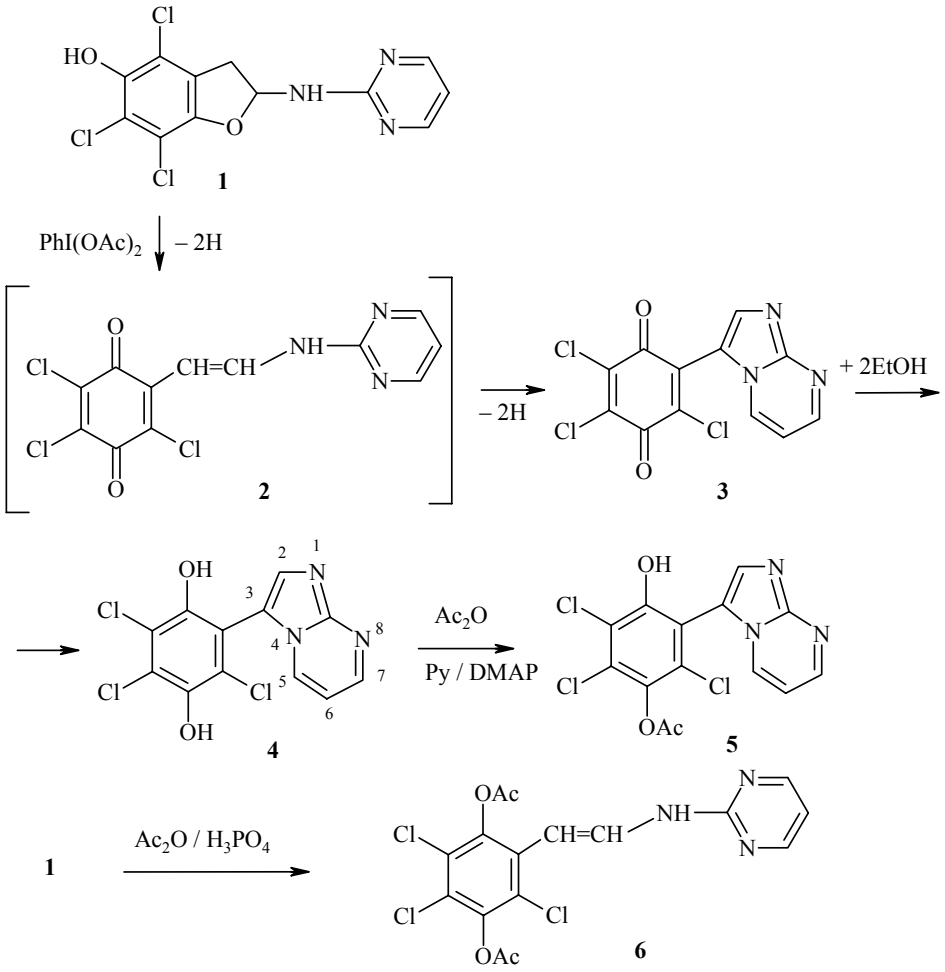

Formation of the intermediate compound **2** is confirmed by the ^{1}H NMR spectrum of a sample taken 5 min after the beginning of the reaction. This spectrum contains, apart from the proton signals of the starting material and reaction product, signals corresponding to the –CH=CH–NH unit (*E*-configuration). This unit occurs in the structure of 2-[N-2-(2,5-diacetoxy-3,4,6-trichlorophenyl)ethenylamino]pyrimidine (**6**), obtained by acetylation of compound **1** with acetic anhydride in the presence of orthophosphoric acid. The coupling constant (^3J = 15 Hz) between the protons of the ethenyl fragment in the ^{1}H NMR spectrum of compound **6** confirms its *E*-configuration.

In the IR spectrum of the benzoquinone **3** bands for the C=O and C=C groups of the quinone are observed, but bands for the OH group are absent. The benzoquinone **3** is intensely colored and the presence in its UV spectrum of a band at 576 nm indicates the intramolecular charge transfer between the electron-donating heterocycle and the electron-accepting 1,4-benzoquinone fragment (cf [8]).

In the ^{1}H NMR spectra of compounds **4** and **5** the signals of the protons in positions 5, 6, and 7 of the imidazo[1,2-*a*]pyrimidine ring appear as a doublet of doublets. The chemical shifts and the coupling constants of these signals (see Experimental) agree well with the spectrum of 2-(4-methoxyphenyl)-3-benzylaminoimidazo[1,2-*a*]pyrimidine [1] in which there are doublets of doublets: H-5 8.49 (^3J = 6.8, ^4J = 2.0), H-6 6.89 (^3J = 4.1, ^4J = 6.8), H-7 8.37 ppm (^3J = 4.1, ^4J = 2.0 Hz). A singlet is also observed for the proton in position 2 of the imidazo[1,2-*a*]pyrimidone ring, the chemical shift of which agrees with the data in [9, 10].

EXPERIMENTAL

IR spectra of nujol mulls were recorded on a Specord M-80 (1900-1500 cm^{-1}, NaCl prism) and of hexachlorobutadiene mulls (3800-2000 cm^{-1}, LiF prism). Electronic spectra of chloroform solutions ($c = 2.5 \cdot 10^{-5}$ mol/l). ^1H NMR spectra were recorded on a Bruker WH-90 (90 MHz) instrument with TMS as internal standard.

3-(3,5,6-Trichloro-1,4-benzoquinon-2-yl)imidazo[1,2-*a*]pyrimidine (3). Phenyliodoso diacetate (0.80 g, 2.5 mmol) in DMSO (5 ml) was added dropwise over 3 min to a solution of benzofuran **1** (0.33 g, 1 mmol) (prepared according to [6]) in DMSO (5 ml) with stirring (magnetic stirrer) at 20°C. The mixture was stirred for 1 h at 20°C and water (100 ml) was then added. The precipitate of **3** was separated, washed , and dried. The product was treated with methylene chloride (5 ml), the undissolved residue was separated, washed with petroleum ether, and dried. Yield 0.25 g (77%). Deep-blue crystals; mp >250°C (dec.). IR spectrum (thin layer), ν, cm^{-1}: 1686 (C=O), 1624, 1582 (C=C), 1538, 1502. UV spectrum ($CHCl_3$, $c = 2.5 \cdot 10^{-1}$mol/l): λ_{max}, nm (log ε): 302 (4.24), 576 (3.70). ^1H NMR spectrum, see compound **4**. Found, %: C 43.34; H 1.78; Cl 31.98; N 12.32. $C_{12}H_4Cl_3N_3O_2$. Calculated, %: C 43.87; H 1.23; Cl 32.38; N 12.79.

3-(3,4,6-Trichloro-2,5-dihydroxyphenyl)imidazo[1,2-*a*]pyrimidine (4). A solution of benzoquinone **3** (0.33 g, 1 mmol) in ethanol (10 ml) was boiled until the reaction mixture was colorless (~30 min). The solvent was evaporated in vacuum to 2 ml and the solution was kept at 0°C for 20 h. The precipitate of the product **4** was separated, washed with ethanol, and dried . Yield 0.28 g (85%). Gray crystals; mp >200°C (dec).

IR spectrum (thin layer), ν, cm^{-1}: 3120 (OH), 2927 (OH), 1622, 1562, 1530, 1494. ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.07 (1H, dd, $^3J = 4$, $^4J = 6$, H-6); 7.83 (1H, s, H-2); 8.42 (1H, dd, $^3J = 6$, $^4J = 2$, H-5); 8.60 (1H, dd, $^3J = 4$, $^4J = 2$, H-7); 9.70 (1H, br. s, OH); 10.00 (1H, br. s, OH). Found, %: C 43.55; H 2.03; Cl 31.78; N 12.80. $C_{12}H_6Cl_3N_3O_2$. Calculated, %: C 43.60; H 1.83; Cl 32.18; N 12.71.

3-(5-Acetoxy-3,4,6-trichloro-2-hydroxyphenyl)imidazo[1,2-*a*]pyrimidine (5). A mixture of compound **4** (0.33 g, 1 mmol), anhydrous pyridine (4 ml), acetic anhydride (2 ml, 20 mmol), and 4-dimethylaminopyridine (0.025 g, 0.2 mmol) was stirred at 20°C for 1 h, then at 50-60°C for 2 h, and was finally boiled for 1 h. After cooling, water (50 ml) was added, the precipitate was separated, washed with water, and dried. After crystallization from ethanol plus activated charcoal, colorless crystals of compound **5** were obtained. Yield 0.25 g (68%); mp ~260°C (dec). IR spectrum (thin layer), ν, cm^{-1}: 2560 (br, OH···N), 1778 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.92 (3H, s, CH_3); 7.11 (1H, dd, $^3J = 4$, $^4J = 6$, H-6); 7.73 (1H, s, H-2); 8.49 (1H, dd, $^3J = 6$, $^4J = 2$, H-5); 8.64 (1H, dd, $^3J = 4$, $^4J = 2$, H-7); 10.95 (1H, br. s, OH). Found, %: C 44.94; H 2.14; Cl 28.72; N 11.15. $C_{14}H_8Cl_3N_3O_3$. Calculated, %: C 45.13; H 2.16; Cl 28.55; N 11.28.

2-[N-2-(2,5-Diacetoxy-3,4,6-trichlorophenyl)ethenylamino]pyrimidine (6). Benzofuran **1** (0.33 g, 1 mmol), acetyl anhydride (5ml), and orthophosphoric acid (3 drops) were heated at 100°C for 1 h. The mixture was cooled and water (50 ml) was added. After 12 h, the precipitate was filtered off, washed with water and dried to give colorless crystals of **6** (0.36 g, 86%). After recrystallization from benzene and then from 1:3 benzene–carbon tetrachloride; mp 184-185°C (dec). IR spectrum (thin layer), ν, cm^{-1}: 3210 (NH), 1775 (C=O), 1638 (C=C), 1517. ^1H NMR spectrum ($CDCl_3$ + DMSO-d_6), δ, ppm (*J*, Hz): 2.33 (3H, s CH_3); 2.39 (3H, s, CH_3); 6.02 (1H, d, $^3J = 15$, CH); 6.70 (1H, t, $^3J = 5$, H-5 Het); 8.13 (1H, dd, $^3J = 15$, $^4J = 12$, CH); 8.34 (2H, d, $^3J = 5$, H-4 Het, H-6 Het); 8.60 (1H, br. d, $^3J = 12$, NH). Found, %: C 46.10; H 2.86; Cl 25.50; N 9.94. $C_{16}H_{12}Cl_3N_3O_4$. Calculated, %: C 46.12; H 2.90; Cl 25.53; N 10.09.

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