

Short communication

Synthesis of 2,4,5-triaryl-imidazoles catalyzed by $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ under heterogeneous system

Majid M. Heravi*, Khadijeh Bakhtiari, Hossein A. Oskooie, Shima Taheri

Department of Chemistry, School of Sciences, Azahra University, Vanak, Tehran, Iran

Received 7 June 2006; received in revised form 16 August 2006; accepted 16 August 2006

Available online 30 August 2006

Abstract

The synthesis of 2,4,5-triaryl-imidazoles from benzyl, aldehydes and NH_4OAc , as ammonia source, in the presence of catalytic amount of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ supported onto acidic alumina in very good yields under heterogeneous system is reported.

© 2006 Elsevier B.V. All rights reserved.

Keywords: 2,4,5-Triaryl-imidazoles; Heterogeneous system; $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$

1. Introduction

The benzimidazole scaffold is a useful structural motif for displaying chemical functionality in biologically active molecules [1]. Optimization of benzimidazole-based structures has resulted in marketed medicines such as Omeprazole [2] and Pimobendan [3] and lead compounds in a wide range of therapeutic areas (e.g. casein kinase [4], hepatitis C virus [5]). In addition, many of the substituted diaryl imidazoles are known as inhibitors of P38 MAP kinase [6]. Therefore, preparation of benzimidazoles has been attracted considerable attention in recent years.

Recently, efficient synthesis of imidazoles from aldehydes, 1,2-diketones, and NH_4OAc in acetic acid have been reported [7]. The synthesis of 2,4,5-triaryl-imidazoles from aryl aldehydes and 1,2-diketones or α -hydroxy ketone in the presence of ionic liquid [8(a)] and silica sulfuric acid [8(b)] have also been described. A variety of solid supports such as alumina, KSF, silica gel, bentonite, montmorillonite K10 and KSF were tested for the synthesis of 2,4,5-triaryl-imidazoles under microwave irradiation [9].

Recently, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ was shown to be an effective promoter for the Biginelli three-component condensation reaction [10]. It has also been reported as a mild useful and inexpensive Lewis

acid catalyst for the synthesis of α -aminonitriles [11(a)] and formal hydrochromination of alkynes [11(b)].

One important aspect of clean technology is the use of environmentally friendly catalysts—typically a solid catalyst that can be easily recovered when the reaction is complete. Employing such an approach results in minimal pollution and waste material production. The application of such catalysts to fine chemical manufacturing is likely to be increasingly important in the future.

Very recently, we have reported the microwave assisted synthesis of 2,4,5-triaryl-imidazoles in solvent-free system in the presence of $\text{NH}_4\text{OAc}/\text{NaHSO}_4$ supported onto silica gel [12].

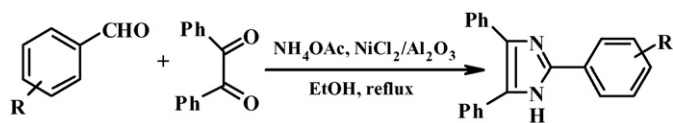
As a part of our program aiming at developing new methodologies for the preparation of heterocyclic compounds containing nitrogen [13], and in continuation of our interest in heterogeneous catalyzed organic reaction [14], here we would like to report our investigation concerning the direct synthesis of 2,4,5-triaryl-imidazoles.

2. Results and discussion

In this paper, we describe an efficient and practical route for the synthesis of benzimidazoles under heterogeneous system using $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ supported onto acidic alumina, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}/\text{Al}_2\text{O}_3$, (Scheme 1) as catalyst.

In a model reaction, in the presence of the catalyst, the mixture of benzaldehyde (1 mmol), benzil (1 mmol) and NH_4OAc (1.2 mmol), as ammonia source, stirred and refluxed in ethanol.

* Corresponding author. Tel.: +98 9121329147; fax: +98 2188047861.
E-mail address: mmh1331@yahoo.com (M.M. Heravi).



Scheme 1.

The corresponding product obtained in 94% yield. Different kinds of substituted benzaldehydes were also subjected to heterogeneous reaction in the presence of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}/\text{Al}_2\text{O}_3$ in EtOH. This method provides 2,4,5-triaryl benzimidazoles directly, in relatively short reaction times and good yields.

We found that, the heterocyclization reaction is facilitated by increasing the temperature, so the reaction proceeded in ethanol under reflux condition to give a high yield at a relative short reaction time.

In all cases, complete conversion was observed after appropriate time and the products were readily isolated in very high yields (Table 1).

To illustrate the need of catalyst, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}/\text{Al}_2\text{O}_3$, for this reaction, experiments were conducted in which the reaction of benzaldehyde and NH_4OAc with benzil was studied in the absence of catalyst. The reaction was not completed even after 24 h. Obviously, the catalyst is an essential component of the reaction.

Although the reaction occurs without alumina, the reaction times are very long, taking several hours to go to completion. Therefore, we think that alumina acts as an effective heterogeneous surface for this reaction. It also makes work-up easy.

We found that for aldehydes bearing either electron-releasing or electron withdrawing substituents in the *ortho*, *meta* or *para* positions the reaction proceeded very efficiently in all cases but

for electron withdrawing substituents longer reaction times need to drive the reaction to completion.

In conclusion, the present work describes an efficient new methodology for the synthesis of a class of benzimidazoles by one-pot reaction of aldehydes, benzil and ammonium acetate. The cheapness and the availability of the reagents, easy and clean work-up and good yields make the method attractive for the synthesis of various 2,4,5-triaryl benzimidazoles.

3. Experimental

Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. All the products are known compounds; they were characterized by IR, ^1H NMR and mass spectral data. All melting points compared satisfactorily with those reported in the literature [15].

3.1. Preparation of 2,4,5-triaryl-imidazoles: typical procedure

A mixture of benzaldehyde (1 mmol), benzil (1 mmol) and NH_4OAc (1.2 mmol), as ammonia source, and $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (0.1 mmol)/ Al_2O_3 (0.05 g) stirred and refluxed in ethanol. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered and the filtrate was cooled to room temperature and the corresponding pure product obtained in 94% yield. Different kinds of substituted benzaldehydes were also subjected to heterogeneous reaction in the presence of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}/\text{Al}_2\text{O}_3$ in EtOH and the corresponding imidazole was obtained. The results are summarized in Table 1.

Table 1
Synthesis of 2,4,5-triaryl benzimidazoles catalyzed by $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}/\text{Al}_2\text{O}_3$

Entry	Aldehyde	Time (min)	Yield ^a (%)	mp (°C)	
				Found	Reported
1		25	94	272–273	275 [15(a)]
2		40	90	258	261–263 [15(c)]
3		35	92	229–231	233 [15(b)]
4		90	89	235–238	240 [15(b)]
5		120	91	313–315	–
6		60	90	226–228	230–232 [15(c)]
7		45	86	259	261.5–263.5 [15(d)]

^a Yields refer to isolated products.

References

- [1] D.S.V. Vliet, P. Gillespie, J. Scicinski, *Tetrahedron Lett.* 46 (2005) 6741.
- [2] P. Lindberg, P. Nordberg, T. Alminger, A. Brandstorm, B. Wallmark, *J. Med. Chem.* 29 (1986) 1327.
- [3] R. Mannhold, *Drugs Future* 10 (1985) 570.
- [4] M.A. Pagano, M. Andrzejewska, M. Ruzzene, S. Sarno, L. Cesaro, J. Bain, F. Meggio, Z. Kazimierczuk, L.A. Pinna, *J. Med. Chem.* 47 (2004) 6239.
- [5] P.L. Beaulieu, Y. Bousquet, J. Gauthier, J. Gillard, M. Marquis, G. McKeercher, C. Pellerin, S. Valois, G. Kukulj, *J. Med. Chem.* 47 (2004) 6884.
- [6] J.C. Lee, J.T. Laydon, P.C. McDonnell, T.F. Gallagher, S. Kumar, D. Green, D. McNulty, et al., *Nature* 372 (1994) 739.
- [7] S.E. Wolkenberg, D.D. Wisnoski, W.H. Leister, Y. Wang, Z. Zhao, C.W. Lindsley, *Org. Lett.* 6 (2004) 1453.
- [8] (a) S.A. Siddiquo, U.C. Narkhede, S.S. Palmikar, T. Daniel, R.J. Lahoti, K.V. Srinivasan, *Tetrahedron* 61 (2005) 3539;
(b) A. Shaabani, A. Rahmati, *J. Mol. Catal. A: Chem.* 249 (2006) 246.
- [9] (a) A.Y. Usyatinsky, Y.L. Khmel'nitsky, *Tetrahedron Lett.* 41 (2000) 5031;
(b) Y. Xu, L.-F. Wan, H. Salehi, W. Deng, Q.-X. Guo, *Heterocycles* 63 (2004) 1613;
(c) R.B. Sparks, A.P. Combs, *Org. Lett.* 6 (2004) 2473.
- [10] (a) J. Lu, H. Ma, *Synlett* (2000) 63;
(b) J. Lu, Y. Bai, *Synthesis* (2002) 466.
- [11] (a) S.K. De, *J. Mol. Catal. A: Chem.* 225 (2005) 169;
(b) K. Takai, S. Sakamoto, T. Isshiki, T. Kokumai, *Tetrahedron* 62 (2006) 7534.
- [12] H.A. Oskooie, Z. Alimohammadi, M.M. Heravi, *Heteroatom Chem.* 17 (2006), in press.
- [13] (a) M.M. Heravi, M. Rahimzadeh, M. Bakavoli, M. Ghassemzadeh, *Tetrahedron Lett.* 45 (2004) 5747;
(b) M.M. Heravi, M. Rahimzadeh, M. Bakavoli, M. Ghassemzadeh, *Tetrahedron Lett.* 46 (2005) 1607;
(c) M.M. Heravi, F. Derikvand, F.F. Bamoharram, *J. Mol. Catal. A: Chem.* 242 (2005) 173;
(d) M.M. Heravi, Kh. Bakhtiari, F.F. Bamoharram, *Catal. Commun.* 7 (2006) 373;
(e) M.M. Heravi, M. Tajbakhsh, A.N. Ahmadi, B. Mohajerani, *Monatsh. Chem.* 137 (2006) 175.
- [14] (a) M.M. Heravi, D. Ajami, M. Ghassemzadeh, *Synthesis* (1999) 339;
(b) M.M. Heravi, D. Ajami, M.M. Mojtahedi, M. Ghassemzadeh, *Tetrahedron Lett.* 40 (1999) 561;
(c) M.M. Heravi, R. Hekmat Shoar, L. Pedram, *J. Mol. Catal. A: Chem.* 231 (2005) 89.
- [15] (a) D. Davidson, M. Weiss, M. Jelling, *J. Org. Chem.* 2 (1937) 319;
(b) A.H. Cook, D.C. Jones, *J. Chem. Soc.* (1941) 278;
(c) J.G. Lombardino, E.H. Wiseman, *J. Med. Chem.* 17 (1974) 1182;
(d) D.M. White, J. Sonnenberg, *J. Org. Chem.* 29 (1964) 1926.