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Synthesis of (*E*)-2-(4,7-dichloroquinolin-2-yl)-3-dimethylamino-2-propene-1-al and its use as a Synthetic Intermediate

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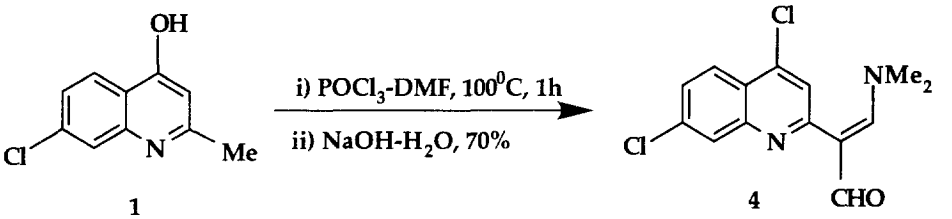
Abstract: A novel synthesis is described for (*E*)-2-(4,7-dichloroquinolin-2-yl)-3-dimethylamino-2-propene-1-al (**4**), which reacts with nucleophiles to yield heterocycle-substituted 4,7-dichloroquinolines (**5-7**).

N^4-(7-chloro-4-quinolinyl)-N^1,N^1-diethyl-1,4-pentanediamine (chloroquine) is an exceptionally safe and effective antimalarial, although its value has been compromised by the increasing prevalence of chloroquine resistance.[1,2] To synthesize potential alternative antimalarials, we required an enaminaldehyde-substituted 4,7-dichloroquinoline. We describe the synthesis of this intermediate (**4**), and demonstrate its utility for the synthesis of heteroaromatic compounds (**5-7**) and novel analogs of chloroquine (**8**). The lack of information available in the literature on this compound (**4**) is the rationale for this report.

7-Chloro-4-hydroxy-2-methyl quinoline, **1**, the precursor of compound **2** was synthesized in good yield from *m*-chloroaniline by condensation with ethyl acetoacetate in the presence of catalytic HCl to produce an intermediate compound (ethyl 3-(3-chloro)anilino-2-butenoate), followed by ring closure in boiling phenyl ether, and recrystallization from EtOAc-EtOH.[3] The subsequent reaction of compound **1** with the Vilsmeir reagent $[Me_2NCHCl]^+$ $[PO_2Cl_2]^-$ yielded an intermediate, which was then converted to compound **4** (Scheme 1).[4,5] Although the mechanism responsible for synthesis of compound **4** has not yet been established, it likely results from the stepwise reaction of two chloromethylenedimethylamine cations with the C-2 methyl of compound **1**. Reactivity of the C-2 methyl is presumably enhanced by conjugation with the ring nitrogen. The use of cold aqueous NaOH yielded primarily compound **4** (step ii of Scheme 1), whereas water alone yielded a mixture of products.

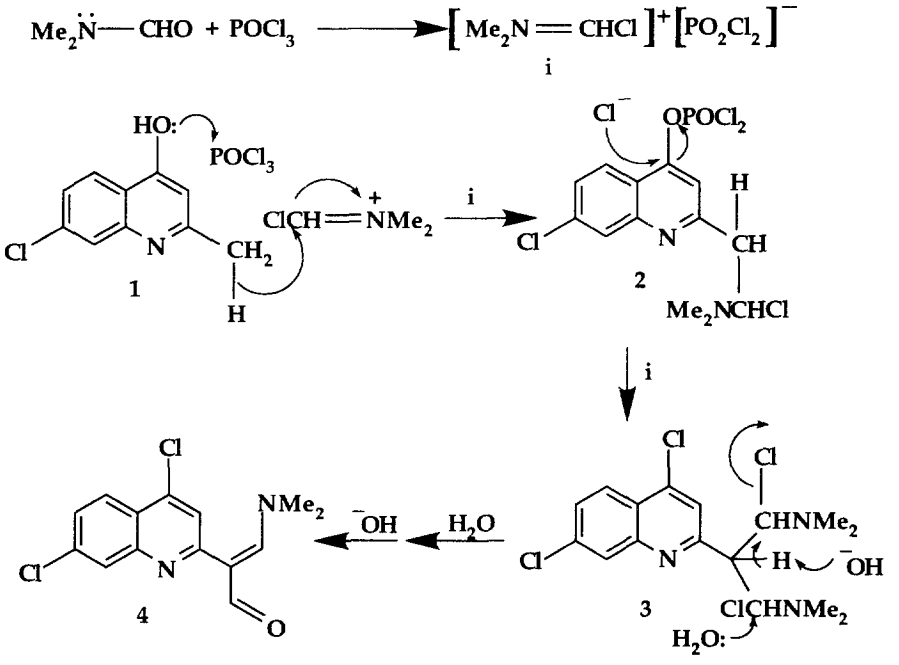
Scheme 1



1 4

A plausible mechanism for the formation of compound **4** is presented in Scheme 2. According to this scheme, alkali-induced transformation of the proposed intermediate (**3**) to compound **4** can be explained by hydrolysis leading to the formation of an aldehyde, which then facilitates the *in situ* elimination of HCl. The structure of compound **4** was assigned on the basis of spectral data,[6] including an NMR spectrum which demonstrated characteristic singlets at 9.20, 7.05, 3.25 and 2.60 ppm for the aldehyde, methine and two methyl protons, respectively. Both the ^{1}H NMR and ^{13}C NMR data indicated that the product (**4**) existed as only one of the two possible stereoisomers (*E*- or *Z*-). The *E*- stereochemistry for compound **4** was

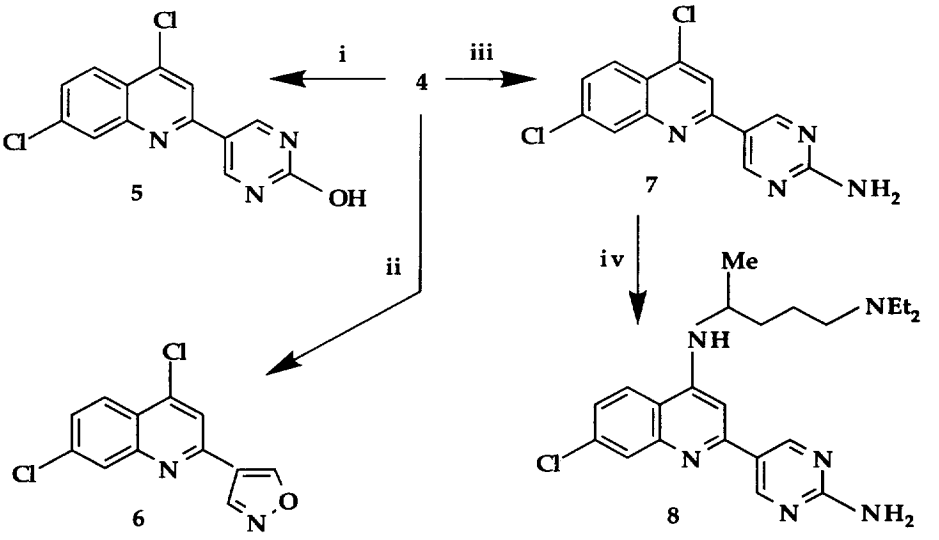
Scheme 2



determined from its X-ray crystal structure.[7] This configuration is also consistent with previous reports in the literature for comparable enaminones.[8] The planarity of the enaminaldehyde side chain favors the delocalization of π–electrons and is thus consistent with the *E*- configuration.

The presence of the enaminaldehyde in compound **4** also makes that compound an excellent intermediate for the synthesis of heterocyclic compounds. We present three examples of 1,3 and 1,2 nucleophiles which condensed readily with compound **4** to produce heteroaromatic compounds (Scheme 3). Reaction of compound **4** with urea, hydroxylamine or guanidine produced compounds **5-7**, respectively, in good yields. The aminopyrimidine-substituted chloroquine analog (**8**) was synthesized from compound **7** using a modification of methods reported previously in the literature (step iv of Scheme 3).[9] Spectral data confirmed the structures assigned to compounds **5-8**.[10]

Scheme 3



Reagents: i) Urea, K_2CO_3, EtOH, reflux, 2h (74%); $NH_2OH.HCl$, K_2CO_3, MeOH, 70^{0}C, 1h (70%); iii) $H_2NC(=NH)NH_2.HCl$, K_2CO_3, EtOH, reflux, 2h (82%); iv) $CH_3CH(NH_2)(CH_2)_3NEt_2$, PhOH, trace amount KI, 145-160^{0}C, 10h (40%).

This report describes a novel synthesis of compound **4**, and demonstrates the value of **4** in the production of heterocycle-substituted 4,7-dichloroquinolines.

Acknowledgments

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4. In a typical experiment, DMF (0.87 mol) was added to $POCl_3$ (0.26 mol) at 5-10°C with stirring. After 30 min, compound **1** was added slowly and the mixture was heated to 100°C for 60 min while being monitored with silica gel TLC (5% MeOH-$CHCl_3$, R_f 0.7). After quenching with ice and adding cold 35% NaOH, the product was filtered, washed with water, dried, and crystallized from MeOH-EtOAc (1:2 v/v) (yield ~70%; M.P. 201-202°C [uncorrected]).
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6. Spectral data for **4**: ^{1}H NMR ($CDCl_3$) δ 2.60 (s, 3H, CH_3), 3.25 (s, 3H, CH_3), 7.05 (s, 1H, =CH), 7.50 (d, J = 9 Hz, 1H, C^6-H), 7.78 (s, 1H, C^8-H), 8.05 (s, 1H, C^3-H), 8.12 (d, J = 9Hz, 1H, C^5-H), 9.20 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 41.45, 47.35, 112.79, 122.11, 123.07, 124.55, 125.23, 127.65, 138.46, 141.20, 149.05, 156.60, 160.42, 188.23. FTIR (KBr, cm^{-1}) 1630 (CHO). GCMS *m/z* 295 (M^+).
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10. Spectral data for **7**: ^{1}H NMR ($(CD_3)_2SO$, ppm) δ 3.50 (bS, 2H, NH_2), 7.52 (dd, J=9, 1.5 Hz, ArH), 7.99 (d, J=1.5 Hz, 1H, ArH), 8.08 (d, J= 9 Hz, 1H, ArH), 9.01 (s, 2H, ArH). FTIR (KBr, cm^{-1}) 3148.02, 3329.34, 1664.67, 1587.51. MS *m/z* 291 (M^+).

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