A New Synthesis of *o*-Nitrobenzylketones. Intermediates for the Synthesis of 2-Substituted Indoles

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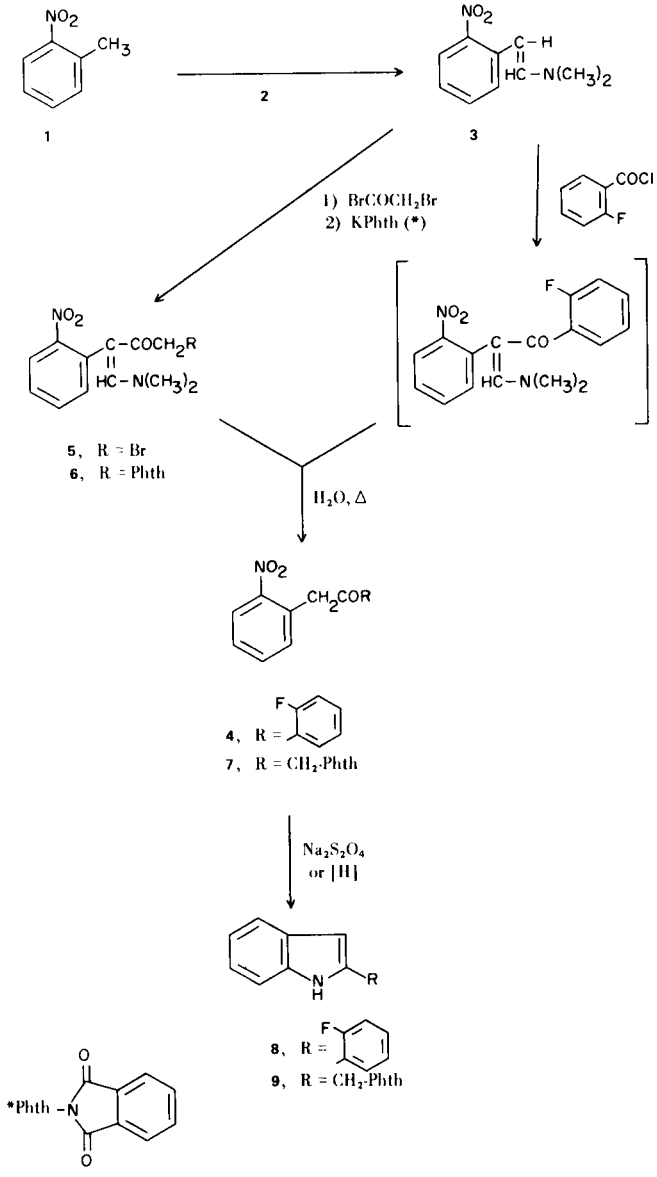
The synthesis of indoles by the reductive cyclization of *o*-nitrobenzylcarbonyl compounds is well documented (1). Since this procedure provides a convenient route to 2-substituted indoles that are otherwise difficultly accessible, it seemed to us that a new approach towards the synthesis of *o*-nitrobenzylketones would be of value in broadening the scope of this reaction. An attractive candidate as the starting material for such a synthesis appeared to be the enamine which would result from condensation of *o*-nitrotoluene with an acetal of *N,N*-dimethylformamide (2). Acylation of this enamine (3), followed by hydrolysis would be expected to yield a β-hydroxymethyl ketone which could readily decarbonylate to form the final *o*-nitrobenzyl ketone.

Chart I



We now wish to describe the synthesis of 2-alkyl or 2-aryl substituted indoles utilizing *o*-nitrobenzyl ketones obtained *via* the reaction sequence described above. Thus, reaction of *o*-nitrotoluene (**1**) with *N,N*-dimethylformamide diethyl acetal (**2**) in refluxing dimethylformamide solution resulted in the formation of *trans*-β-dimethylamino-2-nitrostyrene (**3**) (4,5). Treatment of **3** with *o*-fluorobenzoyl chloride followed by direct hydrolysis of the reaction mixture effected the desired three-step sequence of acylation, hydrolysis and deformylation to give 2′-fluoro-2-(2-nitrophenyl)acetophenone (**4**). Similarly, bromoacetylation of **3** gave the acylenamine **5** which was isolated in 71% yield. Compound **5** was converted in a straightforward fashion to the phthalimido derivative **6** and this in turn was hydrolyzed and decarbonylated to the ketone **7**. Reduction of compounds **4** and **7**, either catalytically or with sodium hydrosulfite, gave the desired indoles **8** and **9**, respectively.

EXPERIMENTAL

All melting points are corrected. Ir spectra were determined with a Beckmann IR-9 spectrophotometer, nmr with a Varian A-60 spectrometer, mass spectra with a CEC 21-100 spectrometer and ultraviolet spectra in ethanol with a Cary Model 14 spectrophotometer. The uv ε values refer to ε x 10^{-3}.

trans-β-Dimethylamino-2-nitrostyrene (**3**).

A solution of 34.3 g. (0.25 mole) of 2-nitrotoluene in a mixture of 37 g. (0.25 mole) of *N,N*-dimethylformamide diethylacetal (**2**) and 100 ml. of dimethylformamide was heated under reflux for 26 hours. The dark reaction mixture was concentrated by first removing the lower boiling components on a rotary evaporator and then distilling the unreacted 2-nitrotoluene at *ca.* 75°/0.2 mm. The residual dark, red liquid (35 g., 72%), the

structure of which has previously been documented (4.5), was used directly in the experiments below without further purification.

2′-Fluoro-2-(2-nitrophenyl)acetophenone (**4**).

To a stirred solution of 26.2 g. (0.136 mole) of **3** and 13.7 g. (0.136 mole) of triethylamine in 150 ml. of benzene was added dropwise 21.8 g. (0.136 mole) of 2-fluorobenzoyl chloride. The resultant mixture was stirred and heated under reflux for 15 hours. Sufficient water was then added to dissolve the salts which had precipitated and the organic layer was separated and concentrated. The oil obtained was dissolved in a mixture of 150 ml. of dioxane-50 ml. of water and the resultant solution was heated under reflux for 18 hours and then concentrated. The residue was extracted with dichloromethane, dried and evaporated to an oil. The oil was dissolved in a small volume of cold ethanol and scratched to initiate crystallization. After refrigeration, filtration gave 18.5 g. of crude **4**. Filtration over 200 g. of florisil with benzene as the eluant yielded 16 g. (45%) of **4** as white crystals, m.p. 84-86°. Recrystallization from carbon tetrachloride gave white prisms, m.p. 85-86°; nmr (DMSO-d_6): δ 4.86 (d, 2H, J = *ca.* 2.3 Hz); ir (chloroform): 1695 cm^{-1} (C=O).

Anal. Calcd. for $C_{14}H_{10}FNO_3$: C, 64.86; H, 3.89; N, 5.40. Found: C, 65.02; H, 4.03; N, 5.48.

α-Bromoacetyl-β-dimethylamino-2-nitrostyrene (**5**).

To a stirred, ice-cooled solution of 38.4 g. (0.2 mole) of **3** and 16 g. (0.2 mole) of pyridine in 200 ml. of ether was added dropwise 40.4 g. (0.2 mole) of bromoacetyl bromide dissolved in 50 ml. of ether. After stirring in an ice-bath for 1.5 hours, the suspension was filtered and the solid was washed with ether. The somewhat oily solid was partitioned between dichloromethane-water and the organic layer was separated, washed, dried, and evaporated to dryness. The solid was recrystallized from dichloromethane-hexane to give amber needles, m.p. 125-127°. The yield of **5** was 44.6 g. (71%); nmr (DMSO-d_6): δ 2.78 (s, 6H), 4.16 (s, 2H), 7.76 (s, 1H); ir (chloroform) 1658 (C=O); mass spectrum, molecular ion at 312; π max 215 nm (infl.) (ϵ, 13.5), 250 (infl.) (6) and 317 (16.4).

Anal. Calcd. for $C_{12}H_{13}BrN_2O_3$: C, 46.02; H, 4.18; N, 8.95. Found: C, 45.84; H, 4.48; N, 8.92.

α-Phthalimidoacetyl-β-dimethylamino-2-nitrostyrene (**6**).

To a stirred suspension of 18.5 g. (0.1 mole) of potassium phthalimide in 700 ml. of warm DMF was added 31.4 g. (0.1 mole) of **5**. The resultant solution was stirred at room temperature for 2 hours and then was poured into 1 l. of ice-water. The precipitated solid was filtered, washed with water and recrystallized from methanol-dichloromethane to give 30 g. (79%) of **6** as orange prisms, m.p. 230-233°. The microanalytical sample was obtained by an additional recrystallization from methanol-dichloromethane, m.p. 237-239°.

Anal. Calcd. for $C_{20}H_{17}N_3O_5$: C, 63.32; H, 4.52; N, 11.08. Found: C, 63.34; H, 4.36; N, 11.24.

1-(2-Nitrophenyl)-3-phthalimido-2-propanone (**7**).

A solution of 22.8 g. (0.06 mole) of **6** in a mixture of 950 ml. of dioxane and 50 ml. of water was heated under reflux for 70 hours and then evaporated at reduced pressure. The residue was extracted with dichloromethane, washed, dried, and filtered over florisil. Elution with dichloromethane gave 10.6 g. (54%) of **7** as a tan solid, m.p. 179-182°. Recrystallization from methanol-dichloromethane yielded white needles, m.p. 181-183°; nmr (DMSO-d_6): δ 4.52 (s, 2H), 4.82 (s, 2H).

Anal. Calcd. for $C_{17}H_{12}N_2O_5$: C, 62.96; H, 3.73; N, 8.64. Found: C, 63.02; H, 3.76; N, 8.71.

2-(2-Fluorophenyl)indole (**8**).

To 15.6 g. (0.06 mole) of **4** dissolved in a mixture of 150 ml. THF-150 ml. ethanol-100 ml. water was added portionwise, 24 g. of sodium hydrosulfite. The mixture was stirred and heated on the steam bath for 10 minutes and after an additional 100 ml. of water was added, stirring was continued at room temperature for 20 minutes. At this point, more sodium hydrosulfite (16 g.) was added portionwise and after warming, the mixture was stirred at room temperature for 20 minutes and evaporated at reduced pressure to remove the organic solvents. The solid which separated was filtered and washed with water. This aqueous filtrate was treated with 100 ml. of 6 *N* hydrochloric acid and heated on the steam bath for 15 minutes. The resultant suspension was filtered and the two solids were combined and recrystallized from hexane (small amount undissolved was discarded) to give 5.9 g. (46%) of **8** as white needles, m.p. 97-98°; ir (chloroform) 3490 (N-H); uv: π max 225 nm (ϵ, 23.7), 240 (18.6), and 3.11 (27.55).

Anal. Calcd. for $C_{14}H_{10}FN$: C, 79.60; H, 4.77; N, 6.63. Found: C, 79.89; H, 4.72; N, 6.61.

N-(2-Indolylmethyl)phthalimide (**9**).

A.

Using the same procedure employed for the synthesis of **8**, 10 g. (0.03 mole) of **7** was reduced with 20 g. of sodium hydrosulfite in a mixture of 300 ml. of ethanol-250 ml. of THF and 250 ml. of water. After removing the organic solvents, the aqueous solution was filtered and the resultant solid was suspended in 250 ml. of 8 *N* sulfuric acid-300 ml. of chloroform and warmed on the steam bath for 5 minutes. The organic layer was separated, washed, dried, and concentrated to give 3.3 g. of **9** as an off-white solid. Treatment of the original aqueous filtrate with sulfuric acid-chloroform in the same fashion gave an additional 0.9 g. of product. The total yield of **9** was 4.2 g. (50%), m.p. 215-219°. Recrystallization from acetonitrile gave pale-yellow needles, m.p. 226-228.5°; nmr (DMSO-d_6): δ 5.00 (s, 2H), 6.35 (broad, 1H, indole 3-H); ir (chloroform): 3460 cm^{-1} (N-H).

Anal. Calcd. for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 74.01; H, 4.25; N, 10.14.

B.

A solution of 20.7 g. (0.064 mole) of **7** in 200 ml. of DMF was treated with *ca.* 10 g. of Raney nickel catalyst and the mixture was reduced in a Parr apparatus at an initial pressure of 46 psi. After hydrogen absorption ceased, the mixture was filtered and the DMF filtrate was evaporated to dryness. The residual solid was recrystallized from acetonitrile-dichloromethane to yield 11.4 g. (65%) of **9**, m.p. 215-220°, identical in all respects to the product obtained by method A.

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