Direct Conversion of Hydroxy Aromatic Compounds to Heteroarylamines via a One-Pot Smiles Rearrangement Procedure

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8-Hydroxyquinoline (**9**) was converted to 8-aminequinoline (**10**) in a one-pot procedure involving alkylation with 2-bromo-2-methylpropionamide (**2**) followed by Smiles rearrangement and hydrolysis, in 41% yield. The scope and limitations of this new procedure were explored with additional hydroxyquinolines.

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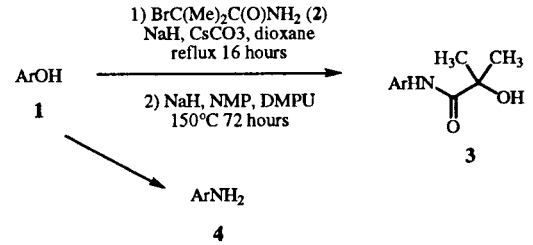
Introduction.

The Smiles rearrangement [1-4] is a useful procedure for converting an aromatic substituent *via* an intramolecular rearrangement which proceeds by nucleophilic displacement. A specific example of the Smiles rearrangement is one method for converting hydroxy aromatic compounds to their corresponding amino aromatic compounds [5-7]. We have recently described a one-pot procedure for converting hydroxy aromatic compounds **1** to the corresponding *N*-aryl-2-hydroxypropionamides **3**, using an alkylation-rearrangement procedure (Scheme I) [8]. Thus, **1** was treated with 2-bromo-2-methylpropionamide (**2**) and three equivalents each of sodium hydride and cesium carbonate in dioxane at reflux for 16 hours. After the reflux period, *N*-methylpyrrolidinone, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (10:1 ratio) and another equivalent of sodium hydride were added and the new mixture was heated at 150° for 72 hours to produce the 2-hydroxy-2-methyl-*N*-arylpropionamides **3** directly. In this report we describe the direct conversion of certain hydroxy aromatic compounds to the corresponding amino aromatic compounds **4** using these same conditions.

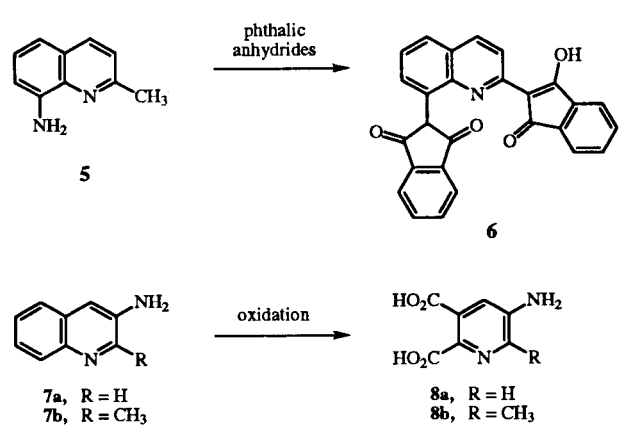
Scheme I. Smiles Rearrangement



Aminoquinolines are useful starting materials for the preparation of heterocycles. 8-Aminoquinaldine (**5**), for example, has been used to prepare quinophthalone pigments *e.g.*, **6** [9], as shown in Scheme II. 3-Aminoquinoline (**7a**) and 3-aminoquinaldine (**7b**) have been oxidized to the corresponding 5-aminopyridine-2,3-dicarboxylic acids **8a** and **8b** [10], respectively, which are highly functionalized pyridine building blocks. Pyridine-2,3-dicarboxylic acids, in turn, have been used as starting materials for the preparation of 2-(2-imidazolinyl)nicotinic acid herbicides [11-12]. Thus, we chose to study the conversion of hydroxyquinolines to aminoquinolines using our Smiles rearrangement procedure, as both a real and a model system of interest.

In addition, aminoquinolines have biological activity. The 3-, 5-, 6- and 8-aminoquinolines are antimalarial agents [13].

Scheme II

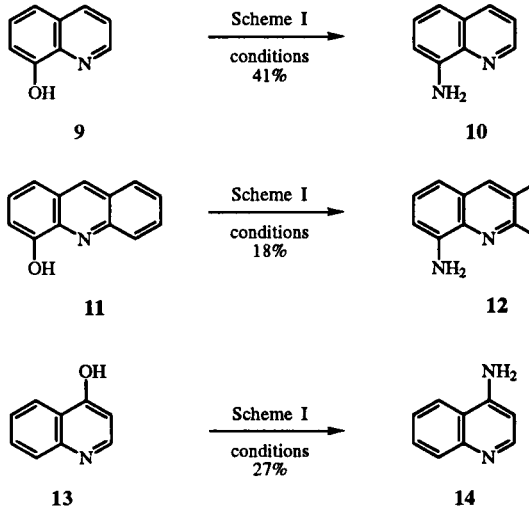


Results and Discussion.

In Scheme III are shown conversions of 8-hydroxyquinoline (**9**), 4-hydroxyacridine (**11**) and 4-hydroxyquinoline (**13**) to their corresponding amino compounds **10**, **12** and **14** using the conditions of Scheme I. While these conversions proceed in only moderate yields, it is significant that these transformations of hydroxy heteroaromatic compounds to amino heteroaromatic compounds are formally three-step procedures which proceed in one pot. Thus, these transformations involve alkylation of the hydroxy heteroaromatic compound with 2-bromo-2-methylpropionamide, Smiles rearrangement of the resulting 2-aryloxypropionamide to the corresponding 2-hydroxy-2-methyl-*N*-arylpropionamide, and *in situ* hydrolysis of the latter to the amino heteroaromatic compound.

Scheme III. Direct Conversions of Hydroxyquinolines to Aminoquinolines

Scheme III

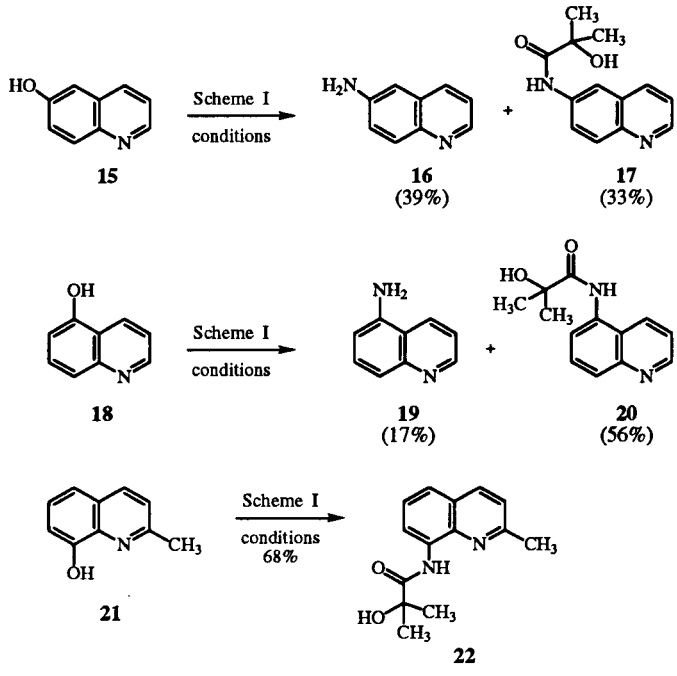


The amino heteroaromatic compounds produced by the reaction shown in Scheme III were the only products isolated from the reaction mixtures. The yields shown are unoptimized. The examples demonstrate that starting materials may have the hydroxy groups positioned on either ring of the quinoline, and that an acridine is also a suitable substrate.

Additional reactions which we studied with hydroxy heteroaromatic compounds are shown in Scheme IV. Treatment of 6-hydroxyquinoline (**15**) under the conditions of Scheme I gave a mixture of 6-aminoquinoline (**16**) and the corresponding 2-hydroxy-2-methylpropionamide **17** which was separated by flash chromatography to give these components in respective yields of 39% and 33%. Likewise, when 5-hydroxyquinoline (**18**) was exposed to these reaction conditions, 5-aminoquinoline (**19**) and its corresponding 2-hydroxy-2-methylpropionamide **20** were isolated in 17% and 56% yields, respectively. Interestingly, 8-hydroxyquinaldine (**21**) afforded only the 2-hydroxy-2-methylpropionamide **22** in 68% yield, and no 8-aminoquinaldine. The mass balances for all transformadons shown in Scheme IV were quite good.

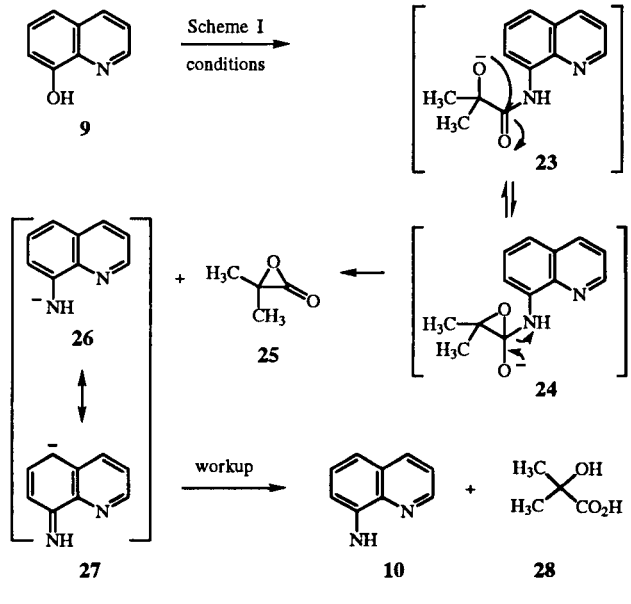
We feel that the propensity for hydroxyquinolines to be converted to aminoquinolines under the described conditions is related to the electron-deficient nature of the quinolines. Thus, the facile amide hydrolysis may be explained by the mechanism shown in Scheme V, as depicted for 8-hydroxyquinoline (**9**). Oxyanion **23** might be in equilibrium with oxyanion **24**, which could decay to stabilized aminoquinoline anion **26** by loss of a suitably electron-deficient leaving group. It makes intuitive sense that 8-hydroxyquinaldine does not produce the corresponding aminoquinaldine: the electron-donating methyl group may offset the electron-deficient nature of the quinoline and cause the

Scheme IV



intermediate anion corresponding to **23** <=> **24** to stay intact. However, it is unclear why hydroxyquinolines **9** and **13** (and **11**) give rise to only the corresponding aminoquinolines while **15** and **18** produce mixtures of aminoquinolines and unhydrolyzed 2-hydroxy-2-methylpropionamides.

Scheme V



The methodology described here may prove extremely useful to those engaged in the synthesis and use of amino heteroaromatic compounds. The conditions which have been developed for the one-pot conversion of hydroxyquinolines

to aminoquinolines may be the conditions of choice for other electron-deficient systems as well.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Tlc analyses were performed with EM Science silica gel 60 F_{254} plates, with visualization by uv irradiation. Flash chromatography was performed with EM Separations silica gel 60 (0.040-0.063 mm). The nmr spectra were recorded on a Varian VXR 300, Gemini-300 or EM-390 spectrometer. The ir spectra were recorded on a Perkin-Elmer Model 1800 or Mattson Galaxy 5020 FT-IR spectrophotometer. The ms data were collected on a Finnigan MAT 4600 or MAT TSQ-700 spectrometer. Steroids were purchased from Berlichem; other reagents were purchased from Aldrich Chemical Company.

2-Bromo-2-methylpropionamide (**2**).

To a vigorously stirring mixture of 42.0 g (0.180 mole) of bromoisobutyryl bromide and 500 ml of hexane at 0° was added 80 ml of concentrated aqueous ammonium hydroxide in portions over a 30-minute period. After an additional 30 minutes of stirring at 0°, the resulting white precipitate was collected, washed with cold water and air-dried. Crystallization from chloroform-hexane (200 ml-20 ml) afforded 31.2 g (100%) of **2** as shiny white plates, mp 146-148° (lit [7] mp 147-148°).

One-Pot Conversion of 8-Hydroxyquinoline (**9**) to 8-Aminoquinoline (**10**).

To a solution of 537 mg (3.70 mmoles) of 8-hydroxyquinoline (**9**) in dioxane (20 ml) was added 300 mg (12.2 mmoles) of dry sodium hydride and 4.00 g (12.2 mmoles) of cesium carbonate. The mixture was stirred at room temperature for 30 minutes, then 2.03 g (12.2 mmoles) of 2-bromo-2-methylpropionamide was added and the resulting mixture was heated at reflux for 16 hours. After the reflux period, *N*-methylpyrrolidone (20 ml), 1,3-dimethyl-3,4,5,6-tetrahydro-(1*H*)-pyrimidinone (2 ml) and 100 mg (4.07 mmoles) of dry sodium hydride were added and the resulting mixture was stirred and heated at 150° for 72 hours. The mixture was cooled and partitioned between water (50 ml) and ethyl acetate (100 ml). The aqueous layer was extracted with ethyl acetate (100 ml) and the combined organic extracts were washed with water (2 x 50 ml), dried (sodium sulfate) and concentrated to leave *ca.* 3 g of residue. Chromatography (30:70:1::ethyl acetate:hexane:triethylamine) gave 220 mg (41%) of 8-aminoquinoline (**10**) as an off-white solid, m.p. 65-67° (lit [14] mp 62.5-64°); ^{1}H nmr (deuteriochloroform): δ 8.76 (dd, J = 4.23, 1.75 Hz, 1 H), 8.06 (dd, J = 8.20, 1.96 Hz, 1 H), 7.37-7.30 (m, 2 H), 7.15 (dd, J = 8.01, 1.30 Hz, 1 H), 6.92 (dd, J = 7.51, 1.42 Hz, 1 H), 4.98 (br s, 2 H, NH_2); ms: (electron impact) m/z 144 (molecular ion).

Anal. Calcd. for $C_9H_8N_2$: C, 74.98; H, 5.59; N, 19.43. Found: C, 74.88; H, 5.67; N, 19.26.

One-Pot Conversion of 4-Hydroxyacridine (**11**) to 4-Aminoacridine (**12**).

To a solution of 722 mg (3.70 mmoles) of 4-hydroxyacridine (**11**) in dioxane (20 ml) was added 300 mg (12.2 mmoles) of dry sodium hydride and 4.00 g (12.2 mmoles) of cesium carbonate. The mixture was stirred at room temperature for 30 minutes, then 2.03 g (12.2 mmoles) of 2-bromo-2-methylpropionamide was added and the resulting mixture was heated at reflux for 16 hours. After the reflux period, *N*-methylpyrrolidone (20 ml), 1,3-dimethyl-3,4,5,6-tetrahydro-(1*H*)-pyrimidinone (2 ml) and 100 mg (4.07 mmoles) of dry sodium hydride were added and the resulting mixture was stirred and heated at 150° for 72 hours. The mixture was cooled and partitioned between water (50 ml) and ethyl acetate (100 ml). The aqueous layer was extracted with ethyl acetate (100 ml) and the combined organic extracts were washed with water (2 x 50 ml), dried (sodium sulfate) and concentrated to leave *ca.* 3 g of residue. The brown oil was chromatographed (1:9 then 3:7::ethyl acetate:hexane) to give 130 mg (18%) of 4-aminoacridine (**12**) as a brown solid, mp 98-100° (lit [15] mp 105-106°); ir (potassium bromide): 3377 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.66 (s, 1 H), 8.23-8.19 (m, 1 H), 7.98-7.95 (m, 1 H), 7.74-7.69 (m, 1 H), 7.53-7.48 (m, 1 H), 7.34 (d, J = 1.72 Hz, 1 H), 6.94 (d, J = 3.32 Hz, 1 H), 5.23 (br s, 2 H, NH_2); ms: (chemical ionization/ammonia) 195 (M + H$^+$).

Another fraction (90 mg of material) contained the rearrangement product by nmr, but the gc-ms showed only m/z 113. The starting 4-hydroxyacridine was also recovered (90 mg, 12%).

One-Pot Conversion of 4-Hydroxyquinoline (**13**) to 4-Aminoquinoline (**14**).

To a solution of 537 mg (3.70 mmoles) of 4-hydroxyquinoline (**13**) in dioxane (20 ml) was added 300 mg (12.2 mmoles) of dry sodium hydride and 4.00 g (12.2 mmoles) of cesium carbonate. The mixture was stirred at room temperature for 30 minutes, then 2.03 g (12.2 mmoles) of 2-bromo-2-methylpropionamide was added and the resulting mixture was heated at reflux for 16 hours. After the reflux period, *N*-methylpyrrolidone (20 ml), 1,3-dimethyl-3,4,5,6-tetrahydro-(1*H*)-pyrimidinone (2 ml) and 100 mg (4.07 mmoles) of dry sodium hydride were added and the resulting mixture was stirred and heated at 150° for 72 hours. The mixture was cooled and partitioned between water (50 ml) and ethyl acetate (100 ml). The aqueous layer was extracted with ethyl acetate (100 ml) and the combined organic extracts were washed with water (2 x 50 ml), dried (sodium sulfate) and concentrated to leave *ca.* 3 g of residue. The brown oil was distilled by Kugelrohr to remove residual *N*-methylpyrrolidone and 1,3-dimethyl-3,4,5,6-tetrahydro-(1*H*)-pyrimidinone. Chromatography (9:1::chloroform:methanol then 7:3::chloroform:methanol) gave 140 mg (26%) of 4-aminoquinoline (**14**) as an off-white solid, mp 146-148° (lit [16] mp 154-155°); ^{1}H nmr (deuteriochloroform): δ 8.30 (d, J = 6.20 Hz, 1 H), 8.22 (d, J = 8.39 Hz, 1 H), 7.78 (d, J = 8.89 Hz, 1 H), 7.68-7.62 (m, 1 H), 7.49-7.38 (m, 3 H), 6.59 (d, J = 5.99 Hz, 1 H); ms: (electron impact) m/z 144 (molecular ion).

One-Pot Conversion of 6-Hydroxyquinoline (**15**) to 6-Aminoquinoline (**16**).

To a solution of 537 mg (3.70 mmoles) of 6-hydroxyquinoline (**15**) in dioxane (20 ml) was added 300 mg (12.2 mmoles) of dry sodium hydride and 4.00 g (12.2 mmoles) of cesium carbonate. The mixture was stirred at room temperature for 30 minutes, then 2.03 g (12.2 mmoles) of 2-bromo-2-methylpropionamide was added and the resulting mixture was heated at reflux for 16 hours. After the reflux period, *N*-methylpyrrolidone (20 ml), 1,3-dimethyl-3,4,5,6-tetrahydro-(1*H*)-pyrimidinone (2 ml) and 100 mg (4.07 mmoles) of dry sodium hydride were added and the resulting mixture was stirred and heated at 150° for 72 hours. The mixture was cooled and

partitioned between water (50 ml) and ethyl acetate (100 ml). The aqueous layer was extracted with ethyl acetate (100 ml) and the combined organic extracts were washed with water (2 x 50 ml), dried (sodium sulfate) and concentrated to leave *ca.* 3 g of residue. The brown oil was distilled by Kugelrohr to remove residual *N*-methylpyrrolidone and 1,3-dimethyl-3,4,5,6-tetrahydro-(1*H*)-pyrimidinone. Chromatography (70:30:1::ethyl acetate:hexane:triethylamine) gave 210 mg (39%) of 6-aminoquinoline (**16**) as a brown solid, mp 111-113° (lit [17] mp 116°); ^{1}H nmr (deuteriochloroform): δ 8.66 (dd, J = 4.27, 1.63 Hz, 1 H), 7.93-7.87 (m, 2 H), 7.26 (dd, J = 8.24, 4.23 Hz, 1 H), 7.16 (dd, J = 9.05, 2.69 Hz, 1 H), 6.90 (d, J = 2.74 Hz, 1 H), 3.97 (br s, 2 H, NH_2); ^{13}C nmr (deuteriochloroform): δ 146.8, 144.5, 143.5, 133.7, 130.6, 129.7, 121.5, 121.4, 107.4; ms: (chemical ionization/ammonia) 145 (M + H$^+$).

Further chromatography gave 250 mg (33%) of the rearrangement product **17** as a brown solid, mp 162-165°; ir (potassium bromide): 1674 (CO), 3308 (OH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 9.02 (br s, 1 H, NH), 8.82 (dd, J = 4.35, 1.66 Hz, 1 H), 8.46 (d, J = 2.51 Hz, 1 H), 8.14-8.10 (m, 1 H), 8.06 (d, J = 9.12 Hz, 1 H), 7.60 (dd, J = 9.0, 2.49 Hz, 1 H), 7.38 (dd, J = 8.35, 4.33 Hz, 1 H), 3.20 (br s, 1 H, OH), 1.62 [s, 6 H, $C(CH_3)_2$]; ^{13}C nmr (deuteriochloroform): δ 174.7, 149.2, 145.4, 136.0, 135.5, 130.0, 128.8, 123.2, 121.6, 115.7, 74.3, 28.0; ms: (chemical ionization/ammonia) 231 (M + H$^+$).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.57; H, 6.36; N, 11.76.

One-Pot Conversion of 5-Hydroxyquinoline (**18**) to 5-Aminoquinoline (**19**).

To a solution of 537 mg (3.70 mmoles) of 5-hydroxyquinoline (**18**) in dioxane (20 ml) was added 300 mg (12.2 mmoles) of dry sodium hydride and 4.00 g (12.2 mmoles) of cesium carbonate. The mixture was stirred at room temperature for 30 minutes, then 2.03 g (12.2 mmoles) of 2-bromo-2-methylpropionamide was added and the resulting mixture was heated at reflux for 16 hours. After the reflux period, *N*-methylpyrrolidone (20 ml), 1,3-dimethyl-3,4,5,6-tetrahydro-(1*H*)-pyrimidinone (2 ml) and 100 mg (4.07 mmoles) of dry sodium hydride were added and the resulting mixture was stirred and heated at 150° for 72 hours. The mixture was cooled and partitioned between water (50 ml) and ethyl acetate (100 ml). The aqueous layer was extracted with ethyl acetate (100 ml) and the combined organic extracts were washed with water (2 x 50 ml), dried (sodium sulfate) and concentrated to leave *ca.* 3 g of residue. Chromatography (7:3::ethyl acetate:hexane) gave 90 mg (17%) of 5-aminoquinoline (**19**) as a brown solid, mp 98-100° (lit [18] mp 108-109°); ^{1}H nmr (deuteriochloroform): δ 8.89 (dd, J = 4.13, 2.06 Hz, 1 H), 8.18 (dd, J = 8.49, 0.93 Hz, 1 H), 7.60-7.48 (m, 2 H), 7.35 (dd, J = 8.56, 4.26 Hz, 1 H), 6.83 (dd, J = 7.13, 1.31 Hz, 1 H), 4.21 (br s, 2 H, NH_2); ^{13}C nmr (deuteriochloroform): δ 150.2, 149.1, 142.2, 130.0, 129.5, 120.1, 119.6, 118.7, 110.0; ms: (chemical ionization/methane) 145 (M+H$^+$).

Further chromatography gave 480 mg (56%) of the rearrangement product **20**, mp 177-179°; ir (potassium bromide): 1649 (CO), 3371 (OH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 9.37 (br s, 1 H, NH), 8.90 (dd, J = 4.26, 1.58 Hz, 1 H), 8.21 (d, J = 8.22 Hz, 1 H), 8.09 (d, J = 7.80 Hz, 1 H), 7.96 (d, J = 8.66 Hz, 1 H), 7.70 (apparent t, J = 8.06 Hz, 1 H), 4.01 (br s, 1 H, OH), 1.63 [s, 6 H, $C(CH_3)_2$]; ^{13}C nmr (deuteriochloroform): δ 175.3, 150.1, 148.4, 132.3, 129.55, 129.46, 122.1, 120.9, 120.O, 47.8, 27.9; ms: (chemical ionization/methane) 231 (M + H$^+$).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 68.17; H, 6.13; N, 12.32.

One-Pot Conversion of 8-Hydroxyquinaldine (**21**) to **22**.

To a solution of 722 mg (3.70 mmoles) of 8-hydroxyquinaldine (**21**) in dioxane (20 ml) was added 300 mg (12.2 mmoles) of dry sodium hydride and 4.00 g (12.2 mmoles) of cesium carbonate. The mixture was stirred at room temperature for 30 minutes, then 2.03 g (12.2 mmoles) of 2-bromo-2-methylpropionamide was added and the resulting mixture was heated at reflux for 16 hours. After the reflux period, *N*-methylpyrrolidone (20 ml), 1,3-dimethyl-3,4,5,6-tetrahydro-(1*H*)-pyrimidinone (2 ml) and 100 mg (4.07 mmoles) of dry sodium hydride were added and the resulting mixture was stirred and heated at 150° for 72 hours. The mixture was cooled and partitioned between water (50 ml) and ethyl acetate (100 ml). The aqueous layer was extracted with ethyl acetate (100 ml) and the combined organic extracts were washed with water (2 x 50 ml), dried (sodium sulfate) and concentrated to leave *ca.* 3 g of residue. The brown oil was chromatographed (3:7::ethyl acetate:hexane) to give 610 mg (68%) of the product **22** as an off-white solid, mp 143-144°; ^{1}H nmr (deuteriochloroform): δ 10.99 (br s, 1 H, NH), 8.76-8.73 (m, 1 H), 8.03 (d, J = 8.26 Hz, 1 H), 7.48-7.45 (m, 2 H), 7.32 (d, J = 9.21 Hz, 1 H), 2.80 (br s, 1 H, OH), 2.75 (s, 3 H, Ar-CH_3), 1.62 [s, 6 H, $C(CH_3)_2$]; ^{13}C nmr (deuteriochloroform): δ 174.9, 157.4, 138.2, 136.3, 133.5, 126.2, 126.1, 122.4, 121.6, 116.3, 74.2, 28.1, 25.4; ms: (chemical ionization, ammonia) 245 (M + H$^+$).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.78; H, 6.56; N, 11.37.

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