



Substituted quinolinones. 21. Efficient *N*-alkylation of 4-chloro-6-methylquinolin-2(1*H*)-one under phase transfer catalysis conditions

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ABSTRACT

Selective and efficient *N*-alkylation reaction of 4-chloro-6-methylquinolin-2(1*H*)-one with certain active halo-methylene compounds have been carried out using phase transfer catalysis (PTC) technique. Tetrabutylammonium bromide (TBAB), PTC catalyst, and potassium carbonate, base catalyst, were utilized to prepare eleven new 1-alkyl-4-chloro-6-methylquinolin-2(1*H*)-ones. Structure of new compounds was established on lights of their analytical and spectral data. © 2014 Trade Science Inc. - INDIA

KEYWORDS

Alkylation reaction;
Halo-methylene compounds;
Quinolin-2(1*H*)-one;
Tetrabutylammonium
bromide;
Phase transfer catalysis.

INTRODUCTION

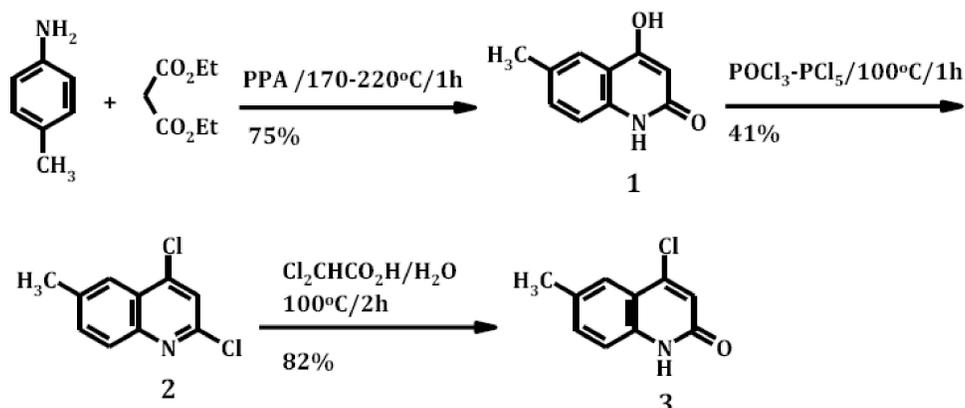
In the last few years, an increasing interest in the synthesis of new functionalized quinolin-2(1*H*)-ones, associated with inspiring biological applications, has been recognized. Many 1,4-disubstituted quinolin-2(1*H*)-ones proved to be accompanied with important broad spectrum of pharmacological activities^[1-6]. In particular, 4-chloro-6-methylquinolin-2(1*H*)-one was selected as key-compound due to the biological activity associated with quinolinones and chloroquinolines^[7-9]. On the other hand, chemically, methyl group in the position-6 might have the highest mesomeric repelling effect (+M), rendering nitrogen at position-1 more active towards alkylation reactions. Thus this position has higher activation effect, compared to either position-5 or position-7. In such *N*-alkylation process, the methyl substituent at position-6 has a preference more than that in position-8 due to the shielding steric effect of the position-8 on substitution at the position-1. In connec-

tion to our program work which deals with substituted quinolinones^[10,11], our attention was directed to obtain new *N*-substituted quinolinone derivatives of expected biological activity especially as antimalarial and antiparasitic.

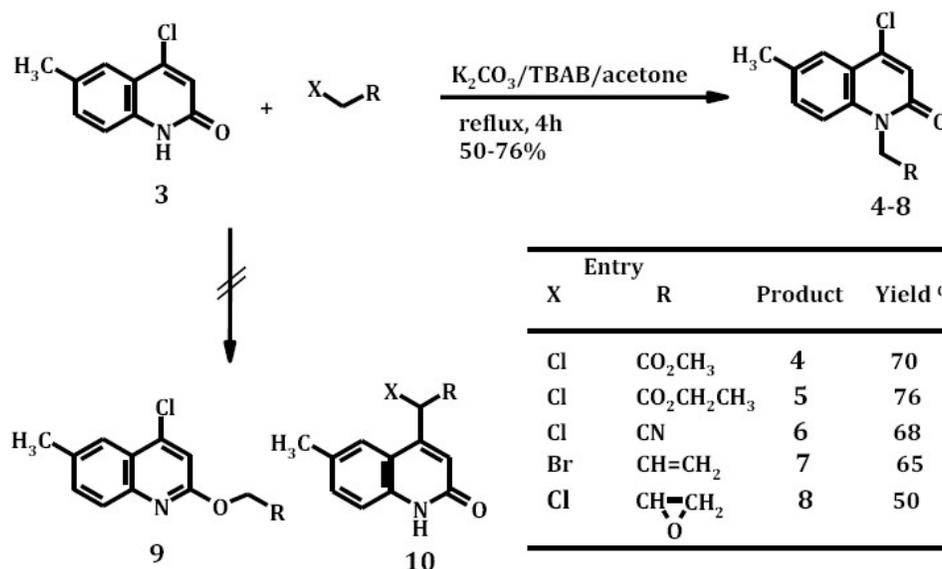
RESULTS AND DISCUSSION

4-Hydroxy-6-methylquinolin-2(1*H*)-one (**1**), which is readily available *via* condensation of *p*-toluidine with diethyl malonate using polyphosphoric acid (PPA)^[12], was used as a starting material. Treatment of the compound (**1**) with a mixture of phosphorus pentachloride and phosphoryl chloride gave 2,4-dichloro-6-methylquinoline (**2**), which was subjected to hydrolysis under acidic condition to give the desired key-compound 4-chloro-6-methylquinolin-2(1*H*)-one (**3**)^[13] (Scheme 1).

The reaction of the chloroquinolinone (**3**) was examined under classic alkylation condition, using the ap-



Scheme 1 : Preparation of the chloroquinolinone (3)



Scheme 2 : Reaction of the chloroquinolinone (3) with halo active methylene compounds

appropriate alkyl halide and potassium hydroxide as base catalyst. The main products obtained are the *N*-alkylated quinolinone. However the overall yields were not satisfactory (range 1–5%). This low yield motivated us to apply phase transfer catalysis (PTC) technique which was proved to improve yields of such alkylation reaction^[14]. Thus, the chloroquinolinone (3) was treated with some active methylene halides namely; methyl chloroacetate, ethyl chloroacetate, chloroacetonitrile, 3-bromopropene (allyl bromide), and 2-chloromethyloxirane (epichlorohydrine), in presence of potassium carbonate as base catalyst and tetrabutylammonium bromide (TBAB) as phase transfer catalyst, in dry acetone as solvent. The IR spectra of the five products (4–8) revealed the presence of amide C=O stretching absorption band at ν 1649 \pm 8 cm⁻¹, confirming *N*-substitution of the quinolinone moi-

ety. The ¹H NMR spectrum of the methyl acetate derivative (4) showed three singlet signals at δ 2.42 which was attributed to C6–CH₃, at δ 5.10 due to N–CH₂–CO, and at δ 6.97 due to the proton at C3–H. Also three protons were detected in the ordinary aromatic region; two of them appeared as doublet signals at δ 7.44, 7.65 and one as a singlet at δ 7.86, corresponding to C7–H, C8–H, and C5–H respectively. These results suggested that substitution takes place at position 1. The mass spectrum fragmentation pattern of compound (4) is in good accordance with the proposed formula (Figure 1).

¹H NMR spectrum of the ethyl acetate derivative (5) revealed triplet and quartet signals at δ 1.28 and 4.16 due to chemical shifts of OCH₂CH₃ protons, in addition to three singlet signals at δ 2.39, 5.07 and 6.83 due to characteristic chemical shifts of 6–CH₃,

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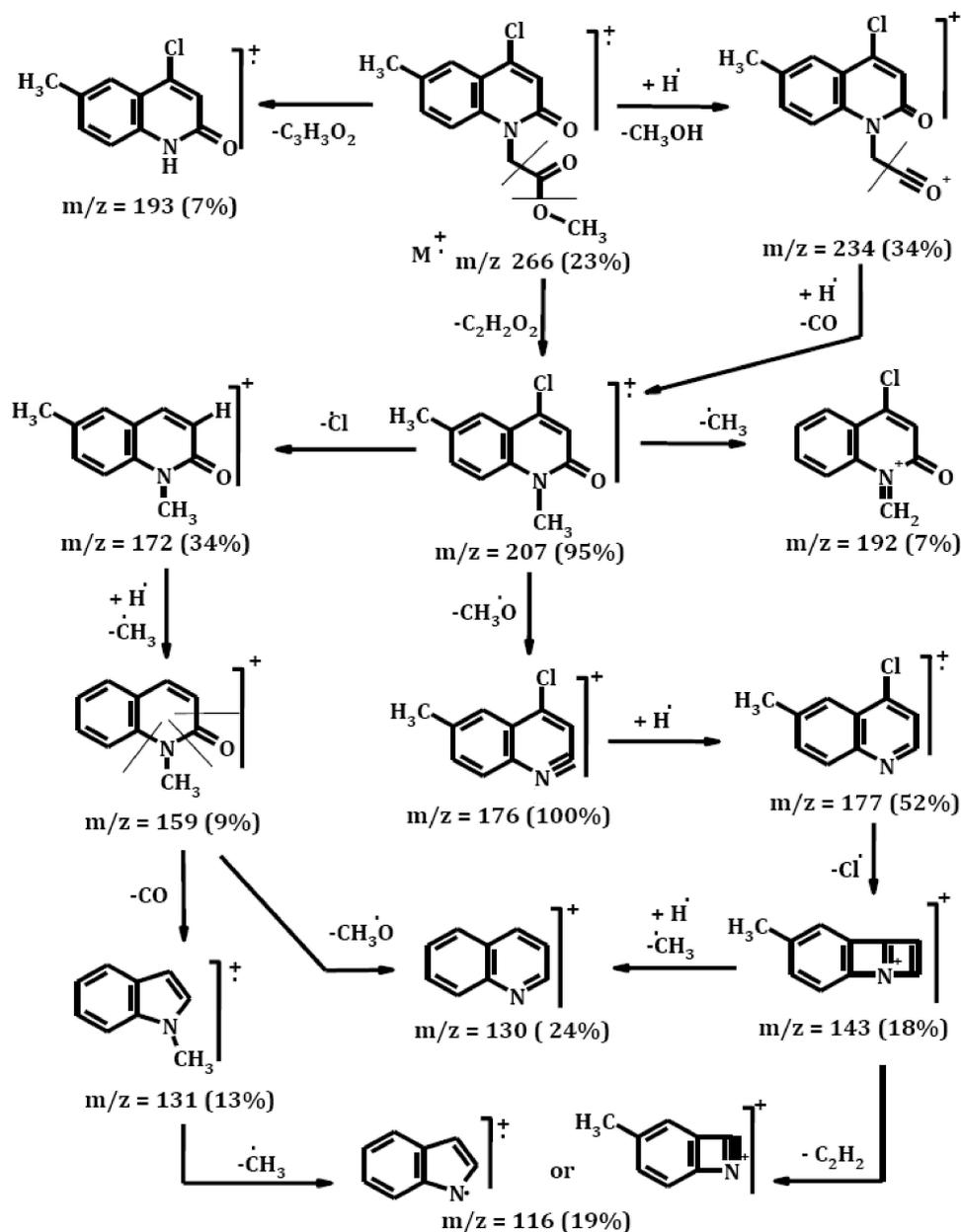


Figure 1: Mass spectrum fragmentation pattern of the methyl acetate derivative (4)

$\text{NCH}_2\text{CO}_2\text{Et}$, and C3-H. The three aromatic protons were observed as two doublets at δ 6.99, 7.34 referred to C7-H, C8-H, respectively, and one singlet peak at δ 7.75 corresponding to C5-H. ^{13}C NMR spectrum of compound (5) is in perfect agreement the proposed structure. Also the mass spectra fragmentation pattern of compound (5) is coincident with its suggested formula (Figure 2).

The acetonitrile derivative (6) (Scheme 2), which was obtained from chloroacetonitrile showed, in its IR spectrum, the presence of a cyano function at ν 2252 cm^{-1} . ^1H NMR spectrum of acetonitrile derivative (6)

revealed a singlet peak at δ 5.41 due to NCH_2CN , and another singlet peak at δ 7.00 due to the proton on position-3.

1-Allyl-4-chloro-6-methylquinolin-2(1H)-one (7) is the product that obtained from allylation of the chloroquinolinone (3), using allyl bromide. IR of this product revealed the presence of an amide $\text{C}=\text{O}$ appeared at ν 1645 cm^{-1} , without any indication for existence of N-H group. ^1H NMR spectrum of the N-allyl derivative (7) showed the specific set of signals due to the allyl grouping. Thus, the chemical shift of N-methylene protons appeared at δ 4.91 as doublet of doublet

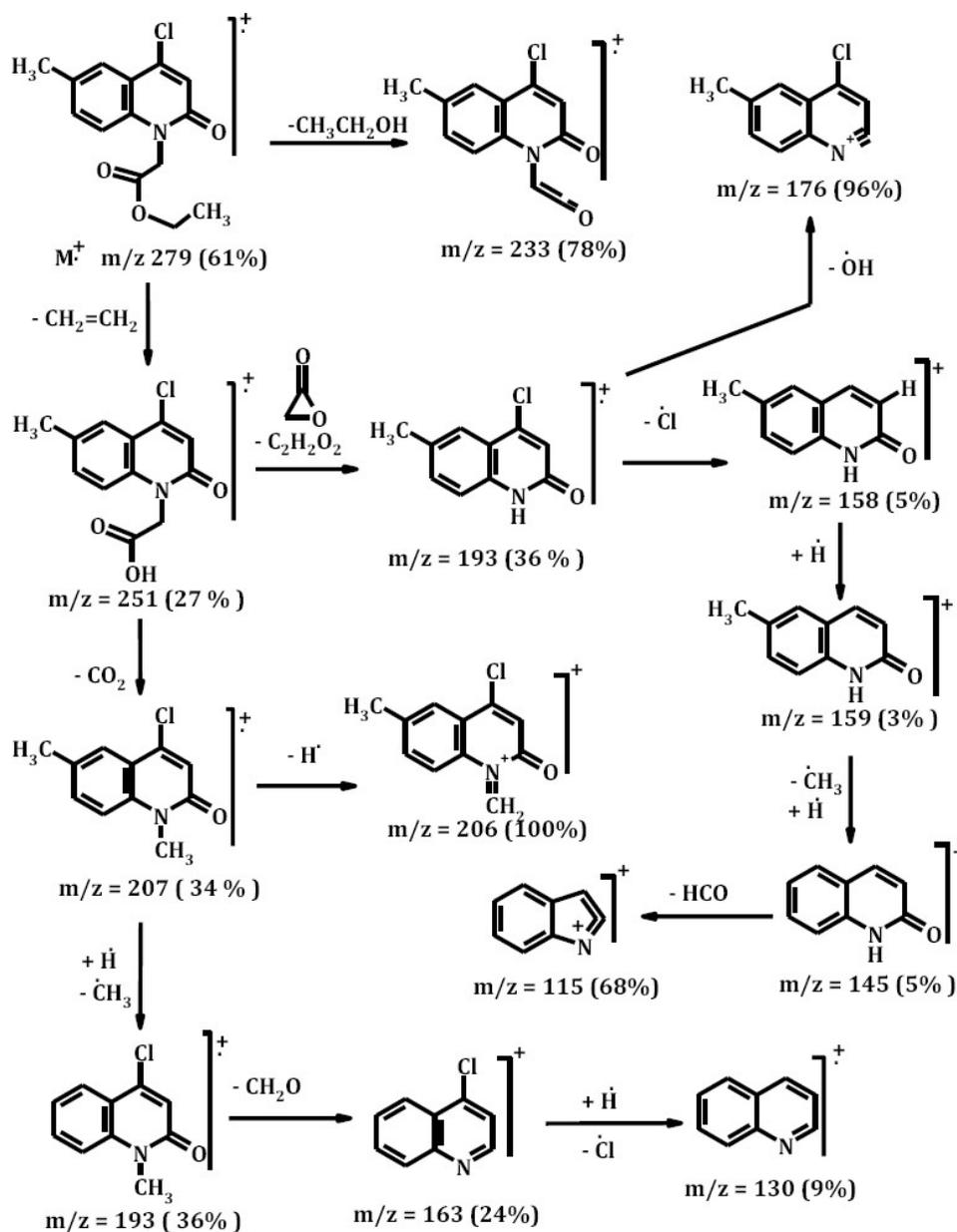


Figure 2 : Mass spectra fragmentation pattern of the ethyl acetate derivative (5)

of doublet due to $(N-CH_aH_a-CH_d=CH_bH_c; J 4.6, 2.4$ Hz). Both of the two methene protons (H_bH_c) were observed as doublet of quartet ($J 10.6, 2.4$ Hz) at δ 5.00 and 5.19. Also an olefinic signal was observed as doublet of doublet of triplet at δ 5.84 due to the proton of $(N-CH_aH_a-CH_d=CH_bH_c; J 7.2, 10.6, 2.4$ Hz). This coupling constant analysis of allylic system was found in agreement with the reported in similar N-allyl derivatives^[15].

Mass fragmentation pattern strongly confirmed the anticipated structure of 4-chloro-6-methyl-1-(oxiran-2-ylmethyl)-quinolin-2(1H)-one (8). Its IR spectrum re-

vealed the absence of N-H group, and the presence of C=O, a result which supported the N-alkylation postulation. ¹H NMR spectrum revealed a doublet of doublet signal at δ 3.94 due to N- CH_2 , a doublet signal at δ 4.93 referred to methene of oxirane ($-CH-CH_2-O-$), and a multiplet at δ 5.00 due to methine of oxirane ($CH_2-CH-CH_2-O$). In all alkylation processes there are no indication for formation of the competitive O-alkylated products (9) (Scheme 2). This is in agreement with the reported results in literature^[16]. Also spectral data as well as elemental microanalysis excluded existence of C-Nucleophilic substitution at position-4

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which could lead to the 4-substituted quinolinone products (**10**) (Scheme 2).

The mechanism of the phase transfer catalyzed *N*-alkylation of chloroquinolinone (**3**) is similar to our previous reported PTC alkylation of 2-hydroxypyrido[1,2-*a*]pyrimidin-4-one^[14] (Figure 3).

Oxidation of the *N*-allylquinolinone (**7**) with aqueous basic potassium permanganate gave the corresponding 4-chloro-1-(2,3-dihydroxypropyl)-6-methylquinolin-2(1*H*)-one (**11**). The same diol derivative (**11**) was obtained on hydrolysis of the oxirane derivative (**8**) using aqueous potassium carbonate (Scheme 3). IR spectrum of the diol (**11**) revealed a broad band of H-bonded hydroxyl groups at ν 3388 cm^{-1} . ¹H NMR spectrum showed a doublet signal at δ 3.20 corresponding to two methylene protons of (NCH₂CH(OH)CH₂(OH)). In addition, two signals appeared at δ 3.44, and 4.39 attributed to (NCH₂CH(OH)CH₂(OH)) protons. The two broad signals at δ 5.48 and 5.88 (exchangeable with deuterium on addition of D₂O) was attributed to the pres-

ence of two alcoholic protons. The characteristic proton at position-3 was observed at δ 6.70 and aromatic region revealed existence of three protons at δ 7.20–7.80.

Acid hydrolysis of the esters (**4**) and/or (**5**), using (2*M*) hydrochloric acid, gave to the acetic acid derivative (**12**), in fair yield (Scheme 4). IR spectrum of the acetic acid derivative (**12**) revealed the presence of stretching vibration of carboxylic O–H, appeared at ν 3419–2580 cm^{-1} , in addition to carboxylic C=O bond at ν 1719 cm^{-1} . ¹H NMR spectrum showed a singlet signal at δ 5.00 attributed to (N–CH₂CO₂H). The proton at position-3 appeared at δ 6.99 whilst the aromatic proton at position-7 were observed as two doublets at δ 7.44, 7.56, and the distinctive proton at position-5 observed as singlet at δ 7.79. The chemical shift of the proton of carboxylic group appeared as a broad signal at δ 13.17 (exchangeable with deuterium on addition of D₂O).

Heating of the acetic acid derivative (**12**), above its melting point, led to decarboxylation giving rise to 4-

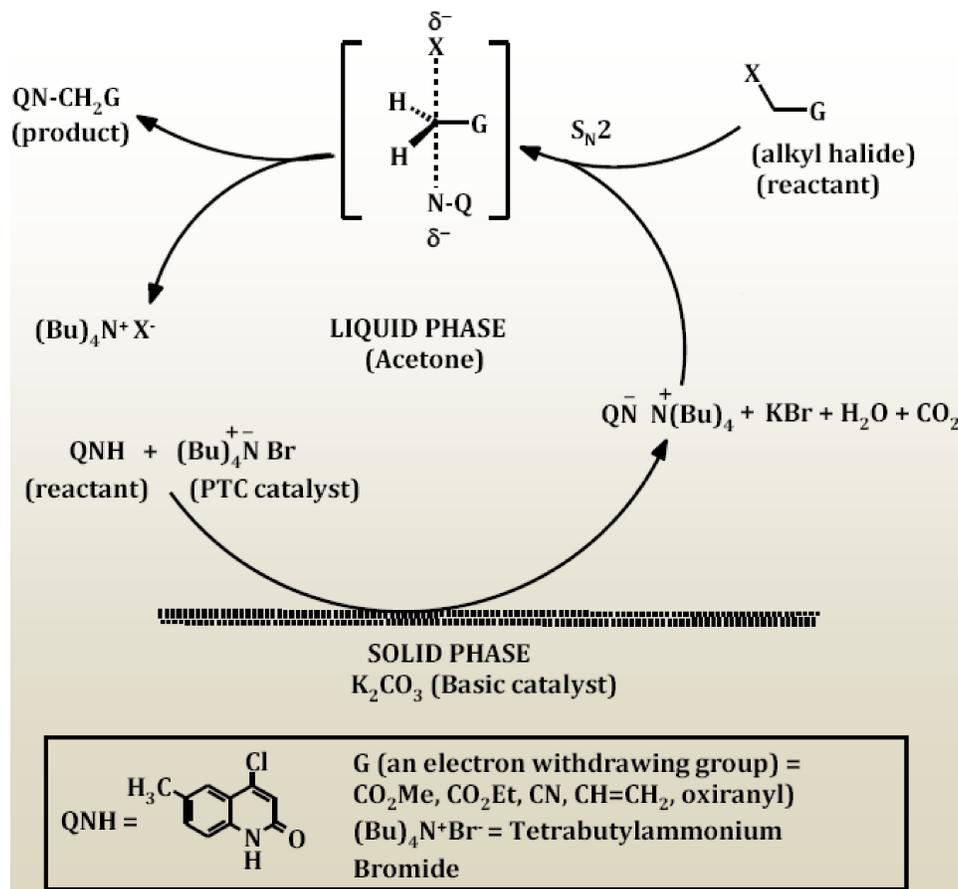
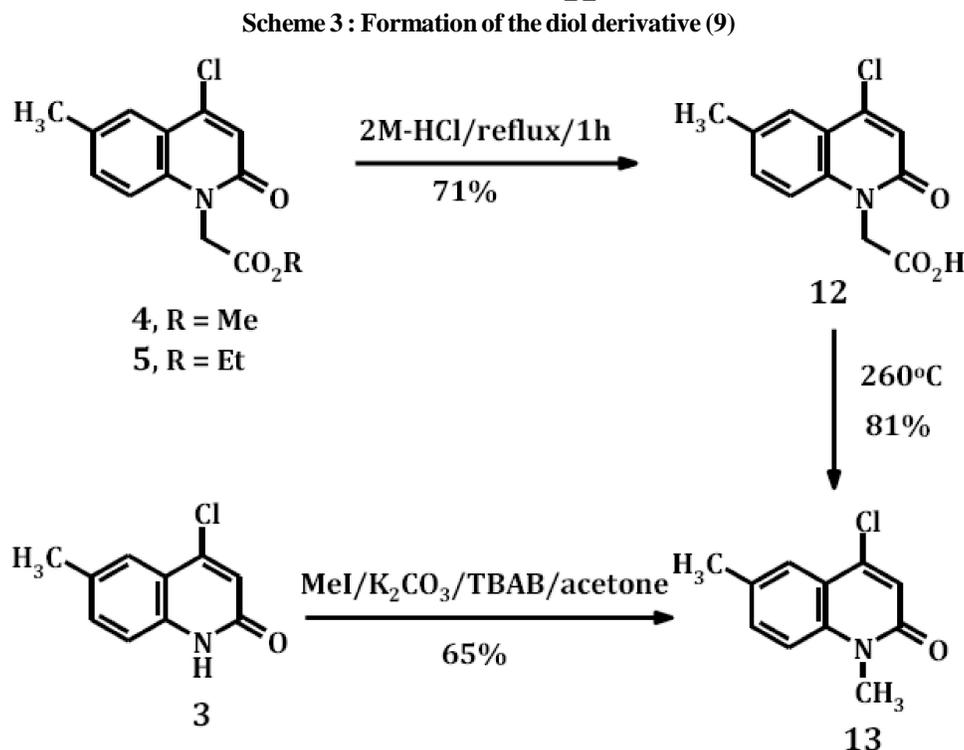
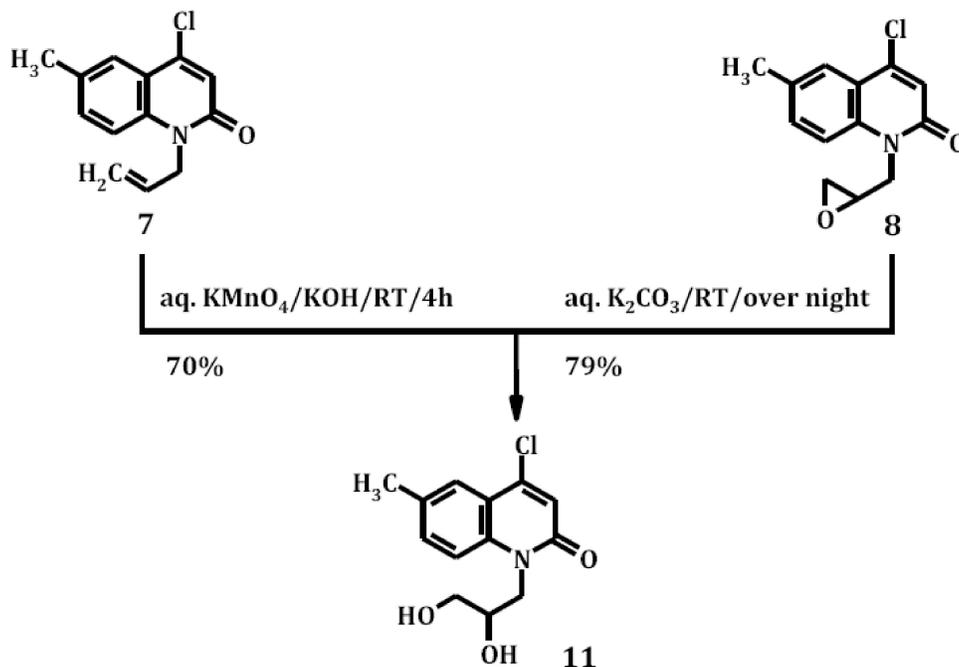


Figure 3 : Mechanism of PTC alkylation of the chloroquinolinone (**3**)

chloro-1,6-dimethylquinolin-2(1*H*)-one (**13**). The structure of the dimethylquinolinone (**13**) was inferred from its spectral data as well as analytical results. ¹H NMR spectrum presented an additional signal at δ 3.60, which is distinctive for N-CH₃ protons. A doubtless structure confirmation for the dimethylquinolinone (**13**) was achieved *via* preparation of the compound (**13**) by *N*-

methylation of 4-chloro-6-methylquinolin-2(1*H*)-one (**3**), under PTC conditions, using methyl iodide and potassium carbonate in presence of TBAB (Scheme 4).

In conclusion, alkylation reaction of 4-chloro-6-methylquinolin-2(1*H*)-one, with active halomethylene compounds, under phase transfer catalysis using solid



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potassium carbonate and tetrabutylammonium bromide (TBAB) as PTC reagent proved to be effective and selective. Thus, alkylation selectively takes place on the nitrogen at position 1 with fair yields (50–76%).

EXPERIMENTAL

Melting points were determined on a digital Stuart-SMP3 apparatus. IR spectra were taken on a Perkin-Elmer FT-IR 1650 in KBr disks. ¹H NMR spectra were recorded on Varian Gemini-200 NMR-spectrometer (200 MHz), using DMSO-*d*₆ or CDCl₃ as solvents and TMS as internal reference. Mass spectra were determined on a Shimadzu GC-MS-QP 1000EX mass spectrometer at 70 eV. Elemental microanalyses were performed on a Perkin Elmer CHN-2400 Analyzer. All reactions were monitored by thin-layer chromatography (TLC) on 0.2-mm silica gel F-254 (Merck) plates, using UV light (254 and 366 nm) for detection. 4-Hydroxy-6-methylquinolin-2(1H)-one (**1**)^[12] and 4-chloro-6-methylquinolin-2(1H)-one (**3**)^[13] were prepared according to the literature methods.

PTC-Alkylation of 4-Chloro-6-methylquinolin-2(1H)-one (**3**). General procedure

To a mixture of the chloroquinolinone (**3**) (1.93 g, 10 mmol) and the proper alkylating agent (30 mmol), namely; methyl chloroacetate (2.63 mL), ethyl chloroacetate, (3.2 mL), chloroacetonitrile (1.89 mL), allyl bromide (2.55 mL), epichlorohydrine (2.33 mL), in dry acetone (50 mL), tetrabutylammonium bromide (TBAB) (0.31 g, 1.25 mmol) and potassium carbonate (2.76 g, 20 mmol) were added. Then the mixture was heated under reflux on a water-bath for 4h and filtered off while hot. The filtrate solution was evaporated under reduced pressure till dryness and the solid residue that obtained was crystallized to give the compounds (**4–8**).

Methyl (4-Chloro-6-methyl-2-oxo-1,2-dihydroquinolin-1-yl)acetate (**4**)

Yield 70%; mp 115–117 °C (EtOH). IR ν (KBr, cm⁻¹) 3050, 2997, 1753 (C=O_{ester}), 1657 (C=O_{quinolone}), 1221, 1131 (C-O-C); ¹H NMR δ (200 MHz, CDCl₃) 2.42 (s, 3H, 6-CH₃), 3.69 (s, 3H, OCH₃), 5.10 (s, 2H, NCH₂CO), 6.97 (s, 1H, 3-H), 7.44 (d, 1H, J=8 Hz, 7-H), 7.65 (d, 1H, J=8Hz, 8-H), 7.86 (s, 1H, 5-H); MS EI (m/z) 267 (20.6) (M⁺), 268

(6.8), 266 (23.4), 265 (46.6), 234 (33.5), 233 (71.5), 232 (76.9), 208 (27.4), 206 (95.8), 205 (83.3), 177 (52.2), 176 (100), 141 (44.3), 115 (54.2), 114 (48.9), 89 (28.8), 71 (17.6), 63 (23.5), 50 (18.2), 51 (19.4); Anal: calculated for C₁₃H₁₂ClNO₃ (265.70) C, 58.77; H, 4.55; N, 5.27%, Found; C, 58.60; H, 4.50; N, 5.10%.

Ethyl (4-Chloro-6-methyl-2-oxo-1,2-dihydroquinolin-1-yl)acetate (**5**)

Yield 76%; mp 137–138 °C (EtOH). IR ν (KBr, cm⁻¹) 3052, 1745 (C=O_{ester}), 1657 (C=O_{quinolone}), 1220, 1197, 1134 (C-O); ¹H NMR δ (200 MHz, CDCl₃) 1.28 (t, 3H, OCH₂CH₃), 2.39 (s, 3H, 6-CH₃), 4.16 (q, OCH₂CH₃), 4.99 (s, 2H, NCH₂CO), 6.83 (s, 1H, 3-H), 6.99 (d, 1H, 7-H), 7.34 (d, 1H, 8-H), 7.75 (s, 1H, 5-H); ¹³C NMR (75 MHz) δ 13.95, 20.89, 60.41, 62.46, 112.18, 122.47, 127.04, 132.99, 133.82, 135.21, 142.66, 144.01, 159.38, 168.35; MS EI (m/z) 279 (46.6) (M⁺), 280 (11.4), 233 (100), 195 (67.3), 143 (56.3), 89 (46.7), 51 (42.2); Anal: calculated for C₁₄H₁₄ClNO₃ (279.73) C, 60.11; H, 5.04; N, 5.01%, Found; C, 60.00; H, 4.90; N, 5.20%.

2-(4-Chloro-6-methyl-2-oxo-1,2-dihydroquinolin-1-yl)acetonitrile (**6**)

Yield 68%; mp 155–157 °C (EtOH) IR ν (KBr, cm⁻¹) 3052, 2993, 2252 (C≡N), 1659 (C=O_{quinolone}), 1593; ¹H NMR δ (200 MHz, DMSO-*d*₆) 2.44 (s, 3H, 6-CH₃), 5.41 (s, 2H, NCH₂CN), 7.00 (s, 1H, 3-H), 7.66–7.80 (m, 3H, H_{arom}); MS EI (m/z) 232 (8.5) (M⁺), 233 (2.1), 207 (100), 192 (18.4), 164 (34.3), 130 (20.6), 102 (22.6), 89 (16.6), 76 (45.3), 63 (25.4), 51 (46.7); Anal: calculated for C₁₂H₉ClN₂O (232.67) C, 61.95; H, 3.90; N, 12.04%, Found; C, 61.70; H, 3.80; N, 11.70%.

1-Allyl-4-chloro-6-methylquinolin-2(1H)-one (**7**)

Yield 65%; mp 173–174 °C (H₂O). IR ν (KBr, cm⁻¹) 3071, 2974, 1645 (C=O_{quinolone}), 1561; ¹H NMR δ (200 MHz, DMSO-*d*₆) 2.45 (s, 3H, 6-CH₃), 4.91 (ddd, $J_{ad}=4.6$, $J_{ab,ac}=2.4$ Hz, 2H, NCH₂), 5.00–5.12 (dq, $J_{bd}=10.6$, $J_{bc}=2.4$ Hz, 1H, CH_bH_c=CH_d), 5.19–5.24 (dd, $J_{cd}=17.2$, $J_{cb,ba}=2.4$ Hz, 1H, CH_bH_c=CH_d), 5.84–6.00 (ddt, $J_{db}=10.6$, $J_{dc}=17.2$, $J_{da}=4.6$ Hz, 1H, CH_aH_a–CH_d=CH_bH_c), 6.90 (s, 1H, 3-H), 7.26 (d, 1H, 7-H), 7.42 (d, 1H, 8-H), 7.80 (s, 1H, 5-H); MS EI (m/z) 234

(M⁺) (25.7), 235 (6.8), 233(47.9), 217 (100), 218 (93.9), 216 (20.6), 176 (17.5), 141 (22.5), 114 (22.5), 102 (13.9), 75 (31.2), 62 (23.4), 51 (16.8); Anal: calculated for C₁₃H₁₂ClNO (233.70) C, 66.81; H, 5.18; N, 5.99%, Found; C, 66.60; H, 5.00; N, 5.70%.

4-Chloro-6-methyl-1-(oxiran-2-ylmethyl)quinolin-2(1H)-one (8)

Yield 5076%; mp 125–127 °C (Acetone). IR ν (KBr, cm⁻¹) 3083, 1641 (C=O_{quinolone}), 1562, 919, 856 (C–O_{epoxide}); ¹H NMR δ (200 MHz, DMSO-*d*₆) 2.42 (s, 3H, 6-CH₃), 3.94 (dd, 2H, NCH₂), 4.93 (d, 2H, CH₂CHOCH₂), 5.00 (m, 1H, CHCH₂O), 6.86 (s, 1H, 3-H), 7.27–7.70 (m, 3H, H_{arom}); MS EI (m/z) 250 (20.5) (M⁺), 251(5.3), 249 (49.5), 219 (22.1), 209 (22.2), 194 (26.6), 193 (100), 115 (33.6), 51 (32.2); Anal: calculated for C₁₃H₁₂ClNO₂ (249.70) C, 62.53; H, 4.84; N, 5.61%, Found; C, 62.50; H, 4.70; N, 05.40%.

4-Chloro-1-(2,3-dihydroxypropyl)-6-methylquinolin-2(1H)-one (11)

Procedure a

A mixture of the allyl derivative (7) (0.234 g, 1 mmol), and aqueous solution of potassium permanganate (20 mL, 1N), potassium hydroxide (10 mL, 2N) was stirred at room temperature for 2 hr. The mixture was filtered off, and the filtrate was concentrated to one third of its initial volume to give solid precipitate. The precipitate was filtered, washed with cold water (25 mL) then ethanol (25 mL) several times, and crystallized from DMSO. Yield 70%; mp 277–278 °C. IR ν (KBr, cm⁻¹) 3388 (b, H-bonded OH), 1643 (C=O_{quinolone}); ¹H NMR δ (200 MHz, DMSO-*d*₆) 2.41 (s, 3H, 6-CH₃), 3.20 (d, 2H, NCH₂), 3.44 (d, 2H, CHOHCH₂OH), 4.39 (m, 1H, CHOHCH₂OH), 5.48 (b, 1H, CH₂OH), 5.88 (b, 1H, CHOH), 6.70 (s, 1H, C3-H), 7.20–7.80 (m, 3H, H_{arom}); MS EI (m/z) 267 (1.2) (M⁺), 254 (3.4), 253 (6.3), 252 (8.1), 251 (6.2), 233 (40.1), 222 (13.2), 219 (23.4), 194 (39.8), 185 (15.6), 193 (73.3), 192 (100), 173 (17.2), 165 (11.3), 159 (20.2), 144 (12.8), 129 (18.6), 102 (13.5), 77 (17.2); Anal: calculated for C₁₃H₁₄ClNO₃ (267.71) C, 58.33; H, 5.27; N, 5.23%, Found; C, 58.20; H, 5.20; N, 4.90%.

Procedure b

A suspension of the oxirane derivative (8) (0.249 g,

1 mmol), in potassium carbonate solution (10 mL, 1M), was stirred at room temperature overnight. The solid precipitate so formed was filtered and crystallized from DMSO to give the diol (11), yield 79%.

(4-Chloro-6-methyl-2-oxo-1,2-dihydroquinolin-1-yl)acetic acid (12)

A mixture of (2 mmol) of the ester (4) (0.53 g) or (5) (0.56 g) and hydrochloric acid (20 mL, 2N) was heated under reflux for 1 hr. The clear solution that obtained was left to cool and neutralized till pH ~ 6.5, using aqueous sodium carbonate solution (1 M). The precipitate so formed was collected by filtration and crystallized from ethanol. Yield 71%; mp 246–247 °C. IR ν (KBr, cm⁻¹) 3419–2580 (b, OH_{carboxylic}), 1719 (C=O_{carboxylic}), 1623 (C=O_{quinolone}); ¹H NMR δ (200 MHz, DMSO-*d*₆) 2.52 (s, 3H, 6-CH₃), 5.00 (s, 2H, NCH₂), 6.99 (1H, 3-H), 7.44 (d, 1H, 8-H), 7.56 (d, 1H, 7-H), 7.79 (s, 1H, 5-H), 13.17 (b, 1H, OH_{carboxylic}); MS EI (m/z) 251 (26.2) (M⁺), 252 (9.6), 233 (10.4), 219 (5.2), 215 (23.6), 206 (98.6), 194 (29.1), 189 (42.0), 176 (63.3), 164 (15.3), 158 (21.9), 147 (19.6), 142 (63.6), 133 (20.3), 128 (37.8), 117 (26.7), 91 (73.6), 77 (67.4), 69 (36.2), 51 (100), 50 (42.4); Anal: calculated for C₁₂H₁₀ClNO₃ (251.67) C, 57.27; H, 4.01; N, 5.57%, Found; C, 57.20; H, 4.00; N, 05.40%.

4-Chloro-1,6-dimethylquinolin-2(1H)-one (13)

Procedure a

The acid (12) (0.25 g, 1 mmol) was heated in a test tube at 10 degrees above its melting point (to ~ 260 °C). The tube was left to cool and the melt was triturated with diethyl ether (10 mL), then the solid material was filtered, washed, crystallized from dioxane-water (5:1). Yield 81 %; mp 172–174 °C (dioxane/H₂O). IR ν (KBr, cm⁻¹) 3071, 1653 (C=O_{quinolone}), 1602, 1597, 1434; ¹H NMR δ (200 MHz, DMSO-*d*₆) 2.39 (s, 3H, 6CH₃), 3.60 (s, 3H, NCH₃), 6.90 (s, 1H, C3-H), 7.28 (d, 1H, C7-H), 7.44 (d, 1H, C8-H), 7.72 (s, 1H, C5-H); MS EI (m/z) 207 (32.3) (M⁺), 208 (8.6), 193 (100), 192 (43.3), 179 (21.2), 145 (12.6), 117 (18.0), 64 (15.6); Anal: calculated for C₁₁H₁₀ClNO (207.66) C, 63.62; H, 4.85; N, 6.74%, Found; C, 63.60; H, 4.60; N, 6.50%.

Procedure b

To a mixture of compound (3) (1.93 g, 10 mmol),

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methyl iodide (16 mmol, 1 mL), in DMF (30 mL), potassium carbonate (2.76 g, 20 mmol), and TBAB (0.3 g) were added, then the mixture was heated under reflux for 8 hr. Afterwards, the mixture was filtered off, and the filtrate was evaporated to give a solid precipitate. The precipitate was filtered and crystallized from dioxane-water (5:1) to give the 1,6-dimethylquinolinone (**13**), yield 65%.

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