A Facile Preparation of 2-(2-Arylethyl)- and 2-(Aminomethyl)indoles

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An important process for the acid catalyzed cleavage of the benzoyl group from 3-benzoylindoles in high yield is identified and its application for the facile syntheses of 2-substituted indoles is demonstrated by preparing some 2-(2-arylethyl)- and 2-(aminomethyl)indoles from 1,3-dibenzoyl-2-bromomethylindole (**7**).

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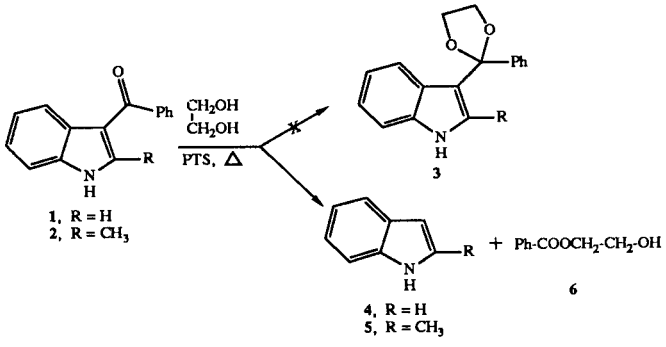
2-Substituted indoles are potential intermediates for the synthesis of many alkaloids and medicinally useful substances [1-10]. While procedures for the preparation of 3-substituted indoles are well established [8-10], there is a need for yet easier access to 2-substituted indoles [8-10]. Recently, allylic bromination of 2-methylindoles was used to synthesize several 2-substituted indoles [11,12]. This involved the protection of the reactive indole 3-position with an ethoxycarbonyl or a phenylthio group during key steps and removal of the protecting group in final steps [11,12].

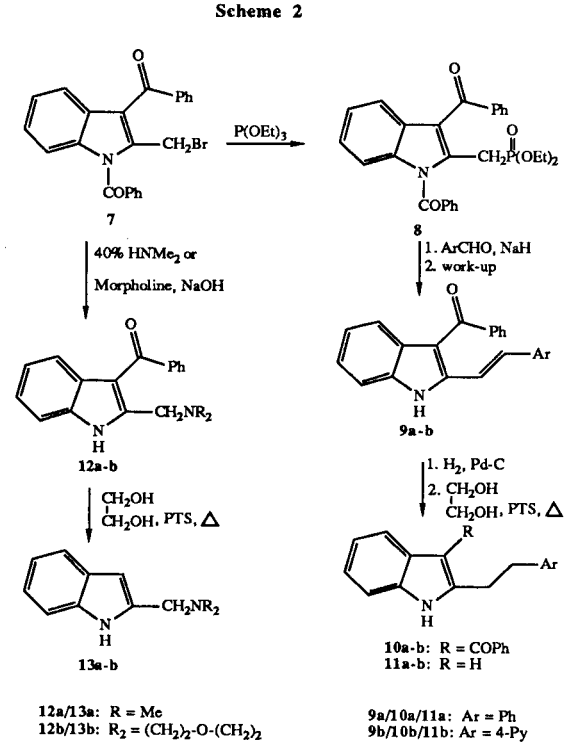
Recent computer modeling studies have shown that indole-based molecules have potential binding sites on sickle hemoglobin [13], and therefore efforts are being made to synthesize several substituted indoles and to study the structure-activity relationships that may exist among these compounds. During this process, we tried to prepare the ethylene ketal of 3-benzoylindole (**1**) adopting standard reaction conditions, using ethylene glycol in boiling benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid. Analysis of the reaction mixture by ^{1}H nmr at frequent intervals over a period of 6 hours did not show the formation of the desired product **3**; instead, it showed the complete disappearance of **1** at the end of 6 hours and the formation of indole (**4**) in 78% yield and 2-hydroxyethyl benzoate (**6**). The structure of **4** was confirmed by comparing it with an authentic sample. The ^{1}H nmr and mass spectral data were in consistent with the structure of **6** and it was confirmed further by hydrolyzing it to benzoic acid. A search of the literature revealed that similar acid catalyzed cleavage of the acetyl group from 3-acetylindole was observed during nitration, but in poor yields [14,15]. The proposed mechanism for cleavage of the acetyl group was to add water to the ketone to form the tetrahedral intermediate in order to facilitate the cleavage [16]. Isolation of product **6** in the present study confirms the same. The improved yield in the present study with the 3-benzoyl group may be due to its improved ability to accommodate the electron deficiency that develops as it is cleaved from the indole 3-carbon [16]. The transfer of the benzoyl group to ethylene glycol was also examined with 3-benzoyl-2-methylindole (**2**) and similar results were obtained to yield 2-methylindole (**5**) and product **6** in good yields.

The synthetic application of this reaction was further

Scheme 1



Scheme 2



utilized for the synthesis of some useful 2-substituted indoles. For this, the readily accessible 1,3-dibenzoyl-2-bromomethylindole [17] (**7**) was reacted with triethyl phosphite at 155-160° to give the phosphonate ester **8** in almost quantitative yield. The Wittig-Horner reaction of compound **8** with benzaldehyde and pyridin-4-carbaldehyde in tetrahydrofuran in the presence of sodium hydride followed by treatment with water gave the corresponding vinylindoles **9a** and **9b** in 65% and 62% respectively. Catalytic hydrogenation of indoles **9a** and **9b** at 40 psi in the presence of 10% palladium on charcoal provided 2-(2-arylethyl)-3-benzoylindoles **10a** and **10b** in 90% and 92% yields. Treatment of these compounds with *p*-toluenesulfonic acid and ethylene glycol, as described earlier, gave 2-(2-arylethyl)indoles **11a** and **11b** in 75% and 71% yields, respectively.

Reaction of **7** with boiling 40% aqueous dimethylamine gave 3-benzoyl-2-(dimethylaminomethyl)indole (**12a**). Similarly, reaction of **7** with morpholine followed by sodium hydroxide hydrolysis gave 3-benzoyl-2-(*N*-morpholinomethyl)indole (**12b**). Compounds **12a** and **12b** on reaction with *p*-toluenesulfonic acid and ethylene glycol gave 2-(dimethylaminomethyl)indole (**13a**) and 2-morpholinomethylindole (**13b**) in 64% and 61% overall yields from **7**, respectively. It was worth noting that the debenzoylation involving substrates with a basic nitrogen (compounds **11a**, **12a**, and **12b**) requires an excess amount of *p*-toluenesulfonic acid to facilitate the completion of the reaction.

In summary, a facile method for the cleavage of the benzoyl group from 3-benzoylindoles in high yield is identified and used for the preparation of some 2-(2-arylethyl)- and 2-(aminomethyl)indoles, useful intermediates for the preparation of alkaloids and medicinally important substances.

EXPERIMENTAL

Melting points were taken in capillary tubes on a Mel-Temp apparatus and are uncorrected. The ir spectra were obtained on a Beckman IR-33 spectrophotometer. The nmr spectra were run on a Chemagnetics A-200 or Nicolet QE-300 or Varian VXR-500S spectrometers using tetramethylsilane as the internal reference. The mass spectral data were obtained on a Finnegan 4000 mass spectrometer.

Formation of Indole (**4**) and 2-Methylindole (**5**).

A mixture of 3-benzoylindole (**1**) or 3-benzoyl-2-methylindole (**2**) [17] (5 mmoles), ethylene glycol (2 ml), and *p*-toluenesulfonic acid (100 mg) in dry benzene (100 ml) was heated under reflux for 6 hours and cooled. Saturated sodium bicarbonate solution (30 ml) was added and the benzene layer was separated. Solvent was distilled from the dried (sodium sulfate) benzene solution and the residue was chromatographed on a silica gel column and eluted with hexane to give products as a colorless oil, which on trituration with hexane became white crystalline powder.

Indole (**4**) was obtained in 78% yield (0.456 g), mp 53-54° (lit [18] 52-54°).

2-Methylindole (**5**) was obtained in 73% yield (0.48 g), mp 59-61° (lit [18] 58-60°).

Further elution of the column with chloroform gave 2-hydroxyethyl benzoate (**6**) as an oil (0.68 g, 82%); ^{1}H nmr (deuteriochloroform, 300 MHz): δ 3.93 (t, 2H, J = 4.6 Hz), 4.43 (t, 2H, J = 4.6 Hz), 7.41 (t, 2H, 7.5 Hz), 7.55 (t, 1H, J = 7.5 Hz), 8.05 (d, 2H, J = 7.5 Hz); ms: (CI) m/z 167 (M + 1, 100). A sample of **6** was hydrolyzed with 20% sodium hydroxide and acidified with concentrated hydrochloric acid to give benzoic acid, comparable with an authentic sample.

Diethyl [2-(1,3-Dibenzoylindolyl)methyl]phosphonate (**8**).

A mixture of 2-bromomethyl-1,3-dibenzoylindole (**7**) [17] (8.36 g, 0.20 mole) and triethyl phosphite (3.65 g, 0.22 mole) was heated at 155-160° under argon for 3 hours and excess triethyl phosphite was distilled under reduced pressure. The oily residue was mixed with hexane (100 ml) and cooled at 5° for 3 hours. The colorless crystalline product formed was filtered and dried (9.03 g, 95%), mp 97-98°; ir (potassium bromide): ν 1685, 1635, 1540, 1440, 1360, 1340, 1260, 1240, 1210, 1010 cm^{-1}; ^{1}H nmr (deuteriochloroform, 500 MHz): δ 1.01-1.08 (t, 6H), 3.85-3.95 (q, 4H), 4.05-4.16 (d, 2H, J = 22.5 Hz), 6.74-7.90 (m, 14H).

Anal. Calcd. for $C_{27}H_{26}NO_5P$: C, 68.20; H, 5.51. Found: C, 68.43; H, 5.49.

2-(2-Arylvinyl)-3-benzoylindoles **9a-b**.

Sodium hydride (0.192 g, 8 mmoles) was added to a well-stirred solution of **8** (1.9 g, 4 mmoles) and benzaldehyde (0.424 g, 4 mmoles) or pyridine-4-carboxaldehyde (0.428 g, 4 mmoles) in dry tetrahydrofuran (50 ml) under argon at -25° and allowed to warm to room temperature. After 24 hours water (10 ml) was added cautiously and the mixture was stirred at 60° for 4 hours. Solvents were evaporated and the residue was partitioned between water (100 ml) and ethyl acetate (100 ml). The organic phase was separated, dried (sodium sulfate) and solvents evaporated. The residue was chromatographed on a silica gel (230-400 mesh, 50 g) column and eluted with 10% ethyl acetate in hexane to give products.

3-Benzoyl-2-(2-phenylvinyl)indole (**9a**) was obtained in 65% yield (0.84 g), mp 159-160°; ir (potassium bromide): ν 3220-3200, 1600, 1570, 1450, 1410, 1220 cm^{-1}; ^{1}H nmr (deuteriochloroform, 300 MHz): δ 7.11-7.58 (m, 14H), 7.80-7.83 (d, 2H, J = 16.2 Hz), 9.47 (s, 1H, NH); ms: (CI) m/z 324 (M + 1, 100).

Anal. Calcd. for $C_{23}H_{17}NO$: C, 85.42; H, 5.30. Found: C, 85.31; H, 5.54.

3-Benzoyl-2-[2-(4-pyridyl)vinyl]indole (**9b**) was obtained in 62% yield (0.80 g), mp 232-233°; ir (potassium bromide): ν 3060-3040, 1610, 1590, 1425, 1410, 1310, 1190, 930 cm^{-1}; ^{1}H nmr (deuteriochloroform, 300 MHz): δ 6.98-7.79 (m, 9H), 8.41-8.50 (m, 3H); ms: (CI) m/z 325 (M + 1, 1.44), 169 (3.05), 85 (100).

Anal. Calcd. for $C_{22}H_{16}N_2O$: C, 81.46; H, 4.97. Found: C, 81.62; H, 4.99.

2-(2-Arylethyl)-3-benzoylindoles **10a-b**.

A solution of vinylindole **9a** or **9b** (0.65 g, 2 mmoles) in ethanol (50 ml) was hydrogenated at 40 psi in the presence of 10% palladium on charcoal for 6 hours and the catalyst was removed by filtration. The filtrate was concentrated to about 10 ml and cooled. The white crystalline product formed was filtered and dried.

3-Benzoyl-2-(2-phenylethyl)indole (**10a**) was obtained in 90% yield (0.585 g), mp 156-157°; ir (potassium bromide): ν 3240-3220,

1610, 1580, 1480, 1450, 1435, 1360, 1325, 1220, 1010, 900, 750 cm^{-1}; ^1H nmr (deuteriochloroform, 300 MHz): δ 2.97-3.04 (t, 2H), 3.23-3.31 (t, 2H), 7.03-7.77 (m, 14H), 8.76 (bs, 1H, NH).

Anal. Calcd. for $C_{23}H_{19}NO$: C, 84.89; H, 5.89. Found: C, 84.73; H, 5.82.

3-Benzoyl-2-[2-(4-pyridyl)ethyl]indole (**10b**) was obtained in 92% yield (0.60 g), mp 193-194°; ir (potassium bromide): ν 3240, 1610, 1580, 1560, 1440, 1425, 1410, 1360, 1220, 1150, 960 cm^{-1}; ^1H nmr (deuteriochloroform, 300 MHz): δ 3.02-3.10 (t, 2H), 3.27-3.35 (t, 2H), 7.00-7.60 (m, 9H), 7.72 (d, 2H), 8.44 (d, 2H), 11.19 (bs, 1H, NH); ms: (CI) m/z 327 (M + 1, 100).

Anal. Calcd. for $C_{22}H_{18}N_2O$: C, 80.95; H, 5.56. Found: C, 81.17; H, 5.48.

2-(2-Arylethyl)indoles **11a-b**.

A mixture of indole **10a** or **10b** (2 mmoles), ethylene glycol (1 ml) and *p*-toluenesulfonic acid (50 mg for **10a** and 450 mg for **10b**) in dry benzene (50 ml) was heated under reflux for 6 hours and worked-up using the method described for **3**. The crude product was purified by flash chromatography on silica gel using hexane-chloroform (1:1) as the eluent.

2-(2-Phenylethyl)indole (**11a**) was obtained in 75% yield (0.33 g), mp 95-96° (lit [12] 95°).

2-[2-(4-Pyridyl)ethyl]indole (**11b**) was obtained in 71% yield (0.315 g), mp 139-140°; ir (potassium bromide): ν 3050-3040, 1525, 1480, 1465, 1094, 1046, 1028, 963 cm^{-1}; ^1H nmr (deuteriochloroform, 300 MHz): δ 3.00 (bs, 4H), 6.18 (s, 1H), 6.96-7.06 (m, 4H), 7.18 (d, 1H), 7.43-7.47 (d, 1H), 7.90 (bs, 1H, NH), 8.42-8.44 (d, 2H); ms: (CI) m/z 223 (M + 1, 100).

Anal. Calcd. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35. Found: C, 81.32; H, 6.31.

3-Benzoyl-2-(dimethylaminomethyl)indole (**12a**).

2-Bromomethyl-1,3-dibenzoylindole **7** (0.836 g, 2 mmoles) was mixed with 40% aqueous dimethylamine (20 ml), heated under reflux for 2 hours and cooled to room temperature. It was extracted with ether (2 x 20 ml), dried (potassium carbonate) and the solvent was evaporated to leave product **12a** as a viscous oil, which solidified on trituration with ethanol (0.47 g, 85%). An analytical sample was prepared by recrystallization from ethanol; mp 110-111°; ^1H nmr (deuteriochloroform, 300 MHz): δ 2.40 (s, 6H, N-Me_2), 3.99 (s, 2H, CH_2-N), 7.01-7.80 (m, 9H), 8.17 (bs, 1H, NH).

Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52. Found: C, 77.84; H, 6.49.

3-Benzoyl-2-(*N*-morpholinomethyl)indole (**12b**).

To a solution of **7** (0.836 g, 2 mmoles) in tetrachloromethane (25 ml), morpholine (0.332 g, 4 mmoles) was added and the mixture was stirred at room temperature for 2 hours. The white crystalline solid (morpholine hydrochloride) formed was filtered and the solvent was evaporated from the filtrate. Sodium hydroxide solution (10%, 10 ml) was added to the residue and the mixture was heated at 80° for 1 hour. It was cooled to room temperature, extracted with ether (2 x 20 ml) and dried (sodium sulfate). Evaporation of solvents gave product **12b** as an oil (0.536 g, 88%). An analytical sample was prepared by preparative thin-layer chromatography using 20% ethyl acetate in chloroform as the eluent; ^1H nmr (deuteriochloroform, 200 MHz): δ 2.52 (t, 4H), 3.73 (t, 4H), 3.87 (s, 2H, CH_2-N), 7.06-7.79 (m, 9H), 9.58 (s, 1H, NH); ms: (CI) m/z 321 (M + 1, 100).

Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.97; H, 6.29. Found: C, 75.18; H, 6.49.

2-(Dialkylaminomethyl)indoles **13a** and **13b**.

A mixture of 3-benzoyl-2-(dialkylaminomethyl)indole **12a** or **12b** (1 mmole), ethylene glycol (1 ml) and *p*-toluenesulfonic acid (225 mg) in dry benzene (20 ml) was heated under reflux for 6 hours and cooled to room temperature. It was worked-up as reported for **3** and the crude product was purified by passing through a column of silica gel using 5% methanol in chloroform as the eluent.

2-(Dimethylaminomethyl)indole (**13a**) was obtained in 75% yield (0.13 g), mp 59-61° (lit [19] 60-61°).

2-(*N*-Morpholinomethyl)indole (**13b**) was obtained in 69% yield (0.15 g) as an oil, mp of picrate 189-190° (lit [11,19] 190-191°).

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