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Multicomponent synthesis of imidazo[1,2-*a*]pyridines using catalytic zinc chloride

Amanda L. Rousseau,* Pulane Matlaba and Christopher J. Parkinson

Discovery Chemistry, Biosciences, CSIR, Private Bag X2, Modderfontein 1645, South Africa

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Abstract—The novel use of zinc chloride to catalyze the one-pot, three component synthesis of imidazo[1,2-*a*]pyridines from a range of substrates using either conventional heating or microwave irradiation is described. This methodology affords a number of imidazo[1,2-*a*]pyridines in reasonable yields and short reaction times without any significant optimization of the reaction conditions.

Imidazo[1,2-*a*]pyridines **1** and the related imidazo[1,2-*a*]-pyrimidines **2** (Fig. 1) have received significant attention from the pharmaceutical industry owing to their interesting biological activities displayed over a broad range of therapeutic classes,[1] exhibiting antibacterial,[2] antifungal,[3] antiviral,[4] and anti-inflammatory[5] properties. They have also been shown to be selective cyclin dependant kinase inhibitors,[6] GABA,[7] and benzodiazepine[8] receptor agonists, and bradykinin B_2 receptor antagonists.[9] Drug formulations containing imidazo[1,2-*a*]pyridines currently available on the market include alpidem **3** (anxiolytic), zolpidem **4** (hypnotic), and zolimidine **5** (antiulcer).[1]

While there are a number of synthetic routes to the imidazo[1,2-*a*]pyridine ring system, the most common approach involves the coupling of 2-aminopyridines with α-halocarbonyl compounds.[1] However, this approach does not readily lend itself to a diversity oriented synthesis.

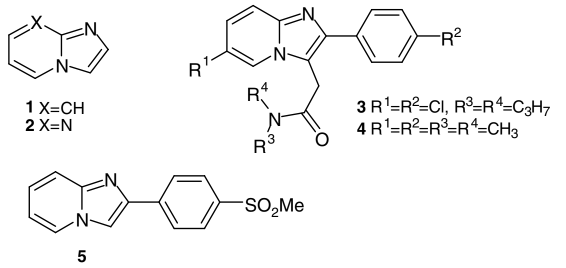
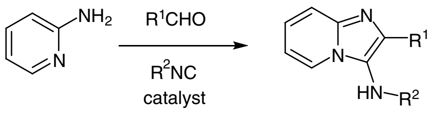


Figure 1.

A more versatile approach uses a three component coupling (3CC) involving the condensation of aldehydes, 2-aminopyridine, and isocyanides (Scheme 1).[10] This robust approach allows for the preparation of a diverse range of products and suited our requirements in the continuation of a synthetic program aimed at kinase inhibitors.

The 3CC reaction is carried out in the presence of an acid catalyst, usually scandium(III) triflate,[11] although there have been reports describing the use of ammonium chloride,[12] acetic acid,[10a] perchloric acid,[10e] or Montmorillonite clay K10[13] to catalyze the reaction. The use of solid supports with a range of acid catalysts in the 3CC reaction has also been described, including the use of excess immobilized glyoxylic acid,[14] toluenesulfonic acid[15] (using an isonitrile resin), and catalytic scandium triflate (using resin bound aldehydes).[10d] Reactions were typically carried out at room temperature (for reactions catalyzed by scandium triflate, acetic acid, toluenesulfonic acid or perchloric acid) or using



Scheme 1.

Keywords: Multicomponent reaction; Imidazo[1,2-*a*]pyridines; Zinc chloride; Montmorillonite K10.

* Corresponding author. Tel.: +27 11 605 2455; fax: +27 11 608 3200; e-mail: arousseau@csir.co.za

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conventional heating (for reactions catalyzed by glyoxylic acid or ammonium chloride). This, however, required long reaction times of 20–72 h.[10–15] The use of microwave reactors has been reported for reactions catalyzed by scandium triflate[11a] and Montmorillonite clay,[13] with reduced reaction times.

In our initial investigations, we hoped to find a general method that would be widely applicable to a range of substrates without extensive optimization, thus allowing for the rapid preparation of a series of imidazo[1,2-*a*]pyridines for biological testing. The reaction of 2-aminopyridine, 2,6-dimethylphenylisocyanide, and benzaldehyde was selected as a test reaction (Scheme 1, $R^1 = Ph$, $R^2 = 2,6\text{-dimethylphenyl}$), and the reaction conditions (catalyst, temperature, solvent, and reaction time) varied (Table 1).

Scandium triflate at ambient temperature gave the desired product in good yield, but required long reaction times as reported[11] (entry 1). In addition to this, scandium triflate is an expensive catalyst, and a loading of 5 mol % corresponds to 25 mass % with respect to 2-aminopyridine. At room temperature, the reaction catalyzed by Montmorillonite clay KSF was very slow (entry 2), and only 20% of the desired product was isolated after 4 days. When the same reaction was carried out in a microwave reactor[16] (with a change to a higher boiling solvent), there was some improvement, but with a substantial increase in uncharacterized by-product formation (entry 3). In addition, multiple solvent washes of the clay were required to recover the product. This reaction was repeated by first forming the imine, and then treating the imine with 2,6-dimethylphenylisocyanide in the presence of the catalyst under microwave conditions (entry 4). With multiple solvent washes of the clay, this gave the desired product in 55% yield in 1 h. However, a one-pot reaction would be preferential.

Therefore, test reactions were carried out separately with both Montmorillonite clay K10 and a novel catalyst for this reaction, zinc chloride, using both conventional heating and microwave irradiation (Table 1, entries 5–8). Both catalysts afforded adequate yields of the desired product in short reaction times. For reactions catalyzed by zinc chloride, the work-up simply involved removal of solvent under reduced pressure, while for reactions catalyzed by Montmorillonite clay, multiple solvent washes of the clay were required to recover the product. As both catalysts are substantially cheaper than scandium triflate (the clay can also be recycled), these methods were used to prepare a collection of imidazo[1,2-*a*]pyridines. This is the first reported use of zinc chloride in the 3CC synthesis of imidazo[1,2-*a*]pyridines.

Without further optimization of the reaction conditions for individual reactions, a range of imidazo[1,2-*a*]pyridines were prepared from 2-aminopyridine using either zinc chloride or Montmorillonite clay K10 as the catalyst (Table 2) in a microwave or an automated parallel reactor. Both catalysts are applicable to a range of substrates, with some limitations.

Reactions with most aldehydes were catalyzed successfully with zinc chloride to afford the corresponding imidazo[1,2-*a*]pyridines. However, the reactions with nicotinaldehyde did not go to completion when zinc chloride was used as the catalyst, and the only product isolated from the reaction was the intermediate imine. Attempts to convert the imine isolated from this reaction (possibly still complexed with zinc chloride) to the desired product using a variety of catalysts afforded only low yields of the product, suggesting that zinc chloride forms a stable complex with this imine once it is formed. In order to overcome this problem, Montmorillonite clay K10 was used as the catalyst in the reactions with nicotinaldehyde, affording the desired imidazo[1,2-*a*]pyridines as shown in entries 5–8 of Table 2. The reactions with furfural were also carried out using the clay catalyst, as we felt that coordination with zinc chloride would also be possible with these products. However, a test reaction carried out with zinc chloride showed that reactions with furfural could, indeed, be catalyzed by zinc chloride.

In general, the use of *p*-methoxybenzaldehyde and 3,4-dimethoxybenzaldehyde gave low yields of the desired products. These oxygenated products were found to be relatively unstable and there was also evidence for decomposition on silica, which contributed to the low yields. This could not be attributed to the presence of zinc chloride, however, as low yields were also obtained with Montmorillonite K10.

Isobutyraldehyde afforded reasonable yields of the desired imidazo[1,2-*a*]pyridines, indicating that zinc

Table 1. Variation of reaction conditions for the 3CC reaction ($R^1 = \text{phenyl}$, $R^2 = 2,6\text{-dimethylphenyl}$)

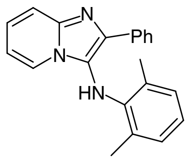
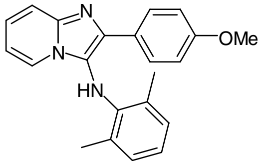
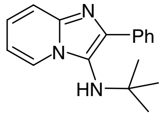
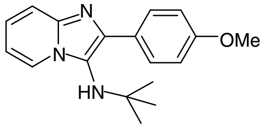
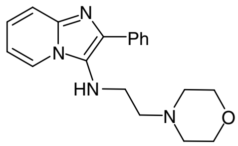
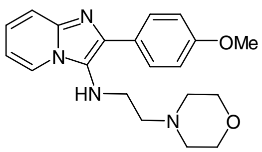
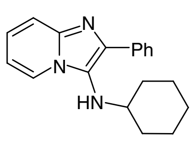
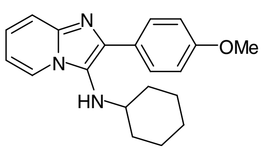
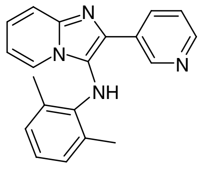
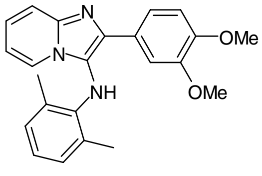
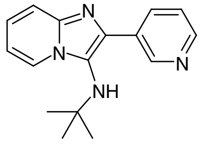
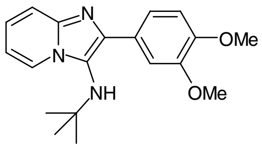
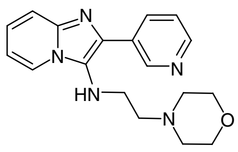
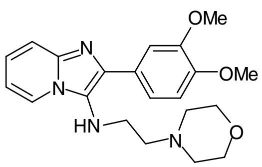
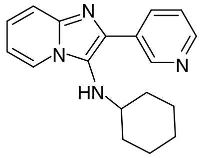
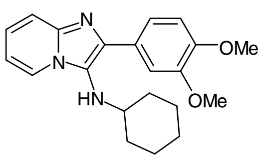
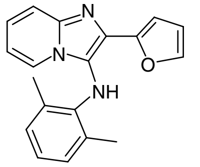
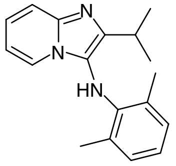
Entry	Catalyst	Solvent	Conditions	Time (h)	Yield (%)
1	$Sc(OTf)_3$	MeOH/DCM	Ambient temperature	48	78
2	Montmorillonite KSF	MeOH/DCM	Ambient temperature	96	20[a]
3	Montmorillonite KSF	1,4-Dioxane	Microwave	2	35[b]
4	Montmorillonite KSF	1,4-Dioxane	Microwave	1	55[c]
5	$ZnCl_2$ (5 mol %)	1,4-Dioxane	Microwave	1	62
6	$ZnCl_2$ (5 mol %)	1,4-Dioxane	Reflux	5	65
7	Montmorillonite K10 (1 mass equiv)	1,4-Dioxane	Microwave	1	61
8	Montmorillonite K10 (1 mass equiv)	1,4-Dioxane	Reflux	5	72

[a] Incomplete reaction.

[b] Formation of multiple products.

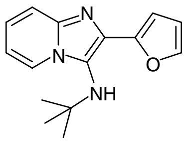
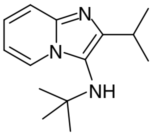
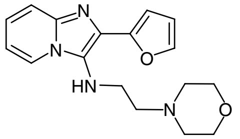
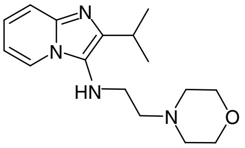
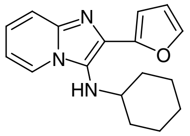
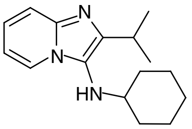
[c] Imine formation carried out first.

Table 2. Imidazo[1,2-*a*]pyridines prepared

Entry	Imidazo[1,2-*a*]pyridine	Reaction conditions	Yield (%)	Entry	Imidazo[1,2-*a*]pyridine	Reaction conditions	Yield (%)
1		$ZnCl_2$, 1,4-dioxane, microwave, 1 h Montmorillonite clay K10, 1,4-dioxane, reflux, 5 h	62 72	13		$ZnCl_2$, 1,4-dioxane, reflux 5 h	28
2		$ZnCl_2$, 1,4-dioxane, microwave, 1 h	60	14		$ZnCl_2$, 1,4-dioxane, reflux 5 h	15
3		$ZnCl_2$, 1,4-dioxane, microwave, 1 h	14	15		$ZnCl_2$, 1,4-dioxane, reflux 5 h	22
4		$ZnCl_2$, 1,4-dioxane, microwave, 1 h	78	16		$ZnCl_2$, 1,4-dioxane, reflux 5 h	27
5		Montmorillonite clay K10, 1,4-dioxane, microwave, 1 h	54	17		$ZnCl_2$, 1,4-dioxane, reflux 5 h Montmorillonite clay K10, 1,4-dioxane, reflux, 5 h	34 41
6		Montmorillonite clay K10, 1,4-dioxane, microwave, 1 h	57	18		$ZnCl_2$, 1,4-dioxane, reflux 5 h	9
7		Montmorillonite clay K10, 1,4-dioxane, microwave, 1 h	20	19		$ZnCl_2$, 1,4-dioxane, reflux 5 h	36
8		Montmorillonite clay K10, 1,4-dioxane, microwave, 1 h	59	20		$ZnCl_2$, 1,4-dioxane, reflux 5 h	75
9		$ZnCl_2$, 1,4-dioxane, reflux 5 h Montmorillonite clay K10, 1,4-dioxane, reflux, 5 h	30 25	21		$ZnCl_2$, 1,4-dioxane, reflux 5 h	20

(*continued on next page*)

Table 2 (*continued*)

Entry	Imidazo[1,2-*a*]pyridine	Reaction conditions	Yield (%)	Entry	Imidazo[1,2-*a*]pyridine	Reaction conditions	Yield (%)
10		Montmorillonite clay K10, 1,4-dioxane, reflux, 5 h	60	22		$ZnCl_2$, 1,4-dioxane, reflux 5 h	53
11		Montmorillonite clay K10, 1,4-dioxane, reflux, 5 h	26	23		$ZnCl_2$, 1,4-dioxane, reflux 5 h	18
12		Montmorillonite clay K10, 1,4-dioxane, reflux, 5 h	73	24		$ZnCl_2$, 1,4-dioxane, reflux 5 h	49

chloride could be utilized as the catalyst in reactions involving aliphatic aldehydes.

In summary, we have described the novel application of zinc chloride, a cheap catalyst, for the one-pot preparation of imidazo[1,2-*a*]pyridines using either conventional heating or microwave irradiation. The work-up is simple and convenient for use in high-throughput synthesis. In cases where coordination is possible, as with the case of aminated aldehydes, Montmorillonite clay K10 can be used as the catalyst.

General procedure for the preparation of imidazo[1,2-a]pyridines using zinc chloride: 2-Aminopyridine (0.125 mg, 1.33 mmol) was dissolved in 1,4-dioxane (2 mL), and treated with zinc chloride (5 mol %, 0.07 mmol), the aldehyde (1.0 equiv, 1.33 mmol), and the isocyanide (1.0 equiv, 1.33 mmol), and heated at reflux for 5 h. After this time the reaction mixture was concentrated under reduced pressure and the crude residue was either treated with ethyl acetate/hexane to afford the product as a precipitate, or was subjected to silica gel column chromatography (30% ethyl acetate/hexane or 5% methanol/chloroform). All products were characterized by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry.

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