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Angel H. Romero

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A modified Procedure for the synthesis of 2-chloroquinoline-3-carbaldehydes using phosphorus pentachloride

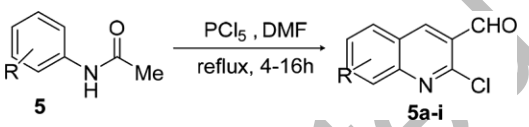
Angel H. Romero[1]

[1]Laboratorio de Química Medicinal y Heterociclos, Departamento de Química, Universidad Simón Bolívar, Valle de Sartenejas, Apartado, Venezuela

Corresponding author Angel H. Romero E-mail: angel.ucv.usb@gmail.com

Abstract

An alternative, convenient and efficient procedure for the synthesis of 2-chloroquinoline-3-carbaldehyde was carried out by the action of Vilsmeier´s reagent on acetanilides using phosphorus pentachloride as chlorinating agent in place of phosphoryl chloride, obtaining good yields for activated acetanilides. The optimal conditions for this reaction requires only 4.5 equivalent of phosphorus pentachloride, 3 equivalent of *N,N*-dimethylformamide and 1 equivalent of the corresponding acetanilide at 100ºC for approximately 4 hours.



5 **5a-i**

KEYWORDS: 2-chloroquinoline-3-carbaldehydes, Vilsmeier´s reagent, phosphorus pentachloride, acetanilides, cyclization

1 INTRODUCTION

2-chloroquinoline-3-carbaldehydes (**1**) are compounds considerable interesting in the chemistry due to their importance as synthetic intermediates for the preparation of large numbers of heterocyclic systems,[1] stereoselective ligands,[2] and compounds with diverse kind of biological activities.[3] These quinolines (**1**) are prepared practically by

two important procedures such as: (i) Vilsmeier-Haack reaction of acetanilides, and (ii) oxidation of the corresponding alcohol (2-chloroquinolin-3-yl)methanol to aldehyde.[1f, 4, 5] However, the first method above mentioned (i) is the most convenient and traditional for the synthesis of 2-chloroquinoline-3-carbaldehydes (**1**); this strategy consists in a multicomponent reaction that involves processes of chloration, formylation and cyclization of acetanilides by the action of the Vilsmeier´s reagent (DMF/$POCl_3$) in $POCl_3$ solution (Scheme 1).[4]

In this reaction, Vilsmeier´s reagent is generated *in situ* and derived of the reaction between *N*,*N*-disubstituted formamides and phosphoryl chloride,[4,6] although this reagent also can be to obtain using chlorinating agent such as phosphorus pentachloride (PCl_5),[7] and tionyl chloride ($SOCl_2$).[8] Particularly, the Vilsmeier´s reagent from PCl_5 produces *in situ* $POCl_3$ (Scheme 2),[7] which could be interesting for reducing the amount of chlorinating agent necessary in the synthesis of 2-chloroquinoline-3-carbaldehydes (**1**) reported by Meth-Cohn,[4] due to that his method requires a large excess of $POCl_3$. Furthermore, another important advantage of the PCl_5 is that it does not require an additional purification.

In addition, the phosphorus pentachloride have been widely used in the chloration of different organic compounds such as *N*-vinylazoles,[9] dialkylcyanamides,[10] triethylamine[11,12], sucrose-6-acetate or sucrose-6-benzoate.[13] Then, considering the above mentioned and well known chlorinating properties of the PCl_5, this work was focused in demonstrating that the PCl_5 can replace to $POCl_3$ in the reaction reported by

Meth-Cohn[4] (Scheme 1) for the synthesis of the 2-chloroquinoline-3-carbaldehydes (**1**). The synthesis of these kind of compounds using PCl_5 have not been reported previously in the literature and represents a novel, modified and alternative procedure.

2 RESULTS AND DISCUSSION

The first step in this work was optimized the reaction conditions searching the optimal amount of PCl_5, working under the same conditions reported in the literature.[4] The results of optimization using the acetanilide as substrate (Table 1) showed that 4.5 equivalent of PCl_5 are enough for obtaining the best yield in this reaction (72%), while amount of PCl_5 below four equivalents provided a decreasing in the yield (42-68%). In addition, it should be noted that when further raising of four equivalent of PCl_5 no significant effect in the yield (62-70%) was observed. However, in this sense, is important to explain that when were used seven equivalent of PCl_5 during the formation of Vilsmeier´s reagent, the reaction solution was turned over saturated due to that PCl_5 is a solid compound, and probably it characteristic could have a small negative effect in the yield of this reaction. In conclusion, these results of optimization were expected due to that in theory this reaction only need three equivalent of chlorinating agent, where an equivalent is involved in the chloration of the corresponding acetanilide and other two equivalents react with DMF, generating two equivalents of Vilsmeier´s reagent. Simultaneously, when PCl_5 reacts with the acetanilide and DMF, there are generated three equivanlent of $POCl_3$ (Scheme 2), which act as solvent in the reaction.

Then, the optimal conditions were applied for the preparation of the series of 2-chloroquinoline-3-carbaldehydes (**5a-i**) using the corresponding acetanilides and the results are summarized in Table 2. The obtained compounds were confirmed by spectra data and melting point reported.[4] The results were practically similar to the results reported by Meth-Cohn,[4] where the activated acetanilides (**Entries 1-6**) showed better yields (yield 49-72%) than the strongly deactivated systems (yield 0-30%) (**Entries 7-9**) under the same reaction conditions of time and heating. This results is no surprisisng due to that the mechanism of this reaction should be exactly same to reported by Meth-Cohn,[4] where the electron-donanting groups in the *meta* position of the acetanilide activates the cyclization process for obtaining the corresponding quinoline, while electron-withdrawing groups decrease the capacity nucleophilic of the arene ring producing an incomplete process of the cyclization.

In summary, this work demonstrated that the phosphorus pentachloride can be used as chlorinating agent for the synthesis of 2-chloroquinoline-3-carbaldehydes by the action the Vilmeier´a reagent on acetanilides following the same procedure reported by Meth-Cohn[4]; representing an alternative, convenient, practical and efficient procedure. Furthermore, the present method has an economical implication towards the raw material cost and becomes highly profitable in the industrial process for the synthesis of these quinolines, due to that there is required less amount of chlorinating agent.

3 EXPERIMENTAL SECTION

General procedure for the synthesis of 2-chloroquinoline-3-carbaldehydes 5a-i:

DMF (12 mmol, 3 equiv.) was cooled at 0ºC in a round flask equipped with a drying tube and phosphorus pentachloride (18 mmol, 4.5 equiv.) was added slowly and the mixture was stirred for 15 minutes keeping the temperature below 0 ºC. To this solution was added in a portion the corresponding acetanilide (4 mmol, 1 equiv.) and the reaction mixture was heated under reflux and stirring for the appropiate time depending of the acetanilide. The resulted mixture was cooled to 0ºC and the solution was poured slowly into ice-water and stirring for ten minutes, obtaining a yellow solid which was filtered, washed several time with cold water and dried under vacuum. Finally, the 2-chloroquinoline-3-carbaldehydes were recristalized according to the literature. [4]

2-chloroquinoline-3-carbaldehyde (5a): Recristalization eluent: Ethyl acetate; Yield 552 mg (72%); yellow pale solid, mp 145-146 ºC. IR (KBr): 3043 (st. C-H), 2872 (st. C-H), 1688 (st. C=O), 1615-1553 (st. C=C) cm^{-1}. ^{1}H-NMR (270 MHz, *J* Hz, $CDCl_3$) δ: 10,55 (s, 1H); 8,76 (s, 1H); 8,07 (d, *J*=8,6; 1H); 7,98 (d, *J*=7,9; 1H); 7,89 (dd, J_1=8,3; J_2=7,7; 1H); 7,64 (dd, J_1=8,3; J_2= 7,9; 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 189,4 (d); 150,3 (s); 140,5 (d); 133,7 (d); 130,6 (s); 129,6 (s); 129,1 (d); 127,7(d); 126,6 (d); 121,2. Anal. Calcd for $C_{10}H_6ClNO$: C, 62,48; H, 3,11; N, 7,23 %. Found: C, 62,68; H, 3,16; N, 7,31 %.

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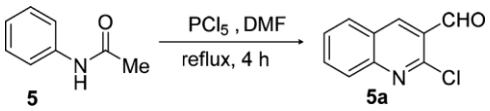
Table 1. Optimization studies according proportions of PCl_5.

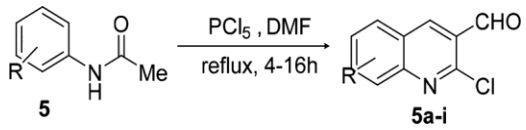


Entry[a]	Equiv. of PCl_5	Yield (%)[b]
1	7.0	63
2	5.0	70
3	**4.5**	**72**
4	4.0	68
5	3.0	42

[a] All reactions were performed used acetanilide (1 mol equiv), DMF (3 mol equiv.) and PCl_5 at 120ºC for 4 h.

[b]Isolated yields of 2-chloroquinoline-3-carbaldehydes after recristalization with ethyl acetate.

Table 2. Results of synthesis of 2-chloroquinoline-3-carbaldehydesgderivates.



Entry	R	t (h)	Yield (%)[a]	Yield (%)[b]	mp (ºC)[c]	mp (ºC)[d]
1	H (**5a**)	4	72	78	145-146	146-147
2	6-CH_3 (**5b**)	4	64	74	121-123	121-123
3	7-CH_3 (**5c**)	4	71	66	142-144	143-144
4	8-CH_3 (**5d**)	16	60	67	133-135	135-136
5	6-OCH_3 (**5e**)	16	49	54	142-144	143-145
6	7-OCH_3 (**5f**)	4	74	65	189-191	190-192
7	6-Br (**5g**)	4	28	30	186-188	189-191
8	7-Cl (**5h**)	4	30	35	156-157	158-159
9	6-NO_2 (**5i**)	4	0	0	____	_____

[a]Yield of reaction conditions: 3 equiv. DMF, 4.5 equiv. PCl_5 and 1 equiv. of the corresponding acetanilide at 120 ºC for 4-16 h.

[b]Yield reported in the literarure using $POCl_3$.[4]

[c]Meltting point obtained for (**5a-h**) in this report.

[d]Melting point reported in the literature.[4]

Scheme 1. Method reported by Meth-cohn for the synthesis of 2-chloroquinoline-3-carbaldehydes (**1**).[4]

Scheme 2. Reaction of N,N-alkylformamide and phosphorus pentachloride (PCl_5).