PEG-mediated synthesis of polyhydroquinoline derivatives under ultrasound irradiation

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Abstract: Hantzsch reaction is classified as a one-pot, four-component process for the synthesis of 1,4-dihydropyridine and polyhydroquinoline derivatives. A green protocol for the promotion of the synthesis of polyhydroquinoline derivatives using polyethylene-glycol (PEG) as a green solvent in the absence of any catalysts under ultrasound irradiation at ambient temperature is demonstrated in this report. High to excellent yields, short reaction times, mild conditions, ambient temperature, inexpensive and availability of the substrates make this procedure an attractive methodology.

Keywords: *Hantzsch reaction; PEG; Catalyst-free; DHPs derivative, ultrasound irradiation*

Introduction:

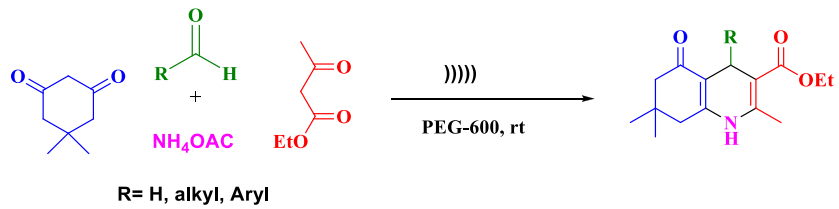
The Hantzsch reaction is classified as a one-pot, three-component process for the synthesis of 1,4-dihydropyridine (DHP) and polyhydroquinoline (PHQ) derivatives. Typically, it is accomplished using an aldehyde, β-dicarbonyls and ammonium acetate or ammonia at high temperature[1]. PHQs are one of the most important classes of heterocyclic scaffolds providing major ligands for biological receptors. PHQs are the source of some valuable drugs which are

very important in pharmacy. For instance, they demonstrate activity for the treatment of angina pectoris and hypertension[2]. Therefore, developing more efficient methods working under mild conditions using more environmentally acceptable catalysts is in high demand[3].

Numerous synthetic methods have been reported for the preparation of PHQ derivatives under thermal, classical or modified conditions. For instance using trimethylsilyl chloride (TMSCl),[4] *P*-TSA,[5] Montmorillonite K10,[6] Co_3O_4-CNTs,[7] Fe_3O_4@chitosan,[8] MCM-41[9] and SBA-15/SO_3H.[10]. However, some of them suffer from drawbacks such as long reaction times, low yields, high catalyst loading, thermal conditions and expensive or difficult preparation of catalyst. Polyethylene-glycol (PEG) is considered as a benign medium due to low vapor pressure, non-flammability, ability to act as a phase transfer catalyst, inexpensive and commercial availability.[11, 12]

Organic synthesis in solvent PEG under catalyst-free conditions is an significant area in modern organic synthesis[12]. Water has been used as green solvent, but utilization is limited because of the hydrophobic nature of organic compounds and the sensitivity of certain catalysts to the moisture.

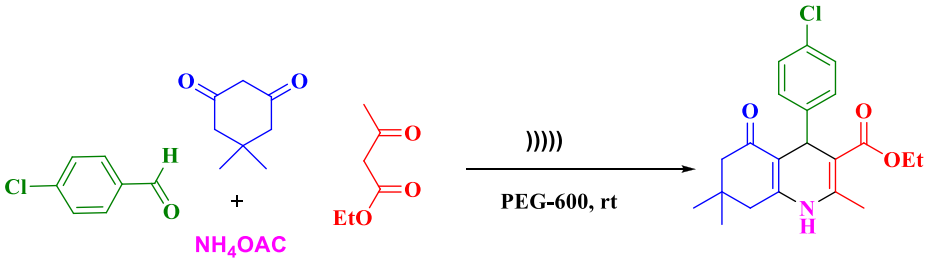
In the initial studies, the reaction of different aldehydes, dimedone, ethyl acetoacetate and ammonium acetate was performed in different solvents without any catalyst to synthesize PHQ derivatives. The reaction in PEG was facile under ultrasound irradiation at ambient temperature (Scheme 1). On the other hand, PEG is an nontoxic, thermally stable, efficient and recyclable solvent for the one-pot four-component condensation of Hantzsch reaction.



Scheme 1: Synthesis of PHQ derivatives using PEG-600 under ultrasound irradiation.

Experimental

A mixture of 4-chlorobenzaldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol) and ammonium acetate (1 mmol) was sonicated in PEG-600 media (2 ml) at ambient temperature under catalyst-free for 30 min to obtain 90% (Scheme 2). Increasing the amount of PEG-600 did not improve the yield. After completion of the reaction as indicated by TLC, the reaction mixture was poured into ice-cold water and extracted with ethyl acetate. Magnesium sulfate was added to organic layer then, filtered to obtain crude product. The crude product recrystallized in hexane.



Scheme 2: Model reaction using PEG-600 under catalyst-free conditions.

Hantzsch condensation of 4-chlorobanzaldehyde, dimedone, ethyl acetoacetate, ammonium acetate in the presence of different solvents was sonicated (P=150 W) at ambient temperature (table 1). Model reaction was promoted in the presence of PEG-600 that played a major role in synthesis of PHQs. It helps to obtain products smoothly in good to excellent yields and short

reaction times. In addition, PEG is available, inexpensive, thermally stable, nontoxic and is used as a green media because of its non-volatility.

Table 1: Synthesis of PHQ derivatives by using of PEG-600 under ultrasound irradiation.

Entry	Aldehyde	Product	Time (min)	Yield (%)	Melting point (°C)	
					Found	Reported
1	4-chlorobenzaldehyde	5a	30	90	243	244-246[13]
2	4-pyridine carbaldehyde	5b	55	84	252-253	256-259[14]
3	Benzaldehyde	5c	45	80	198-200	202-204[15]
4	4-methyl benzaldehyde	5d	65	70	257	260-261[13]

Results and discussion

A ratio of 1:1.1:1 mixture of 4-chlorobanzaldehyde, dimedone, ethyl acetoacetate, ammonium acetate was sonicated in PEG-600 (2 ml) as a green solvent. Electron-withdrawing substituents give the products with higher yields in shorter reaction times than electron-donating substituents. For example, 4-chlorobanzaldehyde gives higher yield than 4-methoxy benzaldehyde also, the group *para*-pyridine carbaldehyde has less steric hindrance than *ortho*- or *matha*-position located (table 1, entry 2, 4). In addition, PEG is a recyclable reagent, therefore slight weight loss of PEG-600 was observed in frequent uses. Using PEG as a solvent reduces the quantity of ethyl acetate in the reaction. This is because of the activation of aldehyde by PEG-600. For the extraction of the mixture of the reaction in water and ethyl acetate, it is better to use rotary evaporator as PEG is soluble in water.

Conclusions

In conclusion, we have reported a sonochemical, facile, catalyst-free and non-thermal method for the Hantzsch reaction. PEG-600 can play a major role in the synthesis of polyhydroquinoline derivatives. Some of the efficient features of this method such as availability, inexpensive, nontoxicity and non-volatility of the solvent motivated us to explore its potential to use in this reaction.

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