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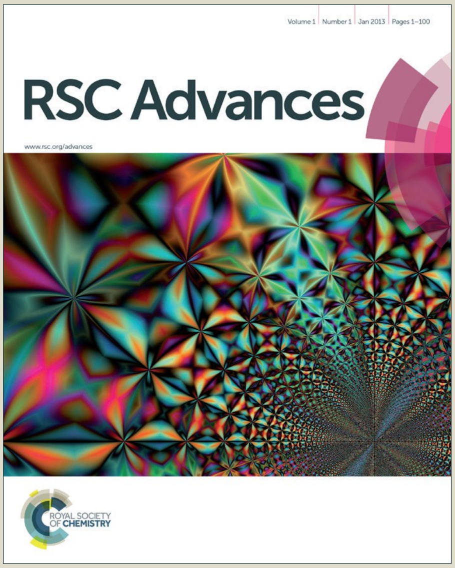

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Copper-catalyzed tandem reaction in ionic liquid: an efficient reusable catalyst and solvent media for the synthesis of fused poly hetero cyclic compounds

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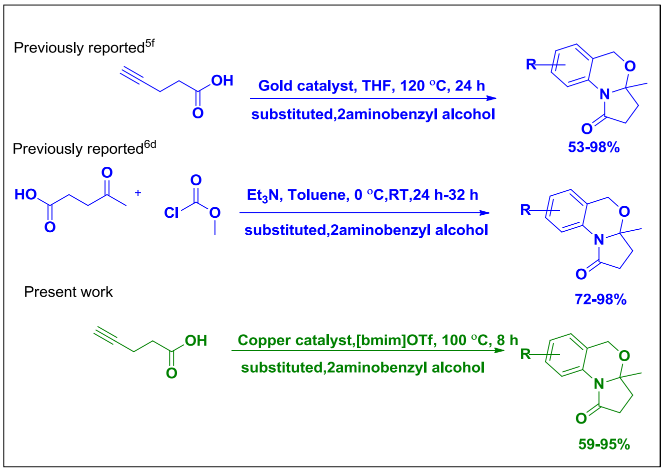
Herein we report Copper catalyzed tandem reaction for the synthesis of therapeutically importantpyrrolo-/pyrido[2,1-b] benzo[d][1,3]oxazin-1-ones from 2-aminobezyl alcohols using alkynoic acids under ligand and base free conditions in presence of green solvent medium [bmim]OTf.The catalyst and solvent were successfully recycled and reused.

Polyheterocyclic molecules are one of most privileged structures in the drug discovery of several leading compounds,which exhibits significant biological properties.[1]Polyheterocyclic compounds particularly containing benzaoxine moieties exhibit potential biological activity by acting as herbicide, plant growth regulators, sedatives and, also exhibit antispasmodic activity with very low toxicity.[2] The research on the synthesis and evaluation of biological properties of angular tricyclicsystemof pyrrolo-/pyrido[2,1-b]benzo[d][1,3]oxazin-1-ones is very limited since the past decades.[3] However, several classical methods were developed to address the above purpose but suffered from disadvantages such as multiple reaction steps, more labor, production of toxic by-products (HBr and CO_2), and high-energy consumption.[7] Domino reactions are the most effective among the synthetic transformation methods, empowering the formation of multiple bonds and cleavage of bond in a single synthetic procedure.[4]The domino reactions reported so far are highly promising in current organic synthesis. Nevertheless, some of these reactions still suffer from limitations such as requirement of expensive metal catalysts (Scheme 1),[5] toxic reagents, usage of volatile organic solvents and additives (Scheme 1),[6] due to which most of the reported methods were unable to follow the green chemistry protocols.[7] Therefore, there is a urgency to develop a new catalytic system for multicomponent reactions using commercially available cost effective catalyst.[8] Herein, cited the reported traditional methods for various Copper catalyzed cascade reactions.[9] Surprisingly, there are no prior examples of Copper-metal-catalyzed routes for the synthesis of pyrrolo-/pyrido[2,1-b]benzo[d][1,3]oxazin-1-ones to promote the domino reactions in ionic liquids. Incontinuation to our research efforts towards the development of Copper catalyzed reactions[10a-b]and ionic liquids in organic synthesis[10c-e]herein we report the one-pot tandem reactions for the synthesis of highly substituted pyrrolo[1,2-a]benzoxazines from 2-amino benzyl alcohols with alkyne-containing carboxylic acids, using $Cu(OAc)_2.H_2O$ in ionic liquid ([bmim]OTf) as solvent at 100 °C with excellent yields (Scheme 1).[11]



Scheme 1: Synthesis of pyrrolo-/pyrido[2,1-b]benzo[d][1,3]oxazin-1-ones

The optimization studies were carried out using 2-amino benzyl alcohol and 4-pentynoic acid as model substrates. The initial set ofexperiments were performed using CuI as metal catalyst, *O*-phenanthrene as ligand in DMF with different bases (K_2CO_3, Cs_2CO_3 and t-BuOK). And the reactions afforded products with lower yields (25-40%) (**Table1,** entries1-3). Next, reactions were performed with other ligands such as ethylene glycol and L-proline underthesimilar conditions which afforded very less yields (19 and 22%) (**Table 1**, entry 4

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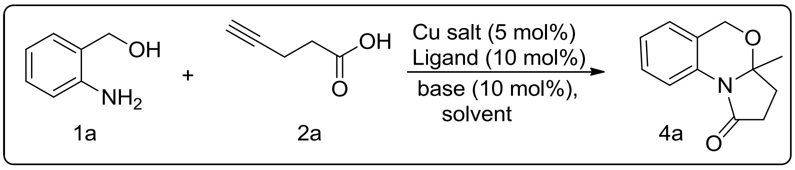
Electronic Supplementary Information (ESI) available

Table 1: Optimization of reaction conditions for the synthesis of fused heterocyclic compounds



Entry	Cu Salt	Ligand	M:L Ratio (mol %)	Base	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]
1	CuI	o-Phen	5:10	K_2CO_3	DMF	120	36	40
2	CuI	o-Phen	5:10	Cs_2CO_3	DMF	120	48	25
3	CuI	o-Phen	5:10	t-BuOK	DMF	120	48	30
4	CuI	ethyleneglycol	5:10	K_2CO_3	DMF	120	36	19
5	CuI	L-proline	5:10	K_2CO_3	DMF	120	48	22
6	Cu_2O	o-Phen	5:10	K_2CO_3	DMF	120	48	31`
7	$CuBr_2$	o-Phen	5:10	K_2CO_3	DMF	120	48	40
8	$Cu(OAc)_2.H_2O$	o-Phen	5:10	K_2CO_3	DMF	120	48	46
9	$Cu(OAc)_2.H_2O$	o-Phen	5:10	K_2CO_3	[bmim]Br	100	20	55
10	$Cu(OAc)_2.H_2O$	-	5:0	-	[bmim]Br	100	20	56
11	$Cu(OAc)_2.H_2O$	-	5:0	-	[bmim]BF_4	100	12	81
12	**$Cu(OAc)_2.H_2O$**	**-**	**5:0**	**-**	**[bmim]OTf**	**100**	**8**	**92**
13	$Cu(OAc)_2.H_2O$	-	2.5:0	-	[bmim]OTf	100	16	83
14	$Cu(OAc)_2.H_2O$	-	10:0	-	[bmim]OTf	100	8	92
15	$Cu(OAc)_2.H_2O$	-	-	-	[bmim]OTf	100	24	-
16	$Cu(OAc)_2.H_2O$	-	5:0	-	[bmim]OTf	RT	36	34
17	$Cu(OAc)_2.H_2O$	-	5:0	-	[bmim]OTf	80	20	83
18	$Cu(OAc)_2.H_2O$	-	5:0	-	[bmim]OTf	120	8	81

Note: Conditions, Substrate 1a (0.5 mmol, 62 mg), 2a (1.25 mmol, 123 mg), solvent (0.5 mL) [a] Isolated yield

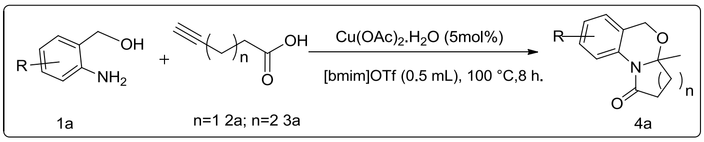
and 5). Further, the effect of different Cu salts such as Cu_2O, $CuBr_2$, and $Cu(OAc)_2.H_2O$ had tested (**Table 1,** entries 6-8).Among all the tested Copper catalysts, $Cu(OAc)_2.H_2O$ was found to be best one and afforded maximum yield (46%) (**Table 1,** entry 8).Further, the effect of solvent has been studied by carrying the same experiment with $Cu(OAc)_2.H_2O$ at 100 °C in[bmim]Br[12]instead of DMF, the yield has been enhanced from 46 to 55% when ionic liquid used as solvent (**Table 1,** entry 9). However similar yield was observed even in the absence of ligand and base. Further, we optimized the reaction using different ionic liquids such as [bmim]BF_4 and [bmim]OTf, as the acidity of the ionic liquid increased, yield (92%) of the product was enhanced (**Table 1**, entries 11 and 12). Among these, [bmim]OTf was found to be best solvent. And 5 mol% of the catalyst was sufficient enough for the complete conversion of the reaction. Further,the optimum quantity of the catalyst (i.e $Cu(OAc)_2.H_2O$) required to obtain maximum yield of the product was studied by varying the mole % of the catalyst (2.5 mol%, 5 mol% and 10 mol%). when we used 2.5 mol%, yield was reduced from 92% to 83% (**Table 1** entry 13),Wherein 10 mol% gave the similaryield (**Table 1** entry 14).However, without catalyst, reaction was not proceeded (**Table 1,** entry 15). Next set of experiments were conducted to study the temperature effect (at room temperature, 80 °C, and 120 °C) and the results reveal that, as we decrease the temperature yield of the reactionalso reduced drastically (**Table 1,** Entries 16 and 17). It should also be noted that the yield has decreased from 92 to 81% when we increase the temperature to 120 °C (**Table 1,** Entry 18).

After successfully optimizing the reaction conditions (**Table 1,** Entry 12), the scope of the study has been extended by employing various substituted 2-aminobenzylalcohols with different alkynoic acids (**Table 2**). The reactions were carried out using various 2-aminobenzyl alcohols with different halogen substituents. The fluoro substituent at meta- and para-position with respect to amino functionality afforded the products in high yields (**Table 2**, entries 1 and 2). The slight variation in the yield could be attributed to the inductive effect of fluorine atom at different positions. Similarly, 2-aminobenzyl alcohols bearing chloro- substituents such as 6-chloro, 5-chloro, 4-chloro (with respect to the alcoholic group) were readily transformed into their respective cyclized products in good to excellent yields (**Table 2**, entries 3-5). The sterically hindered substrates having bromo- and iodo- substituents were also converted into their respective products with moderate to good yields (**Table 2**, entries 6 and 7). Interestingly, it was observed that the substrates with electron withdrawing substituents at 5-F and 5-Cl (with respect to the alcoholic group) gave the high yields (**Table 2**, Entries 2 and 4). Nevertheless, similar trend was not observed in case of substrates with 5-bromo and 5-iodo substituents (**Table 2**, entries 6 and 7) and the steric hindrance could be the reason for the decreasingyield.

Furthermore, it was noticed that the substrates with electron donating groups such as methyl group at 5, 6 position and 4, 5-dimethoxy groups gave products with high yields (**Table 2**, entries 8-10). Then the scope of the reaction was extended to various substituted 2-aminobenzyl alcohols with 5-hexynoic acid under similar optimized conditions. The reactions were successfully took place with both electron releasing as well as deactivating groups and produced the desired products in high yields (entries 11-20).

Majority of the reported method for the synthesis of benzaoxines have been initiated by the transition metal catalysts and the catalytic cycle will be terminated with the help of an acid, which is either internally produced or additionally used.[13a] Here, the reaction might be initiated by $Cu(OAc)_2.H_2O$ where it coordinated with the alkyne moiety of the reactant 4-pentynoic acid, (2a) affording vinyl intermediate **I** *via* loss of one acetic acid molecule. Subsequently, intermediate **I** transformed to enol-lactone **II** (proto-demetalation) with the release of Cu(II) catalyst.[13b] (In order to prove that the intermediate **II** was synthesized and isolated as per the **scheme 3,** further it was subjected [intermediate **II**] to cyclization reaction with 2-aminobenzyl alcohol under optimization reaction conditions and obtained similar yield of the product 4a **scheme 4**).[14]

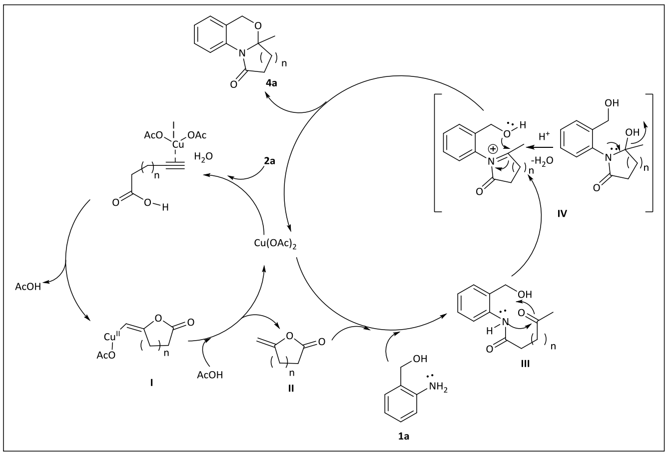
Table 2: Tandem synthesis of fused heterocycles from2-aminobenzyl alcohols



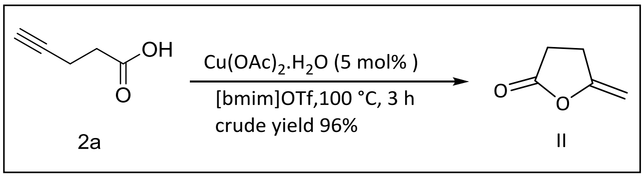
Entry	Substrate	R	n	Product	Yield(%)[a]
1	1b	4-F	2a	4b	81
2	1c	5-F	2a	4c	86
3	1d	6-Cl	2a	4d	72
4	1e	5-Cl	2a	4e	80
5	1f	4-Cl	2a	4f	63
6	1g	5-Br	2a	4g	73
7	1h	5-I	2a	4h	58
8	1i	5-CH_3	2a	4i	95
9	1j	6-CH_3	2a	4j	83
10	1k	4,5-Di-OCH_3	2a	4k	80
11	1l	-	3a	4l	72
12	1m	5-F	3a	4m	78
13	1n	4-F	3a	4n	64
14	1o	6-Cl	3a	4o	63
15	1p	5-Cl	3a	4p	68
16	1q	4-Cl	3a	4q	60
17	1r	5-Br	3a	4r	70
18	1s	5-I	3a	4s	59
19	1t	5-CH_3	3a	4t	76
20	1u	6-CH_3	3a	4u	72

Note: Conditions, Substrate (0.5 mmol), 2a, 3a (1.25 mmol), catalyst (5 mol%, 5 mg), [bmim]OTf, 0.5 mL, 100 °C, 8h.[a] isolated yields.

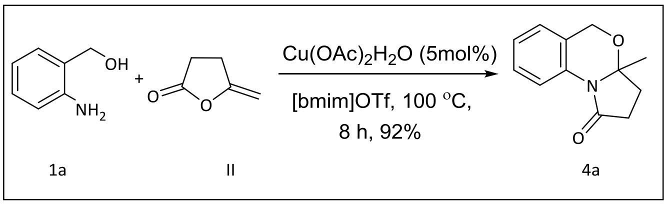
The *in-situ* formed reactive intermediate enol-lactone would undergoes a nucleophilic attack by amino group of the *2*-aminobenzyl alcohol affording ketoamide **III** through intramolecular decyclization. Finally, the ketoamide undergoes cyclization reaction to yield *N*-acyliminium intermediate **IV** in the presence of acidic medium.[6d] Further intermediate **IV** subsequently converted the product 4a.



Scheme 2. Proposed reaction mechanism of copper catalyzed tandem cyclization



Scheme 3. Synthesis of enol lactone II



Scheme4. Synthesis of 4a, using II and 1a, with Cu(OAc)$_2$.H$_2$O

Furthermore, the recyclability and reusability of the developed catalyst and solvent system was tested. It was found that the catalyst as well as solvent, ([bmim]OTf) is recyclable and reusable up to five runs without any significant loss in the catalytic activity. The product was obtained in excellent yields upto five cycles, and results were summarized in table 3.

Table 3: Recyclability experiments for catalyst and Ionic liquid[15]

Run	Time(h)	Yield[a]
1	8	92
2	8	90
3	8	90
4	8	86
5	8	86

Note: Conditions,Substrate (0.5 mmol) 2a, (1.25 mmol), catalyst (5 mol%, 5 mg), [bmim]OTf, 0.5 mL, 100 °C ; [a]Isolated yields

Conclusions

In Summary, we report a facile method for the synthesis of pyrrolo-/pyrido[2,1-b]benzo[d][1,3]oxazin-1-ones *via* Cu catalysed tandem cyclization in green reaction medium. Advantages of this developed method are:

- Offers a convenient, inexpensive, recyclable and reusable catalyst for the preparation of *N*-containing poly heterocyclic compounds using commercially available reagents
- The synthetic strategy follow the formation of two new C-N bonds and a C-O bond by using two simple starting materials
- Target molecules were achieved without formation of any by-products in the reaction mixture

Currently, our group is involved in exploring the additional aspects of developed catalytic system.

Acknowledgment

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Supplementary material is available for this article

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11.**General procedure for 3a-methyl-2,3,3a,5-tetrahydro-1H-benzo[d]pyrrolo[2,1-b][1,3]oxazin-1-one.**

A sealed tube was charged with1.25 mmol (123 mg) of 4-pentynoic acid, 0.5 mL of [bmim]OTf and $Cu(OAc)_2.H_2O$ (5mol%,5 mg). After stirring the above solution for 15min. at room temperature, *2*-aminobenzyl alcohol 0.5mmol (62 mg) was added to the reaction vial and sealed. The reaction mixture was stirred in an oil bath maintained at 100 °C until the completion of reaction. After the completion of reaction, 5mL of water and ethyl acetate were added to the reaction mixture and combined layers were filtered through celite bed and washed with minimum amount of ethyl acetate. The organic layers were separated and concentrated under the reduced pressure. The residue was purified by column chromatography with hexane and ethyl acetate as eluent in a ratio of 4:1 to afford compound 4a with 92%(94.2mg)yield. The aqueous layer was evaporated and dried under vacuum at 70°C for 20 minutes affording the mixture of ionic liquid and catalyst which were further reused for next cycle of experiments.

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14. **General procedure for 5-methylenedihydrofuran-2(3H)-one (enol-lactone).**Charged with 4-pentynoic acid 1.25 mmol (123 mg) in a sealed tube with 0.5 mL of [bmim]OTf as solvent,5 mol% (5mg) of Copper acetate monohydrate withrespect to 4-pentynoic acid was added and the reaction mixture was heated to 100 °C for three hours. Reaction was monitored for its completion, the product was extracted with diethyl ether (3x 5mL) and the combined organic extracts were distilled under vacuum to get crude product (**II**) (118mg) 96%. Subsequently used for the reaction without further purification. The characterization details areavailable in the supporting information.

15. **General procedure for Recyclability of3a-methyl-2, 3, 3a, 5-tetrahydro-1H-benzo[d]pyrrolo[2,1-b][1,3]oxazin-1-one**

After the completion of reaction, 5mL of water and ethyl acetate were added to the reaction mixture and the product was isolated as per above procedure. The aqueous layer was evaporated and dried under vacuum at 70°C for 20 minutes affording the mixture of ionic liquid and catalyst, which was reused for next cycle of experiments.

Graphical Abstract

Copper-catalyzed tandem reaction in ionic liquid: an efficient reusable catalyst and solvent media for the synthesis of fused poly hetero cyclic compounds

Shivaji Naidu and Sabbasani Rajasekhara Reddy*