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Alternate Method for the Synthesis of N-Alkyl/aralkyl-2-(α-hydroxy Alkyl/ aralkyl)benzimidazoles via Regiospecific Acetylation

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Abstract: Acetylation of 1H-2-(α-hydroxyalkyl/aryl)benzimidazoles **2** with Ac_2O results in the regiospecific formation of O-acetoxy derivative **3**, which on alkylation with alkylating agents in nonaqueous media under phase-transfer catalytic conditions affords N-alkyl derivatives **4**. The latter, on hydrolysis in an aqueous basic medium, results in the title compounds **5** in good yields in high purity. Alternatively, **5** can also be obtained by reduction of 1-substituted-2-acetyl/benzoylbenzimidazoles **8** using $NaBH_4$.

Keywords: alkylation, 2-α-hydroxybenzimidazoles, hydrolysis, 2-keto benzimidazoles, $NaBH_4$, regiospecific acetylation

Substituted benzimidazole derivatives exhibit[1] have been shown a wide range of biological properties. They also have commercial application in veterinary medicine as anthelmintic agents and in such diverse human therapeutic areas as anti-ulcerous, antihypertensive, antiviral, antifungal, anticancerous, and antihistaminic agents. They also find application as molecular probes,[2] to name just a few of their uses.

In continuation of our earlier work[3–5] on synthesis of new benzimidazole derivatives with potential biological activity, we have been interested in the

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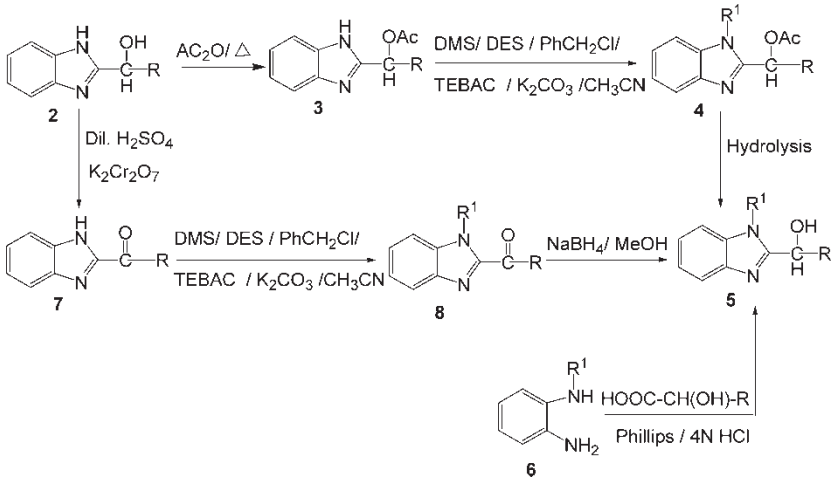
synthesis of N-alkyl/aralkyl-2-sub-(α-hydroxyalkyl/aralkyl)benzimidazoles. The results of our studies in this direction are presented in this communication.

o-Phenylenediamine **1**, on condensation with ($\pm$) lactic acid in 4N HCl (i.e., Phillips condition), gave the previously reported[6] 1H-2-(α-hydroxyethyl)benzimidazole (**2a**, i.e., **2**, R = CH_3). Acetylation of **2a** with acetic anhydride gave an acetyl derivative of **3a**, which could probably be one of the two regiospecific products (i.e., the N-acetyl or O-acetyl derivative of **2a**) based on its mass spectrum and ^{1}H NMR spectrum. Treatment of this product with dimethyl sulphate, in the presence of a base, gave a monomethylated derivative **3a**, which could once again be one of the two probable regioisomers (i.e., N-methylated derivative or O-methylated derivative) based on the starting intermediate being O-acetylated or N-acetylated compound. However, hydrolysis of **3a** with aq. alkali gave N-methyl-2-(α-hydroxyethyl)-benzimidazole **5a$_1$**, an authentic sample of which was also obtained by direct condensation of N-methyl-*o*-phenylenediamine **6a** (i.e., **6**, $R^1 = CH_3$) with ($\pm$) lactic acid under the Phillips condition using the literature procedure.[7] Based on these results, the structure of the regioisomer **2a** was unambiguously assigned as the O-acetyl derivative of 1H-2-(α-hydroxyethyl)benzimidazole.

Thus, reaction of **3a** with diethyl sulphate and $PhCH_2Cl$ gave the corresponding N-ethyl/benzyl derivatives, which on aq. alkaline hydrolysis yielded the respective N-ethyl/benzyl-2-(α-hydroxyethyl)benzimidazoles.[8] This sequence of reactions has been advantageous in preparing N-substituted-2-(α-hydroxyethyl)-benzimidazoles. The reactions of **3a** have also been carried out with **3b** (i.e., R = Ph) (Scheme 1) and similar results were obtained. The compound **3b** itself was prepared from **1** and mandelic acid using the literature[9] procedure. Furthermore, it was found that **5a$_1$** could also be obtained by the reduction of



Scheme 1.

N-methyl-2-acetylbenzimidazole **8a$_1$**, which in turn was prepared by literature methods,[10,11] with $NaBH_4$, thereby establishing in an unambiguous manner the regiospecificity of acetylation of **2a**. All these reactions appear to be very general and have been extended to other derivatives of **8a$_1$**.

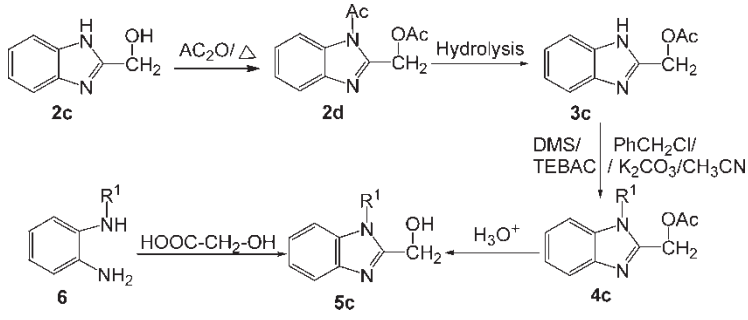
Condensation of **1** with glycolic acid in 4N HCl gave the previously reported[5] 2-hydroxymethylbenzimidazole **2c**. Acetylation of **2c** with acetic anhydride unexpectedly gave a diacetyl derivative of **2c**, as found from its spectral data. This latter product was assigned N-acetoxy-2-(acetoxymethyl)-benzimidazole **2d**, corresponding to simultaneous N- and O-acetylation of **2c**. Further, it was hydrolyzed by hot water, forming a monoacetyl derivative, which may be an N-acetyl or O-acetyl compound. Regiospecific studies were carried out for this compound similar to the previously mentioned sequence of reactions (i.e., alkylation followed by hydrolysis of **4c**). The resultant product **5c** (obtained by hydrolysis of diacetyl compound **2d**) could also be obtained by direct condensation of glycolic acid with **6** under Phillips conditions, which was confirmed by spectral and analytical data. From these studies, the product **3c** was found to be the O-acetyl derivative (Scheme 2).

The advantages of this protocol are regioselective acetylation, followed by alkylation studies in nonaqueous media under phase-transfer catalytic conditions to get the title compounds in good yields.

Alternatively, title compounds could also be prepared by reduction of 1-substituted-2-acetyl/benzoylbenzimidazole using $NaBH_4$ in excellent yields.

EXPERIMENTAL

Melting points are uncorrected and were determined in open capillary tubes in a sulphuric acid bath. Thin-layer chromatography (TLC) was performed on silica-gel G, and spotting was done using iodine or ultraviolet (UV) light. IR spectra were recorded with a Perkin-Elmer 1000 instrument in KBr phase. ^{1}H NMR was recorded on a Varian 200-MHz instrument, and mass



Scheme 2.

spectra were recorded on Agilent LC-MS instrument giving only $M^{+\cdot}$ values using Q + 1 mode.

Typical Procedure for 3

To a solution of **2** (10 mmol), acetic anhydride (11 mmol) was added, and the mixture was heated at 125–130°C under reflux for 2 h. At the end of this period, the reaction mixture was cooled to rt and poured into ice-cold water. The separated product was filtered, washed with water, and dried to obtain **3**. The crude **3** obtained was recrystallized from hot benzene to yield pure **3**.

When **2c** (10 mmol) was treated with acetic anhydride (22 mmol), it resulted in the formation of diacetyl derivative, which was hydrolyzed with water to give the monoacetyl derivative.

Typical Procedure for 4

To a solution of TEBAC (0.2 g) in CH_3CN (20 mL), K_2CO_3 (1.4 g, 10 mmol) was added, and the mixture was stirred at rt. To this mixture, under stirring, a solution of **3** (10 mmol) in CH_3CN (10 mL) was added, followed by alkylating agent (12 mmol). The progress of the reaction was monitored on TLC for the disappearance of **3**. On completion of reaction (~4 h), the mixture was filtered, and insoluble material was washed with CH_3CN (2 × 5 mL). The CH_3CN filterate was evaporated to dryness. The residue was treated with $CHCl_3$ (30 mL) and washed with water (3 × 30 mL), and the $CHCl_3$ layer was evaporated to dryness to obtain the product. The crude product was recrystallized from hot benzene to obtain pure **4**.

Typical Procedure for 5

A mixture of **4** (10 mmol) and aq. NaOH (20%, 10 mL) in MeOH (10 mmol) was stirred at rt for 30 min. The progress of the reaction was monitored on TLC for disappearance of **4**. On completion of the reaction, the mixture was poured into ice-cold water and neutralized with acetic acid. The mixture was extracted with ethyl acetate (2 × 10 mL). The organic layer was dried over anh. Na_2SO_4 and then evaporated to dryness, yielding a crude product. The crude product was recrystallized from ethyl acetate to obtain pure **5**.

Typical Procedure for Reduction of 8

$NaBH_4$ (0.37 g, 10 mmol) was added to MeOH (10 mL) under cooling conditions (5–10°C) and stirred for 5 min. To this, a solution of **7** (10 mmol)

taken in MeOH under cooling conditions was added over a period of 10 min. Then, the reaction mixture was brought to rt and stirred for 2 h. On completion of reaction, as confirmed by TLC, the excess solvent was removed by distillation. The residual reaction mixture was poured into ice-cold water under vigorous stirring. The separated product was filtered, washed with ice-cold water, and dried to obtain **5**.

Data

3a: R = CH_3, R^1 = H; yield = 82%; mp 150–152°C; IR (KBr): 2935, 1745 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ 1.87 (d, 3H, -CH-CH_3*), 2.13 (s, 3H, -O-CO-CH_3), 6.11 (q, 1H, -CH*-CH_3), 7.27–7.8 (m, 4H, aryl protons), 9.92 (bs, 1H, D_2O exchangeable, -NH); $M^+ + 1$:205.

3b: R = C_6H_5, R^1 = H; yield = 80%; mp 170–172°C; IR (KBr): 3025, 1741 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ 2.19 (s, 3H, -O-CO-CH_3), 6.89 (s, 1H, -CH-), 7.14–7.58 (m, 9H, aryl protons), 12.5 (bs, 1H, D_2O exchangeable, -NH); $M^+ + 1$:267.

3c: R = R^1 = H; yield =76%; mp 164 – 166°C; IR (KBr): 2895, 1736 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ 2.15 (s, 3H, -O-CO-CH_3), 5.39 (s, 2H, -CH_2-), 7.26–7.80 (m, 4H, aryl protons), 10.10 (bs, 1H, D_2O exchangeable, -NH).; $M^+ + 1$:191.

4a$_1$: R = R^1 = CH_3; yield = 82%; mp 70–72°C; IR (KBr): 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.8 (d, 3H, -CH-CH_3*), 2.1 (s, 3H, -O-CO-CH_3), 3.8 (s, 3H, -NCH_3), 6.15 (q, 1H, -CH*-CH_3), 7.2–7.7 (m, 4H, aryl protons). $M^+ + 1$:219

4a$_2$: R = CH_3, R^1 = C_2H_5; yield = 68%; mp 150–152°C; IR (KBr): 1742 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.45 (t, 3H, -CH_2-CH_3*), 1.8 (d, 3H, -CH-CH_3*), 2.1 (s, 3H, -O-CO-CH_3), 4.25 (doublet of quartet, 2H, -N-CH_2*-CH_3), 6.15 (q, 1H, -CH*-CH_3), 7.15–7.7 (complex m, 4H, aryl proton; $M^+ + 1$:233.

4a$_3$: R = CH_3, R^1 = CH_2-C_6H_5; yield = 72%; mp 78–80°C; IR (KBr): 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.75 (d, 3H, -CH-CH_3*), 1.8 (s, 3H, -O-CO-CH_3), 5.45 (q, 2H, -CH_2*-Ph), 6.15 (q, 1H, -CH*-CH_3), 6.9–7.9 (m, 9H, aryl protons); $M^+ + 1$:295.

4b$_1$: R = C_6H_5, R^1 = CH_3; yield = 73%; mp 48–50°C; IR (KBr): 1745 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.2 (s, 3H, -O-CO-CH_3), 3.65 (s, 3H, -NCH_3), 7.1 (s, 1H, -CH-), 7.2–7.8 (m, 9H, aryl protons); $M^+ + 1$:281.

4b$_2$: R = C_6H_5, R^1 = C_2H_5; yield = 69%; mp 118–120°C; IR (KBr): 1734 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.23 (t, 3H, -CH_2-CH_3*), 2.2

(s, 3H, -O-CO-CH_3), 4.2 (doublet of quartet, 2H, -N-CH_2*-CH_3), 7.1 (s, 1H,-CH), 7.2–7.8 (m, 9H, aryl protons); M^++1:295.

4b$_3$: R = C_6H_5, R^1 = CH_2- C_6H_5; yield = 74%; mp 98–100°C; IR (KBr): 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.95 (s, 3H, -O-CO-CH_3), 5.35 (dd, 2H, -CH_2-), 7.0 (s, 1H, -CH-), 7.1–7.75 (m, 14H, aryl protons); M^+ + 1:357.

4c$_1$: R = H, R^1 = CH_3; yield = 75%; mp 60–62°C; IR (KBr): 1747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.92 (s, 3H, -O-CO-CH_3), 3.58 (s, 3H, -NCH_3), 5.36 (s, 2H, -CH_2-), 7.15–7.8 (m, 4H, aryl protons); M^+ + 1:205.

4c$_2$: R = H; R^1 = CH_2-C_6H_5; yield = 69%; mp 78–80°C; IR (KBr): 1751 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.9 (s, 3H, -O-CO-CH_3), 5.35 (s, 2H, -CH_2-), 5.44 (s, 2H, -CH_2), 7.0–7.8 (m, 9H, aryl protons); M^+ + 1:281.

5a$_1$: R = R^1 = CH_3; yield = 80/71% (aq. NaOH/$NaBH_4$); mp 80–82°C; IR (KBr): 3145 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.70 (d, 3H, -CH-CH_3*), 3.9 (s, 3H, -NH_3) 5.1 (q, 1H, -CH*-CH_3), 5.45 (bs, 1H, D_2O exchangeable, -OH), 7.1–7.7 (m, 4H, aryl protons); M^+ + 1:177.

5a$_2$: R = CH_3, R^1 = C_2H_5; yield = 75/69% (aq. NaOH/$NaBH_4$); mp 102–104°C; IR (KBr): 3128 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.4 (t, 3H, -N-CH_2-CH_3*), 1.6 (d, 3H, -CH-CH_3*), 4.25 (q, 2H, -N-CH_2*-CH_3), 5.02 (q, 1H, -CH*-CH_3), 7.1-7.6 (m, 4H, aryl protons), 5.4 (bs, 1H, D_2O exchangeable, -OH); M^+ + 1:191.

5a$_3$: R = CH_3, R^1 = CH_2-C_6H_5; yield = 78/68% (aq. NaOH/$NaBH_4$); mp 124–126°C; IR (KBr): 3192 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.65 (d, 3H, -CH-CH_3*), 5.1 (doublet of quartet 1H, -CH*-CH_3), 5.4 (d, 1H, D_2O exchangeable, -OH), 5.65 (s, 2H, -NCH_2Ph), 7.1–7.8 (m, 9H, aryl protons); M^+ + 1:253.

5b$_1$: R = C_6H_5, R^1 = CH_3; yield = 78/70% (aq. NaOH/$NaBH_4$); mp 158–160°C; IR (KBr): 3062 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.45 (s, 3H, -NCH_3), 5.4 (bs, 1H, D_2O exchangeable, -OH), 6.10 (s, 1H, -CH-), 7.1–7.8 (m, 9H, aryl protons); M^+ + 1:239.

5b$_2$: R = C_6H_5, R^1 = C_2H_5; yield = 76/69% (aq. NaOH/$NaBH_4$); mp 162–164°C; IR (KBr): 3058 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ (t, 3H, -CH_2- CH_3*), 4.0 (doublet of quartet, -CH_2*-CH_3), 5.1 (bs, 1H, D_2O exchangeable, -OH), 6.0 (s, 1H, -CH-), 7.1–7.8 (m, 9H, aryl protons); M^++1:253.

5b$_3$: R = C_6H_5, R^1 = CH_2-C_6H_5; yield = 78/69% (aq. NaOH/$NaBH_4$); mp 162–164°C; IR (KBr): 3058 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.38

(dd, 2H, -N-CH_2Ph), 6.2 (s, 1H, -CH-), 6.45 (bs, 1H, D_2O exchangeable, -OH), 6.8–7.7 (m, 14H, aryl protons); $M^+ + 1$:315.

5c$_1$: R = H, $R^1 = CH_3$; yield = 76% (aq. NaOH); mp 96–98°C; IR (KBr): 3065 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.28 (s, 2H, -CH_2-), 3.8 (s, 3H, -NCH_3), 4.88 (s, 1H, D_2O exchangeable, -OH), 7.2–7.7 (m, 4H, aryl protons); $M^+ + 1$:163.

5c$_2$: R = H, $R^1 = CH_2$-C_6H_5; yield = 75% (aq. NaOH); mp 180–182°C; IR (KBr): 3145 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.72 (d, 2H, -CH_2*-OH), 5.55 (s, 2H, -CH_2Ph), 5.72 (improperly resolved triplet, 1H, D_2O exchangeable, -OH), 7.10–7.64 (m, 9H, aryl); $M^+ + 1$:239.

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