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Synthesis of azo derivatives of 4-aminosalicylic acid

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Abstract

For searching a better 4-aminosalicylic acid derivative with higher activity and less side effects against the inflammatory bowel disease, 4-aminosalicylic acid (4-ASA) was protected by benzyloxycarbonyl and acetyl, respectively. The resultant was hydrogenized to remove protective group of amino group, then the product was reacted with $NaNO_2$ to give diazonium salt, which was conjugated with salicylic acid, hydroxybenzene, *N*-salicyloyl glycine acid to get azo derivatives of 4-ASA. The azo derivatives were hydrolyzed under the alkaline condition to get the target products. All compounds were characterized by FT-IR, ^1H NMR, ^{13}C NMR spectra in details. New derivatives of 4-ASA were characterized. The synthetic route was reasonable and feasible.

Keywords: 4-Aminosalicylic acid; Azo derivatives of 4-aminosalicylic acid; Inflammatory bowel disease

Inflammatory bowel diseases (IBD), which include ulcerative colitis and crohn's disease, are chronic inflammatory bowel diseases of unknown etiology. The medication progress has been made recently. Salicylates, corticosteroids, antibiotics, immuno-suppressants are most commonly used to relieve the symptoms of such ailment [1]. Numerous clinical studies have shown that 4-aminosalicylic acid (4-ASA) is highly effective and safe in topical treatment of active ulcerative proctitis or left sided ulcerative colitis [2], yet it is not suitable to be used in the treatment of such disease because it is absorbed rapidly and extensively through the upper intestine before it reaches to the colonic site [3]. Therefore by modifying the structure of 4-ASA, we synthesized azo derivatives of 4-ASA, which have not been reported yet. The design principal of azo derivatives of 4-ASA were taking advantage of azo moiety as the colonic drug delivery system but adding a therapeutic activity to the carrier [4]. In the colon, azoreductase-containing bacteria would cleave the azo bond releasing 4-ASA which had therapeutic effect in IBD [5]. The selected carriers included salicylic acid, phenyl hydroxide, *N*-salicyloyl glycine acid [6,7].

One route on which we prepared azo derivatives of 4-ASA was started from 4-ASA by protecting amino and hydroxyl groups with benzyloxycarbonyl and acetyl respectively, the resultant was hydrogenized to remove the protective group of amino group, then the product was reacted with $NaNO_2$ to give diazonium salt, which was conjugated with salicylic acid, hydroxybenzene, *N*-salicyloyl glycine to get azo derivatives of 4-ASA **5**–**6** as shown in Scheme 1. Preliminary pharmacodynamic experiments on these compounds were carried out by researchers, and the results showed they had better intestinal anti-inflammatory effects. The experiments will be reported in another paper.

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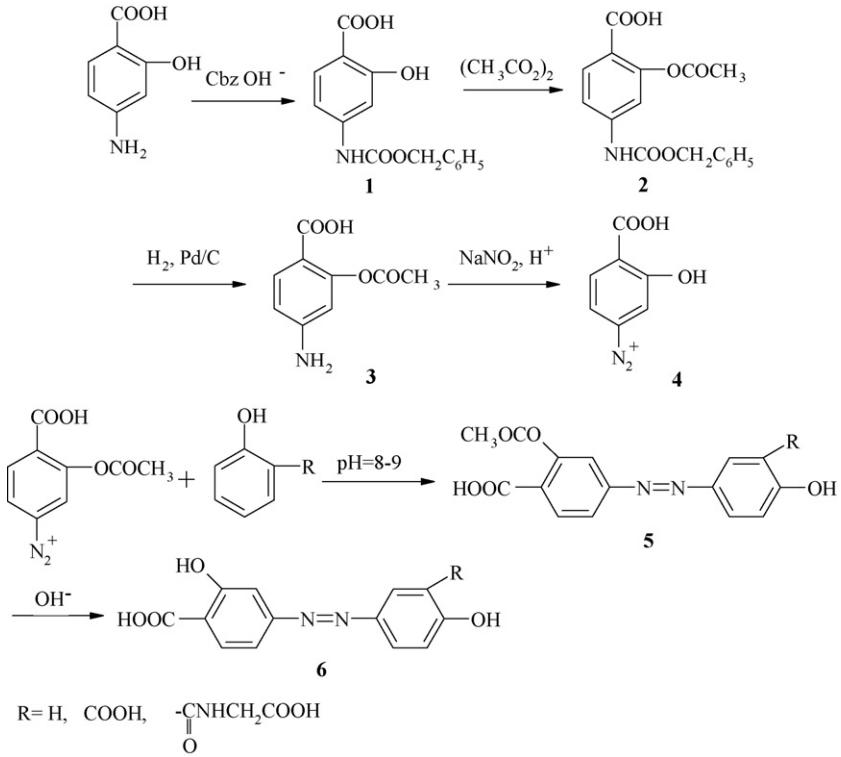

Scheme 1. The synthetic route of azo derivatives of 4-ASA.

1. Experimental

4-Aminosalicylic acid (4-ASA), glycine ethyl ester hydrochloride, benzylchloroformate, acetic anhydride and 10% Pd/C were purchased from Sigma Chemical Co. (St. Louis; MO). All other chemicals were reagent grade and commercially available.

IR spectra was recorded with PE1730 spectrophotometer. ^{1}H NMR spectra and ^{13}C NMR spectra were taken on a Varian (300 MHz) spectrometer. The melting point were measured with X-4 digital display binocular microscope. Pressure reactor (Parr WDF) was used for catalytic hydrogenation.

*1.1. Preparation of 4-[N-(benzyloxycarbonyl)amino]salicylic acid **1***

Benzylchloroformate (carbobenzyloxy chloride) (13.3 g, 78 mmol) was added dropwise gradually to a suspension of 4-ASA (10 g, 65 mmol) in saturated solution of $NaHCO_3$ (250 mL) [8], containing excessive solid $NaHCO_3$ (10 g). The reaction mixture was stirred mechanically 10 h under 0 °C, then was filtered. The filterate was washed three times with ether (30 mL), then acidified with 3 mol/L HCl and extracted with ethyl acetate. The organic phase was dried with anhydrous Na_2SO_4 over night and the solvent was removed by reducing evaporator. The resulting solid was recrystyllized with ethyl acetate and chloroform (1:3) and the crystal was dried under vacuum to give compound **1** (14 g, 75% yield). mp 191–194 °C; IR (KBr, υ cm^{-1}): 3385(N–H), 1263 (C–N), 1744(C=O); ^{1}H NMR (DMSO-d_6, δ ppm): 5. 16(s, 2H, –CH_2–), 7.00–7.70(m, 3H, H-Ph), 7.37(m,5H, –CH_2–Ph), 10.13(s, 1H, –NH–CO–): ^{13}C NMR (DMSO-d_6, δ ppm): 66.3 m (–CH_2–Ph), 104.8–128.6 m (8C, Ph), 109.5 (*Ph*-COOH), 145.9 (*Ph*–NH–), 153.2 (*Ph*–OH), 136.4 (*Ph*–CH_2–), 162.3(–NH–*C*O–), 171.7(Ph–*C*OOH).

*1.2. Preparation of 4-[N-(benzyloxycarbonyl)amino]2-acetoxysalicylic acid **2***

To the suspension of compound **1** (10 g, 35 mmol) in acetic acid (60 mL), acetic anhydride (6 mL, 63.5 mmol) and pyridine (0.3 mL) were added and the mixture was stirred for 24 h. The precipitate was filtered and dried under