

A Novel One Pot Synthesis of 2-Dimethylaminoquinoline Derivatives from Arylazido ketones by Cyclization under Vilsmeier Condition

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Abstract: 1-(2-Azidophenyl)ethanone on treatment with Vilsmeier reagent yields 4-chloro-2-dimethylamino-3-quinolinecarboxaldehyde and 4-chloro-2-dimethylaminoquinoline, whereas 1-(2-azidophenyl)propanone and butanone derivatives give the corresponding 4-chloro-3-alkyl-2-dimethylaminoquinolines and 3-alkyl-4-chloroquinolines. © 1998 Elsevier Science Ltd. All rights reserved.

The halomethyleniminium salts which are reactive intermediates involved in the Vilsmeier-Haack reaction are capable of generating iminium species from numerous carbon,¹ oxygen and nitrogen nucleophiles.² The cyclization of these iminium species provides a facile entry into large number of heterocyclic system.³ Recently, synthesis of various heterocycles under Vilsmeier condition have been reported from our laboratory.⁴

Mild thermal and photolytic decomposition of azides is an important synthetic tool for the construction of nitrogen heterocycles.⁵ In continuation of our interest in exploiting the cyclization potential of azides⁶ under Vilsmeier conditions, we report a novel approach to the synthesis of 2-dimethylaminoquinolines from 1-(2-azidophenyl)ethanone **1a**. The Vilsmeier reaction of **1a** at 90 °C for 3-4 h affords 4-chloro-2-dimethylamino-3-quinolinecarboxaldehyde **2a**⁷ in 35 % yield along with 4-chloro-2-dimethylaminoquinoline **3a**⁸ in 55 % yield.⁹ The substituted 1-(2-azidoaryl)ethanones also furnish the corresponding 2-dimethylaminoquinolines and the results are summarised in Table 1 (Scheme 1).

2-Dimethylaminoquinolines are a class of heterocyclic compounds which possess a potential wide range of biological activities such as antimicrobial and nematocidal,^{10a} antidepressant,^{10b} sedative and antispasmodic.^{10c} Therefore, the success of our strategy prompted us to extend the utility of the reaction for the synthesis of alkyl substituted 2-dimethylaminoquinolines. Towards this end, substituted 1-(2-azidoaryl)propanone and butanone are treated with Vilsmeier reagent at 90 °C for 3-4 h. The reaction proceeds smoothly to furnish the corresponding 3-alkyl-4-chloro-2-dimethylaminoquinolines **5** and 3-alkyl-4-chloroquinolines **6** (Scheme 2) (Table 2).¹¹

Scheme 1

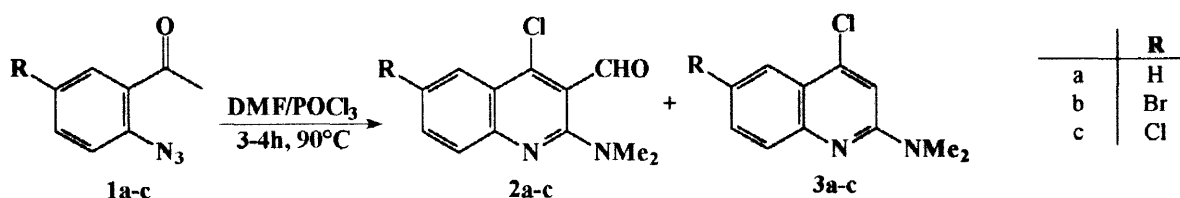
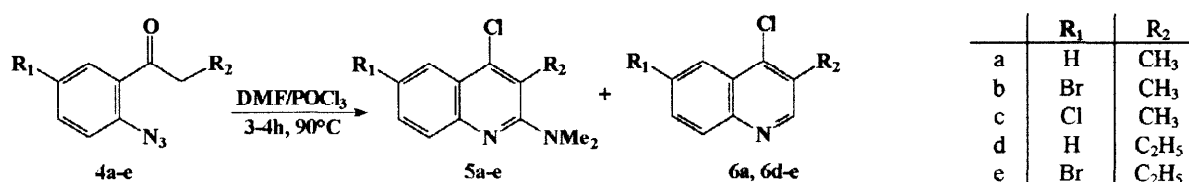


Table 1. Reaction products of 1-(2-azidoaryl)ethanones with Vilsmeier reagent.

S. No.	Substrate	Product ^a	R	% of yield ^b	mp, ° C
1	1a	2a	H	35	103–5
		3a	H	50	– ^c
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: All the products were duly characterised by ¹H NMR, ¹³C NMR, Mass, IR. b: Isolated yield.
c: Liquid.

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

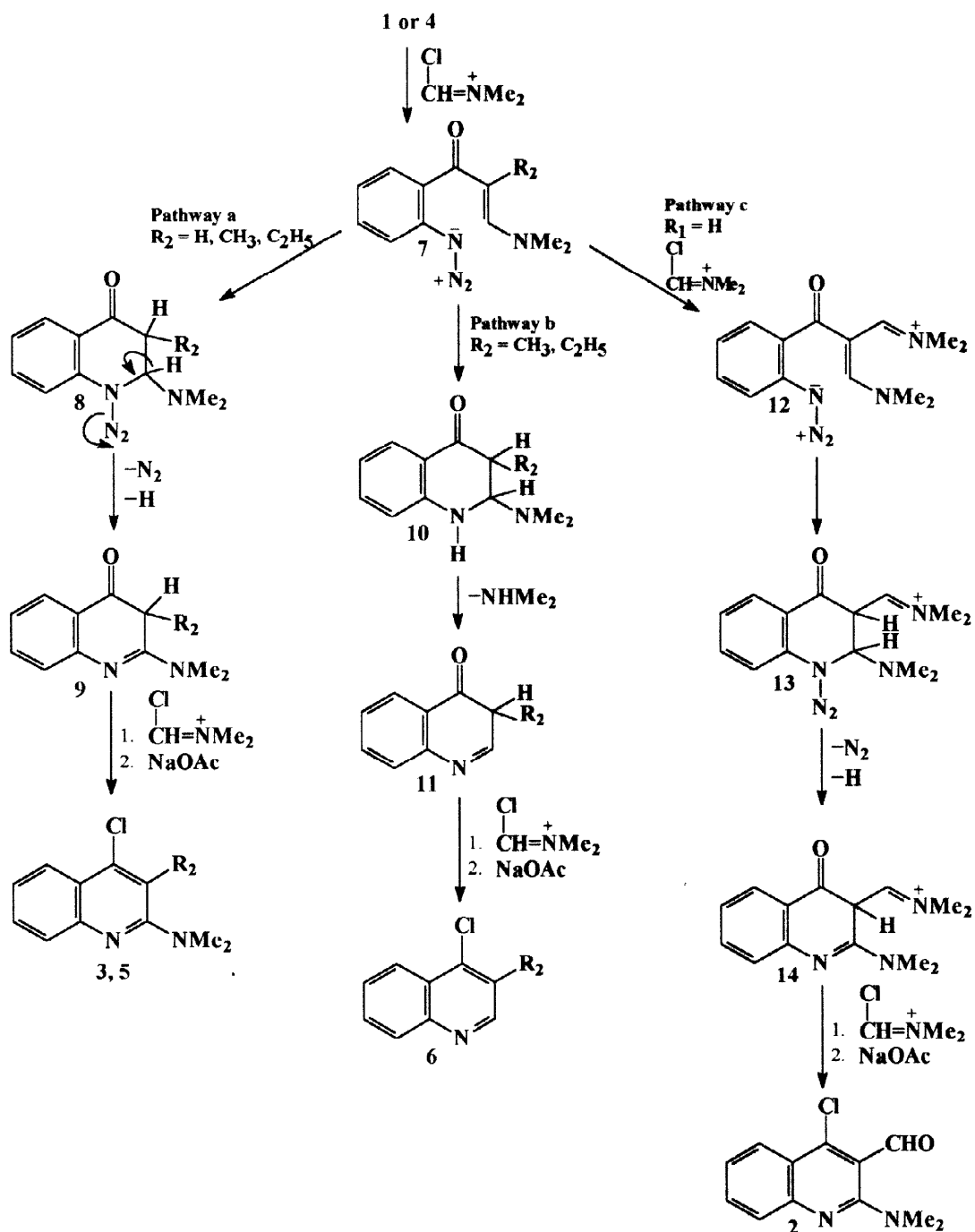
S. No.	Substrate	Product ^a	R ₁	R ₂	% of yield ^b	mp, ° C
1	4a	5a	H	CH ₃	53	– ^c
		6a	H	CH ₃	19	52–4
2	4b	5b	Br	CH ₃	80	41–3
3	4c	5c	Cl	CH ₃	78	59–61
4	4d	5d	H	C ₂ H ₅	24	– ^c
		6d	H	C ₂ H ₅	39	– ^c
5	4e	5e	Br	C ₂ H ₅	30	– ^c
		6e	Br	C ₂ H ₅	36	– ^c

a: All the products were duly characterised by ¹H NMR, ¹³C NMR, Mass, IR. b: Isolated yield.
c: Liquid.

Although it is premature to propose a detailed mechanism at this stage, 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 intermediate 7. The intramolecular attack of iminium species by azides follows through either *pathway a* or *pathway b*. In the case of *pathway a* the cyclic intermediate 8 undergoes elimination of N₂ to give 4-chloro-2-dimethylquinolinamine 3, 5. In the case of *pathway b* the cyclic intermediate 10 undergoes elimination of dimethylamino group to yield 6. In the case of 1-(2-

azidoaryl)ethanone, the reaction also proceeds through *pathway c* to yield the diformylated derivative **12** which undergoes ring closure followed by elimination of nitrogen to give quinolinecarboxaldehydes **2**.

Scheme 3



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- Typical experimental procedure: To a stirred solution of 1-(2-azidophenyl)ethanone **1a** (0.805g, 5mmol) in DMF (3.88mL, 50mmol) at 0-5 °C, POCl₃ (1.86 mL, 20mmol) was added dropwise with stirring over a period of 20-30min. The reaction mixture was stirred at rt for 1h and heated for 4h at 90 °C on a water bath, cooled and neutralised with crushed ice and sodium acetate. The crude solid obtained was filtered and mother liquid was extracted with chloroform (3×50 mL). The combined crude product was chromatographed with (5% ethyl acetate in petroleum ether) to yield **2a** in 35% yield and **3a** in 50% yield. Spectral data of compound **2a**: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₂H₁₁ClN₂O: C, 61.42; H, 4.72; N, 11.94; Found: C, 61.52; H, 4.74; N, 12.01. Compound **3a**: ¹H NMR (300 MHz, CDCl₃) δ 7.98 (d, 1H, *J* = 1.5 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); ¹³C NMR (75 MHz, CDCl₃) 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⁺).
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- Representative spectral data: Compound **5a**: ¹H NMR (300 MHz, CDCl₃) δ 8.04 (d, 1H, *J* = 6.6 Hz), 7.82 (d, 1H, *J* = 8.4 Hz), 7.54 (d, 1H, *J* = 7.5 Hz), 7.36 (t, 1H, *J* = 7.5 Hz), 2.94 (s, 6H), 2.5 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) 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 cm⁻¹; MS *m/e* 220 (M⁺). Compound **6a**: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₀H₈ClN: C, 67.62; H, 4.54; N, 7.89. Found: C, 67.94; H, 4.56; N, 7.90.