Synthesis of a New Mutagenic Benzoazepinoquinolinone Derivative

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Abstract: A novel mutagenic compound **1**, isolated as a Maillard product from tryptophan and glucose, was synthesized using Larock's quinoline formation, where addition of iodonium cation to an acetylene moiety of *N*-propargylaniline triggers subsequent intramolecular electrophilic aromatic substitution to afford quinolines. The key synthetic intermediate **14** was obtained in a good yield when iodonium chloride was employed as an initiator of Larock's method. Conversion of **14** with another six steps, including annulation of a lactam ring and Curtius rearrangement, furnished the target molecule **1**. The synthesized and isolated **1** were identical in comparison of physical and spectral data.

Key words: Larock's quinoline formation, Curtius rearrangement, benzoazepinoquinolinone derivative

The browning reaction that produces melanoidine on heating reducing sugar and amino compounds, such as amino acids and peptides, is referred to the Maillard reaction. The reaction is important for making appetite-stimulating flavors during baking or heating; however, it sometimes yields undesirable compounds, for example, neurotoxic acrylamide produced from asparagine and glucose. Since the Maillard reaction can also produce carcinogenic or mutagenic fused-aromatic compounds as well as neurotoxic amines, a huge number of its products have been identified and assayed to date. Recently, one of the authors and his colleagues isolated a novel mutagenic compound from a Maillard reaction involving L-tryptophan and D-glucose as an amino acid and a sugar, respectively, and initiated by Fenton's reagent. The compound was presumed to be a benzoazepinoquinolinone derivative **1** based on spectroscopic data;[1] however, this was not confirmed with chemical evidence (Figure 1). Therefore, we embarked on the synthesis of **1** to confirm its structure and develop a method to provide enough amounts of **1** for further biological analysis.

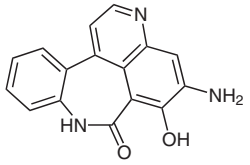

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Figure 1 Structure of compound **1**

Initially, Skraup's quinoline formation[2] was employed in the synthesis of **1** (Scheme 1). Namely, starting with 2-nitrophenyl vinyl ketone (**2**)[3] and 3,5-dimethyl-4-methoxyaniline (**3a**), easily produced from commercially available 2-nitrobenzaldehyde (**4**) and 2,6-dimethyl-4-nitrophenol (**5**), respectively, the quinoline derivative **6** was prepared according to Skraup's protocol. Although the yield was low, **6** was obtained; however, subsequent oxidation of the methyl groups resulted in unfertilized under all conditions tested.

Moreover, neither 3,5-dimethoxycarbonyl-4-methoxytoluene (**3b**) nor 3,5-dimethoxymethyl-4-methoxytoluene (**3c**) was a good substrate for Skraup's method. Since these difficulties could not be overcome, another strategy was needed.

After several attempts, our retrosynthetic analysis of **1** finally reached a promising strategy that employs Larock's quinoline formation, that is, the annulation reaction of *N*-(2-alkynyl)aniline with an appropriate electrophile.[4] Stated it concretely, 2-iodonitrobenzene (**7**) was first treated with propargyl alcohol in the presence of a palladium catalyst to afford 2-nitrophenylpropargyl alcohol (**8**), of which the hydroxyl group was converted to bromide **9** with carbon tetrabromide and triphenylphosphine (Scheme 2). On the other hand, nitration of 2-methoxyisophthalic acid (**10**)[5] and successive methylation of carboxylic acid by a conventional method gave dimethyl 2-methoxy-5-nitroisophthalate (**11**), the nitro group of which was reduced to an amino group by catalytic hydrogenation to afford dimethyl 5-amino-2-methoxyisophthalate (**12**). Next, the reaction of **9** and **12** in the presence of potassium carbonate gave the propargylamine derivative **13**.

The propargylamine **13** was transformed to a quinoline derivative **14**[7] using Larock's method, where addition of iodonium cation to an acetylene moiety of *N*-propargylaniline triggers subsequent intramolecular electrophilic aromatic substitution to furnish quinolines (Scheme 3).[4] Herein, iodonium chloride was preferably employed to other iodonium sources, for example, iodine, as an initiator for giving a good yield of **14**. Subsequent reduction of the iodo group of **14** with palladium in the presence of formic acid, followed by catalytic hydrogenation on Pd/C for

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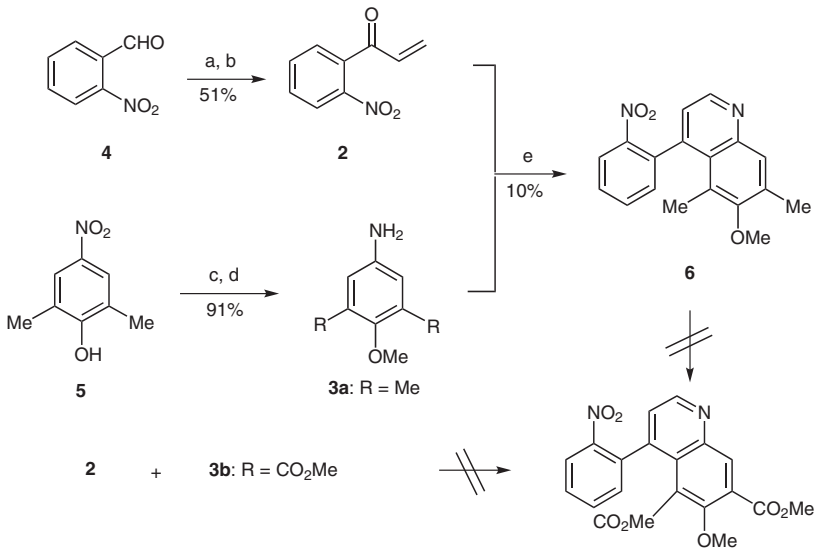

Scheme 1 Early synthetic route to mutagenic compound **1**. *Reagents and conditions*: a: H_2C=CHMgBr (1.5 equiv), THF, –20 °C; b: Dess–Martin periodinane (1.2 equiv), CH_2Cl_2, 0 °C; c: MeI (2.5 equiv), K_2CO_3 (3.0 equiv); acetone, 50 °C; d: Pd/C, H_2, EtOH, r.t.; e: AcOH, sodium 3-nitrobenzenesulfonate (3 equiv).

the reduction of the nitro group yielded amine **15**. Treatment of **15**[8] with methanesulfonic acid at a high temperature provided the ε-lactam derivative **16**,[9] of which the methyl ester was saponified to carboxylic acid and further converted to *tert*-butyl carbamate by Curtius rearrangement with diphenyl phosphoryl azide (DPPA)[6] in *tert*-butyl alcohol to afford compound **17**.[10] In the final step, synchronous cleavage of methyl and Boc protecting groups with boron tribromide furnished the target molecule **1**.[11] The spectral data and physical properties of the synthesized compound were completely consistent with those of the mutagenic component isolated from Maillard medium.

In conclusion, we succeeded in the total synthesis of the mutagenic compound **1**, which was isolated as a Maillard product from tryptophan and glucose, by taking advantage of Larock's quinoline formation. A comparison of spectral data showed that the synthesized and isolated compounds are identical, confirming the structure of **1** shown in Figure 1. Finally, the synthesized form of **1** showed as potent mutagenic activity as **1** isolated from the Maillard medium.

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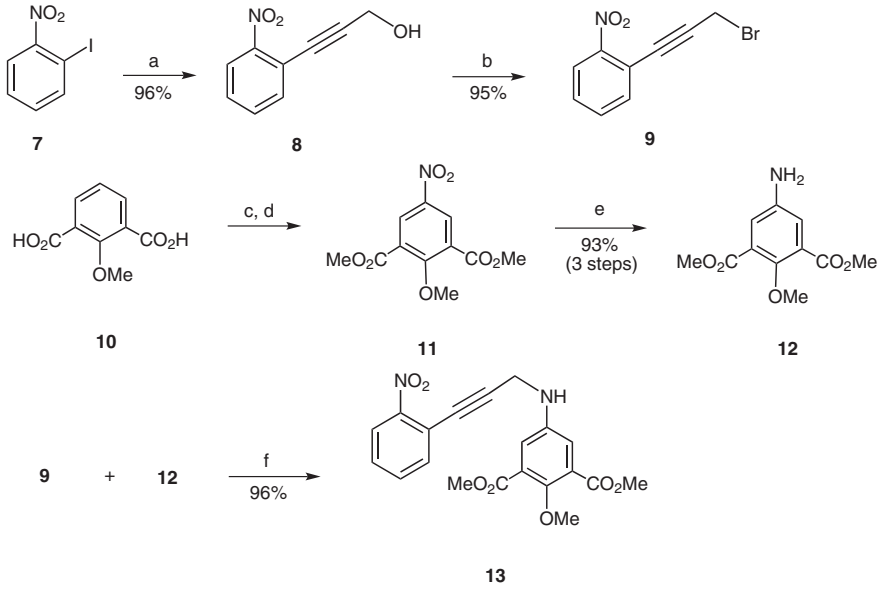
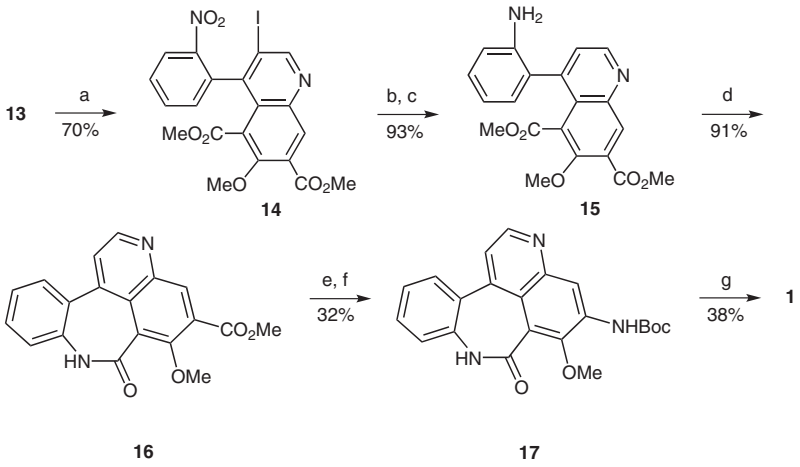


Scheme 2 Synthetic route to propargyl amine (**13**). *Reagents and conditions*: (a) propargyl alcohol (1.8 equiv), $Pd(PPh_3)_2Cl_2$ (2 mol%), CuI (7 mol%), Et_3N, r.t.; (b) CBr_4 (1.2 equiv), Ph_3P (1.2 equiv), CH_2Cl_2, 0 °C; (c) HNO_3, H_2SO_4, r.t.; (d) 5% HCl in MeOH, 70 °C; (e) Pd/C, H_2, *i*-PrOH, 80 °C; (f) K_2CO_3 (1.5 equiv), DMF, r.t.



Scheme 3 Synthetic route of compound **1**. *Reagent and conditions*: (a) ICl (5.6 equiv), $NaHCO_3$ (3.0 equiv), MeCN, 40 °C; (b) $Pd(PPh_3)_4$ (0.2 equiv), HCO_2H (3.0 equiv), Et_3N (3.0 equiv), DMF, 50 °C; (c) Pd/C, H_2, *i*-PrOH, 50–80 °C; (d) MsOH (0.3 equiv), 2-dichlorobenzene, 150 °C; (e) 2 M KOH aq MeOH, r.t.; (f) DPPA (6.3 equiv), Et_3N (9.5 equiv), *t*-BuOH, reflux; (g) BBr_3 (8.7 equiv), CH_2Cl_2, –78 °C.

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(7) **Compound 14**
$NaHCO_3$ (859.8 mg, 10.23 mmol) and ICl (1.0 mL, 19.09 mmol) were added to a soln of **13** (1.35 g, 3.40 mmol) in MeCN (15 mL) at r.t., and the mixture was stirred at 40 °C for 25.5 h. The reaction mixture was quenched with a sat. aq soln of $Na_2S_2O_3$, and diluted with a sat. aq soln of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc = 2:1) to afford **14** (1.25 g, 70%). Yellow crystals; mp 194–195 °C (hexane–EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.25 (s, 1 H), 8.75 (s, 1 H), 8.41 (dd, *J* = 8.0, 1.3 Hz, 1 H), 7.82 (dt, *J* = 8.0, 1.3 Hz, 1 H), 7.75 (dt, *J* = 8.0, 1.7 Hz, 1 H), 7.28 (br d, *J* = 8.0 Hz, 1 H), 4.00 (s, 3 H), 3.81 (s, 3 H), 3.23 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 164.7, 156.8, 155.3, 147.9, 143.5, 136.6, 135.2, 133.9, 133.2, 130.7, 127.2, 126.0, 125.8, 124.8, 101.3, 70.9, 64.1, 52.8, 52.2. IR (KBr): 1730, 1608, 1525, 1471, 1438, 1344, 1248, 1213, 1168 cm^{-1}. MS (70 eV): *m/z* (%) = 522 (100) [M$^+$], 491 (16), 400(12), 335 (37), 275 (32). HRMS: *m/z* calcd for $C_{20}H_{15}IN_2O_7$ [M$^+$]: 521.9924; found: 521.9931.

(8) **Compound 15**
Tetrakis(triphenylphosphine) palladium (5.0 mg, 0.004 mmol), Et_3N (12 μL, 0.087 mmol), and formic acid (2.7 μL, 0.065 mmol) were added to a soln of **14** (22.7 mg, 0.043 mmol) in *N*,*N*-dimethylformamide (1 mL) at r.t., and the mixture was stirred at 50 °C for 3 h. The reaction mixture was poured into a sat. aq soln of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc = 1:1.5) to afford deiodine compound (16.8 mg, 98%). A suspension of the above compound (15.7 mg, 0.040 mmol) and 10% Pd/C (3.1 mg) in 2-PrOH (1.0 mL) was stirred for 0.5 h at 50 °C and for another 1 h at 80 °C under a hydrogen atmosphere. The mixture was filtered with Celite, and the filtrate was concentrated in vacuo to remove the organic solvent. The residue was purified by column chromatography on silica gel (hexane–EtOAc = 1:1.5) to afford **15** (13.8 mg, 95%). Pale yellow crystals; mp 198–199 °C (hexane–EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.96 (d, *J* = 4.2 Hz, 1 H), 8.76 (s, 1 H), 7.39 (d, *J* = 4.2 Hz, 1 H), 7.24 (ddd, *J* = 8.1, 7.4, 1.3 Hz, 1 H), 6.99 (dd, *J* = 8.1, 1.3 Hz, 1 H), 6.84 (dt, *J* = 7.4, 1.3 Hz, 1 H), 6.80 (dd, *J* = 8.1, 1.3 Hz, 1 H), 4.01 (s, 3 H), 3.89 (s, 3 H), 3.53 (br, 2 H), 3.27 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 165.1, 154.6, 150.4, 145.5, 144.5, 144.3, 136.4, 131.1, 129.9, 127.3, 126.9, 126.5, 126.1, 122.7, 117.9, 115.8, 64.2, 52.7, 52.2. IR (KBr): 3436, 3381, 2950, 1728, 1643, 1606, 1487, 1448, 1248, 1224, 1149 cm^{-1}. MS (70 eV): *m/z* (%) = 366 (44) [M$^+$], 306 (100), 291 (67), 275 (52), 259 (85), 219 (56), 203 (43), 102 (34), 77 (16). HRMS: *m/z* calcd for $C_{20}H_{18}N_2O_5$ [M$^+$]: 366.1215; found: 366.1207.

(9) **Compound 16**
A soln of **15** (66.8 mg, 0.182 mmol) and MsOH (3.5 mL, 0.055 mmol) in *o*-dichlorobenzene (2.0 mL) was stirred at 150 °C for 2 h. The reaction mixture was poured into a sat. aq soln of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc = 1:2) to afford **16** (55.6 mg, 91%). Yellow crystals; mp 190–191 °C (hexane–EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.89 (d, *J* = 4.5 Hz, 1 H), 8.50 (s, 1 H), 8.03 (s, 1 H), 7.60 (d, *J* = 4.5 Hz, 1 H), 7.45 (ddd, *J* = 7.9, 7.1, 1.3 Hz, 1 H), 7.33 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.27 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1 H), 7.13 (dd, *J* = 8.4, 1.3 Hz, 1 H), 4.13 (s, 3 H), 3.98 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 165.7, 162.9, 149.6, 142.6, 142.1, 136.8, 135.0, 132.1, 131.8, 130.7, 130.2, 129.0, 125.9, 121.6, 121.4, 116.3, 63.9, 52.7. IR (KBr): 3058, 2950, 1735, 1660, 1591, 1475, 1286, 1195, 1120 cm^{-1}. MS (70 eV): *m/z* (%) = 334 (100) [M$^+$], 317 (96), 305 (46), 277 (29), 246 (27), 218 (31), 203 (49), 102 (44).

HRMS: *m/z* calcd for $C_{19}H_{14}N_2O_4$ [M$^+$]: 334.0953; found: 334.0947.

(10) **Compound 17**

An aq soln of KOH (2 M, 1.0 mL) was added to a soln of **16** (89.3 mg, 0.267 mmol) in MeOH (0.4 mL), and the mixture was stirred at r.t. for 8.5 h. The reaction mixture was concentrated in vacuo to remove the solvent. The residue was dissolved in H_2O, and the pH was adjusted to 6 with an aq soln of 2 M HCl. The mixture was extracted with $CHCl_3$ and EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH = 2:1) to afford a carboxylic acid derivative (62.2 mg, 73%). Diphenyl phosphoryl azide (0.8 ml, 3.76 mmol) and Et_3N (0.8 ml, 5.74 mmol) were added to a soln of the above compound (192.5 mg, 0.601 mmol) in *t*-BuOH (3.0 mL) at r.t., and the mixture was refluxed for 27.5 h. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (hexane–EtOAc = 1:1) to afford **17** (103.7 mg, 44%). Pale yellow crystals; mp 108–109 °C (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.84 (s, 1 H), 8.81 (d, *J* = 4.6 Hz, 1 H), 8.49 (s, 1 H), 7.51 (s, 1 H), 7.44 (d, *J* = 4.6 Hz, 1 H), 7.42 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1 H), 7.35 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.26 (ddd, *J* = 7.6, 7.2, 1.2 Hz, 1 H), 7.14 (dd, *J* = 8.0, 1.2 Hz, 1 H), 4.16 (s, 3 H), 1.56 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 156.0, 152.1, 148.9, 144.4, 141.4, 135.0, 133.6, 132.0, 130.8, 130.2, 125.7, 125.5, 121.3, 120.1, 119.0, 112.9, 81.3, 63.4, 28.3 (3 C). IR (KBr): 3433, 2978, 1732, 1657, 1591, 1523, 1479, 1353, 1336, 1234, 1155 cm^{-1}. MS (70 eV): *m/z* (%) = 391 (5 [M$^+$], 335 (11), 291 (27), 274 (13), 262 (27), 57 (100), 41 (52). HRMS: *m/z* calcd for $C_{22}H_{21}N_3O_4$ [M$^+$]: 391.1532; found: 391.1538.

(11) **Compound 1**

A soln of BBr_3 in CH_2Cl_2 (1 M, 170 μL, 0.170 mmol) was added to a soln of **17** (13.4 mg, 0.034 mmol) in CH_2Cl_2 (0.4 mL) at –78 °C, and the mixture was stirred at –78 °C for 2 h. The mixture was poured into a sat. aq soln of $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was roughly purified with preparative thin-layer chromatography (hexane–EtOAc = 1:5) and the powder obtained was further purified by washing with $CHCl_3$ and MeOH to afford **1** (3.5 mg, 38%). Ocher powder; mp (dec.). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 15.23 (s, 1 H), 10.42 (s, 1 H), 8.51 (d, *J* = 4.6 Hz, 1 H), 7.43 (dd, *J* = 1.5, 8.0 Hz, 1 H), 7.41 (dd, *J* = 1.5, 8.0 Hz, 1 H), 7.30 (d, *J* = 4.6 Hz, 1 H), 7.29 (dd, *J* = 1.5, 6.9 Hz, 1 H), 7.24 (dt, *J* = 1.5, 8.0 Hz, 1 H), 7.20 (s, 1 H), 5.82 (s, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.1, 157.5, 147.3, 144.9, 141.4, 140.6, 137.1, 131.7, 130.2, 128.0, 125.6, 120.7, 120.3, 117.9, 111.8, 104.5. IR (KBr): 3469, 3298, 3193, 1637, 1593, 1521, 1469, 1409, 1353, 1313, 1286, 1259 cm^{-1}. MS (70 eV): *m/z* (%) = 277 (100) [M$^+$], 259 (63), 231 (40), 204 (32), 177 (18), 102 (11), 77 (7). HRMS: *m/z* calcd for $C_{16}H_{11}N_3O_2$ [M$^+$]: 277.0851; found: 277.0856.