Journal of Saudi Chemical Society (2016) **20**, 138–150

King Saud University

Journal of Saudi Chemical Society

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ORIGINAL ARTICLE

$ZrOCl_2 \cdot 8H_2O$: An efficient and recyclable catalyst for the three-component synthesis of amidoalkyl naphthols under solvent-free conditions

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Received 15 April 2012; accepted 23 June 2012
Available online 29 June 2012

KEYWORDS

$ZrOCl_2 \cdot 8H_2O$;
Amidoalkyl naphthol;
Three-component reaction;
Solvent-free condition

Abstract An efficient synthesis of amidoalkyl naphthols from the reaction of β-naphthol and various aromatic aldehydes and amides using $ZrOCl_2 \cdot 8H_2O$, an environmentally friendly catalyst under a thermal solvent-free green procedure is described. This simple protocol offers advantages such as shorter reaction times, simple work-up and excellent yield. The catalyst $ZrOCl_2 \cdot 8H_2O$ can be reused. The reusability of the catalyst has been studied for the synthesis of various amidoalkyl naphthols.

1. Introduction

Multi-component reactions (MCRs) have attracted considerable attention in the organic syntheses as they can produce target products in a single operation without isolating the intermediates and thus reducing the reaction times and energy (Domling and Ugi, 2000; Zhu and Bienayme, 2005). Therefore, the design of novel MCRs has attracted great attention from the research groups working in medicinal chemistry and drug discovery. Some of the examples of MCRs includes Bigenilli (Slimi et al., 2011), Ugi (Keating and Armstrong, 1995), Passerini (Kobayashi et al., 1998) and Mannich (Zhao et al., 2004) reactions. Nevertheless, development and discovery of new MCRs are still in demand.

o-Quinone methides (*o*-QMs) have emerged as interesting molecules due to their toxicological properties against both normal and cancerous cells and also proposed intermediary in the formation of many biologically important polymers (Brousmiche, 1998). *o*-QMs also act as intermediates for the synthesis of antitumour agents (Song et al., 2006). One of the tandem reactions which involves the *in situ* generation of *o*-QMs and their reaction with acetamide or benzamide gives amidoalkyl naphthols (Khosropour et al., 2005). 1-Amidoalkyl naphthols can be easily hydrolysed to 1-aminoalkyl naphthol, which shows biological activities like depressor and brady-cardiac effect (Shen et al., 1999; Dingermann et al., 2004). This 1-aminoalkyl alcohol-type ligand has been used for asymmetric synthesis and also as a catalyst (Hulst et al., 1996; Li et al., 1999).

1-Amidoalkyl-2-naphthols can be also converted into 1,3-oxazine derivatives (Damodiran et al., 2009). 1,3-Oxazines have potentially different biological activities including antibiotic (Kusakabe et al., 1972), antitumour (Remillard et al.,

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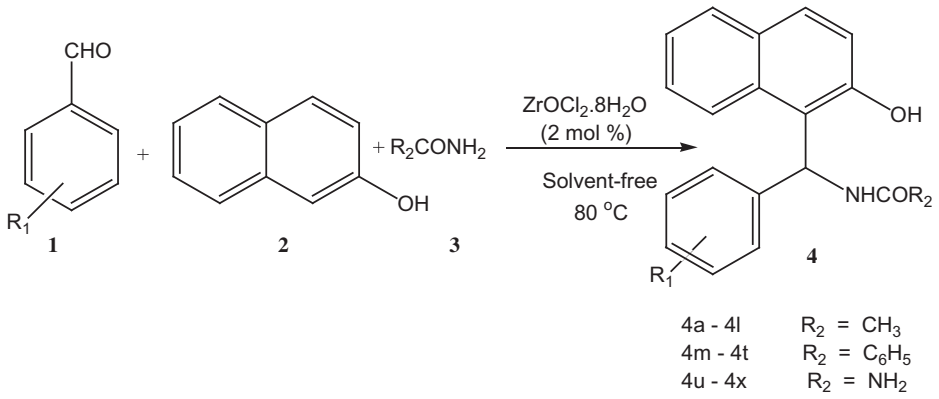
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

1319-6103
http://dx.doi.org/10.1016/j.jscs.2012.06.003



Scheme 1 Synthesis of amidoalkyl naphthols in the presence of $ZrOCl_2{\cdot}8H_2O$ (2 mol%) under solvent-free conditions.

1975), analgesic (Lesher and Surrey, 1955), anticonvulsant (Mosher et al., 1953), antipsychotic (Peglion et al., 1997), antimalarial (Ren et al., 2001), antianginal (Benedini et al., 1995), antihypertensive (Clark et al., 1983), and antirheumatic properties (Matsuoka et al., 1997). One-pot multi-component condensation of β-naphthol with aromatic aldehydes and amide derivatives or acetonitrile has been used as a practical synthetic route towards 1-amidoalkyl-2-naphthols.

Several Lewis and Brønsted acids have been applied to catalyse this transformation, such as silica gel supported $-SO_3H$ functionalized benzimidazolium based ionic liquid (Kotadia and Soni, 2012), wet cyanuric chloride (Mahdavinia and Bigdeli, 2009), trityl chloride (Khazaei et al., 2010), $H_3PW_{12}O_{40}$ (Dorehgiraee et al., 2009), N-(4-sulphonic acid)-butyl triethylammonium hydrogensulphate (Hajipour et al., 2009), 1-butyl-3-methylimidazolium hydrogen sulfate (Sapkal et al., 2009), bismuth nitrate (Wang et al., 2012), $H_4SiW_{12}O_{40}$ (Supale and Gokavi, 2010), montmorillonite K-10 clay (Kantevari et al., 2007), $Ce(SO_4)_2$ (Selvam and Perumal, 2006), iodine (Das et al., 2007), $K_5CoW_{12}O_{40}.3H_2O$ (Nagarapu et al., 2007), *p*-TSA (Khodaei et al., 2006), sulphamic acid (Patil et al., 2007a,b), cation-exchanged resins (Patil et al., 2007a,b), silica sulphuric acid (Srihari et al., 2007), SiO_2–$FeCl_3$ (Shaterian and Yarahmadi, 2008), SiO_2–$HClO_4$ (Shaterian et al., 2008), polyphosphate ester (Moghanian and Ebrahimi, 2014), amberlite IR-120 (Forouzani and Ghasemnejad-Bosra, 2011), $Sr(OTf)_2$ (Su et al., 2008), molybdophosphoric acid (Jiang et al., 2008), 1-hexanesulphonic acid sodium salt (Niralwad et al., 2011), P_2O_5 (Nandi et al., 2009), Thiamine hydrochloride (Lei et al., 2009) and sulphonic acid functionalized imidazolium salts (Zolfigol et al., 2011).

However, some of these catalysts suffer from the drawback of prolonged reaction times, toxic reagents, and low yields. The recovery and reusability of the catalyst are also a problem. Therefore, the cleaning processes and utilizing eco-friendly, heterogeneous, and green catalysts, which can be simply recycled at the end of reactions have been under permanent attention. The demand for environmentally benign procedure with heterogeneous and reusable catalyst (Anastas and Warner, 2000) promoted us to develop a safe alternate method for the synthesis of amidoalkyl naphthols. This is an active ongoing research area and there is a scope for further improvement towards mild reaction conditions and improved yields.

Recently, the use of $ZrOCl_2{\cdot}8H_2O$ as a catalyst in organic synthesis has increased considerably. $ZrOCl_2{\cdot}8H_2O$ is a commercially available solid chemical. Due to its low toxicity (LD_{50} [$ZrOCl_2{\cdot}8H_2O$ oral rate] = 2950 mg/kg), low costs, ease of handling, high activity, $ZrOCl_2{\cdot}8H_2O$ is the potential green catalyst or reagent which is of importance from different views (Firouzabadi and Jafarpour, 2008). $ZrOCl_2{\cdot}8H_2O$ is effectively used as a catalyst in organic reactions, such as the synthesis of 5-aryl-2-oxazolidinones from aziridines and CO_2 (Wu et al., 2009), nitration of phenolic compounds (Shi et al., 2005), acylation of alcohols, phenols, amines and thiols (Ghosh et al., 2005), esterification of carboxylic acids and alcohols (Sun et al., 2006), Michael addition of amines and indoles to α, β-unsaturated ketones (Firouzabadi et al., 2006), Biginelli reaction (Rodriguez-Dominguez et al., 2007), Mannich-type reactions (Eftekhari-Sis et al., 2006), synthesis of xanthenedione derivatives (Mosaddegh et al., 2012). Zirconyl chloride was also proven to be highly effective for the synthesis of β-acetamido ketones (Ghosh et al., 2006), enaminones and enamino esters (Zhang et al., 2007), α-aminophosphonates (Bhagat and Chakraborti, 2008) and homoallylic alcohols or amines (Shen et al., 2008). Furthermore, $ZrOCl_2{\cdot}8H_2O$ is regarded to be an ionic cluster of $[Zr_4(OH)_8(H_2O)_{16}]Cl_8{\cdot}12H_2O$; and whereby the zirconium cation cluster $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ is usually thought to be the active species for the Lewis acid-catalysed reactions.

As a part of our ongoing research devoted to the development of useful synthetic methodologies (Mansoor et al., 2011, 2015), herein we report an efficient and practical method for the synthesis of 1-amidoalkyl-2-naphthol derivatives through a coupling reaction of aldehyde, β-naphthol, amide/urea in the presence of $ZrOCl_2{\cdot}8H_2O$ as catalyst (Scheme 1).

2. Experimental

2.1. Apparatus and analysis

All chemicals were purchased from Aldrich Chemical Co. and solvents were used without further purification. Analytical thin-layer chromatography was performed with E. Merck silica gel 60F glass plates. Visualization of the developed chromatogram was performed by UV light (254 nm). Column chromatography was performed on silica gel 90, 200–300 mesh. Melting points were determined with Shimadzu DS-50 thermal