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ORIGINAL ARTICLE

$TiCl_4$: An efficient catalyst for one-pot synthesis of 1,2-dihydro-1-aryl-naphtho-[1,2-*e*][1,3]oxazin-3-one derivatives and their drug score analysis

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Abstract Multi-component, economical and efficient synthesis of 1,2-dihydro-1-aryl-naphtho[1,2-*e*][1,3]-oxazin-3-one derivatives (**4a**–**k**) with an excellent yield is described through a one-pot condensation of β-naphthol, aromatic aldehydes and urea in presence of catalytic amount of $TiCl_4$ (10 mol%) under conventional heating and microwave irradiation. The role of catalyst in the conversion of reactants to the final compounds is described. All the compounds have been characterized by spectral (IR, ^1H, ^{13}C NMR and Mass) and analytical data. The pharmacological parameters of title compounds were also analyzed for their bioavailability by Osiris property explorer.

1. Introduction

The naphthalene nucleus is commonly found in the compounds of commercial importance. A number of pharmaceutical and agricultural agents have a naphthalene framework. Therefore, the synthesis of aromatic condensed naphthoxazinone derivatives has received considerable attention because of their broad spectrum of biological properties (Patel et al., 1999; EI-Shafei and Badr Eldin, 1994; Girgis, 2000; Waxman and Darke, 2000). Particularly, naphthalene condensed 1,3-oxazin-3-one derivatives have exhibited antibacterial properties (Latif et al., 1982). In spite of their importance from biological and synthetic points of view, relatively few methods describe the synthesis of naphthalene condensed 1,3-oxazin-3-one derivatives (Latif et al., 1982; Ikeda et al., 1980) including condensation of aminoalkylnaphthols as precursors with phosgene in the presence of triethylamine (Szatmari et al., 2004). Carbonyl diimidazole was used instead of phosgene for the preparation of these

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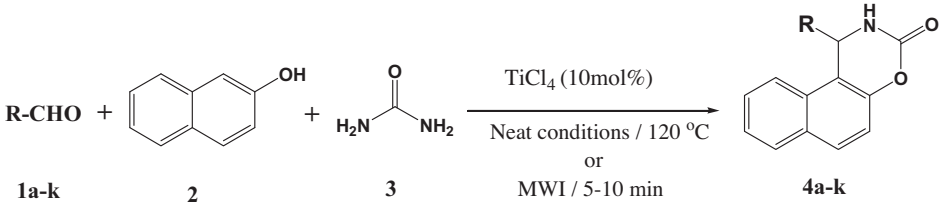
compounds (Cimarelli et al., 2004). Also, it can be synthesized by the multicomponent condensation of aldehyde, β-naphthol and urea in the presence of PTSA as a catalyst (Dabiri et al., 2007). Even though various procedures are reported, disadvantages *viz*., low yields, use of excess of reagents, catalysts and use of toxic organic solvents existed. Therefore, it is necessary to develop an alternative route for the synthesis of naphthalene condensed-1,3-oxazin-3-one derivatives.

In recent years, a tremendous upsurge of interest in various chemical transformation processes by catalysts under mild conditions has offered important advantages in organic synthesis. One of those acidic catalysts is $TiCl_4$ which has been explored as powerful catalyst for various organic transformations such as synthesis of α-amino phosphonates (Thirupathi Reddy et al., 2007), Biginelli reaction (Valizadeh et al., 2008), olefination of aldehydes (Basavaiah and Rao, 2002) and synthesis of imidazo [1,2-*a*]pyridine derivatives (Cai et al., 2006). The reported route is an efficient, convenient and novel method for the condensation of β-naphthol with aldehyde and urea in the presence of $TiCl_4$ (10 mol%) to afford condensed 1,3-oxazin-3-one derivatives in good yields (Scheme 1).

2. Results and discussion

During the course of our investigation, we first explored the effect of solvents and catalysts on a typical condensation of aldehyde (**1a**), β-naphthol (**2**) and urea (**3**) to afford oxazin-3-one derivative (**4a**). It can be emphasized that all the catalysts and solvents used could promote the reaction to a certain extent except $FeSO_4{\cdot}7H_2O$ and $CuSO_4{\cdot}5H_2O$. Although $FeCl_3{\cdot}6H_2O$, $NiCl_2{\cdot}6H_2O$ and $SnCl_4{\cdot}5H_2O$ have exhibited good catalytic activity, the water insoluble solids or salts formed from these catalysts when treated with water make the work-up procedure more complicated. It is obvious that $TiCl_4$ demonstrated superior catalytic activity and was the best catalyst among those examined. However, the reaction could be completed in a short time and afforded the desired product in excellent yield when it was carried out under the solvent free condition. In order to further evaluate the influence of $TiCl_4$, this reaction was carried out using different amounts of $TiCl_4$ (mol%) under neat conditions at 120 °C. Therefore, maximum yield (75%) was possible when titanium chloride was used as a catalyst in the neat condition and the remaining catalysts have exhibited moderate to least activity. It was observed that the reaction hardly proceeded in the absence of $TiCl_4$. The increase in the amount of $TiCl_4$ (mol%) afforded higher yield. When the amount of catalyst increased to 10 mol%, the yield was significantly increased up to 95%. However, an excess of $TiCl_4$ did not help to increase the yield. On the contrary, more than 10 mol% of catalyst resulted in slightly lower yield.

These optimization results prompted us to select 10 mol% of $TiCl_4$ for further study. Moreover, application of microwave irradiation has opened a new prospective in synthetic organic chemistry, not only in terms of high yield and selectivity but also ease of reaction conditions and rate of acceleration (Verma, 2003). Hence, microwaves have been applied to accelerate reaction rates for a variety of chemical transformations. In this line, to our surprise it was observed that, when 4-flourobenzaldehyde (**1b**) was irradiated with β-naphthol (**2**) and urea (**3**) in the presence of $TiCl_4$ (10 mol%) under microwave irradiation, the reaction was completed within 5 min followed by simple work-up to afford 1,2-dihydro-1-aryl-naphtho[1,2-*e*][1,3]-oxazin-3-one (**4b**) (96% of yield) (Table 1).



Scheme 1 Three component coupling reaction of aromatic aldehyde, β-naphthol and urea to yield the title compounds **4a–k.**

Table 1 Synthesis of 1,2-dihydro-1-aryl-naphtho [1, 2-*e*] [1, 3]-oxazin-3-ones **4a–k** in the presence of $TiCl_4$ (10 mol%).

Entry	R1	Method A Time (min)	Yield (%)	Method B Time (min)	Yield (%)	MP (°C)
4a	4-$CH_3C_6H_4$-	55	95	4	96	168–170
4b	4-F-C_6H_4-	55	85	5	96	202–204[#]
4c	3-F-C_6H_4-	60	80	6	86	259–251
4d	C_6H_5-	50	75	5	85	220–222[#]
4e	$CH_2O_2C_6H_3$-	55	72	8	82	232–234
4f	4-OH-C_6H_4-	50	85	10	90	181–183[#]
4g	4-Cl-C_6H_4-	58	70	5	85	210–212[#]
4h	3-Cl-C_6H_4-	62	68	6	82	193–195
4i	4-NO_2-C_6H_4-	70	60	9	80	188–190
4j	2-NO_2-C_6H_4-	65	86	8	78	195–197
4k	4-OCH_3-C_6H_4-	55	75	4	85	186–188[#]

[#] Ikeda et al. (1980).

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