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Nucleophilic, Heterocyclic, Carbene-Catalyzed, Solvent-Free, One-Pot Synthesis of Polyhydroquinolines via Multicomponent Hantzsch Reaction: An Efficient and Ecofriendly Approach

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NUCLEOPHILIC, HETEROCYCLIC, CARBENE-CATALYZED, SOLVENT-FREE, ONE-POT SYNTHESIS OF POLYHYDROQUINOLINES VIA MULTICOMPONENT HANTZSCH REACTION: AN EFFICIENT AND ECOFRIENDLY APPROACH

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Abstract A simple, efficient, and ecofriendly one-pot method has been reported for the synthesis of polyhydroquinolines in excellent yield using nucleophilic heterocyclic carbene

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as catalyst. The generalized approach is the Hantzsch four-component reaction of aromatic aldehyde, ethyl acetoacetate, cyclic 1,3-diketone, and ammonium acetate.

Keywords Hantzsch reaction; nucleophilic heterocyclic carbene (NHC); one-pot reaction; polyhydroquinolines

INTRODUCTION

Dihydropyridine (DHP) is a common feature of various bioactive^[1] compounds such as antihypertension drugs,^[2] vasodialators, bronchodialators, antiatherosclerotics, and geroprotective, hepatoprotective,^[3,4] antitumor, and antidiabetic agents. Recent studies have revealed that 1,4-DHPs also exhibit several other medicinal applications, which include neuroprotectants, platelet antiaggregrators, and cerebral antischaemic agents^[5] in the treatment of Alzheimer disease, chemosensitizers^[5] in tumor therapy, drug resistance modifiers,^[6] antioxidants,^[7] and drugs for the treatment of urinary urge incontinence.^[8] These examples clearly demonstrate the remarkable potential of novel DHP derivatives as sources of valuable drugs. Further, 4-aryl-1,4-DHPs have been explored for their calcium channel activity and are well known Ca²⁺ channel blockers.^[9–11] Amlodipine and nicardipine are specific examples of 1,4-DHP containing biologically active heterocyclic compounds (Scheme 1).

The success of these calcium antagonists has led to the development of several novel synthetic strategies along with improved classical methods of preparation, which include the use of microwaves,^[12,13] ionic liquids,^[14] metal triflates,^[15] solvent reflux at high temperature,^[16] TMSCl-NaI,^[17] InCl₃,^[18] I₂,^[19] SiO₂/HClO₄,^[20] SiO₂/NaHSO₄,^[21] ceric ammounium nitrate (CAN),^[22] Na- and Cs-norit carbons,^[23] tetrabutylammonium hydrogen sulfate,^[24] fermenting Baker's yeast,^[25] and application of organocatalysts,^[26] solar thermochemical method,^[27] potassium dodecatungstocobaltate trihydrate,^[28] thiamine hydrochloride,^[29] and triphenylphosphine.^[30] However, conditions such as the use of high temperature, expensive metal precursors, and longer reaction time limit these methods to great extent. In this context, the replacement of toxic and volatile organic solvents as reaction media with environmentally acceptable alternatives such as water, preferential use of organocatalyst, and solvent-free synthesis is an area of tremendous importance in modern organic synthesis. Thus the development of simple, more efficient, and green methods for the preparation of 1,4-DHP derivatives is an active area of research.



Scheme 1. Some biologically active heterocycles containing 1,4-DHP ring

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It is well known that thiamine hydrochloride (vitamin B_1) is an inexpensive and nontoxic reagent containing a pyrimidine ring and a thiazole ring. Hydrogen on the carbon between S and N (i.e., at position 2) is acidic enough to be removed by the base, thereby providing required functionality to carry out several reactions in our body (and other living organisms), which include decarbonylation of pyruvic acid to acetaldehyde and conversion of pyruvic acid to acetoin. Vitamin B_1 (VB₁) analogs have been used as powerful catalysts for many carbon–carbon and carbon–heteroatom bond-formation reactions. Because most of the Hantzsch reactions are reported using Lewis acids or protic catalysts, only some nucleophiles such as triphenylphosphine, a Lewis base, are used as catalysts in the Hantzsch reaction. With the elucidation of active compound of VB₁ as a nucleophilic carbene/zwitterions, we had the opportunity to explore for the first time a thiazolium-based nucleophilic heterocyclic carbene as a green catalyst for the synthesis of polyhydroquinolines (PHQs) using Hantzsch condensation reaction.

RESULTS AND DISCUSSION

We found thiazolium ion (NHC), a basic, soft, and reusable ecofriendly species, can be used for the preparation of large number of PHQs in considerably short time with good yields. To compare its efficiency with various catalytic systems, we have used a range of catalysts. The results are summarized in Table 1. As evident from Table 1, thiazolium NHC shows comparatively better yield in considerably less time. The amount of catalyst is also comparatively very low, almost less than one-tenth in comparison to most of the other catalysts. We have used these catalysts for the synthesis of PHQs, but the best results were obtained when NHC was used as a catalyst under solvent-free condition. See Scheme 2.

To estimate the influence of NHC concentration on reaction time and percentage yield, the amount of catalyst was varied from 0 to 10 mol%. As shown in Table 1 (entries 8–13), elevated amounts of catalyst improved the product yield and shortened

Entry	Catalyst	Solvent	Catalyst amount (mol%)	Time (h)	Yield (%)
1	None	Ethanol	0	24	36
2	$ZnCl_2$	-Do-	150	12	44
3	AlCl ₃	-Do-	200	12	43
4	FeCl ₃	-Do-	200	12	48
5	NdCl ₃	-Do-	25	12	76
6	La(OTf) ₃	-Do-	15	15	84
7	Yb(OTf) ₃	-Do-	5	5	90^b
8	NHC	Solvent-free	0	4	Trace
9	-Do-	-Do-	1	45 min	74
10	-Do-	-Do-	2	45 min	83
11	-Do-	-Do-	3	40 min	89
12	-Do-	-Do-	5	20 min	92
13	-Do-	-Do-	10	20 min	92

Table 1. Comparative account of the effects of different catalysts^a

^{*a*}Benzaldehyde (1 mmol), ethylacetoacetate (1 mmol), dimedone (1 mmol), and ammonium acetate (1 mmol) + 60 °C.

^bSee Ref. 37.



Thiamine hydrochloride

Thiamine

N-Heterocyclic Carbene

Scheme 2. Generation of N-heterocyclic carbene.



Scheme 3. General reaction for the synthesis of polyhydroquinoline.

the reaction time. When catalyst concentration was $1 \mod \%$, the yield was found to be 74% in 45 min, but when the catalyst concentration was increased to 5 mol%, the yield was found to be 92% in 20 min. Further increase in concentration of catalyst (10 mol%) did not show any significant improvement in the yield. Therefore, the one-pot condensation was carried out taking 5 mol% as catalyst concentration.

To examine the extent of the catalyst's application in condensation reaction (Scheme 3), we have applied the optimized catalyst concentration (i.e., $5 \mod \%$ thiazolium ion) to a large number of aromatic aldehydes having both electron-withdrawing and electron-donating substituents, at 60 °C. It was found that almost all studied aldehydes react efficiently to give excellent yields in shorter reaction time (as shown in Table 2). We have also used aliphatic aldehydes for the Hantzsch condensation using NHC as promoter of the reaction and found that these aliphatic

Entry	R_1	Product	Time (min)	Yield (%)
1	Ph	4a	20	92
2	4-OMe-Ph	4b	25	92
3	4-Cl Ph	4c	25	94
4	4-Me- Ph	4d	25	90
5	3-NO ₂ Ph	4 e	25	88
6	2-Cl Ph	4 f	30	90
7	3,4 OMePh	4g	25	92
8	4-OH. 3-OMe Ph	4h	30	89
9	2.4-Cl Ph	4 i	20	92
10	C_6H_{11} Ph	4i	25	89
11	C ₂ H ₅ CHCH ₃	4k	25	86
12	C ₂ H ₅	41	30	88

Table 2. Synthesis of polyhyroquinolines in presence of catalytic amounts of NHC^a

^aAraldehydes + ethylacetoacetate + dimedone + ammonium acetate + NHC (5 mol%).

aldehydes also react smoothly to produce corresponding dihydropyridines in excellent yields with just 5 mol% of NHC.



Scheme 4. Mechanistic pathway for the synthesis of product 4.

The plausible mechanistic pathway for the synthesis of product **4** is shown in Scheme 3. Identity of the products was confirmed by comparison of the physical and spectral data (IR and ¹H NMR) with those of the reported compounds^[19–30] (see the supporting information).

CONCLUSION

In summary, we have reported that thiazolium ion (nucleophilic heterocyclic carbene) is a highly efficient and green catalyst for the synthesis of PHQs by means of four-component condensation of an aldehyde, β -dicarbonyl compounds, and ammonium acetate in one pot. This method is applicable to a wide range of substrates including aromatic and aliphatic, providing the corresponding PHQs in excellent yields. The present methodology offers many advantages such as reduced reaction time and economic viability of the catalyst compared with other conventional catalysts. Most importantly, the proposed method seems to be one of the best examples of green methodology.

EXPERIMENTAL

Preparation of Catalyst (NHC)

Thiamine hydrochloride (0.5 g) was dissolved in 1.6 ml of water and 6 ml of 95% ethanol was added. The solution was cooled in an ice bath and then 1 ml of 3M NaOH was added dropwise with stirring in a manner such that the temperature remained below 20 °C. Intense yellow-colored solution changed to pale yellow solution, resulting in the formation of thiazolium ion (N-heterocyclic carbene).

Synthesis of PHQs (4a-I) Using NHC as Catalyst

Aldehyde (5 mmol), ethylacetoacetate (5 mmol), dimedone (5 mmol), and ammonium acetate (5.2 mmol) were added to 5 mol% of NHC, and the resulting mixture was heated to 60 °C for an appropriate time (monitored by thin-layer chromatography, TLC). The reaction mixture, after being cooled to room temperature, was poured into cold water and extracted with ethylacetate. The organic layer was washed with brine and dried over Na₂SO₄ under reduced pressure (formation of crude yellow products). The products were purified by recrystallization from ethanol to afford PHQs in 90–96% yield.

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SUPPLEMENTARY DATA

General information and spectral data can be accessed on the publisher's website.

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