One-Pot Solvent-Free Synthesis of Polyhydroquinolines Promoted by In/SiO_2 Composite Catalyst

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INTRODUCTION

Hantzsch multicomponent reaction has been recognized as important synthetic method to access the 1,4-dihydropyridines (1,4-DHPs) with high atomic economy.[1] These compounds exhibit a wide-range of biological activities, specially as calcium channel blockers and useful drugs for the treatment of heart diseases.[2]

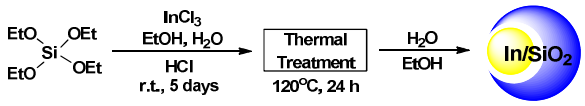
Polyhydroquinolines (PHQs) derivatives are structurally related compounds that can be obtained *via* a non-symmetrical Hantzsch reaction.

The utilization of Lewis acid catalysts in these syntheses is an alternative to surpass drawbacks such as long reaction times, harsh conditions and low yields. Moreover, heterogeneous catalysts are of easy handling and fast isolation from the reaction, minimizing additional work-up procedures.[3]

In the present work we describe the preparation of a novel In/SiO_2 composite and its application as heterogeneous Lewis acid catalyst in a solventless multicomponent Hantzsch reaction.

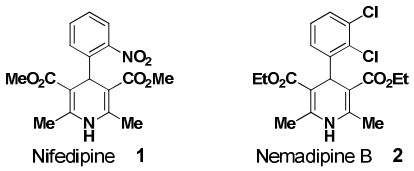
RESULTS AND DISCUSSION

The Indium/Silica hybrid composite was prepared by the Sol-Gel method using $InCl_3$ as metal source (Scheme 1).[4] The process of gelification was carried out on air at room temperature followed by thermal treatment and washes with H_2O and EtOH.



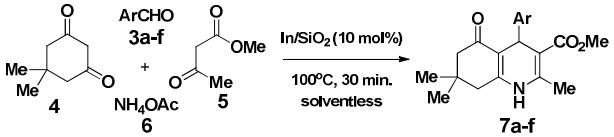
Scheme 1. Sol-Gel Synthesis of hybrid In/SiO_2 composite.

The hybrid material was analyzed by EDS which showed 1:18 atomic ratio of In/Si (0,94 mmols of In/g of composite). The specific surface area was determined by the BET method as being 326 ± 10 m^2g^{-1}. The range of pore diameter minor than 2 nm was determined by BJH method. Two known bioactive 1,4-DHPs, *Nifedipine* (**1**) and *Nemadipine B* (**2**) were synthesized by mixing the reagents in presence of 10 mol% of In/SiO_2 under neat condition, at 100°C over 30 minutes period (Scheme 2). The catalyst was isolated from the crude mixture by a simple filtration process.



Scheme 2. Bioactive 1,4-DHPs *via* In/SiO_2 composite.

We extended the same methodology to the synthesis of a series of PHQs **7a-f** with different aromatic substituents (Scheme 3). The results are shown in Table 1, below.



Scheme 3. Synthesis of Polyhydroquinolines **7a-f**.

Table 1. Synthesis of Polyhydroquinolines.

Ent.	Ar	PHQ (7)	Yield (%)
1	Ph	**7a**	60
2	4-MeO-C_6H_4	**7b**	62
3	3,4-$(MeO)_2$-C_6H_3	**7c**	69
4	2,3,4-$(MeO)_3$-C_6H_3	**7d**	63
5	3-NO_2-C_6H_4	**7e**	71
6	1-Naphtyl	**7f**	84

Recycle experiments with the recovered catalyst were performed for the synthesis of **7b** for additional three times affording the product in similar yields.

CONCLUSION

The synthesized new In/SiO_2 hybrid composite material proved to be an efficient and recyclable Lewis acid heterogeneous catalyst to the synthesis of 1,4-DHPs and PHQs through the Hantzsch multicomponent reaction in solvent-free conditions.

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REFERENCES

[1] Trost, B. M. *Science* **1991**, *254*, 1471.
[2] Bossert, F. *et al. Angew. Chem, Int. Ed. Engl.* **1981**, *20*, 762.
[3] Antonyraj, C. A. *et al. Appl. Catal. A: Gen.* **2008**, *338*, 121.
[4] Hench L. L.; West, J. K. *Chem.Rev.***1990**, *90*, 33.