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An Efficient KSF Montmorillonite Catalyzed One-pot Synthesis Of Polyhydroquinoline Derivatives Under Solvent-free Conditions

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ABSTRACT

An efficient and environmentally benign procedure for the preparation of polyhydroquinoline derivatives via one-pot condensation in the presence of Montmorillonite KSF under solvent-free condition is described in this paper. Operational simplicity, ease of handling and recycling of the catalyst, high yields and solvent free reaction path with the short reaction time are the key features of this protocol. © 2007 Trade Science Inc. -INDIA

KEYWORDS

KSF Montmorillonite;
 Hantzsch reaction;
 Heterogeneous catalyst;
 Polyhydroquinoline;
 Solvent-free.

INTRODUCTION

Environmental concern in research and industry are increasing with the increasing pressure to reduce the amount of pollutants produced, including organic solvents whose recoveries mandated by ever more strict laws. Hence the challenge for sustainable environment calls for the use of clean procedures, which can avoid the use of harmful solvents. Avoiding organic solvents during the reaction in organic synthesis leads to a clean, efficient, and economical technology (green chemistry); safety is largely increased, work-up is considerably simplified and cost is reduced. The absence of solvents coupled with the high yields and short reaction times make these procedures very attractive for synthesis^[1].

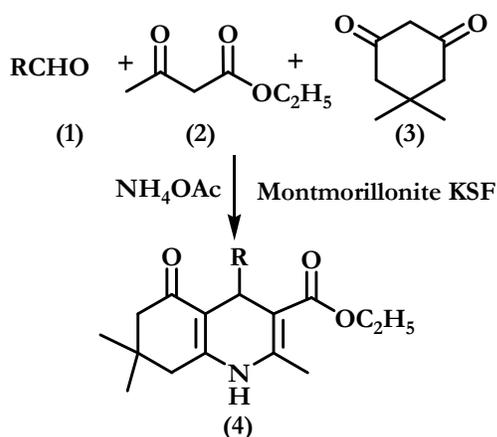
A recent computational analysis of the comprehensive medicinal chemistry database showed the

4-aryl-1,4-dihydropyridines (1,4-DHP) framework to be among the most prolific chemo-types found^[2]. In view of the importance of polyhydroquinoline derivatives, many classical methods for their synthesis using conventional heating and refluxing approaches in the presence of an organic solvent were reported^[3-8]. These methods, however, involves long reaction times, harsh reaction conditions and the use of a large quantity of volatile organic solvents. Therefore, the search continues for the better catalyst and an efficient and versatile method for the preparation of polyhydroquinolines and the progress in this field is remarkable including the promotion of microwave^[9], TMSCl^[10], ionic liquids^[11-12], polymers^[13-14], Lewis acids^[15-16], and HClO₄-SiO₂^[2].

In recent years heterogeneous catalysts are gaining more importance due to environmental-economic factors. Montmorillonite clay's are layered silicates

and are among the numerous inorganic supports for reagents used in organic synthesis. These are non-toxic, non-corrosive, economical and recyclable. They can be used as an efficient and versatile catalyst for various organic reactions viz. Knoevenagel synthesis of coumarin-3-carboxylic acids^[17], synthesis of α -aminonitriles^[18], Aza-Diels-Alder reaction^[19], conversion of D-glycols into furan-diol^[20]. The possibility of performing multi-component reactions under solvent-free conditions with a heterogeneous catalyst could enhance their efficiency from an economic as well as an ecological point of view, prompted us to introduce this article.

Song et al^[21] performed synthesis of polyhydroquinoline derivatives catalysed by montmorillonite K10 in ethanol at reflux temperature. However application of KSF Montmorillonite clay for the synthesis of polyhydroquinoline derivatives is yet to be explored. In continuation of our work aiming at developing selective and environmental friendly methodologies^[22], herein we wish to report a facile Hantzsch condensation in the presence of KSF montmorillonite, under solvent-free conditions, for the synthesis of polyhydroquinoline derivatives in excellent yields. This method is quite superior over the Song et al's work in term of reaction time and being a solvent-free route. To understand the role of KSF montmorillonite and optimize the reaction condition, condensation of 2-chlorobenzaldehyde, 5,5-dimethylcyclohexane-1,3-dione, ethyl acetoacetate and ammonium acetate was performed (SCHEME 1) under various reaction conditions as mentioned in TABLE 1. It was found that



SCHEME 1

TABLE 1: Optimization of reaction condition(R= 2-ClC₆H₄)

Entry	Reaction condition	Time(min)	Yield ^a (%)
1	Stirring at RT without catalyst	180	0
2	Catalyst/Stirring at RT	180	20
3	Stirring at 90°C without catalyst	180	30
4	Catalyst/Stirring at 90°C	5	92
5	Catalyst/Grinding	30	65

^aYield of isolated product

TABLE 2: Synthesis of polyhydroquinoline derivatives via hantzsch condensation under solvent-free conditions

Entry	R	Time (Min)	Yield ^a (%)	Mp (°C)	
				Observed	Literature
a	C ₆ H ₅	20	86	226 - 228	227-229 ^[11]
b	4-OCH ₃ C ₆ H ₄	8	92	260 - 262	260-261 ^[11]
c	4-CH ₃ C ₆ H ₄	10	90	268 - 270	267-268 ^[11]
d	2-ClC ₆ H ₄	5	92	208 - 210	208-210 ^[11]
	2-ClC ₆ H ₄	5	90 ^b	208 - 210	208-210 ^[11]
	2-ClC ₆ H ₄	5	91 ^b	208 - 210	208-210 ^[11]
e	3-NO ₂ C ₆ H ₄	10	92	178 - 180	178-179 ^[2]
f	4-ClC ₆ H ₄	15	90	246 - 248	246-247 ^[11]
g	4-NO ₂ C ₆ H ₄	8	88	246 - 248	242-244 ^[11]
h	4-(CH ₃) ₂ NC ₆ H ₄	12	92	232 - 234	229-231 ^[12]
i	4-OH-3-OCH ₃ C ₆ H ₄	15	90	232 - 234	235-237 ^[11]
j	2-Thienyl	10	87	246 - 248	248-250 ^[11]

^aYield of isolated product ; ^bRecycled catalyst was used.

the reaction in the presence of a catalytic amount of KSF montmorillonite at 90°C gives excellent yield, that too in a short reaction time. Re-usability of the catalyst was studied by performing model reaction using 2-chlorobenzaldehyde as an aldehyde and it was observed that catalyst could be reused up to 3 times effectively. The catalyst was recovered by simple filtration and the recovered catalyst was reused for three times without any significant decrease in activity after being washed with ethanol and activated at 120°C for 4 hrs.

We have selected the optimized reaction conditions to examine the generality of this protocol. Various aromatic and heterocyclic aldehydes were selected to undergo the Hantzsch condensation in the presence of KSF montmorillonite. Benzaldehyde, thiophene-2-carbaldehyde and other aromatic aldehydes containing electron-withdrawing groups (such as nitro group, chloro group) or electron-donating groups (such as alkoxy group, dimethylamine group) were employed and reacted well to give the corresponding polyhydroquinoline derivatives in excellent yields (TABLE 2).

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In conclusion, we have developed a simple and efficient method for the synthesis of polyhydroquinoline derivatives via Hantzsch condensation using KSF montmorillonite catalyst under solvent-free conditions. The mildness of the conversion, experimental simplicity, compatibility with various functional groups, high yields, short reaction time and the easy workup procedure employed, makes this procedure very attractive to synthesize a variety of polyhydroquinoline derivatives.

EXPERIMENTAL

General experimental procedure

All the reagents and aromatic aldehydes were obtained from commercial suppliers and were further purified before use. Melting points were determined by open capillary method and are uncorrected. IR spectra were recorded on Perkin-Elmer IR spectrophotometer in KBr disc. ¹H-NMR spectra were recorded on Bruker Avance II 400 NMR spectrometer. All the products were characterized by IR, ¹H NMR spectra as well as melting point comparison with the reported data.

Typical procedure for the synthesis of polyhydroquinoline derivatives

Mixture of aldehyde(1mmol), 5,5-dimethylcyclohexane-1,3-dione(1mmol), ethyl acetoacetate (1mmol), ammonium acetate(1.5mmol) and KSF montmorillonite(50mg) was heated at 90°C with stirring for 5-20min. and the solid product gradually formed. After completion of the reaction as indicated by TLC, the resulting solid product was treated with EtOAc followed by water and a brine solution. An organic layer was dried over anhydrous Na₂SO₄ and concentrated under vacuum to afford the crude product. The pure product was obtained by recrystallization using absolute alcohol. All the products were identified by comparison of analytical data with those reported in the literature. Spectral data for some compounds are given below.

Catalyst recycle

After completion of the reaction, solid residue was dissolved in ethyl acetate. Catalyst was sepa-

rated by filtration, washed with absolute alcohol and dried. Catalyst was activated by calcination at 120°C for 4hrs. Catalyst was recycled up to three times without any significant loss in its activity.

Analytical and spectral data

Ethyl 1,4,5,6,7,8-hexahydro-4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate

Melting point: 260-262°C; IR(KBr): 3270, 2950, 1700, 1650, 1600, 1495, 1380, 1215, 1030, 765cm⁻¹; ¹H-NMR (400MHz, CDCl₃+DMSO-d₆, δ): 0.93 (s, 3H, CH₃), 1.05 (s, 3H, CH₃), 1.21 (t, 3H, CH₃), 2.11-2.28(m, 4H, 2×CH₂), 2.34 (s, 3H, CH₃), 3.72 (s, 3H OCH₃), 4.06 (q, 2H, CH₂), 4.99 (s, 1H, CH), 6.73 (d, 2H, ArH), 6.76 (s, 1H, NH), 7.21 (d, 2H, ArH).

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