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Two-Step Synthetic Route to 10-Substituted Isoalloxazines

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Abstract: 10-Substituted isoalloxazines were synthesized in two steps starting from 1,2-phenylenediamine. Monoalkylation of the diamine resulted in 2-amino-*N*-alkylanilines, which were subsequently condensed with alloxan in boric acid and acetic acid to give 10-substituted isoalloxazines.

Keywords: Flavin mimic, flavoenzyme, isoalloxazines, monoalkylation

Flavin coenzymes represented by FAD (flavin adenine dinucleotide) and FMN (flavin mononucleotide) play important roles in a wide variety of redox reactions through interactions with apoproteins.[1–4] There has been considerable debate over the reaction pathways and mechanisms utilized by these flavoproteins because of the complexity of the native enzymatic systems.[5–9] Synthetic models play a crucial role here, as they help us to understand the individual interactions and reaction pathways, which become somewhat difficult with the complex flavoenzyme systems. Isoalloxazines have been widely used by many groups as synthetic models for flavin to observe the effects of individual interactions on flavoenzyme behavior.[10–14] As a result, 10-substituted isoalloxazines have been synthesized via a number of routes.[12–18] However, the methods involve expensive starting materials as well as a number of synthetic steps. We report here a simple two-step method for the synthesis of 10-substituted isoalloxazines.

Our synthetic strategy involves the selective monoalkylation of 1,2-phenylenediamine followed by cyclization of the 2-amino-*N*-alkylanilines with

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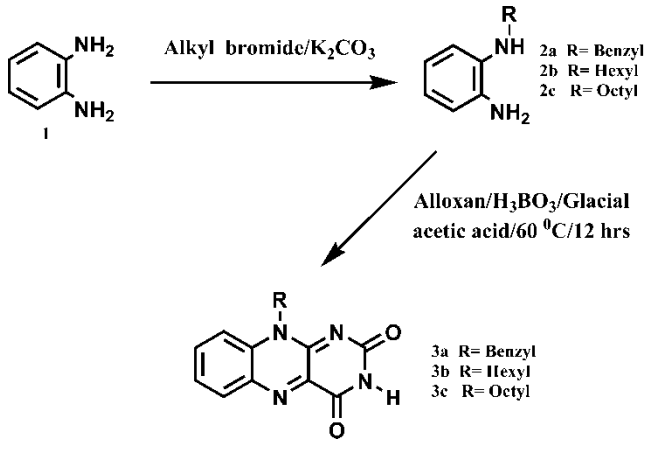

Scheme 1.

alloxan in acidic conditions. Alkylation of a primary amino group normally results in the formation of secondary, tertiary and quaternary amine salts. However, the monoalkylated product can be selectively obtained by using amines in large excess. Thus, 2-amino-*N*-alkylanilines were synthesized by the reaction of alkyl bromides with an excess of 1,2-phenylenediamine and anhydrous potassium carbonate in dry methanol for 12 h. The reaction mixture was concentrated in vacuo, and the residue was flash chromatographed on silica gel (230–400 mesh) using hexane–ethyl acetate (9 : 1) as eluent to obtain pure 2-amino-*N*-alkylanilines in 50–60% yields. The products were characterized by IR and ^{1}H NMR. The unreacted 1,2-phenylenediamine was recovered by using methanol as a eluent. The cyclocondensation of 2-amino-*N*-alkylanilines with alloxan in boric acid and acetic acid resulted in the formation of 10-alkylated isoalloxazines. Acetic acid was removed in vacuo, and the residue was flash chromatographed on silica gel (230–400 mesh) using $CHCl_3$–MeOH (97 : 3) as eluent to obtain pure 10-alkylated isoalloxazines in 45–50% yields. The products were characterized by various spectroscopic data including IR, ^{1}H, ^{13}C NMR, and mass spectrometry. This is a more efficient synthetic route because it not only helps in reducing at least one synthetic step in the preparation of 10-alkylated isoalloxazines but also is more economical because of inexpensive starting materials (Scheme 1).

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Nicolet Protégé 460 FTIR spectrometer, using potassium bromide pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Spectrospin DPX 300. Tetramethylsilane was used as internal reference, and the chemical shifts are expressed as

displacement (δ) in ppm downfield from tetramethylsilane. Mass spectrum for **3a** was recorded on a quadrupole mass spectrometer (VG Platform-II) using acetonitrile–water (1 : 1) as mobile phase. Mass spectra for **3b, c** were recorded on a Quadrupole-TOF Ultima on ESI mode using acetonitrile containing 0.1% formic acid. Elemental analyses were taken on a Perkin-Elmer 2400C elemental analyzer. Column chromatography was carried out using Spectrochem silica gel 230–400 mesh for flash chromatography. The solid compounds were dried under vacuum in the presence of P_2O_5.

General Procedure for the Synthesis of 2-Amino-*N*-alkylanilines

o-Phenylenediamine **1** (4.00 g, 37 mmol) was dissolved in methanol (20 ml). To this, benzyl bromide (1.36 g, 8.0 mmol) and K_2CO_3 (3.0 g, 21.7 mmol) were added. The reaction mixture was allowed to stir at rt for 20 h. The solvent was evaporated, and the residue was flash chromatographed on a silica-gel column (230–400 mesh) [5–20% (v/v) ethyl acetate in hexane] to give 2-amino-*N*-benzylaniline **2a** as a dark brown viscous liquid.

General Procedure for the Synthesis of 10-Alkyl Isoalloxazines

2-Amino-*N*-benzylaniline **2a** (0.59 g, 3.0 mmol) was dissolved in acetic acid (10 ml), and the contents were heated to 50 °C. To this, a preheated (50 °C) mixture of alloxan monohydrate (0.48 g, 3.0 mmol) and boric acid (0.22 g, 3.5 mmol) in acetic acid was added. The reaction mixture was stirred overnight at 50–55 °C. Acetic acid was removed in vacuo, and the solid obtained was flash chromatographed on a silica-gel column (230–400 mesh) [1–3% (v/v) methanol in chloroform] to give the product **3a** as bright yellow solid.

Data

1-(*N*-Benzylamino)-2-aminobenzene (2a): Yield 0.78 g, 50%; IR ν_{max} (KBr)/cm^{-1} 3335, 1057; δ_H (300 MHz, $CDCl_3$) 7.37–7.23 (m, 5H, Ph), 6.81 (m, 1H, Ph), 6.68 (m, 3H, Ph), 4.26 (s, 2H, $-CH_2Ph$), 3.37 (br, 3H, $-NH-$ and $-NH_2$).

10-Benzylisoalloxazine (3a): mp 273–276 °C; yield 0.40 g, 45%; IR ν_{max} (KBr)/cm^{-1} 3446, 1717, 1683, 1243; δ_H (300 MHz, DMSO-d_6) 11.47 (s, 1H, NH), 8.16 (d, 1H, Ph), 7.84–7.79 (m, 1H, Ph), 7.68–7.57 (m, 2H, Ph), 7.36–7.25 (m, 5H, Ph), 5.90 (br s, 2H, $-CH_2Ph$); ^{13}C NMR (DMSO-d_6) δ 47.22, 116.71, 126.18, 126.90, 127.60, 128.74, 131.86, 132.38, 134.62, 134.89, 139.38, 151.23, 155.91, 159.89; ESI mass: 327.38 ($M^+ + Na$), 305.40 ($M^+ + H$). Anal. calcd. for $C_{17}H_{12}N_4O_2$: C, 67.10; H, 3.97; N, 18.41. Found C, 67.12; H, 4.17; N, 18.27.

1-(*N*-Hexylamino)-2-aminobenzene (2b): Yield 0.90 g, 57%; IR ν_{max} (KBr)/ cm^{-1} 3330, 2920, 1599, 1515, 1453, 1265, 730; δ_H (300 MHz, $CDCl_3$) 6.83–6.79 (m, 1H, Ph), 6.71–6.62 (m, 3H, Ph), 3.39–3.28 (br m, 3H, –NH– and $-NH_2$), 3.10–3.04 (t, 2H, $-CH_2$), 1.70–1.61 (m, 2H, $-CH_2$), 1.43–1.26 [m, 6H, $-(CH_2)_3$], 0.91–0.85 (t, 3H, $-CH_3$).

10-Hexylisoalloxazine (3b): mp 246-247 °C; yield 0.44 g, 48%; IR ν_{max} (KBr)/cm^{-1} 3440, 2920, 1715, 1681, 1240; δ_H (300 MHz, $CDCl_3$) 10.51 (s, 1H, NH), 8.24–8.21 (d, 1H, Ph), 7.88–7.82 (m, 1H, Ph), 7.60–7.54 (m, 2H, Ph), 4.62 (t, 2H, $-CH_2$), 1.84–1.74 (m, 2H, $-CH_2$), 1.45–1.18 [m, 6H, $-(CH_2)_3$], 0.86–0.81 (t, 3H, $-CH_3$); ^{13}C NMR (DMSO-d_6) δ 13.88, 22.03, 25.82, 26.41, 30.97, 44.20, 116.34, 125.95, 131.83, 132.35, 134.88, 134.97, 138.66, 150.35, 155.71, 159.75; ESI-LRMS calcd. for $(C_{16}H_{18}N_4O_2 \cdot H)^+$ 299.159, found 299.106. Anal. calcd. for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found C, 64.85; H, 6.20; N, 18.47.

1-(*N*-Octylamino)-2-aminobenzene (2c): Yield 0.93 g, 60% IR ν_{max} (KBr)/ cm^{-1} 3329, 3044, 2923, 1599, 1513, 1454, 1268, 737; δ_H (300 MHz, $CDCl_3$) 6.84–6.80 (m, 1H, Ph), 6.72–6.64 (m, 3H, Ph), 3.40-3.30 (br m, 3H, –NH– and $-NH_2$), 3.11–3.06 (t, 2H, $-CH_2$), 1.71–1.61 (m, 2H, $-CH_2$), 1.42–1.28 [m, 10H, $-(CH_2)_5$], 0.90–0.86 (t, 3H, $-CH_3$).

10-Octylisoalloxazine (3c): mp 248–249 °C; yield 0.43 g, 50%; IR ν_{max} (KBr)/cm^{-1} 3443, 2922, 1714, 1683, 1242; δ_H (300 MHz, $CDCl_3$) 8.54 (s, 1H, NH), 8.35–8.33 (d, 1H, Ph), 7.96–7.91 (m, 1H, Ph), 7.66–7.64 (m, 2H, Ph), 4.71 (t, 2H, $-CH_2$), 1.87 (br m, 2H, $-CH_2$), 1.58–1.28 [m, 10H, $-(CH_2)_5$], 0.88 (t, 3H, $-CH_3$); ^{13}C NMR (DMSO-d_6) δ 13.98, 22.13, 26.19, 26.48, 28.65, 28.78, 31.24, 44.23, 116.38, 125.99, 131.86, 132.39, 134.91, 135.00, 138.70, 138.99, 150.38, 155.76, 159.80; ESI-LRMS calcd. for $(C_{18}H_{22}N_4O_2 \cdot H)^+$ 327.182, found 327.160. Anal. calcd. for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.17. Found C, 66.45; H, 7.06; N, 16.91.

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