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Synthesis of Thiazolidinone Derivatives from 4-amino-2-chloroquinoline

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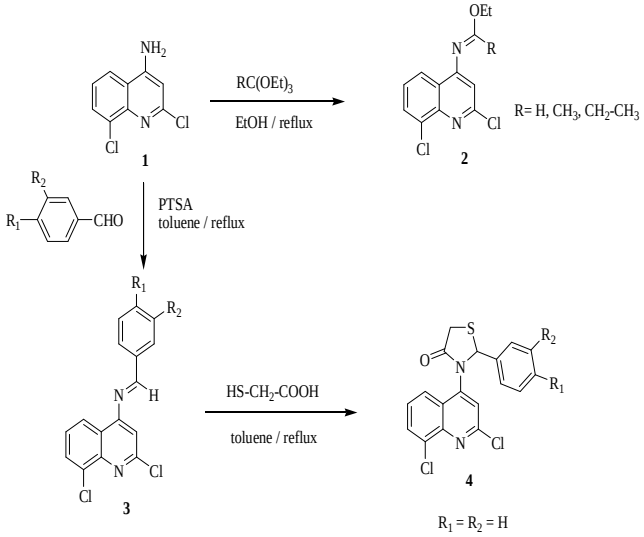
ABSTRACT: This paper describes the synthesis of N-ethoxymethylidene-2,8-dichloroquinolin-4-amine 2(a-c) derivatives from 4-amino-2-chloroquinoline 1. Also describes the synthesis of N-benzylidene-2,8-dichloroquinolin-4-amine 3a (a-c) and 3-(2,8-dichloroquinolin-4-yl)-2-phenylthiazolidin-4-one from 4-amino-2-chloroquinoline 1.

Keywords: 4-amino-2-chloroquinoline; Thiazolidinone.

INTRODUCTION: The synthesis, design and production of new molecules having the value as therapeutic agent for human is the main objective of organic and medicinal chemistry. There are various biologically active molecules which is isolated from plants having five-membered rings, containing hetero atoms. The thiazolidinone derivatives are associated with several biological activities[1-3]. The structure of 4-imino thiazolidinones and 4-thiazolidinones are widely studied for their pharmacological activieties[4,5]. The 4-thiazolidinone derivatives are known to shows antimycobacterial[6]. Anti-fungal[7], anti-tuberculosis[8, 9], anti-convulsant[10], anti-inflammatiry[11-13], anti-HIV[14-16], activities. Peptidoglycan is an essential component of the cell wall of both Gram-negative bacteria and Gram-positive. The derivatives of 4-Thiazolidone have been reported as novel inhibitors of the bacterial enzyme which was precursor for the biosynthesis of peptidoglycan.

RESULTS AND DISCUSSION: The 4-hydroxyquinolin-2(*1H*)-one starting compound was synthesized by literature know procedures from commercially available substituted aniline. Which is on further chlorination, azide reaction and reduction gave 4-amino-2-chloroqunoline in good yield. On refluxing 4-amino-2-chloroqunoline and triethyl orthoformate or triethyl othoacetate or triethyl orthopropionate in ethanol furnished compound **2**(a-c) in good yield. The structures of compound were established by spectral and analytical data. For instance IR of **2a** showed the presence of aliphatic CH stretching frequency at 3010 cm^{-1} and C=N at 1660 cm^{-1}. The ^1H NMR spectrum of **2a** in $CDCl_3$ showed highly deshielded singlet at δ 8.30 ppm assignable for N=CH olefin proton. The remaining protons were resonance at expected chemical shifts and splitting pattern.

Table 1: Estimated Distance (cm) for Letter and Digit Stimuli.



	R_1	R_2
3a	H	H
3b	NO_2	H
3c	OCH_3	OCH_3

Similarly 4-amino-2-chloroqunoline was on reaction with aromatic aldehyde in presence of PTSA in toluene at boiling temperature furnished compound **3**(a-c) in good yield. The structure of **3**(a-c) were established by spectral and analytical data. For instance IR at **3a** showed the presence of aromatic C-H stretching at 2950 cm^{-1}. The ^1H NMR spectrum in $CDCl_3$ showed

singlet at δ 8.32 ppm was assignable for N=CH proton. The remaining protons were show the resonance at expected chemical shifts and splitting patternThe N-benzylidene-2,8-dichloroquinolin-4-amine **3a** on refluxing with thioglycolic acid in presence of one equivalent anhydrous $ZnCl_2$ in ethanol furnished compound **4** in good yield. The purification of product becomes difficult when excess amount of catalyst was used but it did not alter the reaction rate. Same reaction in absence of $ZnCl_2$ proceeds very slowly, while no reaction was observed in presence of anhydrous $AlCl_3$ or H_2SO_4 as catalyst. The structure of compound **4** was established by spectral and analytical data. All compounds were showed the analytical and expected spectral data given in the experimental part.

EXPERIMENT:

GENERAL: Common chemicals and reagents are commercially available or prepared by standard literature procedures and used without further purification. The melting points were measured in open capillary tube method on Barnstead Electro Thermal melting point (Mod. No. IA-9200) apparatus. The IR spectra of compounds were recorded on Shimadzu IR-408. ^{1}H NMR spectra were recorded on VARIAN XL-300 instrument 25 ^{o}C. The protiated solvents-$CDCl_3$ and DMSO-d_6 were used to mesure spectra. The TMS compound was used as an internal standard reference. Coupling constants (*J*) are quoted to the nearest 0.1 Hz and chemical shift (δ-scale) are quoted in parts per million (ppm) and following abbreviation are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Column chromatography was performed using silica gel with particle size (60-120 mesh, Merck). All reactions were monitored by TLC carried out 0.2 mm silica gel 60 F_{254} (Merck) plates using 254 and 366 nm UV light for detection.

Synthetic Procedures:

Synthesis of 2-chloroquinolin-4-amine, 1: The required starting compound 4-amino-2-chloroquinoline was synthesized from commercially available substituted aniline by literature know procedures[17-20].

(E)-N-ethoxymethylidene-2,8-dichloroquinolin-4-amine, 2a: 4-amino-2-chloroquinoline **1** (0.003, mol) and triethyl orthoformate (0.004 mol) were refluxed in ethyl alcohol for 2h. The reaction progress was monitored by TLC till the 4-amino-2-chloroquinoline was consumed. After completion, the reaction mixture was poured in cold water. The obtained solid was filtered, washed with water, dried and recrystallized from ethanol 70% / water to give title compound **3a** (0.72 gm, 90%) as yellow colored prisms.; *Rf* (toluene) 0.5, mp 117 ^{o}C; IR (KBr): γ 3010, 2990, 1660, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.56 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 4.40 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 6.73 (s, 1H, C_3H), 7.38 (t, J = 7.0 Hz, 1H, C_6H), 7.7 (d, J = 7.0 Hz, 1H, C_7H), 7.8 (d, J = 7.0 Hz, 1H, C_5H), 8.3 (s, 1H, N=CH).

(E)-N-ethoxyethylidene-2,8-dichloroquinolin-4-amine, 2b: Recrystallized from ethanol / water to afford yellow prisms; Yield (0.71 gm, 85%); *Rf* (toluene) 0.6; mp 112 ^{o}C; IR (KBr): γ 3010, 2985, 1650, 1530 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.50 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.1 (s, 1H, CH_3), 4.38 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 6.70 (s, 1H, C_3H), 7.40 (t, J = 7.2 Hz, 1H, C_6H), 7.69 (d, J = 7.2 Hz, 1H, C_7H), 7.9 (d, J = 7.0 Hz, 1H, C_5H).

(E)-N-ethoxypropylidene-2,8-dichloroquinolin-4-amine, 2c: Recrystallized from ethanol to afford yellow prisms, Yield (0.71 gm, 80%); *Rf* (toluene) 0.63; mp 101 ^{o}C; IR (KBr): γ 3015, 2990, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.1 (t, J = 6.9 Hz, 3H, CH_2CH_3), 1.52 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.2 (q, J = 6.9 Hz, 2H, CH_2CH_3), 4.39 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 6.75 (s, 1H, C_3H), 7.38 (t, J = 7.0 Hz, 1H, C_6H), 7.70 (d, J = 7.0 Hz, 1H, C_7H), 7.80 (d, J = 7.0 Hz, 1H, C_5H).

(E)-N-benzylidene-2,8-dichloroquinolin-4-amine 3a: A mixture of 4-amino-2-chloroquinoline **1**(0.003 mol), benzaldehyde (0.004 mol) and catalytic amount of PTSA in toluene was refluxed for 10h. The progress of the reaction was monitored by TLC till the 4-amino-2-chloroquinoline was consumed. After completion, the solvent was evaporated in vacuo and the residue was taken up with ethyl acetate. The organic layer was washed with sodium hydrogen carbonate and then with brine. The organic layer was dried over sodium sulfate and the solvent removed under reduced pressure to give crude product. The formed crude product was filtered off, dried and further purified by column chromatography using silica gel eluting with toluene gave title compound **3a** as yellow colored prisms. Recrystallized from ethanol / water to afford yellow prisms yield (0.85 gm, 79 %): *Rf* (toluene / acetone 9:1) 0.73, mp 198 ^{o}C; IR (KBr): γ 2950, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.98 (s, 1H, C_3H), 7.1 (d, J = 7.0 Hz, 2H, ArH), 7.2 (m, 3H, ArH), 7.43 (t, J = 7.2 Hz, 1H, C_6H), 7.79 (d, J = 7.2 Hz, C_7H), 7.95 (d, J = Hz, 1H, C_5H), 8.32 (s, 1H, N=CH).

(E)-N-(4-nitrobenzylidene)-2,8-dichloroquinolin-4-amine 3b: Recrystallized from ethanol to afford radish yellow prisms; Yield (0.78 gm, 65 %); *Rf* (toluene / ethyl acetate 9:1) 0.33; mp 218 ^{o}C; IR (KBr): γ 2972, 2918, 1630, 1573 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ 6.98 (s,

1H, C_3H), 7.2 (d, J = 7.0 Hz, 2H, ArH), 7.32 (d, 2H, ArH), 7.43 (t, J = 7.2 Hz, 1H, C_6H), 7.78 (d, J = Hz, 1H, C_7H), 7.99 (d, J = 7.2 Hz, 1H, C_5H), 8.3 (s, 1H, N=CH).

(E)-N-(3,4-dimethoxybenzylidene)-2,8-dichloroquinolin-4-amine, 3c: Recrystallized from ethanol to afford yellow prisms, yield (0.84 gm, 67 %); *Rf* (toluene / ethyl acetate 9:1) 0.43; mp 205 ^oC; IR (KBr): γ 3030, 2975, 2920, 1635 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.98 (s, 6H, $2OCH_3$), 6.70 (s, 1H, CH), 6.90 (s, 1H, C_3H), 6.92 (s, 1H, ArH), 7.36 (m, 2H, ArH), 7.63 (t, 1H, J = 6.9 Hz, C_6H), 7.9 (d, J = 6.9 Hz, 1H, C_7H), 8.2 (d, J = 6.9 Hz, 1H, C_5H), 8.4 (s, 1H, N=CH)

3-(2,8-dichloroquinolin-4-yl)-2-phenylthiazolidin-4-one, 4: The compound (E)-N-benzylidene-2,8-dichloroquinolin-4-amine **3a** (71 g, 0.002 mol) was reflux with thioglycolic acid (0.207 g, 0.003 mol) in presence of anhydrous $ZnCl_2$ (0.135 g, 0.001 mol) in dry ethanol (20 mL) for 5h. The progress of the reaction was monitored by TLC (toluene/ethyl acetate 2:8) till the reactant was consumed. After completion of the reaction, the reaction mixture was cooled to room temperature, the solid obtained was filtered, washed with water, dried and recrystallized from ethanol to furnished compound **4** (0.44gm, 59%) as yellow colored prisms. *Rf* (toluene/ethyl acetate 2:8); mp. 238 ^oC; IR (KBr): γ 3012, 1695 (C=O), 1546, 13309, 1170 cm^{-1}.; ^1H NMR (DMSO-*d6*) δ 4.30 (s, 2H, CH_2), 4.83 (s, 1H CH), 6.98 (s, 1H, C_3H), 7.43 (t, J = 7.2 Hz, 1H, C_6H), 7.78 (d, J = 7.2 Hz, 1H, C_7H), 8.32 (d, J = 7.2 Hz, 1H, C_5H).

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