# Efficient route to 3-methoxymethylquinoline – A precursor of 5-methoxymethylquinolinic acid

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**Dedicated to Professor C. W. Rees, CBE, FRS on the occasion of his 75th birthday**

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**Abstract**

An efficient process for preparing 3-methoxymethylquinolines, commencing from substituted anilines and 3-chloropropionyl chloride, has been developed. Reaction of substituted anilines with 3-chloropropionyl chloride in the presence of sodium carbonate produced 3-chloro-*N*-(substituted phenyl)propionamide, which was treated with dimethylformamide and phosphorus oxychloride (Vilsmeier Reaction) at 85°C to give 2-chloro-3-chloromethyl substituted quinoline. Selective methoxylation of this dichloro intermediate with sodium methoxide in methanol at 45 °C gave 2-chloro-3-methoxymethyl substituted quinoline, which was dehalogenated by palladium catalyzed hydrodehalogenation to give 3-methoxymethyl substituted quinoline in nearly quantitative yield.

**Keywords:** Quinolinic acids, 3-methoxymethylquinoline, 3-chloropropionyl chloride, anilines, Vilsmeier formylation, hydrodehalogenation

## Introduction

Imidazoline based herbicides (Figure 1) are used for both total and selective vegetation control. We have studied the synthesis of one of these, imazamox. A key intermediate in the preparation of imazamox is 5-methoxymethyl-2,3-pyridinedicarboxylic acid. Two approaches to this intermediate have been published in the literature, one starting from 5-methyl-2,3-pyridinedicarboxylic acid, via esterification, bromination, quaternization, methoxylation and hydrolysis[1] (Scheme 1); and the other starting from 8-chloro-3-methylquinoline via bromination, quaternization, methoxylation, and oxidation[2] (Scheme 2).

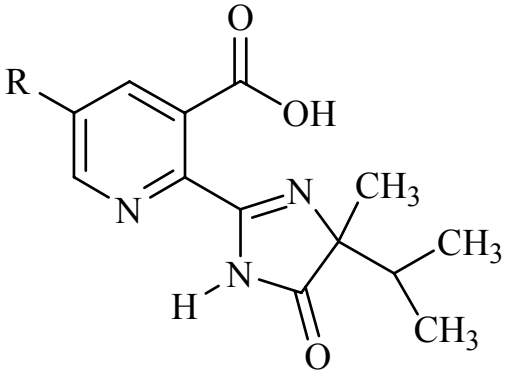
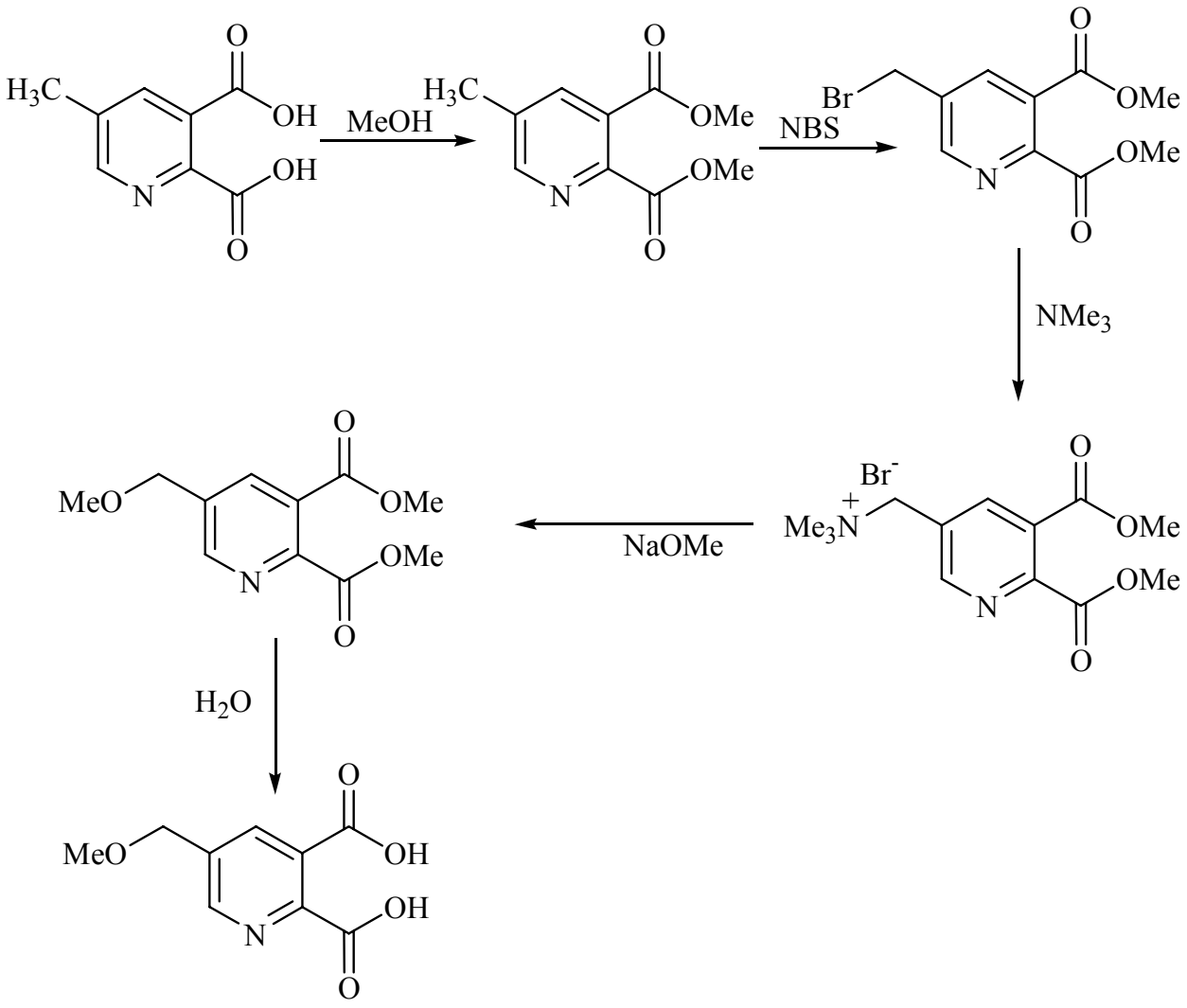
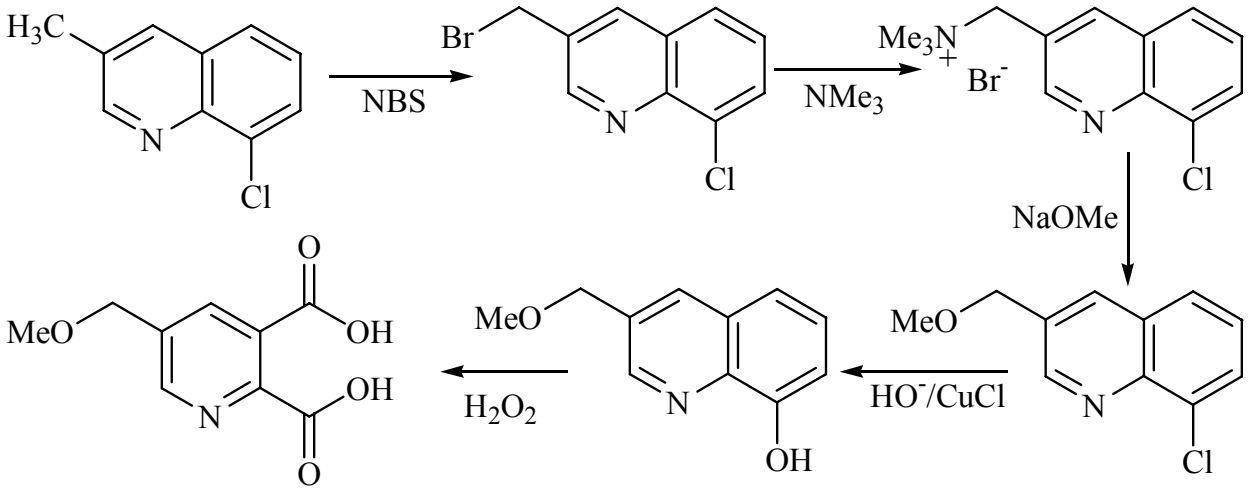


**Figure 1.** Imadazoline herbicide. R=H – Imazapur (Arsenal$^{R}$ ); R=$CH_3$ – Imazameth (Cadre$^{R}$ ); R=$CH_3CH_2$ – Imazaeth (Pursuit$^{R}$ ); R=$CH_3OCH_2$ – Imazamox (Raptor$^{R}$ ).



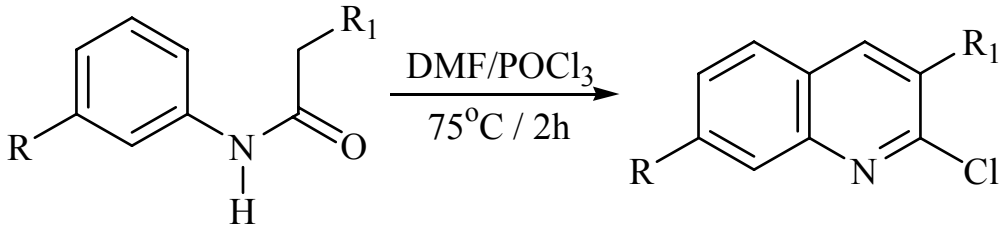
**Scheme 1**




**Scheme 2**

The difficulties (such as high cost of NBS, non recyclablity of succinimide, and dibromo byproduct formation) encountered with the bromination step in each of the above led us to look for better approaches to the key intermediate 5-methoxymethyl-2,3-pyridinedicarboxylic acid.

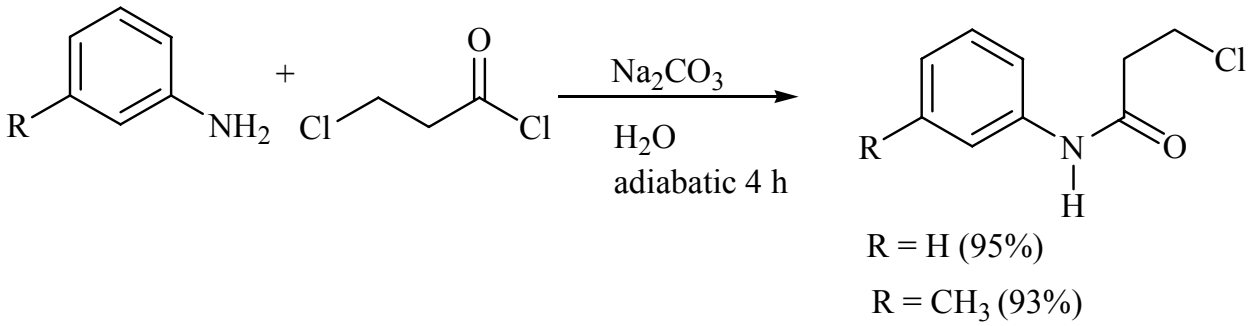
We considered that the introduction of the methoxymethyl group might be achieved from a corresponding chloromethyl group, by starting the synthesis with 3-chloropropionyl chloride and an aniline derivative to make the acylanilide **1**. Treatment of **1** with a Vilsmeier reagent (N,N-dimethylformamide and phoshorus oxychloride) by the method of Meth-Cohn[3] should give 2-chloro-3-chloromethylquinolines in good yields (Scheme 3).




**Scheme 3**

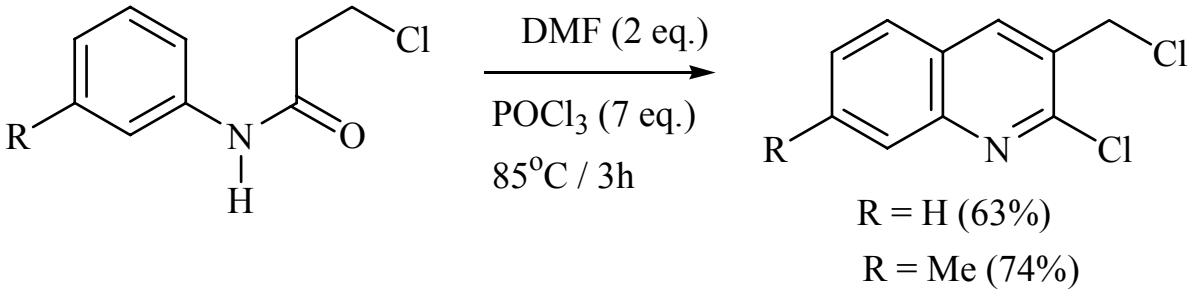
## Results and Discussion

The acylation of the anilines with 3-chloropropionyl chloride was done at ambient temperature for 4 h in the presence of sodium carbonate to neutralize the hydrochloric acid generated. The yields of these reactions were in the 90's (Scheme 4).



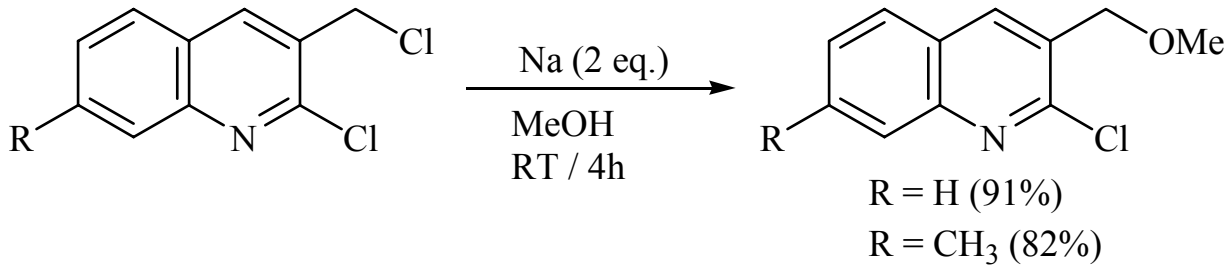

**Scheme 4**

The Vilsmeier procedure was carried out on these acylanilides to give 2-chloro-3-chloromethylquinolines (Scheme 5).



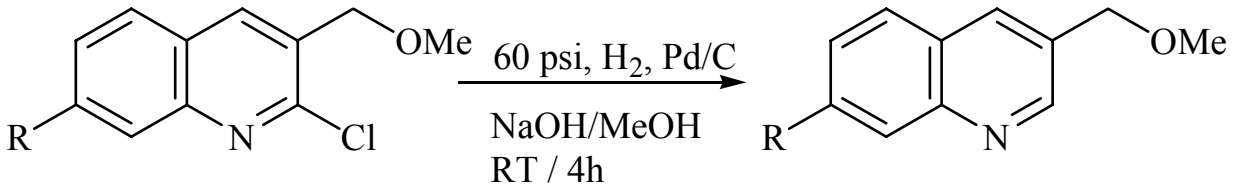

**Scheme 5**

The Vilsmeier reaction products 2-chloro-3-chloromethylquinolines were reacted with two equivalents of sodium methoxide in methanol at ambient temperature to give 2-chloro-3-methoxymethylquinolines in high yields (Scheme 6).




**Scheme 6**

The dehalogenation of 2-chloro-3-methoxymethylquinolines (R = H, Me), was achieved with hydrogen and palladium on a carbon catalyst in quantitative yield (Scheme 7).




**Scheme 7**

The 3-methoxymethylquinolines thus produced could be converted into 5-methoxymethyl-2,3-pyridinedicarboxylic acid by ozonolysis as has been reported in the literature for other quinoline derivatives.[4,5]

## Summary

An efficient process for preparing 3-methoxymethylquinolines, commencing from substituted anilines and 3-chloropropionyl chloride, has been developed. Reaction of substituted anilines with 3-chloropropionyl chloride in the presence of sodium carbonate produced 3-chloro-*N*-(substituted phenyl)propionamide, which was treated with dimethylformamide and phosphorus oxychloride (Vilsmeier Reaction) at 85°C to give 2-chloro-3-chloromethyl substituted quinoline. Selective methoxylation of this dichloro intermediate with sodium methoxide in methanol at 45°C gave 2-chloro-3-methoxymethyl substituted quinoline, which was dehalogenated by palladium catalyzed hydrodehalogenation to give 3-methoxymethyl substituted quinoline in nearly quantitative yield.

## Experimental Section

**General Procedures.** The NMR spectra were recorded on a Bruker AC 300 MHz instrument. All the compounds mentioned in this paper are known compounds and their full characterization data have been either previously reported in the literature or their structure confirmed in our labs using $^{1}$H NMR, $^{13}$C NMR, and GCMS.

**Preparation of 3-chloro-*N*-(phenyl)propionamide.** A one liter, four-neck round bottom flask was equipped with a mechanical stirrer, thermometer, reflux condenser, and an addition funnel. The flask was charged successively with water (340 g), potassium carbonate (76.1 g, 0.55 mole), and aniline (93 g, 1.0 mole). Agitation was started and 3-chloropropionyl chloride (139.9 g, 1.1 mole) was added via an addition funnel over a 2 hour period while maintaining the temperature under 30°C. After the addition the mixture was stirred at room temperature for an additional 2 hours. The solids which formed were collected by vacuum filtration, washed with 6N HCl (1 X

300 mL) and water (1 X 500 mL), and dried. The product thus obtained weighed 175 g (95 % yield),and agreed with all the data reported in the literature.[6]

**Preparation of 2-chloro-3-chloromethylquinoline.** A one liter, four-neck round bottom flask was equipped with a mechanical stirrer, thermometer, reflux condenser, and an addition funnel. The flask was charged with dimethylformamide (70.9 g, 0.761 mole). After cooling to 0-5$^{o}$C, phosphorus oxychloride (408.6 g, 2.66 moles) was added drop wise via an additional funnel over a 1.5 hour period while the temperature was maintained around 10-15$^{o}$C. A white precipitate formed during the course of the addition. After the addition, the mixture was allowed to stir adiabatically for 30 minutes. The amide intermediate prepared above (69.9 g, 0.381 mole) was added in portions over a 5 minute period. The mixture was stirred at room temperature for 20 minutes and then heated to 80-85$^{o}$C. This was maintained for an additional 3 hours with stirring. After cooling to room temperature, the mixture was poured in small portions onto crushed ice (800 g). The light yellow solids, which precipitated were collected by vacuum filtration, washed with water (2 X 1000 mL), 10% NaHCO3 (1 X 500 mL), and water (1 X 1000 mL) again. The solids were air dried to give 51 g (63% yield) of the product. The product obtained from this reaction agreed with the literature data reported, where the same product was made from $PCl_5$ chlorination of 2-chloro-3-methylquinoline.[7]

**Preparation of 2-chloro-3-methoxymethylquinoline.** A one liter four-neck round bottom flask was equipped with a mechanical stirrer, thermometer and reflux condenser. The flask was charged with methanol (600 mL). Agitation was started and sodium (13.3 g, 0.578 mole) chunks were added in small portions over a 1 hour period. After the addition, the solution was allowed to cool to 35$^{o}$C and the dichloro intermediate (94.1 g, 0.444 mole) prepared was added in one portion. The resulting suspension was heated to 45-50$^{o}$C and maintained at this temperature with stirring for 3-4 hours. After cooling to room temperature, water (500 mL) was added. The solids, which precipitated were collected by vacuum filtration, rinsed with water (2 X 200 mL), and dried. The product thus obtained weighed 84 g (91% yield). The product thus obtained agreed with the proton NMR spectra taken in our labs and this compound is already known in the literature.[8] $^{1}$H-NMR (δ, ppm) 8.20 (s, 1H, H-4), 7.95 (d, J = 8Hz, 1H, H-8), 7.65 (d, J = 8Hz, 1H, H-5), 7.60 (m, 1H, H-7), 7.40 (m, 1H, H-6), 4.50 (s, 2H, $CH_2$), 3.50 (s, 3H, $CH_3$).

**Preparation of 3-methoxymethylquinoline.** A 1.4 liter stainless steel shaker bomb was charged with 5% Pd/C (3.2 g, 50% wet), methanol (400 mL), and 50% caustic (44.2 g, 0.553 mole). After cooling to room temperature, 2-chloro-3-methoxymethylquinoline (76.5 g, 0.369 mole) prepared above was added in one portion. The bomb was sealed and continuously shaken under a hydrogen pressure of 60 psig at room temperature for 4 hours. The catalyst was filtered off and the filtrate was rotary evaporated to remove most of the methanol. Toluene (300 mL) was added to the residue and the whole mixture was washed with water (1 X 100 mL). The top layer was rotary evaporated to remove toluene to give 63.6 g (99.5% yield) of the crude product as a brown liquid. The product, 3-methoxymethylquinoline, was distilled from the crude product as a colorless liquid with a boiling point of 128$^{o}$C at 2 mm Hg. The proton and carbon NMR agreed with its structure. $^{1}$H-NMR (δ, ppm) 8.75 (s, 1H, H-1), 8.00 (d, J = 8Hz, 1H, H-5), 7.90 (s, 1H,

H-4), 7.60 (d, J = 8Hz, 1H, H-8), 7.50 (t, J = 8Hz, 1H, H-7), 7.35 (t, J = 8Hz, 1H, H-6), 4.45 (s, 2H, $CH_2$), 3.30 (s, 3H, $CH_3$). $^{13}$C-NMR (δ, ppm) 150.4 (2-C), 147.6 (9-C), 134.2 (4-C), 130.7 (3-C), 129.1 (8-C), 129.0 (5-C), 127.6 (7-C), 126.5 (6-C) [the 10-C quaternary carbon signal is totally not observed and is expected to be fully overlapping with 129.0 ppm signal]. Further confirmation of the structure was obtained when this molecule was ozonalized to give 5-methoxymethylquinolinic acid, a known compound.[1]

## References

1. Strong, H. L. Eur. Pat. 0 747 361 A1; issued Dec. 11, 1996; filed June 4, 1996; to American Cyanamid Company.
2. Marmor, R. S.; Strong, H. L. Eur. Pat. 0 744 399 A2; issued Nov. 27, 1996; filed May 16, 1996; to American Cyanamid Company.
3. Meth-Cohn, O.; Rhouati, S.; Tarnowski, B. A. *Tetrahedron Lett*. **1979**, 4885.
4. O'Murchu, C. *Synthesis* **1989**, 880.
5. Strong, H. L.; Cortes, D. A.; Ahmed, Z. US Patent 5,281,713; issued Jan 25, 1994; filed Oct 23, 1992; to American Cyanamid Company.
6. Walsh, D. A. U.S. Patent 5,057,524; issued Oct 15, 1991; filed Feb 8, 1990; to A. H. Robins Company Inc.
7. Korodi, F. *J. Heterocyclic Chem*. **1991**, *28*, 1549.