Synthesis of Mutagenic Heteroaromatics: 2-Aminoimidazo[4,5-f]quinolines

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(Received September 22, 1981)

Two potent mutagens, 2-amino-3-methylimidazo[4,5-f]quinoline and 2-amino-3,4-dimethylimidazo[4,5-f]quinoline, were synthesized.

Keywords—mutagen; 2-amino-3-methylimidazo[4,5-f]quinoline; 2-amino-3,4-dimethylimidazo[4,5-f]quinoline; imidazo[4,5-f]quinoline; cyanogen bromide

Recent studies showed that pyrolysates of foods, proteins, and amino acids contain potent muta-carcinogens. Active compounds were isolated and their structures were determined. For further studies, synthesis of these active compounds is essential. Previously, we established syntheses of 3-amino-5H-pyrido[4,5-b]indoles (Trp-P) isolated from a pyrolysate of tryptophan, 2-aminoimidazo[1,2-a: 3',2'-d]imidazoles (Glu-P) isolated from a pyrolysate of glutamic acid, and 3,4-cyclopentenopyrido[3,2-a]carbazole (Lys-P-1) isolated from a pyrolysate of lysine. Syntheses of alkylated derivatives of Trp-P and Glu-P were also completed. More recently, two new potent heteroaromatic mutagens were isolated from broiled sardines, and their structures were determined as 2-amino-3-methylimidazo[4,5-f]quinoline (IQ, 1a) and 2-amino-3,4-dimethylimidazo[4,5-f]quinoline (Me₂IQ, 1b). Syntheses of these mutagens were also reported. We here describe a simple and high yield synthesis of 1a and 1b.

1a and 1b were synthesized in overall yields of 35% and 30%, respectively, from 6-aminoquinoline (2a) and 6-amino-7-methylquinoline (2b). 2a is commercially available. 2b was synthesized by means of the Skraup synthesis from 5-acetamido-2-nitrotoluene, which was obtained in good yield by nitration of m-acetylaminobenzene. N-Methylation of 2a and 2b was performed by formylation with HCOOH-(CH₃CO)₂O followed by reduction with LiAlH₄; yields were 77% and 91%, respectively. When similar reactions were applied to 6-amino-5-nitroquinolines, the yields of 6-methylamino derivatives were poor. 6-Methylaminono- and 7-methyl-6-methylaminoquinoline were mono-nitrated in H₂SO₄-HNO₃ selectively at the 5-position of the quinolines in yields of 81% and 68%, respectively. For the reduction of the nitro group to an amino group, Pd-C-catalyzed reduction (for 6-methylamino-5-nitroquinoline;
3a) or SnCl₂–HCl treatment (for 7-methyl-6-methylamino-5-nitroquinoline; 3b) was successful. The Pd-C-catalyzed reduction in more acidic media (in CH₃CO₂H) gave a better result. Condensation of amines 4a and 4b with BrCN gave the desired aminoimidazoles in 72% and 70% yields, respectively. Recrystallization from solvents containing dilute hydrobromic acid gave the hydrobromides of 1a and 1b. Spectral data of the synthetic 1a and 1b as well as crystal data were consistent with those described for authentic samples isolated from broiled sardines. The present synthesis of 1a and 1b is simple and unambiguous as regards the position of the N-methyl group. This made the synthesis of a metabolite of 1a possible.

Experimental

2-Amino-3-methylimidazo[4,5-f]quinoline (IQ, 1a)—A mixture of (CH₃CO₂)₂O (4.4 g) and HCOOH (40 ml) was added to a solution of 6-aminoquinoline (2a, 3.96 g) in HCOOH (40 ml), and the whole was stirred at room temperature for 2 h. The reaction mixture was evaporated to dryness and the residue was washed with aqueous K₂CO₃ and recrystallized from AcOEt to give 4.12 g (87%) of 6-formamidoquinoline (mp 115°C, M⁺ 172). Reduction of the formyl group (4.12 g) was performed with LiAlH₄ (1.5 g) in tetrahydrofuran (THF) (400 ml) at 0°C. The reaction mixture was acidified with conc. HCl and then basified with aqueous K₂CO₃. The organic layer was evaporated to dryness and the residue was recrystallized from AcOEt to give 3.05 g (80.3%) of 6-methylaminoquinoline (400°C, mp 174°C, [α]D 174°) (CDCl₃; δ, 2.85 (s), 4.45 (s), 6.57 (d, J = 3 Hz), 6.96 (dd, J = 8 Hz, 3 Hz), 7.20 (dd, J = 5 Hz, 10 Hz), 7.64 (d, J = 8 Hz), 7.85 (dd, J = 10 Hz, 2 Hz), 8.60 (dd, J = 5 Hz, 2 Hz)). This amine (3.05 g) was treated with 100 ml of 10% H₂SO₄ (10 ml–10 ml) at 0°C (10 min). The reaction mixture was basified with aqueous K₂CO₃ and extracted with CHCl₃. The extract was concentrated, and recrystallization of the residue from CH₂Cl₂–n-C₄H₁₀ gave 2.9 g (80.5%) of 6-methylamino-5-nitroquinoline (3a, mp 122–124°C, PMR (CDCl₃); δ, 3.50 (s), 3.75 (s), 6.63 (dd, J = 6 Hz, 8 Hz), 7.65 (d, J = 9 Hz), 8.21 (dd, J = 8 Hz, 2 Hz), 8.35 (d, J = 9 Hz), 8.97 (dd, J = 2 Hz, 6 Hz)). Next, 5.5 g of 3a was reduced in CH₃COOH (250 ml) with H₂ gas in the presence of 10% Pd-C (2 g) at room temperature for 7 h. The mixture was filtered, the filtrate was evaporated to dryness, and the residue was washed with aqueous K₂CO₃. Recrystallization from AcOEt gave 3.7 g (78%) of 6-amino-6-methylamino-quinoline (4a, PMR (DMSO-d₆); δ, 3.40 (s), 5.80 (s), 6.14 (s), 7.19–7.56 (m), 8.78 (dd, J = 9 Hz, 2 Hz), 8.90 (dd, J = 5 Hz, 2 Hz)). 4a (3.7 g) was treated with 3 g of BrCN in MeOH (200 ml) at room temperature for 3 h. The mixture was then concentrated, and recrystallization of the residue from EtOH containing dilute HBr gave 3.1 g (72%) of 1a-HBr·H₂O mp >300°C. (Anal. Calcd. for C₉H₈N₂·HBr·H₂O: C, 44.46; H, 3.47; N, 18.86; Found: C, 44.32; H, 4.19; N, 18.79). To prepare free 1a, 1a·HBr·H₂O was subjected to silica gel column chromatography (AcOEt–MeOH–NH₄OH). Free 1a, mp >300°C (83%) was obtained. The spectral data of 1a thus obtained were identical with those reported for IQ isolated from broiled sardines.

2-Amino-3,4-dimethylimidazo[4,5-f]quinoline (Me-IQ, 1b)—A mixture of HNO₃ and H₂SO₄ (1.5ml–5 ml) was added dropwise to an ice-cooled solution of m-N-acetylaminophenol (5 g) in conc. H₂SO₄ (35 ml). Stirring was continued for 30 min. The reaction mixture was poured into ice-water, and precipitates were filtered off. Recrystallization from AcOEt–CHCl₃ gave 4.89 g (75%) of 5-acetamido-2-nitroloene (PMR (CDCl₃); δ, 2.37 (s), 2.50 (s), 2.85–7.64 (m), 7.97 (d, J = 8 Hz). Next, 10.7 g of 3 was heated in a mixture of glycerol (20 g), H₂SO₄ (15 g), and arsenic acid (8 g) at 130°C for 18 h. The mixture was then basified with aqueous NH₄OH and precipitates were collected. The precipitates were dissolved in EtOH (250 ml) and reduced with H₂ gas in the presence of 2 g of 10% Pd-C for 7 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was subjected to silica gel column chromatography to give 7-methyl-6-aminooquinoline (2b, mp 137–138°C, PMR (CDCl₃); δ, 2.40 (s), 6.99 (s), 7.27 (dd, J = 6 Hz, 8 Hz), 7.66 (s), 7.98 (dd, J = 2 Hz, 8 Hz), 8.42 (dd, J = 2 Hz, 6 Hz)) in a yield of 65%. A mixture of (CH₃CO₂)₂O–HCOOH (3 g–5 ml) was added to solution of 2b (0.93 g) in HCOOH (20 ml). The mixture was stirred for 2 h at room temperature, basified with aqueous NH₄OH, concentrated and extracted with CH₂Cl₂. The extract was concentrated, and recrystallization of the residue from benzene–CHCl₃ gave 1.46 g (90%) of 7-methyl-6-formamidoquinoline (mp 154–156°C). The amide (1.15 g) was reduced with LiAlH₄ (0.47 g) in THF (10 ml). The mixture was acidified with conc. HCl, then basified with aqueous NH₄OH and extracted with AcOEt. The organic layer was evaporated to dryness and the residue was recrystallized from CHCl₃–n-C₄H₁₀ to give the 6-methylaminoquinoline (0.96 g, 90%, PMR (CDCl₃); δ, 2.35 (s), 2.96 (s), 6.70 (s), 7.26 (dd, J = 4 Hz, 8 Hz), 7.62 (s), 8.04 (d, J = 4 Hz), 8.40 (d, J = 4 Hz). The methylanilinium (0.836 g) was dissolved in H₂SO₄ (10 ml) and cooled to 0°C. Next, 0.5 ml of HNO₃ was added and the mixture was stirred for 1 h. The reaction mixture was basified with NH₄OH and extracted with AcOEt. The organic layer was evaporated to dryness and the residue was subjected to silica gel column chromatography. Recrystallization from benzene–n-C₄H₁₀ gave 0.72 g (68%) of 7-methyl-6-methylamino-5-nitroquinoline (3b, PMR (CDCl₃); δ, 2.57 (s), 3.78 (s), 7.76 (d, J = 6 Hz, 8 Hz), 8.32 (s), 8.35 (d, J = 2 Hz, 6 Hz), 9.10 (d, J = 2 Hz, 6 Hz)). Reduction of 3b (0.72 g) was performed in HCl with SnCl₂ (2 g). The reaction mixture was heated for 1 h on a boiling water bath, then cooled to room temperature, and H₂S gas was bubbled through it. The mixture
was basified with NaOH and extracted with AcOEt. The extract was concentrated, and recrystallization of the residue from CHCl₃- n-C₄H₁₀ gave 4b (0.14 g, 80%), mp 218—220°C, PMR (CDCl₃): 6, 2.44 (s), 2.56 (s), 7.19 (dd, J = 6 Hz, 8 Hz), 7.36 (s), 8.05 (dd, J = 2 Hz, 8 Hz), 8.66 (dd, J = 2 Hz, 6 Hz). 4b (0.14 g) was dissolved in EtOH (10 ml), and BrCN (0.12 g) was added. Stirring was continued for 2 h. The mixture was basified with NaOH and extracted with CH₂Cl₂. The extract was subjected to silica gel column chromatography. Recrystallization of the product from CH₂Cl₂ gave brown crystals, 1b, mp 294—296°C. Spectral data of 1b were consistent with those described for Me-IQ isolated from broiled sardines. Recrystallization from MeOH-AcOEt containing dilute HBr gave 1b-HBr salt, mp >300°C in 70% yield (Anal. Calcd for C₁₂H₁₄N₄·HBr: C, 49.16; H, 4.82; N, 19.11; Found: C, 49.29; H, 4.52; N, 18.60).

References and Notes