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Development of an Efficient Process for 4,5,7-Trichloroquinoline, A Key Intermediate for Agrochemical Synthesis

B. Chandrasekhar,* A. S. R. Prasad, S. Eswaraiah,† and A. Venkateswaralu

Process Research and Technology Development, Dr. Reddy's Research Foundation, Bollaram Road, Miyapur, Hyderabad-500 050, India

Abstract:

A short, simple, and industrially feasible process for the preparation of 4,5,7-trichloroquinoline, starting from 3,5-dichloroaniline and acrylonitrile, in essentially three steps, is discussed. This article presents the preparative process, including the impurity profile, of each intermediate.

Introduction

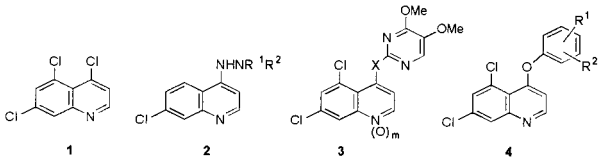
The marked antimalarial activity of a number of quinoline derivatives[1] having an aminoalkyl side chain attached in the fourth position (**2**) led to an investigation of new procedures for the preparation of 4-chloroquinolines, which in turn may be readily converted to the desired drug.[2] One such intermediate, 4,5,7-trichloroquinoline (**1**) (Scheme 1) was described as a useful intermediate for the preparation of pyrimidinylthiopyrimidinyloxy quinoline derivatives (**3**) and phenoxyalkane carboxylates (**4**), which are reported as potent herbicides,[3a] microbicides,[3b,c] and fungicides.[3d−h]

In view of these properties, it has created some interest among synthetic organic chemists, culminating in the development of several synthetic routes.[4a−i]

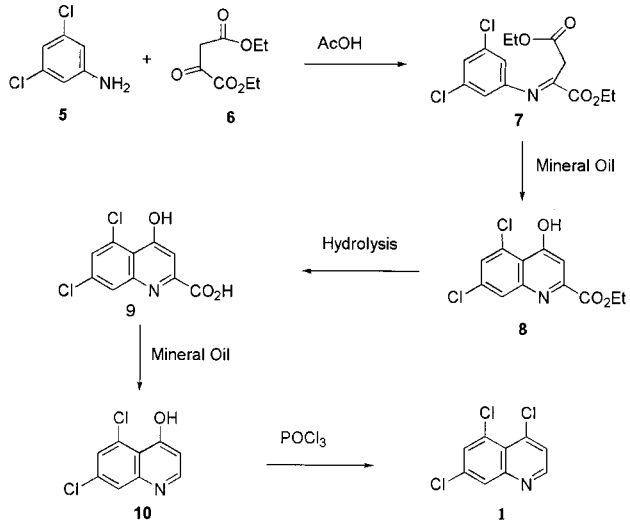
Results and Discussion

Of all the schemes reported in the literature, we selected three routes for study on the basis of their seemingly simple chemistry. The first route[1b] (Scheme 2) consists of five steps. The first step is based on Conrad−Limpach methodology[5] of the reaction of 3,5-dichloroaniline (**5**) and ethyl oxaloacetate (**6**) (β-ketoester) to afford the corresponding Schiff base ethyl β-arylaminomaleate (**7**). The Schiff base on thermal cyclisation in medicinal mineral oil at 250 °C yields 5,7-dichloro-4-hydroxyquinoline-2-carboxylic ethyl ester (**8**), which on hydrolysis yields the corresponding hydroxy acid

Scheme 1



Scheme 2



* Author for correspondence. Telephone: 91-40-3045439. Fax: 91-40-3045438. E-mail: chandrasekharb@drreddys.com.

† Present address: Dr. Reddy's Laboratories, 7-1-27 Ameerpet, Hyderabad-500 016, India.

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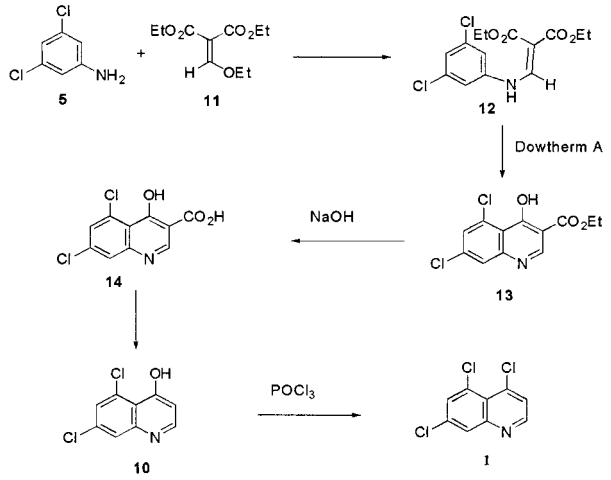
Scheme 3



(**9**), followed by decarboxylation in mineral oil at 270 °C which gives the 5,7-dichloro-4-hydroxyquinoline. Chlorination of **10** with $POCl_3$ results in 4,5,7-trichloroquinoline (**1**).

This route worked very well in terms of chemistry, but we encountered problems in scaling up the process. In addition, we observed the following drawbacks which rendered this route less attractive.

1. Compound **7** (β-anilinoacrylate) is a liquid, the purification of which needs high-vacuum distillation at high temperature, resulting in the partial charring and loss in the yields.

2. In the synthesis, the ring-closure reaction is a high-temperature process, not preferred for scale-up.

3. The use of mineral oil in this high-temperature process also leads to a messy process in work up.

The second route[1c] (Scheme 3) involves the reaction of 3,5-dichloroaniline (**5**) with ethoxymethylene malonic ester (**11**) in the first step.[6,7,4g] The resulting anilinomethylene malonate of the formula (**12**) upon thermal cyclization in Dowtherm or diphenyl ether gives 4-hydroxy-3-carboxyquinoline derivative (**13**). The ester on hydrolysis gives the 4-hydroxyquinoline-3-carboxylic acid (**14**). The thermal decarboxylation of hydroxy acid (**14**) resulted in the formation of 4-hydroxy-5,7-dichloroquinoline (**10**), which on chlorination with phosphorus oxychloride produces 4,5,7-trichloroquinoline (**1**).

Although Scheme 3 appeared to be straightforward with a better overall yield of 15% compared to that of the first route of overall yield 12% (Scheme 2), but the following shortcomings are noted:

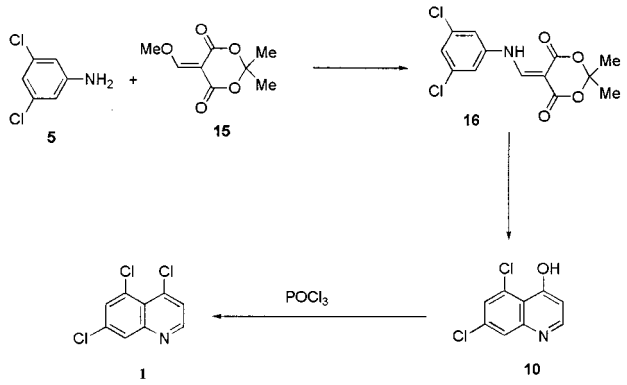
(1) Ethoxymethylene malonic ester (EMME) is relatively expensive.

(2) In this case also the thermal cyclization is not an efficient process due to the product decomposition and reaction work up.

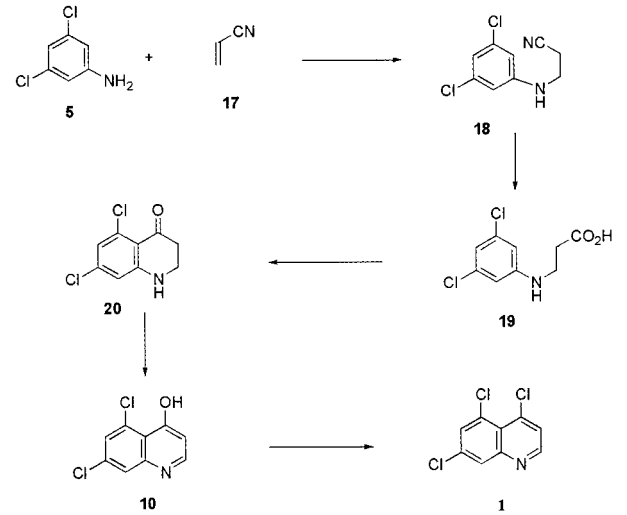
(3) Isolation of (**13**) from Dowtherm A or diphenyl ether appeared to be tedious on large scale.

The third route[4h] (Scheme 4) starts with reaction of 3,5-dichloroaniline (**5**) with Meldrum's acid derivative (**15**),

Scheme 4



Scheme 5



which upon thermolysis undergoes ring opening, elimination of acetone, and subsequent cyclization to give 5,7-dichloro-4-hydroxyquinoline (**10**). Chlorination with phosphorus oxychloride produces 4,5,7-trichloquinoline (**1**).

Even this route is not free from problems. The main drawbacks are the following:

(1) Preparation of Meldrum's acid derivative adds one extra step to the process, and this is also a relatively expensive raw material.

(2) Thermolysis in plant-scale operations leads to product decomposition.

An Alternative Route. A new route has been developed to simplify the process and to make it cost effective and feasible for scale-up operation. This involves five steps and utilizes acrylonitrile in the first step as shown in Scheme 5.

Stage I. Cyanoethylation[8,9] of various alkyl and alkoxy anilines using acrylonitrile in acetic acid medium has been reported in the literature. We observed that β-anilinopropionitriles have been employed as starting materials for the synthesis of various alkyl, alkoxychloro quinolines. Hence, it was decided to employ the β-anilinopropionitrile for the synthesis, which must eliminate decarboxylation step, as the required three-carbon chain comes from acrylonitrile. We

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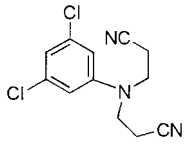
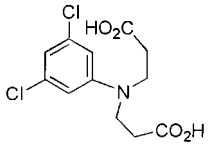
attempted the reaction of 3,5-dichloroaniline (**5**) with acrylonitrile (**17**) at 90−100 °C, and the Michael addition proceeded to near completion affording β-anilinopropionitrile (**18**) in 82% yield and 97% purity (HPLC). The use of acrylonitrile and copper acetate not only simplified the process but also proved to be less expensive. LC−MS analysis of the residue after distillation indicated the presence of the following bis-cyanoethylated aniline (**21**) in traces.



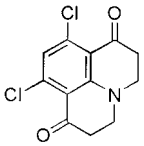
(**21**)

Stage II. β-Anilinopropionitrile (**18**) was hydrolysed in 10% aqueous sodium hydroxide solution and without isolating the sodium salt, the reaction mass was neutralized by treatment with concentrated hydrochloric acid to give β-anilinopropionic acid (**19**) in about 90% yield, with a HPLC purity of ∼99%. The aqueous phase was freeze-dried for LC-MS analysis which revealed the formation of (**22**) as an impurity.



(**22**)

Stage III. The cyclization of β-anilinopropionic acid (**19**) was accomplished in polyphosphoric acid. The reaction was facile, and product **20** was obtained in 80% yield. The purity of the compound **20** is 99%. The LC−MS analysis of the mother liquors indicated the presence of the following impurity (**23**).



(**23**)

Stage IV. 5,7-Dichloro-2,3-dihydroquinolin-4-(1H)-one (**20**) on dehydrogenation[10a−e] with 5% Pd/C in refluxing 1,2-dichlorobenzene gave (**10**) in about 78% yield with 99% HPLC purity. The Pd/C was separated from the precipitated product by extraction with 10% methanolic sodium hydroxide and the insoluble 5% Pd/C was filtered, dried, and recycled three times. The methanolic sodium hydroxide was neutralized with concentrated HCl to obtain pure 5,7-dichloro-4-hydroxyquinoline (**10**). In this way the purification of the compound **10** and separation of Pd/C for recycling was achieved.

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Stage V. The conversion of 5,7-dichloro-4-hydroxyquinoline (**10**) to 4,5,7-trichloroquinoline (**1**) was readily achieved using phosphorus oxychloride. 4,5,7-Trichloroquinoline (**1**) so obtained in 90% yield was of high quality (99% purity by HPLC).

Scale-Up Trials. With the procedure fully optimized, for stage I to stage V of Scheme 5, the scale-up trials were performed at 5−10 kg scale. This route was operated routinely without problems. The expected yields and purities obtained in all stages of the synthesis demonstrate the robustness and viability of the process.

Conclusions

A short, simple, and inexpensive industrially feasible process for the preparation of the 4,5,7-trichloroquinoline has been developed. Preparation of 5,7-dichloro-4-hydroxyquinoline (**10**) and 4,5,7-trichloroquinoline (**1**) have been simplified without compromising on their yield and purity.

Experimental Section

Solvents and reagents were obtained from commercial sources and were used as such without any further purification unless specified. The melting points are recorded on Buchi-535 apparatus and are uncorrected. The ^{1}HNMR spectra were obtained using a 200 MHz Varian Gemini spectrometer using tetramethylsilane as internal standard. Infrared spectra were recorded using a Perkin-Elmer model 1640 instrument. Mass spectra were recorded on an MS Engine-Hewlett-Packard model 5989 at DIP 20 eV. HPLC equipment consisted of a Waters 510 pump, a Waters 486 UV−vis detector, a Waters 746 data module, and a Bondclone C-18 column.

Preparation of 3,5-Dichloroanilino-β-propionitrile (18). Thirty-two and four tenths kilograms of 3,5-dichloroaniline, 10.6 kg of acrylonitrile, and 2.04 kg of cupric acetate monohydrate were suspended in a 100-L reactor. The reaction mass was stirred and heated to 80−90 °C for a period of 6−8 h. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, and the resulting dark mixture was quenched with 40 L of NH_4OH solution until the pH reached 8−8.5. The reaction mixture was extracted with toluene (3 × 200 L), washed with water (3 × 40 L), and distilled. The crude 3,5-dichloroanilino-β-propionitrile was distilled to give 35.1 kg of the pure compound: bp 180−200 °C/3−5 mm, yield 82%, mp 76−78 °C, purity 99% by HPLC [HPLC system: BondcloneC^{18} column; mobile phase: 0.01 M KH_2PO_4/MeOH in 45:55 ratio; flow rate 0.8 mL/min; λ 254 nm, retention time 7.68 min]. IR cm^{-1} 3470, 2250. ^{1}H NMR ($CDCl_3$) δ 2.5 (t, 3H), 3.4 (t, 3H), 4.3 (broad singlet, 1H), 6.7−7.2 (m, 3H). Mass spectrum *m*/*z* 214 corresponding to $C_9H_8Cl_2N_2$.

Preparation of 3,5-Dichloroanilino-β-propionic Acid (19). 3,5-Dichloroanilino-β-propionitrile (**18**) (10.7 kg) and 40 L of 10% sodium hydroxide solution were suspended in a 100-L reactor. The reaction mixture was heated to 90−95 °C for a period of 8−10 h until there was no further evolution of ammonia in the reaction. The reaction mixture was cooled

and then acidified with concentrated hydrochloric acid (10 L) for pH of 5.8−6.0 and extracted with toluene (25 L × 3). The toluene extracts were again washed with water (25 L × 2). The organic layer was concentrated to a volume of 15−20 L, and the precipitated 3,5-dichloroanilino-β-propionic acid (**19**) was filtered, dried to give 10.4 kg of **19**: yield 90%, purity 97% [HPLC system: BondcloneC^{18} 150 mm column; mobile phase: 0.01 M KH_2PO_4/MeOH in 45:55 ratio; flow rate 0.8 mL/min; λ 254 nm, retention time 5.37 min], mp 102−104 °C. IR cm^{-1} 3470, 1720. ^{1}H NMR ($CDCl_3$) δ 2.5−3.6 (t, 2H), 3.2−3.4 (t, 2H), 5.0 (broad singlet, 1H), 6.5−7.4 (m, 3H). Mass spectrum *m*/*z* 233 corresponding to $C_9H_9Cl_2NO_2$.

Preparation of 5,7-dichloro-2,3-dihydroquinolin-4-(1H)-one (20). Phosphorus pentoxide (8 kg) and 6.7 L of orthophosphoric acid were placed into 50-L reactor. The mixture was heated to 100 °C for 2 h, and 4.66 kg of 3,5-dichloroanilino-β-propionic acid (**18**) was added slowly in about 30 min. The reaction mixture was maintained at 90−100 °C for 2 h. Progress of the reaction was monitored by TLC. The reaction mixture was brought to room temperature, chilled water (20 L) was added, and the mixture was extracted with toluene (10 L × 3). The organic layer was washed with water and concentrated to a volume of 4−6 L. The precipitated product was filtered and dried to give 3.4 kg of **20**: yield 80%, purity 98% [HPLC system: BondcloneC^{18} 150 mm column; mobile phase: 0.01 M KH_2PO_4/MeOH in 45:55 ratio; flow rate 0.8 mL/min; λ 254 nm, retention time 5.85 min], mp 184−186 °C. IR (cm^{-1}) 3470, 1720. ^{1}H NMR ($CDCl_3$) δ 2.8 (m, 2H), 3.63 (m, 2H), 6.3 (s, 1H), 7.1 (s, 1H). Mass spectrum *m*/*z* 215 corresponding to $C_9H_7Cl_2NO$.

Preparation of 5,7-Dichloro-4-hydroxyquinoline (10). 5,7-Dichloro-2,3-dihydroquinolin-4-(1H)-one (**20**) (5.37 kg), 0.8 kg of 5% Pd/C, and 12.5 L of 1,2-dichlorobenzene were placed into 50-L reactor. The reaction mixture was stirred and heated to 180−200 °C for 12−14 h, monitoring the progress of the reaction by TLC. The reaction mixture was cooled to room temperature, and the precipitated solid 5,7-dichloro-4-hydroxyquinoline (**10**), was filtered and dried. To separate the Pd/C from the product, the product was extracted with 10% methanolic sodium hydroxide (∼10 L), and the insoluble 5% Pd/C was filtered and dried. The methanolic sodium hydroxide was neutralized with concentrated HCl (∼2.5 L) until the pH reached 5.8−6.0. The precipitated product was filtered and dried to afford 4.13 kg of **10**: yield 78%, purity 97−98% by HPLC [HPLC system: Bondclone C^{18} 150 mm column; mobile phase: 0.01 M KH_2PO_4/MeOH in 45:55 ratio; flow rate 0.8 mL/min; λ 254 nm, retention time 6.85 min], mp 345−48 °C. IR (cm^{-1}) 3450, 1620; ^{1}H NMR ($CDCl_3$ + TFA) δ 7.51 (d, 1H), 7.63 (d, 1H), 8.03 (d, 1H), 8.67 (d, 1H); MS *m*/*z* 213 corresponds to $C_9H_5Cl_2NO$.

Preparation of 4,5,7-Trichloroquinoline (1). 5,7-Dichloro-4-hydroxyquinoline (**10**) (6.39 kg), 30 L of toluene, and 3.1 L of phosphorus oxychloride were placed into a 50-L reactor. The reaction mixture was heated to 120−130 °C under stirring and maintained for 1 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature. The toluene layer was washed with water (9 L × 3) until the pH reached 6−7. The toluene layer was concentrated to a minimum volume of 3−6 L and cooled to 5−10 °C. The precipitated product was filtered and dried to give 6.24 kg of **1**: yield 90%, purity 99% by HPLC [HPLC system: SGE column; mobile phase: hexane/dioxane in 9:1 ratio; flow rate 2 mL/min; λ 254 nm, retention time 3.39 min], mp 104 °C. ^{1}H NMR ($CDCl_3$) δ 7.51 (d, 1H), 7.63 (d, 1H), 8.03 (d, 1H), 8.67 (d, 1H). Mass spectrum *m*/*z* 231 corresponds to $C_9H_4Cl_3N$.

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