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Short Communication

I_2-TEMPO as an efficient oxidizing agent for the one-pot conversion of alcohol to amide using $FeCl_3$ as the catalyst

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ABSTRACT

A high yield one-pot method for the synthesis of amides from alcohols is described. The aldehyde was generated in situ using iodine-TEMPO as oxidizing agent followed by intermediate oxime formation through reaction with NH_2OH•HCl and finally rearrangement of oxime catalyzed by $FeCl_3$.

1. Introduction

Amides are an important class of compounds in biological and chemical systems. Extensive studies have been done on amides by biologists and chemists over the past few decades [1,2]. Because of the pervasive nature of the amides, it constitutes the formation of polymer in a biological system through peptide linkage [3–5]. It is regarded as one of the most important functional groups in organic chemistry. Several “name reactions” and “rearrangements” exist that are used routinely to synthesize amides. Some of these are Schotten–Baumann reaction, Schmidt reaction, Willgerodt–Kindler reaction, Bodroux reaction, Leuckart amide synthesis, Beckmann rearrangement, Chapman rearrangement, etc. [6,7]. Several transition metals are reported for the oxidative conversion of aldehydes to amides [8–13]. However very few reports are present for direct alcohol to amide synthesis. Recently our group has reported a synthetic route for aldehyde to amide conversion using $FeCl_3$ [14]. Recent literature documents the use of Ir [15] and Ru [16–18] complexes for the synthesis of amides directly from alcohols. Metal free processes are also reported for the conversion of alcohols to amides. Togo et al. have reported the use of molecular iodine in aq. ammonia and H_2O_2 for alcohol to amide conversion [19]. The $PhI(OAc)_2$–NaN_3 system was reported by Zhang et al. [20]. The selectivity of amide formation may sometimes be hindered by the formation of side products such as aldehyde, carboxylic acid and nitrile [21,22]. The challenge in this area is to overcome these side reactions.

Many reports exist where TEMPO has been used as oxidant in combination with Cu [23–30], Ru [31] metal or polymer support [32] although Semmelhack's report [23] indicates the inability of Cu-TEMPO complex towards simple primary and secondary alcohols and reactive only with allylic and benzylic alcohols. Miller et al. have used the I_2-TEMPO system for the conversion of alcohols to aldehydes [33]. After receiving excellent results with $FeCl_3$ for aldehyde to amide conversion, we were interested to explore a one-pot method for alcohol to amide conversion using I_2-TEMPO as oxidant and $FeCl_3$ as the catalyst and NH_2OH•HCl as a nitrogen source.

2. Results and discussion

2.1. Screening of oxidant

Since the in situ oxidation of alcohol to aldehyde is critical, we first screened various oxidants taking benzyl alcohol as a model substrate, with $FeCl_3$ as the catalyst, K_2CO_3 as the base, and NH_2OH•HCl as the nitrogen source in ethylenedichloride (EDC) solvent at 90 °C (Table 1).

At first we have tried using a mild oxidant such as H_2O_2 or *t*-BuOOH (solution in water), but unfortunately carboxylic acid was obtained as the product (Table 1, Entries 1 and 2). Next, we used selective oxidants such as $MnO_2/KMnO_4$ and KI/I_2 giving benzaldehyde as the major product along with a formation of oxime in little amount. But the reaction from aldehyde to amide or oxime to amide does not proceed further (Table 1, Entries 3 and 4) as concluded from GC studies of the reaction mixture. Our next attempt was using I_2-TEMPO which successfully produces amide in the presence of Fe(III) (Table 1, Entry 5).

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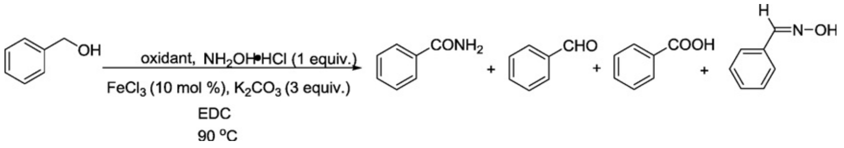
Table 1
Screening of oxidant.



Entry	Oxidant used [a]	GC yield of products (%)			
		Aldehyde	Acid	Oxime	Amide
1	70% H_2O_2 (1 eq.)	0	92	0	0
2	70% *t*-BuOOH (water) (1 eq.)	0	97	0	0
3	$MnO_2/KMnO_4$ (1.5 and 0.5 mmol)	75	0	22	0
4	KI/I_2 (25 mol%, 1 mmol)	72	0	25	0
5	I_2-TEMPO (2 eq., 0.1 mmol)	10	0	0	75

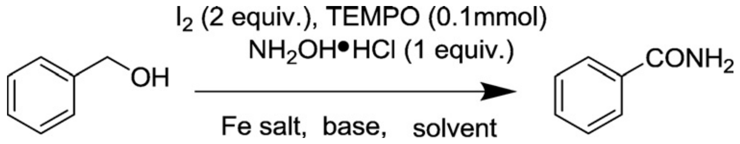
[a] Reaction performed with 10 mol% $FeCl_3$, 3 eq. K_2CO_3, 1 eq. NH_2OH•HCl along with above mentioned amount of oxidant in EDC at 90 °C for a period of 12 h, yield corresponds to the GC yield obtained using internal standard.

2.2. Screening of solvent, base and iron salt

We proceed to optimize other parameters such as the choice of the base, solvent and iron salt taking I_2-TEMPO as the oxidative system and the results have been summarized in Table 2.

From Table 2, it is very clear that among easily available Fe(III) salts (Table 2, Entries 1–7), $FeCl_3$ gives good results with the formation of expected amide product. $FeCl_2$ also produces 70% product in 22 h. Next, we screened a number of inorganic bases to compare their reactivity with $FeCl_3$ (Table 2, Entries 8–12) and we found that K_2CO_3 and Cs_2CO_3 gave almost the same results. We have chosen K_2CO_3, since it is inexpensive. We observed that KO-*t*-Bu, although a very strong base, did not produce better results. Other bases such as NaOH, KOH and Na_2CO_3 were less effective or ineffective (Table 2, Entries 8–10). Among the varieties of solvents tested (Table 2, Entries 13–20), EDC was most effective. EtOAc also gave good yield, but required longer reaction time whereas reaction at lower temperature (80 °C) with EDC produces more amide at the same time. Highly

Table 2
Optimization of solvent, base and catalyst.

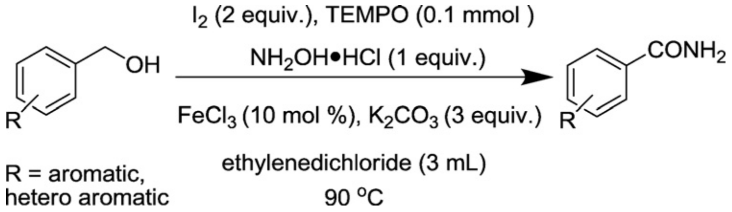


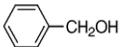
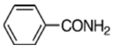
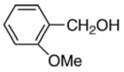
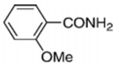
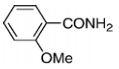
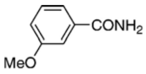
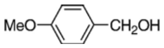
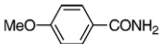
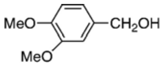
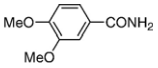
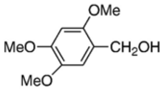
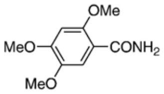
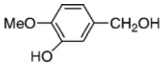
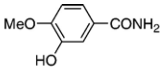
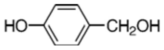
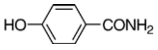
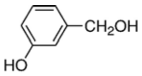
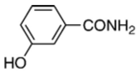
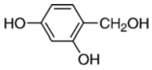
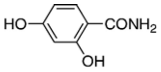
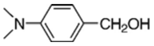
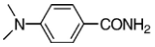
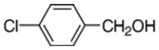
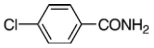
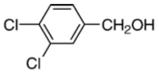
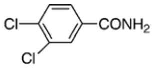
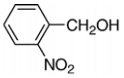
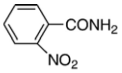
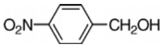
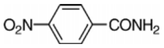
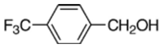
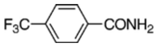
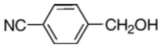
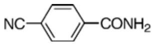
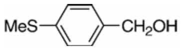
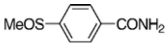
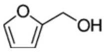
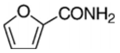
Entry	Fe-salt (10 mol%)	Base (3 eq.)	Solvent	Temp. (°C)	Time (h)[a]	Yield (%)[b]
1	Fe_2O_3	K_2CO_3	EDC	90	24	10
2	$Fe(NO_3)_3\cdot 9H_2O$	K_2CO_3	EDC	90	24	5
3	$Fe_2(SO_4)_3$	K_2CO_3	EDC	90	24	5
4	Mohr's salt	K_2CO_3	EDC	90	24	5
5	$FeCl_3$	K_2CO_3	EDC	90	20	89
6	$FeCl_2$	K_2CO_3	EDC	90	22	70
7	Fe powder	K_2CO_3	EDC	90	30	20
8	$FeCl_3$	NaOH	EDC	90	24	5
9	$FeCl_3$	KOH	EDC	90	24	30
10	$FeCl_3$	Na_2CO_3	EDC	90	24	30
11	$FeCl_3$	Cs_2CO_3	EDC	90	20	90
12	$FeCl_3$	KO-*t*-Bu	EDC	90	22	88
13	$FeCl_3$	K_2CO_3	Toluene	110	24	5
14	$FeCl_3$	K_2CO_3	THF	70	12	–
15	$FeCl_3$	K_2CO_3	EtOAc	80	22	78
16	$FeCl_3$	K_2CO_3	EDC	80	22	85
17	$FeCl_3$	K_2CO_3	CH_3NO_2	110	24	50
18	$FeCl_3$	K_2CO_3	DMF	100	24	40
19	$FeCl_3$	K_2CO_3	DMF	150	24	60
20	$FeCl_3$	K_2CO_3	DMSO	100	24	50
21	$FeCl_3$	K_2CO_3	DMSO	150	24	60
22	–	K_2CO_3	EDC	90	24	–
23	$FeCl_3$	K_2CO_3	EDC	60	29	80
24	$FeCl_3$ (5 mol%)	K_2CO_3	EDC	90	24	50
25	$FeCl_3$ (15 mol%)	K_2CO_3	EDC	90	20	90
26	$FeCl_3$	K_2CO_3 (2 eq.)	EDC	90	20	50
27	$FeCl_3$	K_2CO_3 (4 eq.)	EDC	90	20	90
28	$FeCl_3$	K_2CO_3	H_2O	100	24	50

[a] Monitored using TLC.
[b] Isolated yield after column chromatography of the crude product.

polar solvents such as DMF and DMSO gave poor yield. Even when the temperature was increased up to 150 °C, a very slight improvement in yield was noticed (Table 2, Entries 19 and 21). Next, we have performed a blank experiment without catalyst and no product formation was observed (Table 2, Entry 22). Reducing the temperature from 90 °C to 60 °C leads to the increase in the reaction time (Table 2, Entry 23). We varied the amount of catalyst from 5 mol% to 15 mol% and 10 mol% was found to be the optimum amount

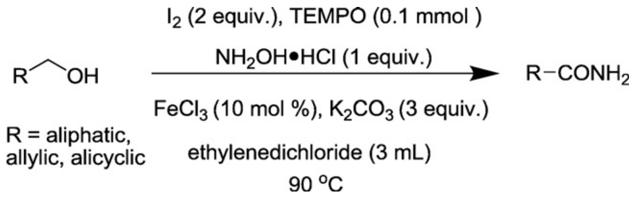
Table 3
$FeCl_3$ catalyzed conversion of benzylic alcohols into aromatic amides.

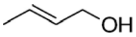
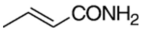
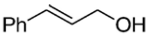
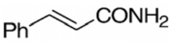
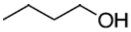
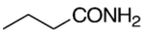
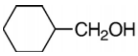
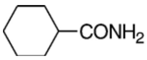
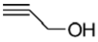
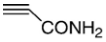
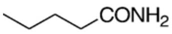
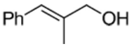
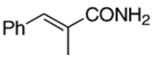
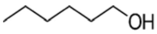
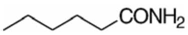
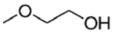
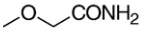


Entry	Alcohol	Amide	Time (h)[a]	Yield (%)[b]
1			20	89
2			15	82
3			17	80
4			14	87
5			9	90
6			8	92
7			15	78
8			16	80
9			19	75
10			12	79
11			15	80
12			19	82
13			20	80
14			24	80
15			24	81
16			30	84
17			32	83
18			25	85
19			15	82

[a] Monitored using TLC.
[b] Isolated yield after column chromatography of the crude product.

Table 4
$FeCl_3$ catalyzed conversion of aliphatic and allylic alcohols into amides.



Entry	Alcohol	Amide	Time (h)[a]	Yield (%)[b]
1			19	85
2			17	82
3			21	81
4			24	78
5			19	75
6			22	79
7			20	82
8			22	80
9			24	77

[a] Monitored using TLC.

[b] Isolated yield after column chromatography of the crude product.

(Table 2, Entries 24 and 25). Similarly, 3 eq. of base is required for best results (Table 2, Entries 26 and 27). As our previous report on $FeCl_3$ uses water as solvent, here also we attempted an experiment with H_2O as solvent at 100 °C (Table 2, Entry 28) but only 50% conversion was observed in 24 h.

In summary, the optimized conditions include I_2-TEMPO (2 eq., 0.1 mmol) as oxidant with $NH_2OH•HCl$ (1 equiv.) as the nitrogen source, $FeCl_3$ (10 mol%) as the catalyst and K_2CO_3 (3 equiv.) as the base in EDC solvent at 90 °C. The grade of these various salts along with impurities has been given in the supporting information.

2.3. Substrate scope

To access the capability of the reaction, various substituted alcohols were subjected to this reaction under the optimized condition. Results are depicted in Tables 3 and 4.

This method tolerates a variety of functional groups including various electron-donating and electron-withdrawing functional groups. All the alcohols are converted to the amides giving good yields within a reasonable time. Substrate containing electron-donating group (Table 3, Entries 2–6) takes less time with high yields of product whereas substrate having strong electron-withdrawing groups such as cyano, nitro, and trifluoromethyl takes more time for completion (Table 3, Entries 15–17). Substrates containing other functional groups like amine and hydroxyl group (Table 3, Entries 7–11) are tolerated well in the reaction media, and do not affect product formation. Similar results were obtained with alcohol having a hetero atom such as furylalcohol (Table 3, Entry 19). But in the sulphide group containing alcohol (Table 3, Entry 18) a slightly different behavior is observed. Sulphide functionality also oxidizes to sulfoxide during the conversion of alcohol to amide which has been confirmed by ESI-MS spectroscopy.

In addition to these, aliphatic and allyl alcohols were also subjected to this methodology (Table 4). These substrates are also converted to the corresponding amide in reasonable time with good yield.

Long chain alcohols such as butyl, pentyl, and hexyl alcohols give amide formation within 20–24 h under similar reaction conditions (Table 4, Entries 3, 6, 8). Crotyl, cinnamyl and allylic alcohols result in amide with better yields (Table 4, Entries 1, 2, 7). Propagylic and cyclohexyl amides form within reasonable time in good yield from the corresponding alcohols (Table 4, Entries 4, 5). Similarly, 2-methoxyethanol also shows the same result of this reaction (Table 4, Entry 9).

ICP-MS studies revealed that the $FeCl_3$ used in this study contained trace amounts of Cu^{2+} as impurity. A control experiment was done as per the standard procedure using benzyl alcohol as the

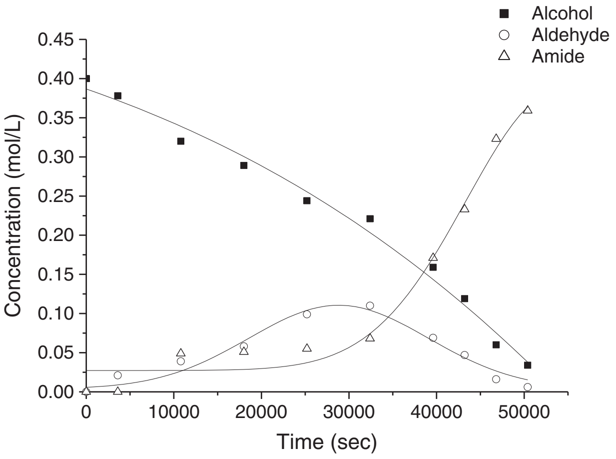


Fig. 1. Concentration versus time in the conversion of *p*-methoxybenzyl alcohol to *p*-methoxy benzamide by $FeCl_3$.

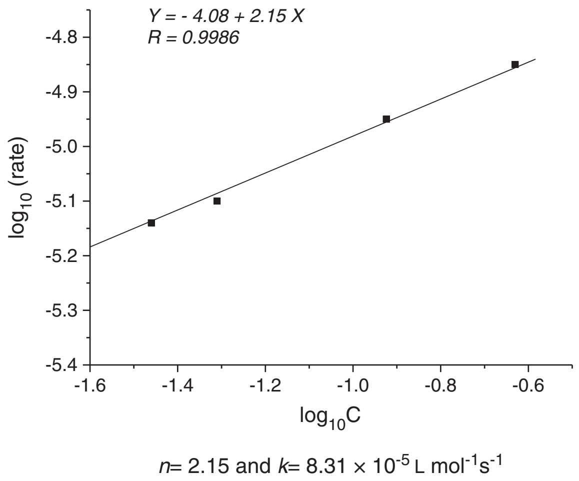


Fig. 2. Van't Hoff differential plot for the conversion of *p*-methoxybenzyl alcohol to *p*-methoxy benzamide by $FeCl_3$.

substrate along with the required concentration of $CuBr_2$ as guided by ICP-MS results, in the absence of $FeCl_3$. We observed less than 5% conversion during the required period of time. In another experiment, we used 99.99% $FeCl_3$ and added $CuBr_2$ as an impurity in trace quantities, keeping other parameters of the experiment identical. In this case the time of reaction and the isolated yield remained almost invariant. These experiments prove that this transformation is catalyzed by $FeCl_3$ alone.

3. Kinetic studies

We have performed the kinetic studies with the following substrates namely *p*-methoxybenzylalcohol, *p*-chlorobenzylalcohol and cinnamyl alcohol. High-Pressure Liquid Chromatography (HPLC) was used to determine the various concentrations of starting materials and product present with respect to time. Fig. 1 shows the concentration vs time plot for the conversion of *p*-methoxybenzyl alcohol to *p*-methoxy benzamide which indicates the steady decrease in the concentration of alcohol with gradual increase in concentration of amide with time while the intermediate aldehyde concentration increases, achieves a steady state and finally decreases to give the product.

The order (n) and rate constant (k) have been calculated by the Van't Hoff differential method. The rate of the reaction at different concentrations has been estimated by evaluating the slope of the tangent at each point of Fig. 1. With this data $\log_{10}$ (rate) vs $\log_{10}$ (concentration) have been plotted in Fig. 2. The order (n) and rate constant (k) evaluated from the slope of the line and its intercept on the $\log_{10}$ (rate) axis. In Fig. 2, as $n = 2.15$, the reaction proceeds with second order kinetics and rate constant $k = 8.31 \times 10^{-5}$ L mol^{-1} s^{-1}. For the other two substrates $n \approx 2$ with rate constants 1.25×10^{-4} and 5.24×10^{-5} L mol^{-1} s^{-1} respectively (see supplementary material for details).

4. Conclusions

In conclusion, I_2-TEMPO serves as an efficient oxidizing agent for the in situ generation of aldehyde for the one-pot synthesis of amides form alcohols catalyzed by $FeCl_3$. Moreover the reactions are selective and no by-product formation is observed. Various aromatic, hetero aromatic, aliphatic, and allylic alcohols tolerate the reaction condition with the formation of the corresponding amides in good yield. Kinetic studies indicate that the reaction follows second order kinetics. Overall, a simple, general and practical one-pot protocol for the conversion of alcohols to amides is described.

5. Experimental

5.1. General consideration

All the reagents were purchased from Aldrich and used as received. All the solvents were purchased from Ranchem, India and purified using standard methods. The products were characterized by recording ^1H, ^{13}C NMR and ESI-MS by using a Bruker Avance 400 MHz instrument and Jeol JMS GC-Mate II instrument. HPLC analysis was done with Waters HPLC instrument fitted with Waters 515 pump and Waters 2487 dual-wavelength absorbance detector.

5.2. Typical experimental procedure

To a stirred solution of alcohol (1 mmol) in ethylenedichloride (3 mL) was added I_2 (507 mg, 2 mmol) and TEMPO (15 mg, 0.1 mmol) followed by K_2CO_3 (414 mg, 3 mmol), $NH_2OH{\bullet}HCl$ (69 mg, 1 eq.) and anhydrous $FeCl_3$ (16 mg, 10 mol%) and the reaction mixture was heated to 90 °C for the appropriate time. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled and was quenched with aqueous solution of sodium sulfite and then the organic layer was extracted in EtOAc. The organic layer was dried over sodium sulfate and evaporated, followed by flash column purification of the crude to obtain the pure product.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2012.04.027.

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