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A NEW ROUTE TO THE SYNTHESIS OF 4-CHLORO-3-METHYLQUINOLINES FROM 1-(2-AMINOPHENYL)-PROPANONES USING VILSMEIER REAGENT.

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Abstract: An efficient one-step synthesis of various substituted 4-chloro-3-methylquinolines from 1-(2-aminophenyl)propanone using Vilsmeier reagent is reported.

Quinoline[1] derivatives are reported to exhibit a wide spectrum of biological activities including chronotropic,[2a] bactericidal,[2b] antitumor,[2c] antimalarial,[2d] anti-inflamatory,[2e] etc. The 4-chloro-3-methylquinoline is reported to be synthesised by a series of rection starting from aniline with diethyloxalpropionate.[3a] Recently various substituted quinolines are prepared by treatment of suitable o-substituted anilines with formaldehyde and electron rich alkenes,[3h] with various ketones,[3c] base

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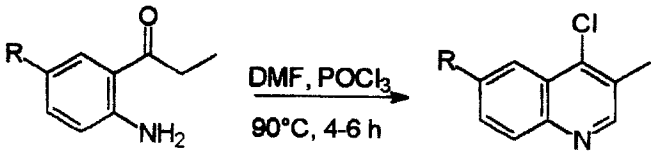


1a-c 2a-c

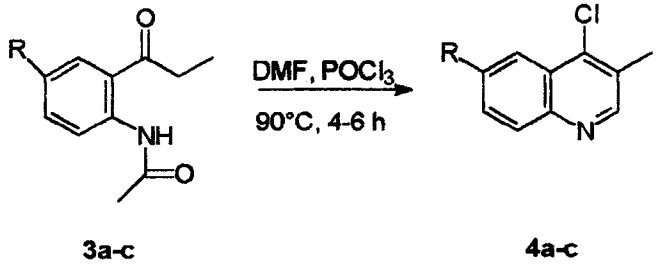
	R
a	H
b	Cl
c	Br

Scheme 1

and alkylating agent,[3d] with N,N-Dimethylacetamide[3e] and with allylic alcohol.[3f] Other methods of synthesis include treatment of N-alkyl, N-arylbenzotriazole with α,ß-unsaturated ether[3g] reaction of ortholithiated N-acylanilines.[3h]

Vilsmeier-Haack-Arnold reaction is a mild method for introduction of formyl group[4] in various activated aromatic and heteroaromatic compounds. The Vilsmeier reagent is also utilised in the synthesis of a large number of heterocyclic compounds.[5] Recently some interesting cyclization reaction under Vilsmeier conditions have been reported from this laboratory.[6] In continuation of our interest in this versatile reagent, we wish to report the synthesis of various substituted 4-chloro-3-methylquinolines **2** from 1-(2-aminophenyl)propanones **1** in good yields (Scheme 1).

Further we were interested to study the scope of this reaction by introduction of acetyl group on nitrogen atom. Accordingly substituted N-[2-(1-oxopropyl)phenyl]acetamide were treated with Vilsmeier reagent at 90°C for 4-6 h to afford the substituted 4-chloro-3-methylquinolines in excellent yields (Scheme 2).



	R
a	H
b	Br
c	NO_2

3a-c **4a-c**

Scheme 2

Table: Reaction products of 1-(2-aminophenyl)propanone and N-[2-(1-oxopropyl)phenyl]acetamide with Vilsmeier reagent.

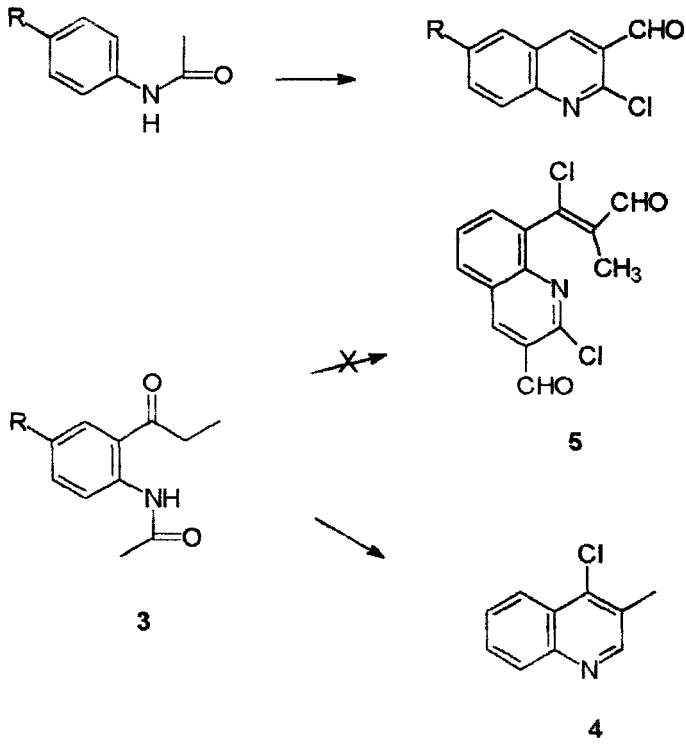
Entry	Product[a]	Yield[b] (%)	mp (°C)
1	**2a**	36	58
2	**2b**	56	104
3	**2c**	68	142
4	**4a**	89	58
5	**4b**	90	142
6	**4c**	75	170

a: All the products were characterised by IR, ^{1}H NMR, ^{13}C NMR and mass spectra.

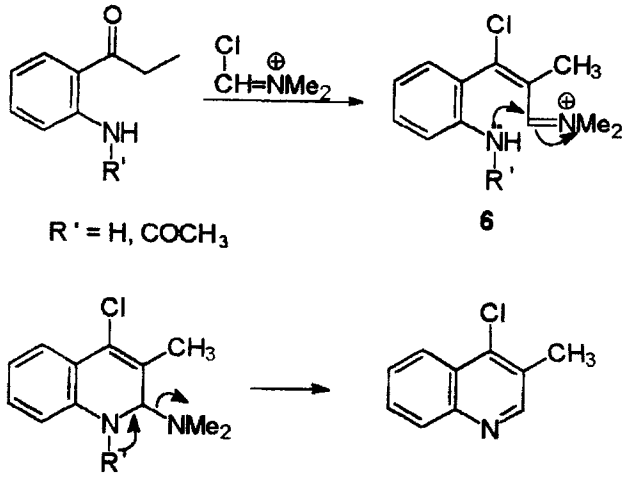
b: Yields reported here are after separation from chromatography.

All the products were characterised by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The overall yields of the product are summarised in the Table.

Acetanilides are reported to undergo Vilsmeier reaction to yield quinolinecarboxaldehydes.[7] But treatment of **3** with Vilsmeier reagent leads to the exclusive formation of **4** and not even traces of **5** is obtained. This indicates that the enolisable methylene group adjacent to the keto group is more readily susceptable to chloroformylation compared to the methylene group adjacent to the amidic carbonyl.



Based on the above findings a plausible mechanism could be proposed for the reaction (Scheme 3). The chloromethyleneiminium salt formed from DMF and



Scheme 3

$POCl_3$ reacted with 1-(2-aminophenyl)propanone or its acetyl derivative to yield the monomethyleneiminium salt **6** which undergoes spontaneous cyclization to give **2** or **4**.

There is a remarkable improvement in the yields of the product formed when free amino group is substituted with acetyl group. This may be due to the susceptibility of free amino group to undergo N-formylation to a greater extent which will interfere with the cyclization. N-acyl group does not undergo formylation at nirogen due to the presence of electron withdrawing group.

Typical experimental procedure:

Preparation of 4-chloro-3-methylquinoline(**4a**): To a stirred solution of N-[2-(1-oxopropyl)phenyl]acetamide (0.764g, 0.004 mole) in DMF (3.508g, 0.048 mole)

cooled to 0°C, $POCl_3$ (4.90g, 0.032 mole) was added dropwise over 30 min. The reaction mixture was stirred at room temperature for 1h and maintained at 90°C for 4h. The resulting mixture was neutralised with crushed ice containing sodium acetate, and left overnight. Solids are separated filtered and purified by passing through the column chromatography (8:2 petroleumether:ethylacetate) to yield **4a** in 89% yield; mp.58°C; MS(m/e): 177(m^+); IR(KBr) 820 cm^{-1}; ^1H NMR(300MHz, $CDCl_3$) δ 8.73(s,1H), 8.22-8.20(d,1H,J=9Hz), 8.09-8.06(d,1H,J=9Hz), 7.72-7.58(m,2H), 2.56(s,3H); ^{13}C NMR(75MHz, $CDCl_3$) δ 152.00, 147.56, 141.01, 129.58, 129.14, 128.78, 127.53, 126.34, 123.75, 17.53.

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