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An improved Bischler indole synthesis to obtain 2-arylindole scaffolds

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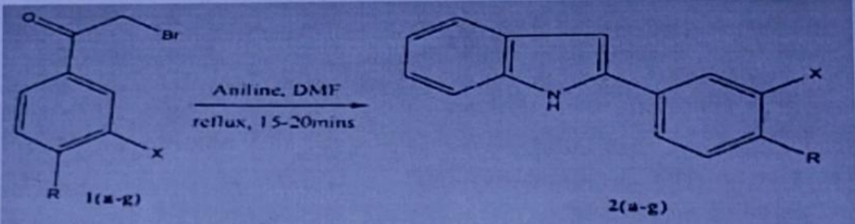
Introduction

2-Phenylindoles are much significant scaffolds in medicinal chemistry because of their wide spread bioactivity. They exist in natural alkaloids and synthetic compounds bearing potent biological activities as well as optoelectronic properties. The indole nucleus has been reported for a broad spectrum of biological activities such as anti-inflammatory[1-3] , anti-convusant[4] , cardiovascular[5] and anti bacterial[6] . And also the indolealkaloids were reported for anti-cancer[7] , anti-tumour[8] , anti-inflammatory, hypoglycemic , analgesic and antipyretic activities[9] . Thus , effective and economical synthesis of indoles from simple starting materials under mild reaction conditions is the remarkable task among organic chemists . Indoles have been syntheszed by various methods[10]. Bartoli indole synthesis, Bischler indole synthesis, Fischer indole synthesis, Hemtsberger indole syntghesis, Julia indole synthesis Larock indole sythesis, Leimrgruber,Batcho indole synthesis, Madelung indole synthesis, Nenitzescu indole synthesis, Ressert indole synthesis, Sunderberg indole synthesis. Most of the methods really on the metal catalysts such as palladium complexes[11] , copper complexes[12] , gold(III) salts[13] and ruthenium complexes[14] for the cyclization step. Various solid catalysts , carboxyl-functionalized ionic liquids and other greener techniques have also been reported for indole synthesis[15]. Besides the well established Fischler indole synthesis, other classical methods such as Bischler indole synthesis from phenacyl bromides and excess of aniline, Batcho-Lemruber indoles synthesis from ortho-nitrotoluenes, Gassmanna indole synthesis from N-haloanilines, Madelung indole synthesis and the reductive indolization of orth-nitrobenzyl carbonyl compounds were also well discussed[16] . The classical Bischler indole synthesis has received little attention over other methods. This is due to the harsh conditions and expensive catalysts to carry out this reaction[17] . On the other hand, Sridharan et al. reported one pot soild state reaction of anilines with phenacyl bromides in the presence of sodium bicarbonate and anilinium bromide as a catalyst under microwave irradiation to obtain 2-arylindoles[18] . In this method the cyclization has been achieved in one step without the isolation of the intermediates, but the preparation of the phenacyl aniline and anilinium bromide from commercially available aniline is still required . With our interest to develop and synthesisze indole nucleus , we explored the Bischler method for the indole cyclization between various α-bromoarylethanones and anilines in dimethylformamide in single step by thermal method within 20 min. The advantage of this method is that reaction proceeded without any catalyst.

Results and discussion

The Bischler indole synthesis is the classical method to obtain 2-arylindoles and in this method the use of excess of aniline is required to afford the targets. Generally the 2-arylindoles have been synthesised from 1:1 molar ratio of aniline and phenacyl bromide. To improve the synthesis methodology we have tried the same synthesis in DMF and used only 1:1 molar ratio of aniline and phenacyl bromide. Aniline (1equi.) was added to solution of α-bromoarylethanones (1 equi.) in dimethyl formamide. The mixture was then refluxed (120 ^{0}C) , an intramolecular electrophilic cyclization between of α-bromoarylethanones and aniline was taken place and afforded 2-phenylindoles. Here, the cyclization has been achieved in the absence of the catalylst Initially, we have carriedd out the reaction in the absence of catalyst using methanol as the solvent, although 2-arylindoles were formed but yied eas less even after long reaction time (24 h). Then the reaction was done in the presence of dimethyl formamide and observed an effective cyclization at the shorter time (15-20 min). The lesser reaction time may be due to the presence of dimethyl formamide (DMF) as an energy transfer agent in relation to its high dipole moment[19] . It has been found that the cyclization was fast in case of α-bromoarylethanones containing chloro and nitro substituents in the ring. Thus our method in DMF without any acidic catalyst has been emerged as the better and esiest way to obtain 2-arylindoles. The obtained products (**2a-g**) were confirmed by their FT-IR, GC-MS and NMR analyses. In the IR spectrum of the compound (**2a**), a N-H stretching vibration was observed at 3444.87 cm^{-1} and the absence of the C-Br stretching vibration at 690 cm^{-1} indicates the formation of 2-



Compd.	R	X
2a	H	H
2b	NH_2	H
2c	Cl	H
2d	CH_3	H
2e	OCH_3	H
2f	H	NO_2
2g	NO_2	H

phenylindole. ^{1}H NMR of compound (**2a**) shown a singlet peak at δ 8.34 ppm corresponding to -NH group and the shift of peak at δ4.723 ppm correspounding to $-CH_2Br$ in the starting material to δ 6.835 ppm correspounding to a proton at C-3 in the cyclized product. Similarly, the ^{1}H NMR spectra of compounds (**2b-g**) shown a singlet peaks at δ 8.2 ppm to 8.7 ppm correspounding to -NH group and the peaks at δ 6.8 ppm to 7.03 ppm correspounding to a proton at C-3 in the cyclized products. All the compounds (2a-g) showed their characteristics molecular ion peaks in GC-MS analyses.

Experimental

Melting points were determined in open capillary tubes, are compared and found to be matching with the literature. The compounds were purified by simple recrystallization technique and purity was confirmed by thin layer chromatography conversion and characterization of the products were done by GC-MS chromatogram [Perkin-Elmer system of GC model clarus 680 and MS model clarus 600 (EI) using helium as carrier gas] . NMR spectra were recorded on Brucker 400 MHz FT-NMR using $CDCl_3$ / DMSO-d_6 as solved. FT-IR spectra were recording on Shimadzu IR Affinity-1 CE model with resolution 4.

Generl procedure for the synthsis of 2-arylindoles :

Aniline (1 mmol) was added to a solution of α-bromoarylethanones (1 mmol) in dimethylformamide (1 mL). The resultant mixture was refluxed for 15-20 min. The reaction was monitored by TLC. The heating was continued till the reactant spot was disappeared. After the completion of reaction, the reaction mixture was poured into ice, brought to room temperature and filtered. The solid products were washed with water and the crude products were recrystallized from hot ethanol.

Yield, melting point, IR, NMR and Mass data :

2-Phenylindole (**2a**) :Yield : 92% ; m.p : 192 ^{0}C ; IR (KBr) (cm^{-1}) : 3442.87 (-NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ : 8.348 (1H, s, -NH), 6.835 (1H, s, -CH), 7.200 (1H, t, -CH), 7.106-7.181 (4H, dd, -CH), 7.312-7.683 (4H, m, -CH) ; ^{13}C NMR (400 MHz, $CDCl_3$) δ : 100.01, 110.89, 120.29, 120.69, 122.38, 125.17, 127.74,129.05,129.28,136.82,137.89; MS (EI) : m/z (relative intensity) : 193.3 (M^+).

2-(4-Aminophenyl)indole (**2a**) : Yield : 80% ; m.p. : 207 ^{0}C; IR (KBr) (cm^{-1}) : 3527.80 (-NH), 3257.77 ($-NH_2$); ^{1}H NMR (400 MHz, DMSO) δ : 8.946 (1H, s, -NH), 5.286 (2H, s, $-NH_2$) , 6.728 (1H, s, -CH), 7.202 (4H, s, -CH), 6.583-7.536 (4H, d, -CH) ; ^{13}C NMR (400 MHz, DMSO) δ : 146.63, 141.93, 130.54, 128.76, 126.22, 118.04, 113.50; MS (EI) : m/z (relative intensity) : 208.8 (M^+).

2-(4-Chlorophenyl)indole (**2c**) : Yied : 84%; m.p. : 193 ^{0}C; IR (KBr) (cm^{-1}) : 3433.29 (-NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ : 8.287 (1H, s, -NH), 6.814 (1H, s, -CH), 7.117-7.912 (8H, m, -CH); 13C NMR (400 MHz, $CDCl_3$) δ : 100.62, 111.08, 120.61, 120.90, 122.83, 126.46, 129.31, 129.37, 131.04, 133.59, 136.82, 137.05; MS (EI) : m/z (relative intensity) : 227.1 (M^+).

2-(-4 Methylphenyl)indole (**2d**) : Yield : 78%; (KBr) (cm^{-1}) : 3433.29 (-NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ : 2.208 (3H, s, $-CH_3$), 6.844-6.880 (1H $_{Arom}$, t), 7.165-7.183 ($4H_{Arom}$, d), 7.238-7.293 ($1H_{Arom}$, t), 7.289 ($1H_{Arom}$, s), 7.673-7.693 (2H $_{Arom}$, d); ^{13}C NMR (400 MHz, $CDCl_3$) δ : 26.85, 122.39,122.99, 126.43, 126.88, 128.44, 129.07, 129.24, 130.39, 131.13, 145.91, 152.35; GC-MS (EI) : m/z (relative intensity) : 207.1 (M^+).

2-(4- Methoxyphenyl)indole (**2e**) : Yield : 86%: IR (KBr) (cm^{-1}) : 3429.43 (-NH) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ : 3.833 (3H, s, $-OCH_3$), 6.842-6.904 ($2H_{Arom,}$ t), 6.921 ($1H_{Arom}$, s), 7.157-7.293 ($4H_{Arom}$, d), 7.729-7.750 ($2H_{Arom}$, d); ^{13}C NMR (400 MHz, $CDCl_3$) δ : 55.35, 113.17, 113.70, 113.74, 119.97, 126.88, 129.24, 130.62, 145.46; GC-MS (EI) : m/z (relative intensity) : 225.2936 (M+2).

2-(3- Nitrophenyl)indole (**2f**) : 79%; m.p. : 176 ^{0}C; IR (KBr) (cm^{-1}) : 3425.58 (-NH); 1H NMR (400 MHz, $CDCl_3$) δ:8.510 (1H, s, -NH), 7.031 (1H, s, -CH), 7.147-7.809 (2H, s, -CH), 7.167 (1H, t, -CH), 7.433-8.299 (6H, d, -CH); ^{13}C NMR (400 MHz, $CDCl_3$) δ : 100.62, 111.80, 120.61, 120.90, 122.83, 126.46, 129.31, 129.37, 131.04, 133.59, 136.82, 137.05; MS (EI) : m/z (relative intensity) : 238.92 (M+1).

2-(4- Nitrophenyl)indole (**2g**) : Yield : 89% : m.p. : 189 ^{0}C; IR (KBr) (cm^{-1}) : 3429.43 (-NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ : 8.4 (1H, s, -NH), 7.032 (1H, s, -CH), 7.150-7.296 (2H, t, -CH), 7.435-8.322 (6H, d, -CH); 13C NMR (400 MHz, $CDCl_3$) δ : 103.48, 111.27, 120.99, 121.39, 123.90, 124.00, 124.59, 125.17, 128.96; MS (EI) : m/z (relative intensity) : 238.22 (M+1).

Conclusion

Thus I have successfully improved the Bischler method for indole synthesis without any catalyst and the generality of this methodology has been confirmed by the synthesis of seven 2-arylindole derivatives.

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