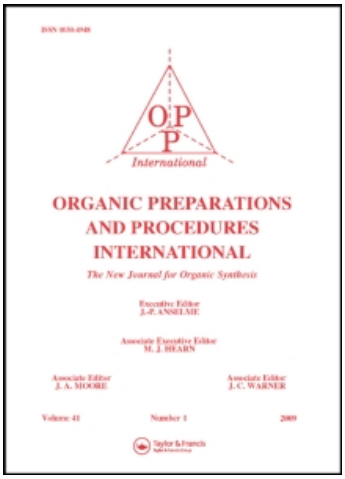

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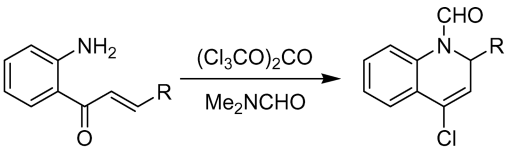
Quinolines and their derivatives occur in numerous natural products. Many quinolines exhibit a broad spectrum of biological activities such as anti-malarials,[1] anti-fungal,[2] anti-depressants,[3] etc. There are many publications concerning the methods for the synthesis of various 2-substituted-4-chloroquinolines,[4–6] but to the best of our knowledge, the synthesis of 2-substituted-4-chloro-*N*-formyl-1,2-dihydroquinolines has rarely been reported so far. Comparatively, the Vilsmeier cyclization of 2′-aminochalcones is a convenient method for the synthesis of 2-substituted-4-chloro-*N*-formyl-1,2-dihydroquinolines.[7] However, the traditional Vilsmeier reagent employs the use of phosphorus oxychloride, which forms inorganic phosphorus salts as by-products.[8] Due to the great importance of quinolines, the development of novel synthetic methods remains an active research area. *bis*-(Trichloromethyl) carbonate (BTC) in combination with DMF, has emerged as a versatile synthetic auxiliary for the synthesis of some important organic compounds.[9–12] Herein, we report a practical route for one-pot synthesis of 2-substituted-4-chloro-*N*-formyl-1,2-dihydroquinolines from the reaction of 2′-aminochalcones with halomethyleniminium salts derived from BTC/DMF (*Scheme 1*).



1 a - k **2 a - k**

a) R = C_6H_5; b) R = *p*-ClC_6H_4; c) R = *m*-ClC_6H_4; d) R = *p*-$MeOC_6H_4$; e) R = *p*-$NO_2C_6H_4$; f) R = *m*-FC_6H_4; g) R = *m*-BrC_6H_4; h) R = 2-F-6-ClC_6H_3; i) R = 2-furyl; j) R = 2-thienyl; k) R = 3,4-diMeC_6H_3.

Scheme 1

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Table 1
Synthesis of 2-Substituted-4-chloro-*N*-formyl-1,2-dihydroquinolines using BTC and DMF

Cmpd[a]	Yield (%)	mp (°C) (*lit*. m.p.)	IR (cm^{-1})	^{1}H NMR (δ)
2a	86	Oil Dense oil[7]	1682 952 759	6.38 (d, 1 H, $J = 6.5$ Hz, 2-H), 6.71 (d, 1 H, $J = 6.5$ Hz, 3-H), 7.23–7.32 (m, 3 H, ArH), 7.39–7.43 (m, 3 H, ArH), 7.54 (d, 1 H, $J = 7.5$ Hz, ArH), 7.60–7.62 (m, 2 H, ArH), 8.83 (s, 1 H, CHO)
2b	92	118–120 (110–119[7])	1675 839 756	6.31 (d, 1 H, $J = 6.5$ Hz, 2-H), 6.40 (d, 1 H, $J = 6.0$ Hz, 3-H), 7.04–7.06 (m, 1 H, ArH), 7.21 (s, 4 H, ArH), 7.26–7.33 (m, 2 H, ArH), 7.71 (m, 1 H, ArH), 8.66 (s, 1 H, CHO)
2c	93	75–77 (77–78[7])	1675 831 761	6.33 (d, 1 H, $J = 6.5$ Hz, 2-H), 6.40 (d, 1 H, $J = 6.0$ Hz, 3-H), 7.08–7.16 (m, 1 H, ArH), 7.14–7.36 (m, 5 H, ArH), 7.71–7.74 (m, 2 H, ArH), 8.68 (s, 1 H, CHO)
2d	82	69–71 (68–69[7])	1687 838 759	3.74 (s, 3 H, MeO), 6.33 (d, 1 H, $J =$ 6.0 Hz, 2-H), 6.40 (d, 1 H, $J = 6.0$ Hz, 3-H), 6.78–6.80 (m, 2 H, ArH), 7.04–7.06 (m, 1 H, ArH), 7.22–7.23 (m, 2 H, ArH), 7.26–7.32 (m, 2 H, ArH), 7.72–7.74 (m, 1 H, ArH), 8.67 (s, 1 H, CHO)
2e	81	151–153	1674 841 757	6.37 (d, 1 H, $J = 6.5$ Hz, 2-H), 6.51 (d, 1 H, $J = 6$ Hz, 3-H), 7.08–7.10 (m, 1 H, ArH), 7.30–7.38 (m, 2 H, ArH), 7.45–7.47 (m, 2 H, ArH), 7.74–7.75 (m, 1 H, ArH), 8.11–8.14 (m, 2 H, ArH), 8.70 (s, 1 H, CHO)
2f	87	Oil	1682 844 759	6.34 (d, 1 H, $J = 6.5$ Hz, 2-H), 6.42 (d, 1 H, $J = 6.5$ Hz, 3-H), 6.92–7.09 (m, 2 H, ArH), 7.08–7.09 (m, 2 H, ArH), 7.22–7.24 (m, 1 H, ArH), 7.25–7.72 (m, 2 H, ArH), 7.73 (d, 1 H, $J = 1.5$, ArH), 8.69 (s, 1 H, CHO)
2g	85	73–75	1685 833 758	6.34 (d, 1 H, $J = 6.5$ Hz, 2-H), 6.41 (d, 1 H, $J = 6.5$ Hz, 3-H), 7.01–7.16 (m, 2 H, ArH), 7.22 (d, 1 H, $J = 7.0$ Hz, ArH), 7.28–7.35 (m, 3 H, ArH), 7.38–7.44 (m, 1 H, ArH), 7.73–7.75 (m, 1 H, ArH), 8.69 (s, 1 H, CHO)

(*Continued on next page*)

Table 1
Synthesis of 2-Substituted-4-chloro-*N*-formyl-1,2-dihydroquinolines using BTC and DMF (*Continued*)

Cmpd[a]	Yield (%)	mp (°C) (*lit*. m.p.)	IR (cm^{-1})	^{1}H NMR (δ)
2h[b]	94	Oil	1687 759	6.09 (d, 1 H, $J = 5.5$ Hz, 2-H), 6.86 (d, 1 H, $J = 1$ Hz, 3-H), 6.87–6.93 (m, 1 H, ArH), 7.13–7.22 (m, 3 H, ArH), 7.25–7.28 (m, 1 H, ArH), 7.36–7.39 (m, 1 H, ArH), 7.70–7.72 (m, 1 H, ArH), 8.80 (s, 1 H, CHO)
2i	84	120–122	1677 849 764	6.38 (d, 1 H, $J = 6.5$ Hz, 2-H), 6.63 (d, 1 H, $J = 6$ Hz, 3-H), 6.87–6.89 (m, 1 H, 5′-H), 6.97–6.98 (m, 1 H, 4′-H), 7.07–7.09 (m, 1 H, ArH), 7.17–7.18 (d, 1 H, $J = 1.5$ Hz, ArH), 7.26–7.34 (m, 2 H, 3′-H and ArH), 7.72–7.74 (m, 1 H, ArH), 8.68 (s, 1 H, CHO)
2j	86	130–132	1687 785	6.37 (d, 1 H, $J = 6.5$ Hz, 2-H), 6.63 (d, 1 H, $J = 6.0$ Hz, 3-H), 6.86- 6.88 (m, 1 H, 5′-H), 6.97 (d, 1 H, $J = 3.0$ Hz, 4′-H), 7.07 (d, 1 H, $J = 7.5$ Hz, ArH), 7.17 (d, 1 H, $J = 5$ Hz, ArH), 7.26–7.33 (m, 2 H, 3′-H and ArH), 7.30 (d, 1 H, $J = 7.5$ Hz, ArH), 8.67 (s, 1 H, CHO)
2k	83	81–83	1672 765	2.18 (s, 6 H, CH_3), 6.32 (d, 1 H, $J = 6.5$ Hz, 2-H), 6.37 (d, 1 H, $J = 6.5$ Hz, 3-H), 6.97–7.01 (m, 2 H, ArH), 7.05–7.07 (m, 2 H, ArH), 7.25–7.30 (m, 2 H, ArH), 7.70–7.72 (m, 1 H, ArH), 8.67 (s, 1 H, CHO)

[a]) Yellow solids unless otherwise stated.

It was determined that the best ratio of 2′-aminochalcone/BTC/DMF in toluene should be 1:2:6. A temperature of 90°C was found to be best to carry out the conversion and a wide range of substituted 2′-aminochalcones were subjected to these conditions to afford a variety of 2-substituted-4-chloro-*N*-formyl-1,2-dihydroquinolines in good to excellent yields (*Table 1*). 2′-Aminochalcones with electron-withdrawing group (*e.g.* 2-F-6-ClC_6H_3 and *p*-ClC_6H_4) were obtained in high yields, while with 2′-aminochalcones bearing electron-donating groups (*e.g.* *p*-$MeOC_6H_4$ and 3,4-diMeC_6H_3), the reaction proceeded in relatively low yields. The structures of the compounds were confirmed by ^{1}H-NMR, IR and MS (*Table 2*). New compounds were further comfirmed by ^{13}C NMR and elemental analysis (*Table 3*).

Table 2
MS, ^{13}C NMR and Elemental Analysis for Unknown Compounds

Cmpd **2**	MS(EI) *m/z* (%)	^{13}C NMR (δ)	Elemental Analysis Found (Calcd)
2e	314 (M^+, 9), 316 ($[M + 2]^+$, 3), 192 (33), 164 (100)	51.8, 118.1, 123.2, 124.1, 126.1, 126.2, 128.3, 130.0, 130.7, 144.1, 161.4	C, 60.78 (61.06); H, 3.51 (3.52); N, 8.91 (8.90)
2f	287 (M^+, 39), 289 ($[M + 2]^+$, 13), 192 (55), 164 (100)	52.1, 114.2, 114.4, 115.3, 115.5, 118.1, 123.0, 124.2, 124.3, 125.9, 129.2, 130.3, 130.4, 134.5, 161.5	C, 66.48 (66.79); H, 3.83 (3.85); N, 4.86 (4.87)
2g	346 (M^+, 28), 348 ($[M + 2]^+$, 34), 350 ($[M + 4]^+$, 9), 192 (70), 164 (100)	52.0, 118.1, 122.9, 124.0, 124.3, 125.9, 126.0, 129.3, 130.3, 131.6, 134.4, 140.2, 161.6	C, 54.82 (55.12); H, 3.17 (3.18); N, 4.01 (4.02)
2h	320 (M^+, 6), 321 ($[M + 2]^+$, 8), 324 ($[M + 4]^+$, 2), 192 (45), 164 (100)	50.7, 115.0, 115.2, 116.0, 121.0, 124.9, 125.7, 125.8, 125.8, 128.5, 129.7, 129.8, 130.3, 162.1	C, 59.45 (59.65); H, 3.12 (3.13); N, 4.37 (4.35)
2i	259 (M^+, 27), 261 ($[M + 2]^+$, 9), 230 (70), 164 (100)	48.1, 118.0, 124.2, 125.9, 126.2, 126.9, 129.3, 130.3, 134.1, 140.7, 160.8	C, 64.54 (64.75); H, 3.86 (3.88); N, 5.40 (5.39)
2j	275 (M^+, 15), 277 ($[M + 2]^+$, 5), 246 (73), 164 (100)	48.1, 118.3, 124.2, 124.2, 125.8, 125.9, 126.2, 126.4, 126.9, 129.3, 130.3, 134.1, 140.7, 160.8	C, 60.76 (60.98); H, 3.64 (3.66); N, 5.09 (5.08)
2k	297 (M^+, 15), 299 ($[M + 2]^+$, 4), 192 (35), 164 (100)	19.5, 19.8, 52.6, 118.1, 124.6, 125.3, 125.7, 128.3, 128.6, 130.0, 130.0, 134.8, 135.4, 136.9, 137.1, 161.5	C, 72.30 (72.60); H, 5.39 (5.42); N, 4.71 (4.70)

In summary, we have developed an efficient intramolecular cyclization of 2′-aminochalcones to 2-substituted-4-chloro-*N*-formyl-1,2-dihydroquinolines by halomethyleniminium salts derived from BTC/DMF. This method provides excellent chemoselectivity, higher yields, and avoids the formation of inorganic phosphorus salts.

Table 3
^{1}H NMR, ^{13}C NMR, MS, and Elemental Analysis for Unknown Compounds **1**

Cmpd **1**	**1f**	**1h**	**1k**
mp(°C)	105.2–106.5	107.5–108.7	99.8–101.1
^{1}H NMR	6.35 (br s, 2 H, NH_2), 6.69–6.72 (m, 2 H, ArH), 7.06–7.11 (m, 1H, ArH), 7.26–7.39 (m, 4 H, ArH), 7.58–7.70 (m, 2 H, CH = CH), 7.83–7.86 (m, 1 H, ArH)	6.43 (br s, 2 H, NH_2), 6.68–6.72 (m, 2 H, ArH), 7.05–7.10 (m, 2 H, ArH), 7.22–7.32 (m, 3 H, CH = CH, ArH), 7.83 (m, 1 H, ArH), 7.90–7.95 (m, 2 H, ArH)	2.30 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 6.33 (br s, 2 H, NH_2), 6.69–6.72 (m, 2 H, ArH), 7.17 (d, 1 H, J = 7.6 Hz, ArH), 7.25–7.30 (m, 2 H, ArH), 7.57 (d, 1 H, J = 15.6 Hz, CH = CH), 7.71 (d, 1 H, J = 15.6 Hz, CH = CH), 7.86–7.88 (m, 1 H, ArH)
^{13}C NMR (δ)	114.3 (d, J = 22 Hz), 115.9, 116.9 (d, J = 21.2 Hz) 117.3, 118.9, 120.2, 124.3 (d, J = 13.7 Hz), 130.4 (d, J = 8.3 Hz), 131.0, 134.5, 137.6, 141.4, 151.1, 161.9 (d, J = 245 Hz) 191.3	114.7 (d, J = 23.5 Hz), 115.9, 117.3., 120.1 (d, J = 10.7 Hz), 126.0, 129.9, 130.0, 130.2, 130.3, 131.2, 132.6, 134.5, 151.2, 163.2, 191.6	19.7, 19.8, 115.9, 117.3, 119.4, 122.0, 126.0, 129.4, 123.2, 131.0, 133.0, 134.1, 137.1, 139.3, 143.3, 150.8, 191.9
MS(EI) *m/z* (%)	241 (M^+, 68), 146 (100)	275 (M^+, 51), 277 ([M+2], 17), 146 (100)	251 (M^+, 100) 146 (100)
Elemental Analysis Found (Calcd)	C, 74.66 (74.67), N, 5.85 (5.81), H, 4.98 (5.01)	C, 65.31 (65.35), N, 5.06 (5.08), H, 4.01 (4.02)	C, 81.21 (81.24), N, 5.54 (5.57), H, 6.69 (6.82)

Experimental Section

Melting points (mp) were determined on a digital melting point apparatus WRS-1B and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker ANANCE III-500 spectrometer in $CDCl_3$ using TMS as an internal standard. Infrared spectra were recorded neat or as KBr pellets on a Thermo Nicolet Avatar 370 spectrophotometer. MS (EI) spectra were acquired on a Finnigan Trace DSQ spectrometer. Elemental analysis was determined

on a Carlo-Erba 1108 instrument. The progress of the reaction was monitored by TLC. The prerequisite 2′-aminochalcones were prepared as previously described.[13]

General Procedure for the Preparation of 2-Substituted-4-chloro-N-formyl-1,2-dihydroquinolines.

A solution of BTC (0.3 g, 1 mmol) in toluene (8 mL) was added dropwise to a solution of DMF (0.3 mL, 3 mmol) in toluene (5 mL) immersed in an ice-water cooled bath. The mixture was stirred for 20 minutes. The temperature was then raised to 20°C and was stirred for an additional 0.5–1 hour. Then substituted 2′-aminochalcones **1** (0.5 mmol) in toluene (10 mL) was added dropwise to the mixture below 5°C, and when the addition was complete, the mixture was heated to 90°C and maintained for 1–3 hours. After completion of the reaction [monitored by TCL (petroleum ether/ethyl acetate = 5:1)], the mixture was poured into ice water and stirred for 1–1.5 hour. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (20 mL × 2). The combined organic layers was washed successively with 10% NaOH (20 mL × 2) and then with brine (20 mL × 3). After evaporation of the organic solvent, the residue was subjected to column chromatography. Elution with petroleum ether/ethyl acetate 20:1) afforded the pure products.

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