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An Efficient Heteropoly Acid-Catalysed Procedure for Synthesis of Quinolines and Naphthyridines

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ABSTRACT

The synthesis of quinolines and 1, 8-naphthyridines was carried out in the presence of HCl and a series of eco-friendly solids including Keggin-type heteropolyacids (HPAs) $H_4SiW_{12}O_{40}.\mathbf{14}H_2O$, $H_4SiMo_{12}O_{40}.\mathbf{14}H_2O$, $H_3PW_{12}O_{40}.\mathbf{13}H_2O$ and $H_3PMo_{12}O_{40}.\mathbf{15}H_2O$ used as catalysts. Using of HPAs exhibit high yields in particular the silicates, SiW_{12} and $SiMo_{12}$ with 73-93% of yield.

Keywords: Polyoxometalates, Quinolines, Naphthyridines, Catalysis.

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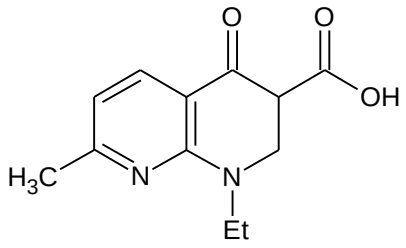
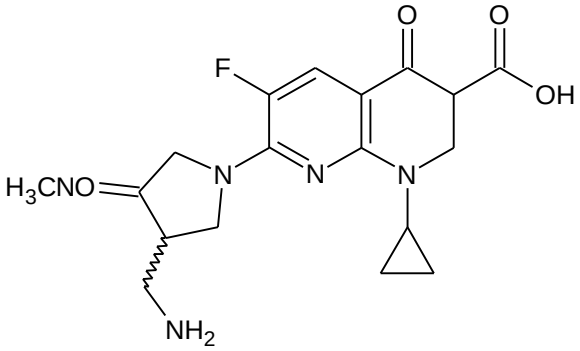
INTRODUCTION

Quinolines derivatives have been found to be a biological versatiles compounds [1], having anti-malarial, anti-bacterial, anti-asthmatic, anti-hypertensive, antiinflammatory, anti-platelet activities and tyro-kinase PDGF-RTK inhibiting [2-4]. In addition, quinolines have been used in the bio-organic and bio-organometallic processes [5]. Due to this broad application domain, the development of effective methodologies for their synthesis has been expanded.

On the other hand, natural and synthetic compounds possessing the naphthyridine structural motif display a wide range of pharmacological and biological activities. For example**,** Nalidixic acid, with a strong antibacterial activity, is used mainly for the treatment of urinary tract infections [6] and Gemifloxacin for its antimicrobial and antibacterial properties [7]. It is known that oximes derivatives of 1, 8-naphthyridine are potential drugs for local anesthesia [8]. Substituted 1,8-naphthyridin-2(1*H*)-one is employed to treat memory disorders, in particular, Alzheimer's disease [9]. It has been also reported that some 3-phenyl-1,8-naphthyridines that include piperidyl, piperazinyl, morpholinyl group or a N-diethanolamine side chain at the 2,7 positions show significant activity as inhibitors of human platelet aggregation induced by collagen and arachidonate [10].



Nalidixic Acid



Gemifloxacin

MATERIALS AND METHODS

CHEMISTRY

Starting materials were obtained from commercial sources and were used without further purification. Solvents were dried and freshly distilled following the usual procedures. Product organic solutions were dried over sodium sulfate prior to evaporation of the solvents under reduced pressure on a rotatory evaporator. Reaction progress was observed by thin layer chromatography making use of commercial silica gel plates (Merck silica gel F254 on aluminium sheets). ^{1}H and ^{13}C NMR spectra were measured at 400.13 and 100.61 MHz respectively using TMS as internal reference. Chemicals shifts are reported in ppm relative to TMS. Signals are quoted s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) and coupling constant (J) values are given in Hz. High Resolution Electro Spray Impact Mass Spectra (HR-ESI-MS) were performed in the Régional Centre physical (Blaise Pascal university of Clermont Ferrand, France).

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SYNTHESIS

Catalysts preparation

Phosphomolybdic acid sample, **$H_3PMo_{12}O_{40}$** was prepared by acidifying the sodium salt, $Na_2HPMo_{12}O_{40}$ that was prepared from an appropriate mixture solution of $HClO_4$ (70%) Na_2MoO_4 and H_3PO_4 [19]. Phosphotungstic acid, **$H_3PW_{12}O_{40}$** was prepared by acidifying the sodium salt, **$Na_3PW_{12}O_{40}$** prepared by heating a mixture of Na_2WO_4 and H_3PO_4 in appropriate molar ratio [19]. Molybdosilicic acid, **$H_4SiMo_{12}O_{40}$** was prepared by heating a solution of HNO_3 (69%), Na_2MoO4 and Na_2SiO_3 in appropriate molar ratio [20] and tungstosilicic acid, **$H_4SiW_{12}O_{40}$** was prepared from an appropriate mixture solution of HCl, Na_2SiO_3 and Na_2WO_4 [21]. All the HPAs formed were extracted with diethyl ether. The heteropolyacids are hydrated at 13-15 water molecules.

General procedure for Friedlander reaction

Method I: A mixture of 2-amino acetophenone and 2-aminocotinaldehyde (1 mmol), α-methylene carbonyl compound (1 mmol) with 1 mL concentrated HCl was carried out under reflux in ethanol. The obtained solid was crystallized in ethanol.

Method II: A mixture of 2-amino acetophenone and 2-aminocotinaldehyde (1.0 mmol), α-methylene carbonyl compound (1 mmol) and catalyst (0.2 g) was carried out under reflux in ethanol (15 mL). After reaction completion, as indicated by TLC. The obtained solid was crystallized in ethanol after washing with water to eliminate any catalyst residue.

8, 9-dihydro-8-méthyl pyrano [4, 3-b] 1, 8-naphthyridin-6-one: yellow solid, Mp = 220-222 °C, ^{1}H NMR (DMSO-d6) δ: 1.56 (d, J = 6.40 Hz, 3H), 3.26 (dd, J = 11Hz, J = 17 Hz, 1H), 3.40 (dd, J = 3Hz, J = 17 Hz, 1H), 4.84 (m, 1H), 7.52 (dd, J = 4Hz, J = 8 Hz 1H), 8.26 (d, J = 8 Hz), 8.90 (s, 1H), 9.16(d, J = 4Hz). ^{13}C NMR (DMSO-d6) δ: 21, 38.71, 74.94, 119.81, 121.78, 122.85, 138.63, 141.47, 156.34, 156.94, 160.80, 164.18. HRMS *m/z* calcd. for $C_{12}H_{10}N_2O_2$ $(M+H)^+$: 215.0821, found: 215.0833.

8, 9-dihydro-8, 8-diméthyl benzo[b] 1, 8-naphthyridin-6(7H)-one: dark yellow solid, Mp= 158-159 °C, ^{1}H NMR (DMSO-d_6) δ: 1.09 (s, 6H), 2.61(s, 2H), 3.22(s, 2H), 7.45(dd, J = 4Hz, J = 8Hz, 1H), 8.24(dd, J = 2Hz, J = 8Hz, 1H), 8.78(s, 1H), 9.12(dd, J = 2Hz, J = 4Hz, 1H). ^{13}C NMR (DMSO-d_6) δ: 27.78, 32.31, 46.31, 51.48, 121.03, 122.46, 125.59, 137.54, 139.41, 155.88, 156.51, 164.28, 197.00. HRMS *m/z* calcd. for $C_{14}H_{14}N_2O$ $(M+H)^+$: 227.1184, found: 227.1187.

$3-(2-hydroxybenzoyl)-1, 8- naphthyridin-2(1H)-one: white solid, Mp = 275-277 °C, ^{1}H NMR(DMSO-d_6) δ: 6.95(dd, J = 4Hz, J = 8Hz, 1H), 7.62(dd, J = 2Hz, J = 8Hz, 1H), 6.98-8.26(m, 4H), 8.18(s, 1H), 8.60(dd, J = 2Hz, J = 4Hz, 1H), 10.98(s, 1H), 12.42(s, 1H). ^{13}C NMR (DMSO-d_6) δ: 102.58, 119-128, 120.67, 121, 137.93, 153.45, 154.31, 158.62, 161.20, 166.38. HRMS *m/z* calcd. for $C_{15}H_{10}N_2O_3$ $(M+H)^+$: 267.2588, found: 267.2592.

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5H-indano [1,2-b][1,8]naphthyridin-6(7H)one: yellow solid, Mp= 280-282, ^{1}HNMR (DMSO-d_6) δ: 7.15(d, J = 7.50 Hz, 1H), 7.50(t, J = 7.50 Hz, 1H), 7.51(dd, J = 4Hz, J = 8Hz, 1H), 7.66(t, J = 7.50 Hz, 1H), 7.77(d, J = 7.50 Hz, 1H), 8.27(dd, J = 2Hz, J = 8 Hz, 1H), 8.40(s, 1H), 9.11(dd, J = 2Hz, J = 4Hz, 1H). ^{13}C NMR (DMSO-d_6) δ: 121.41, 122.54, 122.87, 124.29, 127.66, 132.41, 133.06, 136.08, 137.54, 139.33, 143.688, 154.96, 158.90, 165.57, 190.06. HRMS *m/z* calcd. for $C_{15}H_8N_2O$ $(M+H)^+$: 233.0715, found: 233.0730.

3-methyl-10-phenyl-3, 4-dihydro-1*H*-pyrano [4, 3-*b*] quinolin-1-one: yellow solid, Mp= 285-287 °C**,** ^{1}H NMR (DMSO-d6) δ: 1.49(d, J= 6.22 Hz), 3.41(dd, J = 10.79Hz, J = 16.65Hz, 1H), 3.50(dd, J = 2.92Hz, J = 16.83Hz, 1H), 4.96(s, 1H), 7.01-8.99 (m, 9Harom). ^{13}C NMR (DMSO-d_6) δ: 20.1, 37.56, 117.29, 73.63, 124.9, 126.15-135.67, 157.69, 161.67.
HRMS *m/z* calcd. for $C_{15}H_8N_2O$ $(M+H)^+$: 290.1181, found: 290.1176.

8, 8-dimethyl-5-phenyl-8, 9-dihydrobenzo[*b*][1,8]naphthyridin-6(7*H*)-one: yellow solid, Mp= 246-247 °C, ^{1}H NMR (DMSO-d_6) δ: 1.16(s, 6H), 2.60(s, 2H), 3.81(s, 2H), 7.13-7.52(m, 5H), 7.66(m, 2H), 7.99(m, 1H), 9.05(d, J = 8Hz). ^{13}C NMR (DMSO-d_6) δ: 28.09, 32.74, 42.17, 53.62, 121.81, 123.55-134.47, 136.28, 139.29, 159.34, 163.44, 193.46.
HRMS *m/z* calcd. for $C_{20}H_{18}N_2O(M+H)^+$: 302.1545, found: 302.1530.

RESULTS AND DISCUSSION

The Friedlander reaction, well-known as method for the preparation of quinolines and 1,8-naphthyridines involves a thermal condensation between a 2-aminoaryl ketone and another carbonyl compound possessing a reactive methylene group [11] under acidic or basic conditions [12].

The use of Keggin-type polyoxometalates (POMs) as catalysts in both homogeneous and heterogeneous systems was the subject of several research works. The advantage of such materials is related to their redox and acidic properties which can be controlled at atomic/molecular levels [13, 14]. In previous works, our laboratory has used some heteropolyacids (HPAs) as catalysts in the synthesis of various heterocycls. They showed excellent catalytic activities in several reactions such as the synthesis of substituted 1,4-diazepines and 1,5-benzodiazepines [15], cyclocondensation reaction for the synthesis of 4(3*h*)-quinazolinones [16] and synthesis of calix[4]resorcinarenes [17]. These catalytic performances are related to Brönsted acidity strength, stronger than that of many mineral acids and also to strong oxidative power. On the other hand, heteropolyacids are easy to handle and offer a strong option for efficient and cleaner processing compared to polluting and corrosive liquid acid catalysts as mineral acids [18].

In this work, we report the synthesis of quinolines and 1,8-naphthyridines in the presence of HCl and a series of Keggin-type HPAs as catalysts $H_4SiW_{12}O_{40}.$**14**H_2O, $H_4SiMo_{12}O_{40}.$**14**H_2O, $H_3PW_{12}O_{40}.$**13**H_2O and $H_3PMo_{12}O_{40}.$**15**H_2O noted SiW_{12}, $SiMo_{12}$, PW_{12} and PMo_{12}, respectively.

Two series of Naphthyridines and quinolines derivatives were synthesized **3** from the reaction between product **2** and aromatic aldehyde or ketone **1** in the presence of HCl or

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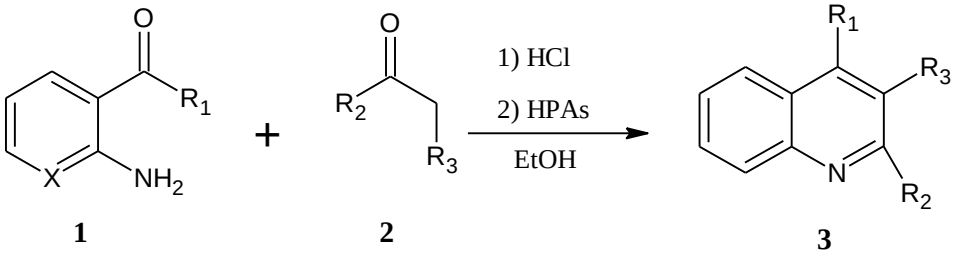
HPAs (SiW_{12}, $SiMo_{12}$, PW_{12} and PMo_{12}) in ethanol under reflux conditions. The product was isolated by filtration and washed with water to eliminate any catalyst residue in the case of HPAs. In the absence$ of catalyst, the reaction did not occur even after a long time (Scheme 1).



1 **2** **3**

X = C, N

R^1 = H, C_6H_5

Scheme 1

Two series of Naphthyridines and quinolines derivatives were synthesized **3** from the reaction between product **2** and aromatic aldehyde or ketone **1** in the presence of a catalytic amount of HCl or HPAs (SiW_{12}, $SiMo_{12}$, PW_{12} and PMo_{12}) in ethanol under reflux conditions. The product was isolated by filtration and washed with water to eliminate any catalyst residue in the case of HPAs. In the absence of catalyst, the reaction did not occur even after a long time (Scheme 1).

Table 1 shows that the yields, towards quinolines (a-d) and naphthyridines (e-f) derivatives obtained from 2-aminobenzophenone or 2-aminocotinaldehyde with α-methylene ketones, depend of the nature of both heteroatom (P (V), Si (IV)) and metallic atom (W(VI), Mo(VI)) of the polyanion. Thus, the silicates, SiW_{12} and $SiMo_{12}$ exhibit higher yields (72-93%) than the phosphates, PW_{12} and PMo_{12} (65-85%). In the case of SiM_{12} or PM_{12} series the tungstates are more active than the molybdates with 68-93% against 65-89% of yields. The catalytic activities are in the order SiW_{12} > $SiMo_{12}$ > PW_{12} > PMo_{12}. It is noted that the catalytic behavior of HCl is generally similar to that of phosphates (PW_{12}, PMo_{12}).

Furthermore, quinolines and naphthyridines derivatives yields are sensitive to α-methylene Ketones nature and the acid strength. Thus, the yields vary from 75 to 93% for SiW_{12}, 72 to 89% for $SiMo_{12}$, 68 to 85% for PW_{12}, 65 to 79% for PMo_{12} and from 55 to 88% for HCl. These results evidenced the high catalytic activity of $SiMo_{12}$ in the synthesis of quinolines and naphthyridines. As, the heteropolyacid is dissociated completely in solution in giving the totality of protons, it appears that the yields are more sensitive to the number of proton that the strength of the acid. It's known in the literature, that the silicates ($H_4SiM_{12}O_{40}$, M: W, Mo) have a Brönsted acidity lower than that of phosphates ($H_3PM_{12}O_{40}$, M: W, Mo) [21]. Consequently, these results suggest that the reaction via Friedlander condensation requires an acidity of Brönsted with a moderate strength.

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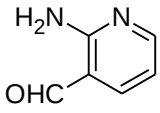
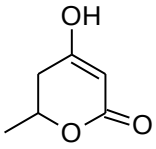
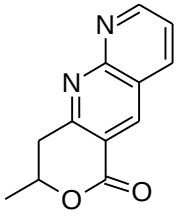
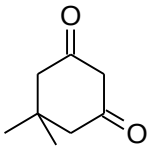
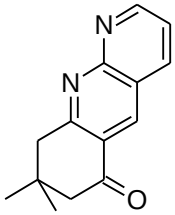
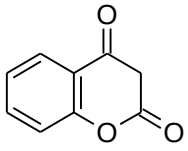
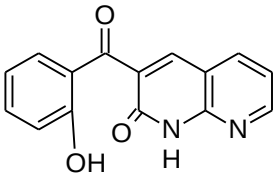
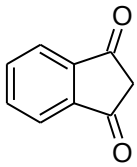
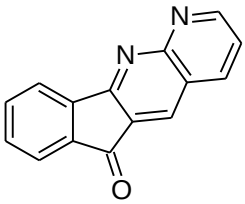
Table 1: Synthesis of Quinoline and Naphthyridines Derivatives Using Equimolar Reactants in Presence of HCl and Various Heteropolyacids Under Refluxing Conditions.

entry	2-Aminoketone (1)	Ketone (2)	Product (3)	Catalyst	Yield (%)
A				HCl $H_3PW_{12}O_{40}$ $H_4SiMo_{12}O_{40}$ $H_4SiW_{12}O_{40}$ $H_3PMo_{12}O_{40}$	65 88 81 78 68
B				HCl $H_4SiW_{12}O_{40}$ $H_4SiMo_{12}O_{40}$ $H_3PW_{12}O_{40}$ $H_3PMo_{12}O_{40}$	71 78 73 72 67
C				HCl $H_4SiW_{12}O_{40}$ $H_4SiMo_{12}O_{40}$ $H_3PW_{12}O_{40}$ $H_3PMo_{12}O_{40}$	69 75 73 69 67
D				HCl $H_4SiW_{12}O_{40}$ $H_4SiMo_{12}O_{40}$ $H_3PW_{12}O_{40}$ $H_3PMo_{12}O_{40}$	88 93 89 85 79

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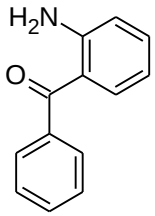
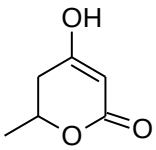
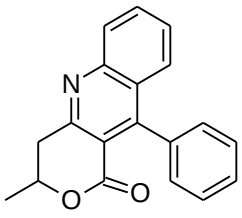
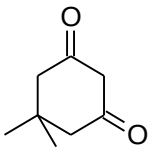
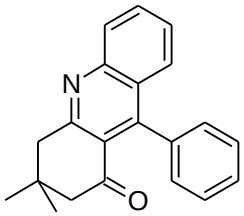
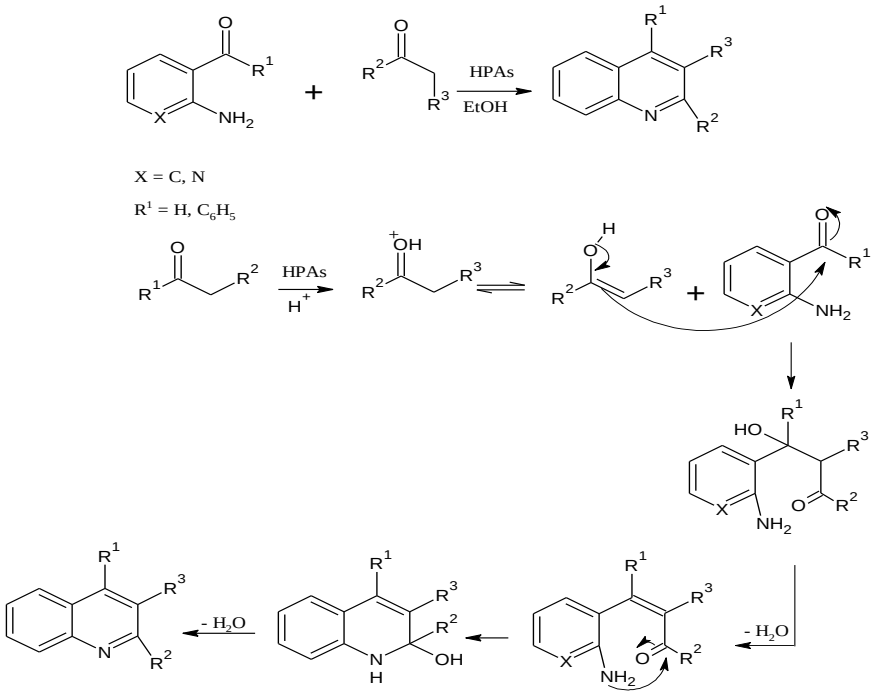
E				HCl $H_4SiW_{12}O_{40}$ $H_4SiMo_{12}O_{40}$ $H_3PW_{12}O_{40}$ $H_4PMo_{12}O_{40}$	55 88 81 78 68
F				HCl $H_4SiW_{12}O_{40}$ $H_4SiMo_{12}O_{40}$ $H_3PW_{12}O_{40}$ $H_4PMo_{12}O_{40}$	68 75 72 68 65

In the Friedlander synthesis, the proton ability of HPA permits to crossed-aldol reaction to take place, creating an amino ketone. This intermediate subsequently condenses with itself, and produced the ring with concomitant formation of the carbon–nitrogen double bond (Scheme 2).



Scheme 2

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CONCLUSION

This study showed that the Keggin-type heteropolyacids (HPAs) are excellent catalysts for the synthesis of quinolines and 1,8-naphthyridines via Friedlander condensation of 2-aminoaryl Ketones with α-methylene Ketones in particular the silicates (SiW_{12}, $SiMo_{12}$) by exhibiting high yields (72-93%) compared to the conventional mineral acid.

The use of Keggin-type HPAs as catalysts can be an alternative compared to liquid mineral acids, due to their easy preparation, their non-toxicity and more they are not corrosive. Furthermore, the strength of acidity can be adjusted in function of the polyanion composition and conditions of organic synthesis.

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