Pergamon

Tetrahedron 54 (1998) 14327–14340

TETRAHEDRON

A novel one-pot synthesis of 2-aminoquinolines from arylazidoketones by cyclization under Vilsmeier conditions

Ramiya R. Amaresh and Paramasivan T. Perumal*

Organic Chemistry Division
Central Leather Research Institute, Adyar, Chennai - 600 020, INDIA.

Received 1 July 1998; revised 15 September 1998; accepted 24 September 1998

Abstract

Studies have been carried out on a new novel method for the synthesis of 2-(*N,N*-disubstituted)aminoquinoline *via* intramolecular electrophilic substitution of methyleniminium salts by azide. Treatment of 1-(2-azidophenyl)ethanone with Vilsmeier reagent (DMF/$POCl_3$) gave 4-chloro-2-dimethylamino-3-quinolinecarboxaldehyde and 4-chloro-2-dimethylaminoquinoline, whereas 1-(2-azidophenyl)propanone and 1-(2-azidophenyl)butanone give unformylated products 4-chloro-3-methyl-2-dimethylaminoquinoline, 4-chloro-3-methylquinoline and 4-chloro-3-ethyl-2-dimethylaminoquinoline, 4-chloro-3-ethylquinoline respectively. The possible mechanisms for the formation of the products are discussed. The effect of the *N,N*-dimethylamino leaving group has been studied using sterically hindered *N*-methylformanilide(MFA), *N*-formylpiperidine(NFP) and *N*-formylmorpholine(NFM) instead of DMF.

Keywords: iminium salt; quinolines; Vilsmeier reagent.

Introduction

Halomethyleniminium salts derived from DMF and $POCl_3$ (the Vilsmeier-Haack-Arnold reaction) is extensively used for formylation of activated aromatic, heteroaromatic[1-4] and fully conjugated carbocyclic systems. The broad synthetic utility of this halomethyleniminium salt is not limited to formylation alone, but has been extented for the synthesis of several β-chloro-vinylaldehyde derivatives[5] from enolisable carbonyl compounds. The halomethyleniminium salt is also suitable for electrophilic substitution often followed by intramolecular cyclization[6-8]. Recently we have described a few new mild methods for the

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00887-4

synthesis of various heterocyclic compounds like indoles[9], quinolines[10,11], quinazolines[12], pyran[13] using the Vilsmeier reagent

Azides are of great value due to their capability of generating nitrenes as well as their functional group interconvertability. The commonly encountered reactions of azides are photolysis, thermolysis, Curtius rearrangement, Schmidt rearrangement, electrophilic and nucleophilic attack. In addition, cyclic products namely triazoles, tetrazoles, aziridines are formed by the cycloaddition of azides to double bonds, triple bonds, allenes and fullerenes[14].

Although various substituted quinolines have been synthesized by both normal[15-17] and reverse[6,18,19] Vilsmeier approach, the synthesis of quinoline derivatives from aryl azides using Vilsmeier reagent is not reported so far. This led us to undertake studies on the synthesis of quinoline derivatives from the aryl azides with appropriately located activated methyl group using Vilsmeier reagent.

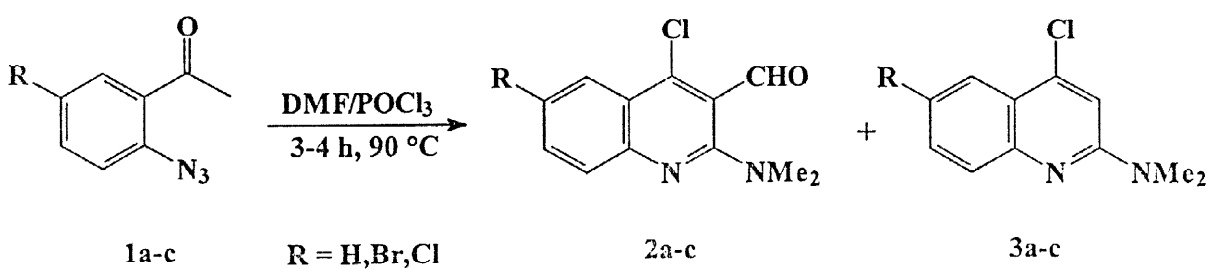
In this paper, we report a novel route to the synthesis of 2-dimethylaminoquinoline, 2-(4-morpholinyl)quinoline, and 2-(1-piperidinyl)quinoline from the reaction of 1-(2-azidoaryl)alkanones with various halomethyleniminium salts derived from DMF, MFA, NFM, NFP with $POCl_3$. The novelty of this synthetic route lies in the intramolecular electrophilic substitution of iminium salt by azide.

Results and Discussion

We have previously described the synthesis of a series of quinoline derivatives[10,11] from 1-(2-aminoaryl)alkanones using Vilsmeier reagent. In continuation of our studies on newer synthetic routes using this reagent, we have carried out studies (i) to synthesize quinoline derivative from 1-(2-azidoaryl)alkanone system, (ii) to demonstrate the intramolecular electrophilic substitution of iminium salt, (iii) to utilise the azido group towards the synthesis of simple heterocycles.

The Vilsmeier reaction of **1a** with 4 equivalents of Vilsmeier reagent (DMF/$POCl_3$) at 90 °C for 4 h affords 4-chloro-2-dimethylamino-3-quinolinecarboxaldehyde **2a** in 35% yield and 4-chloro-2-dimethylaminoquinoline **3a** in 50% yield [20]. Similar reaction was carried out on the substituted 1-(2-azidophenyl)ethanone **1b, 1c** (Scheme 1, Table 1).

Scheme 1



1a-c R = H,Br,Cl 2a-c 3a-c

Table 1. Reaction products of 1-(2-azidoaryl)ethanones with Vilsmeier reagent

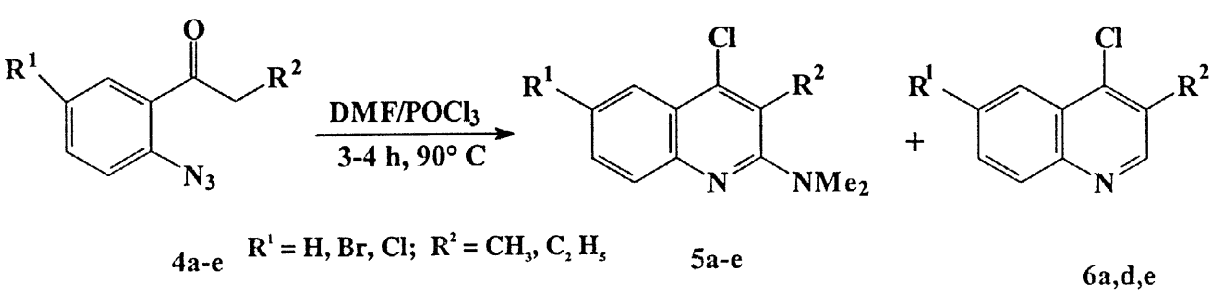
Entry	Substrate	Product	R	Yield[a] (%)	mp (° C)
1	**1a**	**2a**	H	35	103-5
		3a	H	50	-[b]
2	**1b**	**2b**	Br	28	89-90
		3b	Br	26	129-30
3	**1c**	**2c**	Cl	44	134-36
		3c	Cl	44	92-93

a: Isolated yield b: Liquid.

2-Dimethylaminoquinolines are a class of heterocyclic compounds which possess a potential wide range of biological activities such as antimicrobial and nematocidal[21], antidepressant[22], sedative and antipasmodic[23]. The reaction seems to proceed via the enolisable carbonyl methyl group. Initially the carbonyl methyl interacts with halomethyleniminium salt to give monomethyleniminium salt which further reacts with another mole of reagent to afford dimethyleniminium salt, followed by intramolecular nucleophilic attack of iminium salt by azide leading to the cyclic products.

We envisaged the formation 3-alkyl-4-chloro-2-dimethylaminoquinoline alone by changing methyl ketone moiety to ethyl and propyl ketone, since double formylation is prevented by the introduction of ethyl and propyl group. However the results obtained were interesting. Whereas 1-(2-azidoaryl)propanone (**4a-c**) yielded 4-chloro-3-methyl-2-dimethylaminoquinoline **5a-c** and 4-chloro-3-methylquinoline **6a** and 1-(2-azidoaryl)butanone **4d,e** yieled 4-chloro-3-ethyl-2-dimethylaminoquinoline **5d,e** and 4-chloro-3-ethylquinoline **6d,e**. (Scheme 2, Table 2)

Scheme 2



4a-e $R^1 = H, Br, Cl$; $R^2 = CH_3, C_2H_5$ 5a-e 6a,d,e

In the case of 4-chloro and 4-bromo ketone **4b, c** we obtained only aminoquinoline **5 b, c** and not **6 b, c** (Scheme 2), although the reasons are not known.

Table 2. Reaction products of 1-(2-azidoaryl)propanones and butanones with Vilsmeier reagent

Entry	Substrate	Product	R^1	R^2	Yield[a] (%)	mp, (°C)
1	**4a**	**5a**	H	CH_3	53	-[b]
		6a	H	CH_3	19	52-4
2	**4b**	**5b**	Br	CH_3	80	41-3
3	**4c**	**5c**	Cl	CH_3	78	59-61
4	**4d**	**5d**	H	C_2H_5	24	-[b]
		6d	H	C_2H_5	39	-[b]
5	**4e**	**5e**	Br	C_2H_5	30	-[b]
		6e	Br	C_2H_5	36	-[b]

a: Isolated yield b: Liquid.

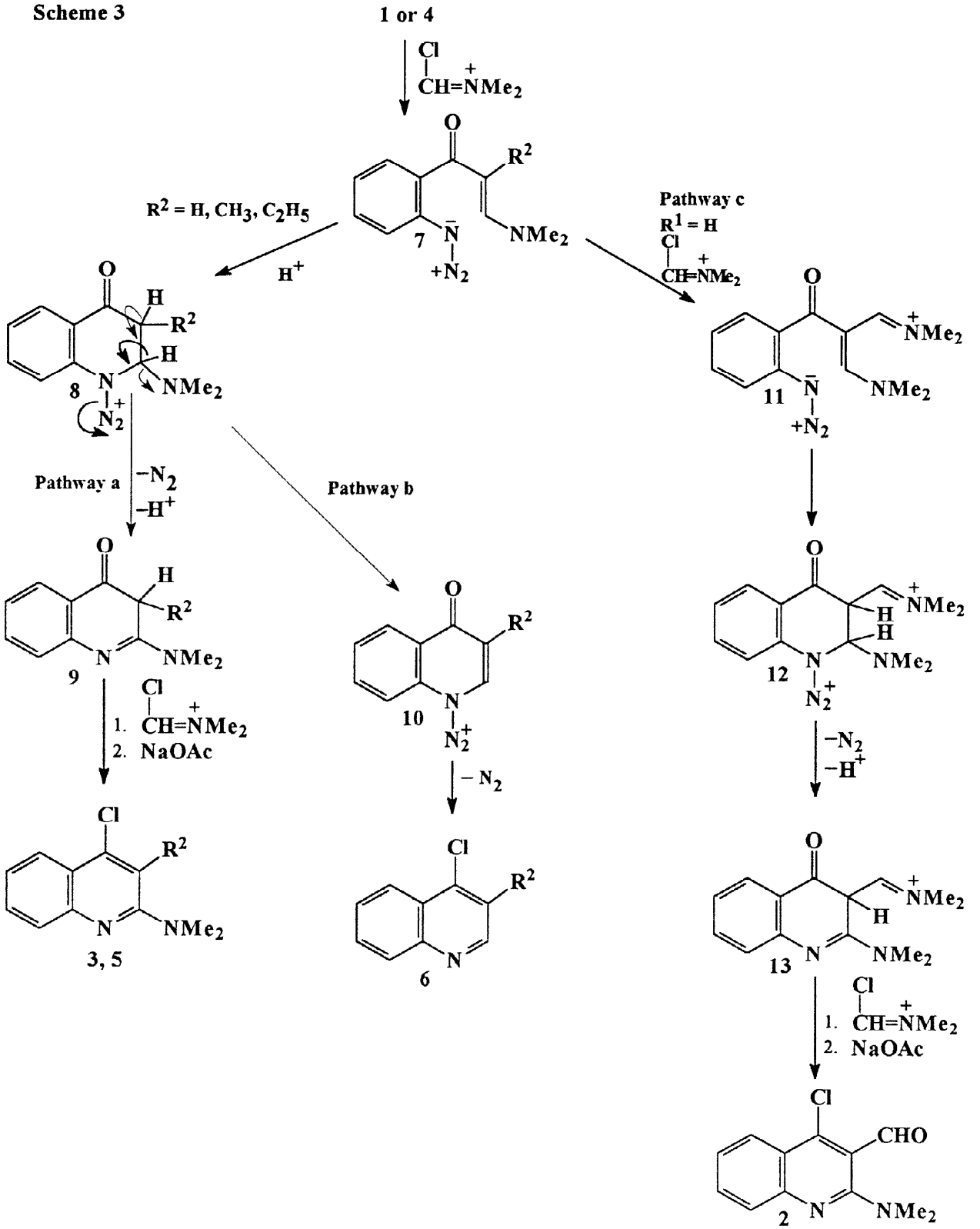
Although it is premature to propose a detailed mechanism, based on the above results a probable sequence of reactions may be proposed (Scheme 3). The azidoketones undergo chloroformylation on treatment with halomethyleniminium salts to yield **7**. The intramolecular attack of iminium species by azides to give **8** which follows either *pathway* **a** or *pathway* **b**. In the case of *pathway* **a** the cyclic intermediate **8** undergoes elimination of N_2 to give 4-chloro-2-dimethylaminoquinoline **3,5**. In the case of *pathway* **b** the cyclic intermediate **8** undergoes elimination of dimethylamino group followed by loss of nitrogen to yield **6**. In the case of 1-(2-azidoaryl)ethanone, the reaction also proceeds through *pathway* **c** to yield the diformylated derivative **11** which undergoes ring closure followed by elimination of nitrogen to give quinolinecarboxaldehydes **2.**

The present study is the first one for the synthesis of 2-dimethylaminoquinoline from 1-(2-azidoaryl)alkanones using Vilsmeier reagent. The 4-chloro-2-dimethylaminoquinoline[24] has been previously prepared by the reaction of hexamethylphosphoramide with activated heteroaryl halides.

In order to study the effect of leaving group, we extended our studies further by introducing more sterically hindered *N,N*-alkylarylamine and *N*-cyclized amines. Vilsmeier reagent derived from sterically hindered formamide and $POCl_3$ has been used to increase yields and to study the reaction mechanisms[18,25].

1-(2-Azidophenyl)ethanone with MFA gave 4-chloro-2-(*N*-methyl-*N*-phenyl)aminoquinoline **14** in 41% yield. Similarly 4-chloro-3-alkyl-2-(1-piperidinyl)quinoline and 4-chloro-3-alkyl-2-(4-morpholinyl)quinoline were synthesized by replacing DMF with *N*-formylpiperidine and *N*-formylmorpholine (Scheme 4). The overall reaction, product and reagents are summarized in Table 3. The probable mechanisms for the formation of 2-(*N*-methyl-*N*-phenyl)aminoquinoline, 2-morpholinyl and 2-piperidinyl quinoline are similar to the previous case. Even when highly sterically hindered formamides were used, the results are similar to DMF.

Scheme 3


1 or 4
Cl
CH=NMe2
R2 = H, CH3, C2H5
H+
Pathway c
R1 = H
Pathway a
−N2
−H+
Pathway b
1. CH=NMe2
2. NaOAc
− N2
3, 5
6
2
7
8
9
10
11
12
13
NMe2
CHO

Scheme 4

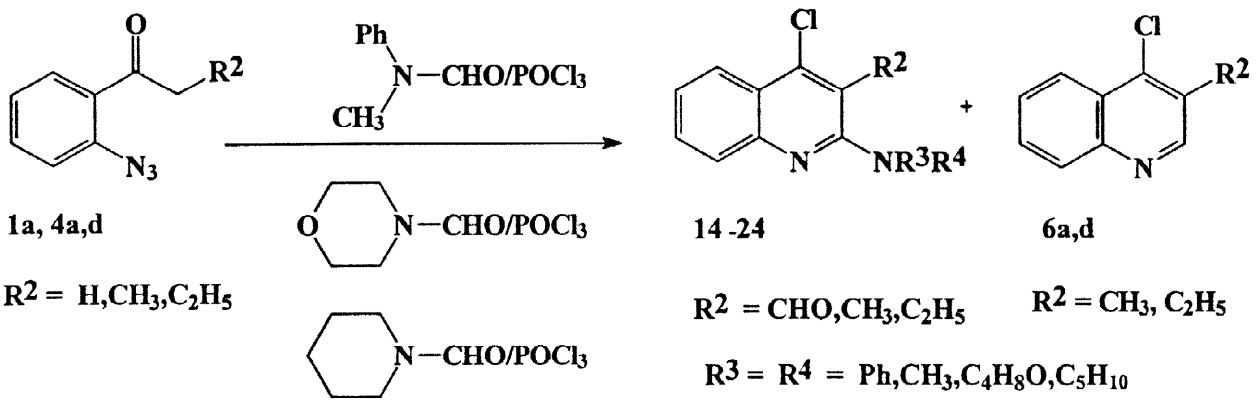


Table 3. Synthesis of various 2-(*N*-methyl-*N*-phenyl)aminoquinoline, 2-morpholinyl and 2-piperidinyl quinolines from 1-(2-azidoaryl)alkanone with Vilsmeier reagent

Substrate	Vilsmeier reagent	Product	R^2	R^3	R^4	Yield[a] (%)	mp. °C
1a	MFA/$POCl_3$	14	H	CH_3	C_6H_5	41	89-91
4a	MFA/$POCl_3$	15	CH_3	CH_3	C_6H_5	46	90-92
		16	CH_3	CH_3	C_6H_4CHO	2	-[b]
4d	MFA/$POCl_3$	17	C_2H_5	CH_3	C_6H_5	29	56-58
		18	C_2H_5	CH_3	$CH_3C_6H_4CHO$	3	121-22
1a	NFM/$POCl_3$	19	CHO	$C_2H_4OC_2H_4$		30	151-2
		20	H	$C_2H_4OC_2H_4$		12	-[b]
4a	NFM/$POCl_3$	21	CH_3	$C_2H_4OC_2H_4$		53	-[b]
		6a				18	52-54
4d	NFM/$POCl_3$	22	C_2H_5	$C_2H_4OC_2H_4$		29	-[b]
		6d				33	-[b]
4a	NFP/$POCl_3$	23	CH_3	C_5H_{10}		53	-[b]
		6a				20	52-54
4d	NFP/$POCl_3$	24	C_2H_5	C_5H_{10}		19	-[b]
		6d				51	-[b]

a: Isolated yield. b: Liquid.

In conclusion, irrespective of the steric effect of amide, the reaction course is controlled only by alkyl derivatives and not by iminium salt derived from various *N,N*-disubstituted amides.

Experimental

Melting points were measured in capillary tubes and are uncorrected. Analytical thin layer chromatography was performed on precoated sheets of silicagel with 0.25 mm thickness containing PF 254 indicator (Merck, Darmstadt). Column chromatography was performed with silica gel 60-120 mesh, neutral alumina (SD fine, Boisar); flash chromatography was performed with silica gel 230-400 mesh (Acmes, Bombay).

1-(2-Azidoaryl)ethanone[26,27] was prepared by following the literature procedure. 1-(2-Aminoaryl)ethanone was diazotised followed by quenching with NaN_3 which leads to azido ketone. Similarly 1-(2-azidophenyl)propanone and butanone were also synthesized.

Synthesis of 2-dimethylaminoquinoline, 2-(*N*-methyl-*N*-phenyl)aminoquinoline, 2-morpholinyl and 2-piperidinyl quinoline

General Procedure

The 1-(2-arylazido)alkanone (5 mmol) was dissolved in 50 mmol of DMF or 60 mmol of *N*-methylformanilide (MFA) or *N*-formylmorpholine (NFM) or *N*-formylpiperidine (NFP), and the solution was cooled to 0 °C. $POCl_3$ (20 mmol or 40 mmol) was added dropwise with stirring over a period of 20-30 min. The reaction mixture was stirred at room temperature for 1h and heated for 3-5h at 90 °C. After the completion of the reaction, the reaction mixture was cooled and treated with ice and then treated with solid NaOAc (25 mmol or 50 mmol). The crude solid was filtered and mother liquid was extracted with chloroform and chromatographed to afford the products in stated yields.

4-Chloro-2-dimethylamino-3-quinolinecarboxaldehyde (2a) and 4-chloro-2-dimethylaminoquinoline (3a)

The title compounds were synthesised from 1-(2-azidophenyl)ethanone according to the general procedure. 1-(2-Azidophenyl)ethanone (0.805 g, 5 mmol), DMF (3.88 ml, 50 mmol) and $POCl_3$ (1.86 ml, 20 mmol) were heated for 4 h at 90 °C. The crude product was chromatographed on neutral alumina (petroleum ether) to afford yellow solid of **2a** (0.409g, 35% yield), mp. 103-5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.12 (d, 1H, J = 8.1 Hz), 7.71-7.61 (m, 2H), 7.34-7.29 (m, 1H), 3.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.37, 159.42, 149.12, 148.26, 132.93, 127.16, 125.11, 123.86, 121.50, 117.13, 41.99; IR (KBr) 2929, 2890, 1676, 1570, 1547, 1476, 1408, 971, 751 cm^{-1}; MS m/e 234 (M^+); Anal. Calcd. for $C_{12}H_{11}ClN_2O$: C, 61.42; H, 4.72; N, 11.94; Found: C, 61.52; H, 4.74; N, 12.01 and **3a** (0.51 g, 50% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, 1H, J = 7.5 Hz), 7.71 (d, 1H, J = 8.4 Hz), 7.58-7.52 (m, 1H), 7.26-7.21 (m, 1H), 6.91 (s, 1H), 3.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.81, 148.63, 142.59, 130.14, 126.45, 123.65, 122.06, 120.33, 108.57, 37.66; IR (Neat) 2928, 2862, 1600, 1547, 1513, 1387, 963, 837, 754 cm^{-1}; MS m/e 206 (M^+): Anal. Calcd. for $C_{11}H_{11}ClN_2$: C, 63.92; H, 5.36; N, 13.55; Found: C, 63.60; H, 5.33; N, 13.48.

6-Bromo-4-chloro-2-dimethylamino-3-quinolinecarboxaldehyde (2b) and **6-bromo-4-chloro-2-dimethylaminoquinoline (3b)**

The title compounds were synthesised from 1-(2-azido-4-bromophenyl)ethanone according to the general procedure. The 1-(2-azido-4-bromophenyl)ethanone (1.20 g, 5 mmol), DMF(3.88 ml, 50 mmol) and $POCl_3$(1.86 ml, 20 mmol), were heated for 4 h at 90 °C. The crude solid product was chromatographed on silica gel (90 : 10 petroleum ether : ethyl acetate) to afford light yellow solid of **2b** (0.436 g, 28% yield), mp. 89–91°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.47 (s, 1H), 8.22 (d, 1H, *J* = 2.4 Hz), 7.69-7.65 (m, 2H), 7.53 (d, 1H, *J* = 9 Hz), 3.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.00, 159.46, 149.92, 148.22, 135.91, 128.86, 127.04, 122.41, 117.40, 116.92, 41.81; IR (KBr) 2940, 2894, 1683, 1578, 1543, 1473, 1394, 979, 821, 704 cm^{-1}; MS m/e 312 (M^+) Anal. Calcd. for $C_{12}H_{10}BrClN_2O$: C, 45.96; H, 3.21; N, 8.98. Found: C, 46.11; H, 3.24; N, 9.00 and dark yellow solid of **3b** (0.37 g, 26% yield), mp. 129–31°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.52 (m, 2H), 6.90 (s, 1H), 3.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.61, 147.52, 141.67, 133.52, 128.34, 126.08, 115.20, 109.43, 37.94; IR (KBr) 2933, 2861, 1598, 1547, 1510, 1394, 973, 834, 753 cm^{-1}; MS m/e 284 (M^+); Anal. Calcd. for $C_{11}H_{10}BrClN_2$: C, 46.27; H, 3.53; N, 9.81. Found: C, 46.02; H, 3.70; N, 9.76.

4,6-Dichloro-2-dimethylamino-3-quinolinecarboxaldehyde (2c) and **4,6-dichloro-2-dimethylaminoquinoline (3c)**

The title compounds were synthesised from 1-(2-azido-4-chlorophenyl)ethanone according to the general procedure. The 1-(2-azido-4-chlorophenyl)ethanone (0.98 g, 5 mmol), DMF (3.88 ml, 50 mmol) and $POCl_3$ (1.86 ml, 20 mmol) were heated for 4 h at 90 °C. The crude solid product was flash chromatographed on silica gel (petroleum ether) to afford dark yellow solid of **2c** (0.59 g, 44% yield), mp. 134–36 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.22 (s, 1H), 7.59-7.49 (m, 2H), 3.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.95, 159.32, 147.42, 146.21, 133.35, 128.67, 123.70, 122.22, 117.51, 41.81; IR (KBr) 2934, 2894, 1683, 1578, 1547, 1474, 1398, 979, 834, 769 cm^{-1}; MS m/e 268 (M^+); Anal. Calcd. for $C_{12}H_{10}Cl_2N_2O$: C, 53.55; H, 3.75; N, 10.41. Found: C, 53.52; H, 3.78; N, 10.26. and light yellow solid of **3c** (0.53 g, 44% yield), mp. 92–93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.56 (d, 1H, *J* = 8.7 Hz), 7.43 (d, 1H, *J* = 8.4 Hz), 6.91 (s, 1H), 3.14 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.98, 149.31, 141.64, 130.83, 128.08, 127.43, 122.75, 120.81, 109.35, 37.82; IR (KBr) 2934, 2854, 1604, 1548, 1514, 979, 834, 759 cm^{-1}; MS m/e 240 (M^+); Anal. Calcd. for $C_{11}H_{10}Cl_2N_2$: C, 54.79; H, 4.18; N, 11.62. Found: C, 55.06; H, 4.20; N, 11.67.

4-Chloro-3-methyl-2-dimethylaminoquinoline (5a) and **4-chloro-3-methylquinoline (6a)**

The title compounds were synthesised from 1-(2-azidophenyl)propanone according to the general procedure. The 1-(2-azidophenyl)propanone (0.88 g, 50 mmol), DMF (3.88 ml, 50 mmol) and $POCl_3$(1.86 ml, 20 mmol) were heated for 4 h at 90 °C. The crude liquid product

was chromatographed on silica gel (90 : 10 petroleum ether : ethyl acetate) to afford **5a** (0.58 g, 53% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, 1H, J = 6.6 Hz), 7.82 (d, 1H, J = 8.4 Hz), 7.56-7.53 (m, 1H), 7.39-7.34 (m, 1H), 2.94 (s, 6H), 2.5 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.41, 147.33, 142.04, 129.03, 127.44, 124.26, 123.61, 122.26, 121.47, 41.83, 17.25; IR (Neat) 2945, 2865, 1583, 1484, 1395, 1362, 1153, 964, 757; MS m/e 220 (M^+) ; Anal. Calcd. for $C_{12}H_{13}ClN_2$: C, 65.30; H, 5.93; N, 12.69. Found: C, 65.63; H, 5.96; N, 12.62 and light yellow solid **6a** (0.17 g, 19% yield), mp. 52–54 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.15 (d, 1H, J = 8.4 Hz), 8.02 (d, 1H, J = 8.1 Hz), 7.64 (t, 1H, J = 7.2 Hz), 7.52 (t, 1H, J = 7.5 Hz), 2.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.95, 147.53, 140.97, 129.54, 129.10, 128.75, 127.49, 126.30, 123.71, 17.49; IR (KBr) 2923, 1552, 1489, 1344, 1301, 1033, 762, 732, 644 cm^{-1}; MS m/e 177 (M^+); Anal. Calcd. for $C_{10}H_8ClN$: C, 67.62; H, 4.54; N, 7.89. Found: C, 67.94; H, 4.56; N, 7.90.

6-Bromo-4-chloro-3-methyl-2-dimethylaminoquinoline (5b)

The title compound was synthesised from 1-(2-azido-5-bromophenyl)propanone according to the general procedure. The 1-(2-azido-5-bromophenyl)propanone (1.27 g, 5mmol), DMF (3.88 ml, 50 mmol), and $POCl_3$ (1.86 ml, 20 mmol) were heated for 4 h at 90 °C The crude solid product was chromatographed on silica gel (90 : 10 petroleum ether : ethyl acetate) to afford light brown solid **5b** (1.2 g, 80% yield), mp. 41–43 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.79 (d, 1H, J = 2.7 Hz), 7.61 (d, 1H, J = 1.5 Hz), 2.95 (s, 6H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.21, 144.36, 142.27, 132.46, 128.83, 125.99, 123.67, 122.24, 118.71, 41.64, 17.35; IR (KBr) 2937, 2855, 1582, 1472, 1407, 1347, 1183, 963, 816; MS m/e 298 (M^+); Anal. Calcd. for $C_{12}H_{12}BrClN_2$: C, 48.11; H, 4.04; N, 9.35. Found: C, 48.30; H, 4.07; N, 9.40.

4,6-Dichloro- 3-methyl-2-dimethylaminoquinoline (5c)

The title compound was synthesised from 1-(2-azido-5-chlorophenyl)propanone according to the general procedure. The 1-(2-azido-5-chlorophenyl)propanone (1.05 g, 5 mmol), DMF (3.88 ml, 50 mmol) and $POCl_3$(1.86 ml, 20 mmol) were heated for 4 h at 90 °C. The crude solid product was chromatographed on silica gel (90 : 10 petroleum ether : ethyl acetate) to afford light grey solid **5c** (1.0 g, 78% yield), mp. 59–61 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, 1H, J = 3.3 Hz), 7.70 (d, 1H, J = 9 Hz), 7.46 (dd, 1H, J = 2.1 Hz, J = 2.1 Hz), 2.93 (s, 6H), 2,46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.91, 148.27, 144.04, 141.15, 129.75, 128.99, 123.99, 123.74, 122.75, 41.78, 17.47; IR (KBr) 2951, 2850, 1582, 1472, 1391, 1350, 1187, 964, 823; MS m/e 254 (M^+); Anal. Calcd. for $C_{12}H_{12}Cl_2N_2$: C, 56.49; H, 4.74; N, 10.98. Found: C, 56.78; H, 4.77; N, 11.02.

4-Chloro-3-ethyl-2-dimethylaminoquinoline (5d) and **4-chloro-3-ethylquinoline (6d)**

The title compounds were synthesised from 1-(2-azidophenyl)butanone according to the general procedure. The 1-(2-azidophenyl)butanone (0.94 g, 5 mmol), DMF (3.88 ml, 50 mmol) and $POCl_3$ (1.86 ml, 20 mmol) were heated for 4.15 h at 90 °C. The crude liquid product was

chromatographed on silica gel (95 : 5 petroleum ether : ethyl acetate) to afford **5d** (0.29 g, 24% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, 1H, *J* = 8.7 Hz), 8.81 (d, 1H, *J* = 8.4 Hz), 7.57-7.55 (m, 1H), 7.40-7.38 (m, 1H), 3.02 (q, 2H), 2.96 (s, 6H), 1.26 (t, 2H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.28, 148.26, 142.46, 131.43, 129.04, 127.50, 124.53, 123.90, 119.67, 42.73, 23.10, 13.07; IR (neat) 2940, 1571, 1460, 1394, 1368, 1152, 963, 757; MS m/e 234 (M^+); Anal. Calcd. for $C_{13}H_{15}ClN_2$: C, 66.52; H, 6.44; N, 11.93. Found: C, 66.18; H, 6.41; N, 11.99. and **6d** (0.52 g, 39% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.13 (d, 1H, *J* = 8.1 Hz), 8.02 (d, 1H, *J* = 8.1 Hz), 7.59 (t, 1H, *J* = 7.2 Hz), 7.52 (t, 1H, *J* = 7.8 Hz), 2.88 (q, 2H, *J* = 7.5 Hz), 1.25 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.40, 147.53, 140.36, 134.18, 129.48, 129.13, 127.45, 126.39, 123.90, 24.89, 14.12; IR (neat) 2970, 1557, 1488, 1361, 758; MS m/e 191 (M^+). Anal. Calcd. for $C_{11}H_{10}ClN$: C, 68.93; H, 5.25; N, 7.30. Found: C, 69.27; H, 5.23; N, 7.27.

6-Bromo-4-chloro-3-ethyl-2-dimethylaminoquinoline (5e) and **6-bromo-4-chloro-3-ethylquinoline (6e)**

The title compounds were synthesised from 1-(2-azido-5-bromophenyl)butanone according to the general procedure. The 1-(2-azido-5-bromophenyl)butanone (1.33 g, 5 mmol), DMF (3.88 ml, 50 mmol) and $POCl_3$ (1.86 ml, 20 mmol) were heated for 4 h at 90 °C. The crude liquid product was chromatographed on silica gel (90 : 10 petroleum ether : ethyl acetate) to afford **5e** (0.47 g, 30% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.62-7.60 (m, 2H), 2.98 (q, 2H), 2.93(s, 6H), 1.26 (t, 2H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.23, 144.30, 140.83, 132.37, 130.06, 129.19, 126.07, 125.00, 117.95, 42.62, 23.23, 12.99; IR (neat) 2934, 1575, 1480, 1393, 1369, 1184, 961, 823; MS m/e 312 (M^+); Anal. Calcd. for $C_{13}H_{14}BrClN_2$: C, 49.78; H, 4.49; N, 8.93. Found: C, 49.53; H, 4.47; N, 8.97 and **6e** (0.48 g, 36% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.27 (s, 1H), 7.85 (d, 1H, *J* = 8.7 Hz), 7.67 (d, 1H, *J* = 8.7 Hz), 2.58 (q, 2H, *J* = 6.9 Hz), 1.26 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.61, 145.97, 139.04, 134.97, 132.57, 131.09, 127.43, 126.15, 121.74, 24.85, 13.92; IR (neat) 2971, 1549, 1479, 1335, 1067, 824, 609; MS m/e 269 (M^+); Anal. Calcd. for $C_{11}H_9BrClN$: C, 48.83; H, 3.35; N, 5.17. Found: C, 49.07; H, 3.33; N, 5.15.

4-Chloro- 2-(*N*-methyl-*N*-phenyl)aminoquinoline (14)

The title compound was synthesised from 1-(2-azidophenyl)ethanone according to the general procedure. The 1-(2-azidophenyl)ethanone (0.82 g, 5 mmol), MFA (4.95 ml, 60 mmol) and $POCl_3$ (3.73 ml, 40 mmol) were heated for 3 h at 90 °C. The crude solid product was chromatographed on silica gel (petroleum ether) to afford yellow solid **14** (0.55 g, 41% yield), mp. 89–92 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, 1H, *J* = 8.4 Hz), 7.81 (d, 1H, *J* = 8.4 Hz), 7.63-7.58(m, 1H), 7.47-7.43 (m, 1H), 7.30 (s, 5H), 6.84 (s, 1H), 3.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.60, 148.57, 145.80, 142.13, 130.40, 130.03, 126.94, 126.72, 126.42, 123.93, 123.10, 121.48, 111.46, 38.67; IR (KBr) 2942, 1588, 1548, 1494, 1473, 1384, 762, 691;

MS m/e 268 (M^+); Anal. Calcd. for $C_{16}H_{13}ClN_2$: C, 71.51; H, 4.88; N, 10.42. Found: C, 72.08; H, 5.09; N,10.73.

4-Chloro-3-methyl-2-(*N*-methyl-*N*-phenyl)aminoquinoline (15) and **4-Chloro-3-methyl-2-[*N*-(4-formylphenyl)-*N*-methyl]aminoquinoline (16)**

The title compounds were synthesised from 1-(2-azidophenyl)propanone according to the general procedure. The 1-(2-azidophenyl)propanone (0.88 g, 5 mmol), MFA (4.95 ml, 60 mmol) and $POCl_3$ (3.73 ml, 40 mmol) were heated for 3 h at 90 °C. The crude solid product was chromatographed on silica gel (90 : 10 petroleum ether : ethyl acetate) to afford colourless solid **15** (0.65 g, 46% yield), mp. 90–92 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, 1H, J = 8.4 Hz), 7.91 (d, 1H, J = 8.1 Hz), 7.63 (t, 1H, J = 7.5 Hz), 7.46 (t, 1H, J = 7.8 Hz), 7.28-7.23 (m, 2H), 7.04-6.99 (m, 1H), 6.90 (d, 1H, J = 7.8 Hz), 3.57 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.32, 149.23, 146.10, 142.34, 129.31, 129.21, 127.85, 125.19, 125.10, 124.16, 123.87, 122.75, 121.35, 41.79, 17.06; IR (KBr) 2968, 1579, 1557, 1491, 1421, 1396, 1349, 1145, 1108, 761, 723, 698; MS m/e 282 (M^+); Anal. Calcd. for $C_{17}H_{15}ClN_2$: C, 72.21; H, 5.35; N, 9.91. Found: C, 72.50; H, 5.38; N, 9.95 and **16** (0.03 g, 2% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.20 (d, 1H, J = 8.1 Hz), 7.96 (d, 1H, J = 8.4 Hz), 7.73-7.57 (m, 4H), 6.73-6.70 (m, 2H,), 3.56 (s, 3H), 2.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.54, 156.77, 152.79, 146.45, 143.70, 131.70, 129.85, 128.68, 128.37, 127.23, 126.94, 125.45, 124.00, 114.88, 38.92, 16.18; IR (neat) 2962, 2923, 2732, 1689, 1602, 1575, 1514, 1483, 1392, 1353, 1168, 1105, 808, 761; MS m/e 310 (M^+) 312 (M + 2). Anal. Calcd. for $C_{18}H_{15}ClN_2O$: C, 69.56; H, 4.86; N, 9.04. Found: C, 69.28; H, 4.84; N, 8.96.

4-Chloro-3-ethyl-2-(*N*-methyl-*N*-phenyl)aminoquinoline (17) and **4-chloro-3-ethyl-2-[N-(4-formylphenyl)-N-methylaminoquinoline (18)**

The title compounds were synthesised from 1-(2-azidophenyl)butanone according to the general procedure. The 1-(2-azidophenyl)butanone (0.98 g, 5 mmol), MFA (4.95 ml, 60 mmol) and $POCl_3$ (3.73 ml, 40 mmol) were heated for 2.3 h at 90 °C. The crude solid product was chromatographed on silica gel (95 : 5 petroleum ether : ethyl acetate) to afford light yellow solid **17** (0.43 g, 29% yield), mp. 56–58 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, 1H, J = 8.4 Hz), 7.94 (d, 1H, J = 8.4 Hz), 7.67-7.62 (m, 1H), 7.53-7.48 (m, 1H), 7.27-7.22 (m, 2H), 7.01-6.96 (m, 1H), 6.89-6.86 (m, 2H), 3.51 (s, 3H), 2.68 (q, 2H, J = 7.5 Hz), 0.95 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.45, 149.65, 147.22, 144.31, 131.93, 129.34, 129.28, 128.08, 125.74, 124.87, 124.07, 122.16, 120.12, 41.44, 23.20, 12.56; IR (KBr) 2939, 1577, 1559, 1489, 1423, 1392, 1348, 1279, 1271, 1149, 748, 701; MS m/e 296 (M^+); Anal. Calcd. for $C_{18}H_{17}ClN_2$: C, 72.84; H, 5.77; N, 9.44. Found: C, 73.25; H, 5.81; N, 9.48. and dark brown solid **18** (0.048 g, 3% yield), mp. 121–22 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.24 (d, 1H, J = 8.1 Hz), 7.98 (d, 1H, J = 8.1 Hz), 7.74-7.60 (m, 5H), 6.68-6.65 (m, 2H), 3.52 (s, 3H), 2.80 (q, 2H, J = 7.5 Hz), 1.11 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.57,

156.78, 153.18, 146.79, 143.62, 133.39, 131.73, 129.93, 128.88, 127.81, 126.07, 124.20, 120.12, 113.81, 39.06, 23.08, 13.53; IR (KBr) 2963, 2928, 2748, 1679, 1601, 1558, 1482, 1349, 1297, 1167, 1100, 822, 758; MS m/e 324 (M^+); Anal. Calcd. for $C_{19}H_{17}ClN_2O$: C, 70.26; H, 5.28; N, 8.62. Found: C, 70.64; H, 5.31; N, 8.66.

4-Chloro-2-(4-morpholinyl)quinoline (20) and **4-chloro-2-(4-morpholinyl)-3-quinoline carboxaldehyde (19)**

The title compounds were synthesised from 1-(2-azidophenyl)ethanone according to the general procedure. The 1-(2-azidophenyl)ethanone (0.82 g, 5 mmol), NFM (6.05 ml, 60 mmol) and $POCl_3$ (3.73 ml, 40 mmol) were heated for 3 h at 90 °C. The crude solid product was flash chromatographed on silica gel (95 : 5 petroleum ether : ethyl acetate) to afford **20** (0.15 g, 12% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, 1H, J = 8.4Hz), 7.70 (d, 1H, J = 8.4 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.30 (t, 1H, J = 7.5 Hz), 7.02 (s, 1H), 3.81 (t, 4H, J = 4.5 Hz), 3.65 (t, 4H, J = 4.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.90, 146.42, 143.41, 130.54, 126.88, 123.84, 123.29, 121.37, 109.15, 66.67, 45.39; IR (neat)2962, 2825, 1615, 1594, 1548, 1497, 1422, 1234, 1111, 959, 758; MS m/e 248 (M^+); Anal. Calcd. for $C_{13}H_{13}ClN_2O$: C, 62.78; H, 5.26; N, 11.26. Found: C, 62.46; H, 5.24; N, 11.21 and dark yellow solid **19** (0.41 g, 30% yield), mp. 151–52 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.4 (s, 1H), 8.18 (d, 1H, J = 8.4 Hz), 7.78-7.67 (m, 2H), 7.44-7.39 (m, 1H), 3.85 (t, 4H, J = 4.2 Hz), 3.42 (t, 4H, J = 4.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.95, 158.00, 148.75, 148.33, 133.03, 127.73, 125.29, 125.23, 122.67, 118.35, 66.70, 51.08; IR (KBr) 2962, 2922, 2870, 1698, 1608, 1562, 1456, 1401, 1118, 909, 761 ; MS m/e 276 (M^+); Anal. Calcd. for $C_{14}H_{13}ClN_2O_2$: C, 60.77; H, 4.73; N, 10.12. Found: C, 61.04; H, 4.77; N, 10.17.

4-Chloro-3-methyl-2-(4-morpholinyl)quinoline (21) and **4-chloro-3-methylquinoline (6a)**

The title compounds were synthesised from 1-(2-azidophenyl)propanone according to the general procedure. The 1-(2-azidophenyl)propanone (0.88 g, 5 mmol), NFM (6.05 ml, 60 mmol) and $POCl_3$ (3.73 ml, 40 mmol) were heated for 4 h at 90 °C. The crude product was chromatographed on silica gel (95 : 5 petroleum ether : ethyl acetate) to afford yellow solid **21** (0.69 g, 53% yield). mp. 95–97 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, 1H, J = 7.8 Hz), 7.84 (d, 1H, J = 8.1 Hz), 7.59 (t, 1H, J = 7.2 Hz), 7.42 (t, 1H, J = 7.2 Hz), 3.88 (br s, 4H), 3.27 (br s, 4H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.91, 146.71, 142.56, 130.83, 129.22, 128.76, 127.95, 125.09, 123.85, 123.32, 66.91, 50.46, 16.68; IR (KBr) 2957, 2860, 1582, 1485, 1405, 1353, 1250, 1227, 1111, 1020, 955, 765; MS m/e 262 (M^+); Anal. Calcd. for $C_{14}H_{15}ClN_2O$: C, 64.0; H, 5.75; N, 10.66. Found: C, 64.30; H, 5.79; N, 10.79 and light yellow solid **6a** (0.16 g, 18% yield).

4-Chloro-3-ethyl-2-(4-morpholinyl)quinoline (22) and **4-chloro-3-ethylquinoline (6d)**

The title compounds were synthesised from 1-(2-azidophenyl)butanone according to the general procedure. The 1-(2-azidophenyl)butanone (0.94g, 5 mmol), NFM (6.05 ml, 60 mmol)

and $POCl_3$ (3.73 ml, 40 mmol) were heated for 3 h at 90 °C. The crude product was flash chromatographed on silica gel (95 : 5 petroleum ether : ethyl acetate) to afford **22** (0.40 g, 29% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, 1H, *J* = 8.1 Hz), 7.85 (d, 1H, *J* = 8.1 Hz), 7.59 (t, 1H, *J* = 6.9 Hz), 7.42 (t, 1H, *J* = 7.5 Hz), 3.88 (br s, 4H), 3.25 (br s, 4H), 2.95 (q, 2H, *J* = 6.9 Hz), 1.29 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.02, 145.70, 142.10, 130.20, 129.86, 128.76, 127.97, 125.83, 124.33, 66.89, 51.37, 24.11, 13.28; IR (neat) 2963, 2848, 1578, 1482, 1404, 1362, 1226, 1117, 958, 858, 759; MS m/e 276 (M^+); Anal. Calcd. for $C_{15}H_{17}ClN_2O$: C, 65.09; H, 6.19; N, 10.12. Found: C, 65.42; H, 6.16; N, 10.17 and **6d** (0.31 g, 33% yield).

4-Chloro-3-methyl-2-(1-piperidinyl)quinoline (23) and **4-chloro-3-methylquinoline (6a)**

The title compounds were synthesised from 1-(2-azidophenyl)propanone according to the general procedure. The 1-(2-azidophenyl)propanone (0.88 g, 5 mmol), NFP(6.71 ml, 60 mmol) and $POCl_3$ (3.73 ml, 40 mmol) were heated for 4 h at 90 °C. The crude product was flash chromatographed on silica gel (95 : 5 petroleum ether : ethyl acetate) to afford **23** (0.69 g, 53% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, 1H, *J* = 8.1 Hz), 7.84 (d, 1H, *J* = 10.5 Hz), 7.57 (t, 1H, *J* = 7.2 Hz), 7.38 (t, 1H, *J* = 7.5 Hz), 3.21 (br s, 4H), 2.47 (br s, 3H), 1.75 (br s, 4H), 1.66 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.17, 145.80, 142.01, 128.89, 127.71, 124.51, 123.84, 123.56, 51.17, 25.98, 24.52, 16.68; IR (neat) 2932, 2850, 1582, 1555, 1483, 1412, 1367, 1234, 1111, 951, 756; MS m/e 260 (M^+); Anal. Calcd. for $C_{15}H_{17}ClN_2$: C, 69.09; H, 6.57; N, 10.77. Found: C, 68.74; H, 6.60; N, 10.83 and light yellow solid **6a** (0.17g, 20% yield).

4-Chloro-3-ethyl-2-(1-piperidinyl)quinoline (24) and **4-chloro-3-ethylquinoline (6d)**

The title compounds were synthesised from 1-(2-azidophenyl)butanone according to the general procedure. The 1-(2-azidophenyl)butanone (0.94 g, 5 mmol), NFP (6.71 ml, 60 mmol) and $POCl_3$ (3.73 ml, 40 mmol) were heated for 3 h at 90 °C. The crude product was chromatographed on silica gel (95 : 5 petroleum ether : ethyl acetate) to afford **24** (0.26 g, 19% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, 1H, *J* = 8.4 Hz), 7.86 (d, 1H, *J* = 8.4 Hz), 7.57 (t, 1H, *J* = 7.2 Hz), 7.41 (d, 1H, *J* = 7.5 Hz), 3.19 (br s, 4H), 2.98 (t, 2H, *J* = 6.0 Hz), 1.74 (br s, 4H), 1.63 (br s, 2H), 1.29 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.60, 145.96, 141.72, 130.61, 129.01, 127.90, 125.52, 124.33, 123.14, 52.33, 26.19, 23.01, 15.25; IR (neat) 2933, 2851, 1578, 1556, 1482, 1405, 1368, 1229, 1114, 956, 759; MS m/e 274 (M^+) Anal. Calcd. for $C_{16}H_{19}ClN_2$: C, 69.93; H, 6.96; N, 10.19. Found: C, 69.58; H, 7.01; N, 10.24 and **6d** (0.49 g, 51% yield).

Acknowledgement : One of the authors (R.R.A) is grateful to University Grants Commission and Council of Scientific & Industrial Research, New Delhi, India for financial assistance.

References

[1] Jones G, Stanforth SP. Org. React. 1997;49:1-330.
[2] Meth-Cohn O, Stanforth SP. In Comprehensive Organic Synthesis, Trost BM, Fleming I. Eds.; Vol.2. Heathcock CH. Vol. Ed. Pergaman, Oxford, 1991:777-794.
[3] Seshadri SJ. Sci. Ind. Res. 1973;32:128-149.
[4] Jutz C. In Adv. Org. Chem. Taylor, E. C. Ed; John. New York: Wiley & Sons, 1976;9:225-342.
[5] Marson CM. Tetrahedron 1992:3659-3726.
[6] Meth-Cohn O, Tarnowski B. Adv. Heterocycl. Chem. 1982;31:207-236.
[7] Meth-Cohn O, Taylor DL. J. Chem. Soc., Chem. Commun. 1995;14:1463-1464.
[8] Meth-Cohn O, Goon S. J. Chem. Soc., Perkin Trans 1 1997:85-89.
[9] Majo VJ, Perumal PTJ. Org. Chem. 1996;61:6523-6525.
[10] Amaresh RR, Perumal PT. Synth. Commun. 1997;27:337-343.
[11] Amaresh RR, Perumal PT. Indian J. Chem. Sect. B. 1997;36B:541-544.
[12] Majo VJ, Perumal PT. Tetrahedron Lett. 1996;37:5015-5018.
[13] Venugopal M, Umarani R, Perumal PT, Rajadurai S. Tetrahedron Lett. 1991;32:3235-3238.
[14] Scriven EFV, Turnbull K. Chem. Rev. 1988;88:297-368.
[15] Meth-Cohn O, Narine B. Tetrahedron Lett. 1978:2045-2048.
[16] Meth-Cohn O, Narine B, Tarnowski BJ. Chem. Soc., Perkin Trans 1 1981:1520-1530.
[17] Chupp JP, Metz SJ. Heterocycl. Chem. 1979;16:65.
[18] Meth-Cohn O, Taylor DL. Tetrahedron Lett. 1993;34:3629-3632.
[19] Lee GT, Amedio JC, Underwood R, Prasad K, Repic O. J. Org. Chem. 1992;57:3250-3252.
[20] For preliminary communication Amaresh RR, Perumal PT. Tetrahedron Lett. 1998;39:3837-3840.
[21] Pfiiester JR. J. Nat. Prod. 1988;5:969-970.
[22] Hino H, Furukwa K, Nagai, Y, Uno, H. Chem. Pharm. Bull. 1980;28:2618-2622.
[23] Granik UG, Zhidkova AM, Kiselev SS, Glushkov RG, Poczhaeva AI, Mashkovski MD. Khim.Farm.Zh. 1978;12:66-71.
[24] Gupton JT, Idoux JP Baher G, Colon C, Crews A, Donald Jurss CD, Rami RC. J. Org. Chem. 1983; 48:2933-2937.
[25] Jackson A, Meth-Cohn O. J. Chem. Soc., Chem. Commun. 1995:1319.
[26] Adger BM, Bradbury S, Keating M, Rees CW, Storr RC, Williams MTJ. Chem. Soc., Perkin Trans. 1 1975: 31.
[27] Takada K, Kan-Woon T, Boulton AJ. J. Org. Chem. 1982;47:4323.