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Behaviour of 2'-Aminochalcones Towards Vilsmeier-Haack Reagent: Synthesis of Some New N-Formyl-2-Aryl/Hetryl-4-Chloro-1,2-Dihydro-4(1h)-Quinilonies

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Abstract

The Vilsmeier-Haack reaction of 2'-aminochalcones provides a convenient approach to 2-aryl / hetryl -4- chloro -N- formyl-1,2-dihydroquinolines.

Keywords : 2'-aminochalcones, Vilsmeier-Haack Reagent, quinolines

Introduction

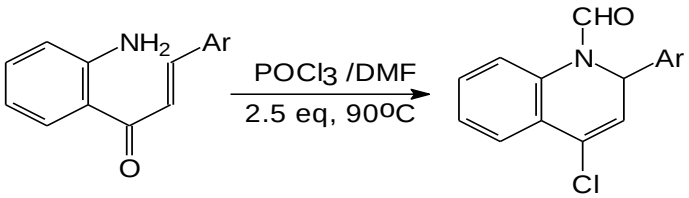
The extensive synthetic utility of traditional Vilsmeier-Haack reagent in organic synthesis is well recognized. Vilsmeier-Haack Arnold reactions that were initially used for the formylation of activated aromatic substrate[1-3] and carbonyl compounds[4] have now evolved into a powerful synthetic tool for the construction of many heterocyclic compounds such as indoles, furans, pyrrols, pyrazoles, oxazoles, pyridines, quinazolines[5-14]. A great deal of work has been reported on the synthesis of various substituted quinolines by both normal[15-17] and reverse vilsmeier approaches[18-20]. The preparation of quinolines is significant from both synthetic as well as biological point of view.

Quinolines and their derivatives occur in numerous natural products[21]. Many quinolines display interesting physiological activities and have found attractive applications as pharmaceuticals and as general synthetic blocks[22,23]. Although many synthesis have been developed for quinolines[24,25] and a wide range of derivatives of quinolines have been synthesized by adopting various methods reported in literature, there has been continuous demand for the development of newer and convenient methods for the synthesis of quinlones. Of the various methods developed so far for the synthesis of quinolines and reduced quinolines, convenient synthesis involving the cyclization of 2'-aminochalcones for the convenient synthesis of 2-Aryl-4-chloro-N-formyl-1,2-dihydroquinoines

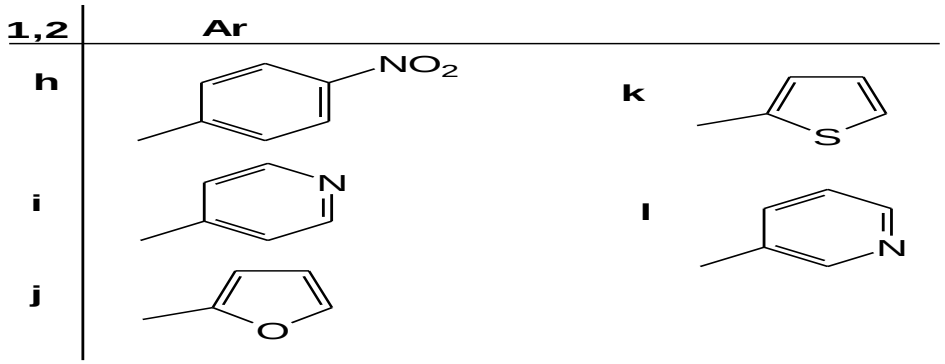
Discussion

Although Balasubramanian et al. carried out Vilsmeier-Haack reaction of seven derivatives of 2'-aminochalcones(Ar= phenyl, p-chlorophenyl, p-tolyl, p-anesyl, o-chlorophenyl, o-tolyl, m-chlorophenyl) 1a-1g, to our surprise no reaction on the chalcones containing electron withdrawing substituent such as $-NO_2$ was investigated. Further, Vilsmeier Haack reaction of hetryl analogs of 2'-aminochalcones has not been reported as yet. The main objective of the present work is to study the scope of method of Balasubramanian et al. for the synthesis of wide variety of 4-chloro-N-formyl-1,2-dihydroquinolines including 2-hetryl analogs.

The chalcones 1h-1l were treated with 2.5 equivalent of Vilsmeier reagent at 90 ^oC for 3h. As expected, reactions proceeded similar to the reported observations affording 2-aryl/hetryl-4-chloro-N-formyl-1,2-dihydroquinolines(2h-2l) Scheme-1



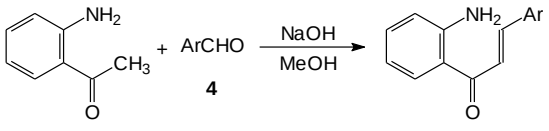
1 **2**



Scheme-1

The spectral data (IR, NMR) and elemental analysis confirmed the synthesis of 2-aryl/hetryl-4-chloro-N-formyl-1,2-dihydroquinolines. The products exhibited carbonyl absorption in the region 1670-1680 cm^{-1}while the spectra were transparent in the region of absorption of NH_2 group. The ^1H NMR spectra of 2 were consistent with their spectrum. Two characteristics doublets and one singlet (each integrating for one proton) appeared at δ 6.3, 6.5 (J=6.3 Hz) and 8.6 were ascribed to the C_3-H, C_2-H and CHO respectively and confirmed the structure 2

2'-Aminochalcones 1 needed for the present investigations were synthesized by condensation of methanolic solution of 2'-aminoacetophenone (3) and corresponding ar/hetaraldehyde 4 (Scheme 2). 2'-Aminochalcones 1 obtained as crystalline solid were confirmed by comparison of their physical and spectral data with already reported in literature. Physical data of 2'-aminochalcones 1 is given in Table I



3 **1**

Table I Physical Data of 2'-Aminochalcones 1

Compound	M.pt. (^oC)	Lit. M.pt.(^oC)[29-31]	Yield (%)
1h	122-124	122-124	79
1i	110-112	112-113	72
1j	139-140	141-142	80
1k	120-121	120-121	83
1l	71-72	72-74	68

Experimental

Melting points were taken in open capillaries and are uncorrected. ^1H NMR spectra were recorded on a Brucker 300 MHz instruments using TMS as internal standard. IR spectra were recorded on a Perkin Elmer 1800 IR spectrophotometer. Elemental analyses were carried out in a Perkin Elmer 2400 instrument. The homogeneity of the compounds was checked through TLC on silica gel plates and spots were located in iodine chamber vapors. Most of common chemicals such as o-aminoacetophenone, substituted ar/hetaraldehyde etc were obtained from commercial suppliers. Phosphorous oxychloride ($POCl_3$) and dimethylformamide were dried according to standard literature procedure.

Preparation of 2'-Aminochalcones [29-31]
General Procedure

To a cold solution of an appropriate ar/hetaraldehyde (0.02 mol) in methanol (100 mL) containing NaOH (5 pellets) was added. 2-Aminoacetophenone (2.70g, 0.02 mol). The solution was allowed to stir at 5 ^oC in ice bath for 8 hrs. The resulting orange precipitate was poured onto ice cold water (200 mL) containing hydrochloric acid (10 mL). The contents were stirred with a glass rod, filtered and washed with water. The crude solid was recrystallised with alcohol.

Reaction of 2'-Aminochalcones With Vilsmeier Reagent General Procedure

To an ice cold magnetically stirred solution of 2'-aminochalcones (0.02 mol) in DMF, $POCl_3$ (2.5 eq) was added drop wise. The reaction mixture was allowed to attain r.t. and was heated over a water bath for 3h, after which it was poured into crushed ice, neutralized with $NaHCO_3$ and extracted with DCM. The organic layer was washed with water and dried over anhydrous Na_2SO_4, filtered and solvent evaporated in vaccuo. The crude reaction product was purified by column chromatography using 2% ethyl acetate in petroleum ether as eluent.

4-Chloro-N-Formyl-2-(4''-Nitrophenyl)-1,2-Dihydroquinoline (2h)

Yield 70% m.p. 134-135 ^oC
IR (ν_{max}, in KBr): 1353, 1557, 1680 cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz, δ): 6.37(d, IH, J=6.3 Hz); 6.56(d, IH, J=6.3 Hz); 7.2-7.3 (m, 2H); 7.68-7.75(m, 3H);7.78-7.81(m,1H);8.19-8.22(m,2H);8.65(s,1H, CHO)
Elemental analysis: Found C 61%, H 3.3%, N 8.4%,; Requires C 61.1%, H 3.5%, N 8.9%

4-Chloro-N-Formyl-2-(4''-Pyridyl)-1,2-Dihydroquinoline (2i)

Yield 65% m.p. 128-130 ^oC
IR (ν_{max}, in KBr): 1678 cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz, δ): 6.36(d, IH, J=6.3 Hz); 6.54(d, IH, J=6.3 Hz); 7.21-7.32 (m, 2H); 7.67-7.79(m, 4H); 8.17-8.23(m, 2H); 8.61(s, 1H, CHO)
Elemental analysis: Found C 66.2%, H 4.03%, N 9.9%,; Requires C 67%, H 4.07%, N 10.4%

4-Chloro-N-Formyl-2-(2''-Furyl)-1,2-Dihydroquinoline (2j)

Yield 64% m.p. 87-89 ^oC
IR (ν_{max}, in KBr): 1679 cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz, δ): 6.16-6.19 (m, !H); 6.23-6.25 (m, !H); 6.37(d, IH, J=6.3 Hz); 6.5(d, IH, J=6.3 Hz); 7.11-7.15 (dd, 1H, J= 1.5, 7.8 Hz); 7.30-7.38(m,

3H); 7.72-7.75(dd, 1H, J= 1.5, 7.8 Hz); 8.7(s, 1H, CHO)

Elemental analysis: Found C 64.5%, H 3.3%, N 5.1%,; Requires C 64.9%, H 3.9%, N 5.4%

4-Chloro-N-Formyl-2-(2"-Thienyl)-1,2-Dihydroquinoline (2k)

Yield 68% m.p. 96-98 ^{o}C

IR (v_{max}, in KBr): 1670 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz, δ): 6.31(d, lH, J=6.3 Hz); 6.56(d, IH, J=6.3 Hz); 6.80-6.83 (dd, 1H, J= 2.1, 5.1 Hz); 6.90-6.91(m, 1H); 7.00-7.02(dd, 1H, J= 1.2, 7.5Hz); 7.10-7.12(dd, 1H, J= 1.2, 5.1Hz); 7.21-7.26 (m, 2H); 7.65-7.68(dd, 1H,J= 2.1, 7.5 Hz) 8.61(s, 1H, CHO)

Elemental analysis: Found C 60.8%, H 2.9%, N 4.7%,; Requires C 61.1%, H 3.6%, N 5.1%

4-Chloro-N-Formyl-2-(3"-Pyridyl)-1,2-Dihydroquinoline (2l)

Yield 63% m.p. 124-126 ^{o}C

IR (v_{max}, in KBr): 1677 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz, δ): 6.35(d, lH, J=6.3 Hz); 6.5(d, IH, J=6.3 Hz); 7.19-7.30 (m, 3H); 7.64-7.76(m, 3H); 8.19-8.21(m, 2H); 8.65(s, 1H, CHO)

Elemental analysis: Found C 65.6%, H 4.0%, N 10.1%,; Requires C 67%, H 4.07%, N 10.4%

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