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One-pot, three-component synthesis of 1-amidomethyl-imidazo[1,2-*a*]pyridines catalyzed by ytterbium triflate

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ABSTRACT

A straightforward method has been developed for the synthesis of 1-amidomethyl-imidazo[1,2-*a*]pyridines by $Yb(OTf)_3$ catalyzed three-component reaction of aldehydes, acetamide, and imidazo[1,2-*a*]pyridines. A series of substituted 3-substituted imidazo[1,2-*a*]pyridines were synthesized in moderate to good yield (21–74%) under mild reaction condition and the catalyst was recycled for four cycles.

Imidazo[1,2-*a*]pyridines are important biologically and pharmaceutically active heterocyclic compounds. They have received considerable attention in the field of pharmaceutical industry owing to their broad range of biological activities. Imidazo[1,2-*a*]pyridine derivatives have been studied for different therapeutic classes such as antifungal,[1] antibacterial,[2] antiviral,[3] anti-rhinoviral,[4] CDK inhibition,[5] aromatase inhibition,[6] K^+-stimulated ATPase inhibition,[7] ligands for peripheral benzodiazepine (PBD) receptors,[8] and β-amyloid (Aβ) aggregate,[9] bradykinin B2 receptor antagonists.[10] Imidazo[1,2-*a*]pyridine nucleus is also core structure of several drug formulations such as alpidem, nicopidem, saripidem, zolimidine, zolpidem, and olprinone, which are presently available in market (Fig. 1).

In recent years multicomponent reactions (MCR) have emerged as a powerful tool in combinatorial chemistry for diversity oriented synthesis of small sized organic compounds of pharmaceutical interest.[11] These reactions offer significant advantages over linear-type conventional synthesis. They retain majority of the atoms of starting materials and thus provide high atom economy and E factor. In addition to the low cost, reduction in overall reaction time and operational simplicity are the other advantages of MCR. Over the past decades, rare earth metals have been used in the diversity of organic transformations as catalysts, especially lanthanide triflates function as efficient Lewis acid catalysts.[12] Moisture insensitiveness, stability, high catalytic activity, and reusability without much loss of activity are distinctive features of metal triflates. From environmental and efficiency point of view lanthanide triflates have become highly attractive Lewis acid catalysts for various chemical reactions. In continuation of our efforts to develop novel reaction methodologies using $Yb(OTf)_3$[13] herein, we report a straightforward and practical $Yb(OTf)_3$ catalyzed one-pot, three-component method for the synthesis of 1-amidomethyl-imidazo[1,2-*a*]pyridines (Scheme 1). Recently, Chaubet et al. have reported the synthesis of polysubstituted 2-amino-1,3-thiazoles via tandem aza-Friedel–Crafts reaction/Hantzsch cyclization.[14] They have achieved *N*-[(aryl)(2-alkyl/arylimidazo[1,2-*a*]pyridin-3-yl)-methyl]thiourea via multicomponent reaction of 2-methylimidazo[1,2-*a*]pyridine, aldehyde and thiourea using $TiCl_4$ or thiamine·HCl as catalyst. To the best of our knowledge, this is the first report on one-pot synthesis 1-amidomethyl-imidazo[1,2-*a*]pyridines (**4**).

Synthesis of imidazo[1,2-*a*]pyridine derivatives (**1a**–**e**) was achieved by reacting appropriately substituted α-bromoacetophenone with 2-aminopyridines.[15] To optimize the reaction conditions for the synthesis of 1-amidomethyl-imidazo[1,2-*a*]pyridines (**4**), initially we attempted condensation of 2-*p*-tolyl-1*H*-imidazo[1,2-*a*]pyridine (**1a**), 4-chloro-benzaldehyde (**2a′**), and acetamide (**3**) using various solvents in the presence of $Yb(OTf)_3$ (Table 1). Two new spots were observed on TLC and the ratio of these spots varied with solvents (Table 1). From ^1H & ^{13}C NMR, IR, and mass data, it was clear that polar spot (by TLC) is expected *N*-((4-chlorophenyl)(2-*p*-toly-l*H*-imidazo[1,2-*a*]pyridin-3-yl)methyl)acetamide (**4aa′**) and non polar one is *bis*(imidazo[1,2-a]pyridine) (**5aa′**).

The structure of (**4aa′**) and **5aa′** was confirmed by ^1H NMR, ^{13}C NMR, and mass data. The ESI-MS spectrum of **4aa′** displayed a peak

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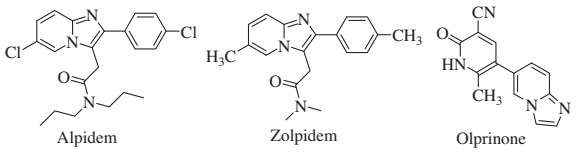
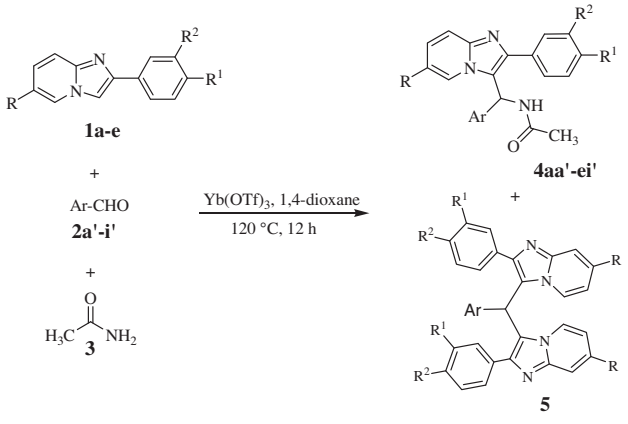


Figure 1. Structure of some imidazo[1,2-*a*] pyridine drug molecules.



1a $R_1 = CH_3$, $R_2 = R = H$
1b $R_1 = OCH3$, $R_2 = R = H$
1c $R_1 = H$, $R_2 = NO_2$, $R = H$
1d $R_1 = Cl$, $R_2 = H$, $R = H$
1e $R_1 = Cl$, $R_2 = H$, $R = Br$

2a' Ar = 4-ClC_6H_4
2b' Ar = 4-$OCH_3C_6H_4$
2c' Ar = 3-$OCH_3C_6H_4$
2d' Ar = 3-OCH_3, 4-$OCH_3C_6H_3$
2e' Ar = C_6H_5
2f' Ar = 3-$NO_2C_6H_4$
2g' Ar = 4-$NO_2C_6H_4$
2h' Ar = 3-Indolyl
2i' Ar = 2-Thiophenyl

Scheme 1. Synthesis of 1-amidomethylimidazo[1,2-*a*]pyridines (**4**) using $Yb(OTf)_3$ as catalyst.

Table 1
Optimization of the reaction conditions[a]

Entry	Solvent	Temp (°C)	Time (h)	Yield[b,c] (%)
1	Toluene	100	15	41 (30)
2	DMF	100	15	44 (25)
3	H_2O	100	15	(10)[d]
4	1,4-Dioxane	100	15	56 (15)
5	1,4-Dioxane	120	12	72 (15)
6	[bmim][BF_4]	120	12	27 (10)
7	[bmim][PF_6]	120	12	75 (5)
8	[bmim][Br]	120	12	28 (5)

[a] Reagents and conditions: **1a** (1 equiv), **2a′** (1 equiv), **3** (1.5 equiv), $Yb(OTf)_3$ (20 mol %).
[b] Isolated yield.
[c] In parenthesis yield of *bis*(imidazo[1,2-*a*]pyridine).
[d] No desired product formed.

at *m*/*z* 389.9 for $[M+H]^+$ ion and a peak at 1682 cm^{-1} was observed for amidic C=O stretching in the IR spectrum. The ^1H NMR spectrum contained a characteristic doublet at δ ~9.17 (d, J = 7.8 Hz, 1H) for amide –NH and a doublet at δ ~6.79 (d, J = 7.8 Hz, 1H) for –CH attached to amide. A peak appeared at δ 170.11 ppm in ^{13}C NMR for C=O of acetamide group along with other carbons of **4aa′** (see Supplementary data). These spectral data are consistent with the structure of **4aa′**. ^1H NMR of compound **5aa′** contained a characteristic singlet at δ ~6.65 ppm and displayed an ion at *m*/*z* 539.2 for $[M+H]^+$ ion in ESI-MS. These spectral data are consistent with the structure of **5aa′**.

To study the effect of solvent on the reaction, we performed the model reaction in different solvents such as 1,4-dioxane, DMF, toluene, water, [bmim][BF_4], [bmim][PF_6], and [bmim][Br]. Among all solvents, [bmim][PF_6] gave best yield of **4aa′** (75%) (Table 1, entry 7). The product was not soluble in non polar solvents such as diethyl ether and thus we were not able to extract it from [bmim][PF_6]. We tried regular water/ethyl acetate work-up, but [bmim][PF_6] is soluble in ethyl acetate and not in water. Lastly, we performed column chromatography of the reaction mass, but in this case also we could not remove ionic liquid completely from the product. Recrystallization using dichloromethane was found to be good method for the removal of ionic liquid but recovery of the product was low. Thus, we selected 1,4-dioxane as solvent of choice for this reaction although it gave relatively lower yield of **4aa′** (72%) than that of [bmim][PF_6].

Table 2
Optimization of different catalysts[a]

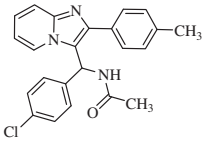
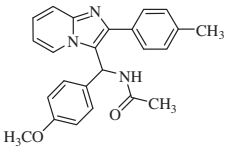
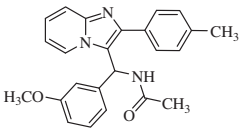
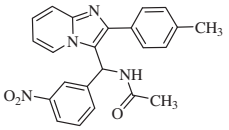
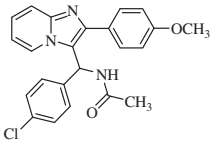
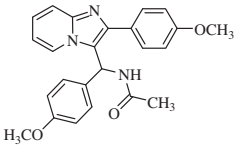
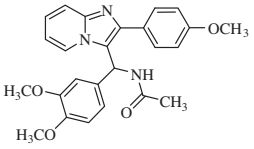
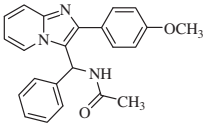
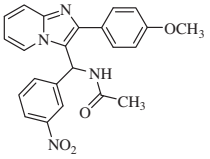
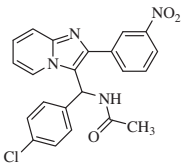
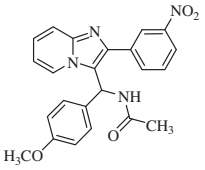
Sr. No.	Catalyst	Catalyst (mol %)	Time (h)	Yield[b] (%)
1	—	—	24	—[c]
2	$Yb(OTf)_3$	20	12	72
3	$Yb(OTf)_3$	10	12	54
4	$Yb(OTf)_3$	5	12	45
5	Mont. K-10	5	15	28
6	AgOTf	20	15	46
7	*p*-TSA	20	12	65
8	$Cu(OTf)_2$	20	15	36
9	$Sc(OTf)_3$	20	15	24
10	$Er(OTf)_3$	20	15	34
11	$Zn(OTf)_2$	20	15	25
12	$La(OTf)_3$	20	15	54

[a] Reagents and conditions: **1a** (1 equiv), **2a′** (1 equiv), **3** (1.5 equiv), 1,4-dioxane (5 mL), 120 °C.
[b] Isolated yield.
[c] No desired product formed.

To find the best catalyst, we screened the model reaction in 1,4-dioxane at standardized condition using different acidic catalysts (Table 2). While there was no conversion observed when the reaction was performed without any catalyst (Table 2, entry 1), other metal triflates such as AgOTf, $Cu(OTf)_2$, $Sc(OTf)_3$, $Er(OTf)_3$, and $Zn(OTf)_2$ gave poor yield of **4aa′**. It is worthy to mention that in all the cases the reaction was incomplete with starting materials remaining in the reaction mixture. Among all metal triflates, $Yb(OTf)_3$ gave highest yield of **4aa′** (72%) whereas *p*-TSA resulted in 65% of **4aa′** among other acidic catalysts used (Table 2, entry 5). The high catalytic activity of $Yb(OTf)_3$ could be explained by the fact that Yb^{+3} is the hardest cation and therefore the most oxophilic, due to its smaller ionic radius, so it can coordinate with oxygen atom of C=O group in aldehyde to make it more electrophilic, leading to the enhancement of rate of reaction. The variation in the loading of the catalyst also affected the yield of **4aa′**. When 5, 10, and 20 mol % of $Yb(OTf)_3$ was used for the model reaction under standardized reaction condition it resulted in 45%, 54%, and 72% yields of **4aa′**, respectively. Further increase in the catalyst loading did not improve the yield of **4aa′**.

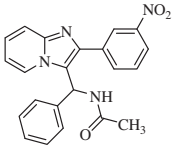
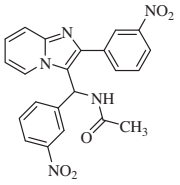
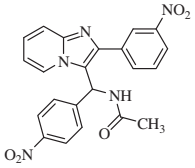
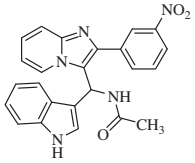
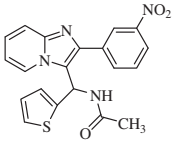
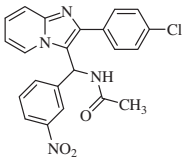
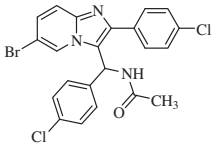
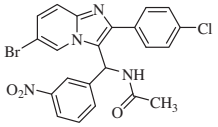
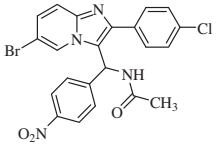
In order to investigate the generality of the reaction, we applied this strategy to various substrates having both electron donating and electron withdrawing groups. The results are summarized in Table 3. The substituent on C-2 phenyl ring of imidazo[1,2-*a*]pyridine (**1**) has predominant effect on product formation. If the substituent is an electron releasing group it decreases the yield of **4** and enhances the yield of **5**. It may be due to the fact that presence of electron rich aryl group at C-2 position increases electron density on the imidazo[1,2-*a*]pyridine nucleus and makes it more nucleophilic to attack on intermediate **6**. In contrast, when the substituent is an electron withdrawing group such as nitro, it gives better yield of **4**. This again may be due to decreased nucleophilicity of the nucleus of imidazo[1,2-*a*]pyridine. Similarly, it was found that aldehydes with electron donating groups resulted in lower yields of **4** as compared to the aldehydes having electron withdrawing groups.

Table 3
Synthesis of 1-amidomethyl-imidazo[1,2-*a*]pyridines using $Yb(OTf)_3$[a,16]

Entry	R^1	R^2	R	Ar	Product[b] (4)		% Yield[c]
1	4-CH_3	H	H	4-ClC_6H_4		**4aa′**	72[d]
2	4-CH_3	H	H	4-$CH_3OC_6H_4$		**4ab′**	36
3	4-CH_3	H	H	3-$CH_3OC_6H_4$		**4ac′**	33
4	4-CH_3	H	H	3-$NO_2C_6H_4$		**4af′**	28
5	4-OCH_3	H	H	4-ClC_6H_4		**4ba′**	62
6	4-OCH_3	H	H	4-$CH_3OC_6H_4$		**4bb′**	49
7	4-OCH_3	H	H	3,4-$(CH_3O)_2C_6H_3$		**4bd′**	39
8	4-OCH_3	H	H	C_6H_5		**4be′**	52
9	4-OCH_3	H	H	3-$NO_2C_6H_4$		**4bf′**	44
10	H	3-NO_2	H	4-ClC_6H_4		**4ca′**	62
11	H	3-NO_2	H	4-$CH_3OC_6H_4$		**4cb′**	59

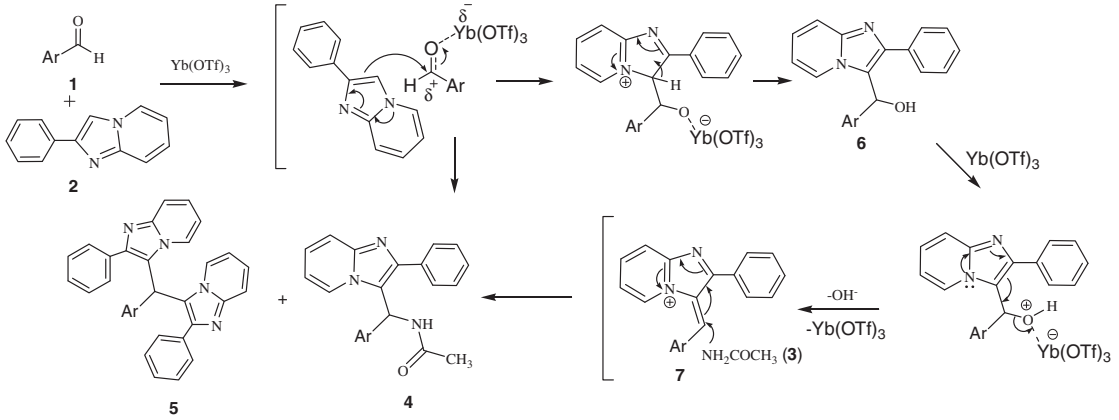
(*continued on next page*)

Table 3 (*continued*)

Entry	R^1	R^2	R	Ar	Product[b] (4)		% Yield[c]
12	H	3-NO_2	H	C_6H_5		**4ce**′	55
13	H	3-NO_2	H	3-$NO_2C_6H_4$		**4cf**′	74
14	H	3-NO_2	H	4-$NO_2C_6H_4$		**4cg**′	65
15	H	3-NO_2	H	C_8H_5N		**4ch**′	39
16	H	3-NO_2	H	C_4H_3S		**4ci**′	29
17	4-Cl	H	H	3-$NO_2C_6H_4$		**4df**′	40
18	4-Cl	H	Br	4-ClC_6H_4		**4ea**′	46
19	4-Cl	H	Br	3-$NO_2C_6H_4$		**4ef**′	30
20	4-Cl	H	Br	4-$NO_2C_6H_4$		**4eg**′	21

[a] Reagents and conditions: compound **1** (1.0 equiv), **2** (1.0 equiv), **3** (1.5 equiv), 1,4-dioxane, 120 °C, 12 h.
[b] All compounds showed satisfactory ^1H NMR, ^{13}C NMR and mass data.
[c] Isolated yield.
[d] Yields for four cycles were 72%, 69%, 68% & 66%, respectively.

As can be seen from Table 3, the method is applicable for different aromatic and heterocyclic aldehydes and substituted imidazo[1,2-*a*]pyridines. It is also noteworthy to mention that when 6-bromo-imidazo[1,2-*a*]pyridine was used, low yield of the corresponding 3-substituted derivative of **4** was obtained (Table 3, compare entries 17 & 19). However, there was no corresponding *bis*(imidazo[1,2-*a*]pyridines) derivative in this case. This might be because of the decreased nucleophilicity of imidazo[1,2-*a*]pyridine nucleus due to the presence of bromo group. To further increase the diversity in the product, we performed the reaction with benzamide instead of acetamide but we did not observe the desired product, instead *bis*(imidazo[1,2-*a*]pyridine) derivative was observed, this may be because of poor nucleophilicity of benzamide compared to acetamide.



Scheme 2. Plausible mechanism for synthesis of 1-amidomethyl-imidazo[1,2-*a*]pyridines.

Based on the product distribution, a plausible reaction mechanism is proposed in Scheme 2. It is expected that in the presence of Lewis acid, aldehyde (**1**) gets activated and is attacked by imidazo[1,2-*a*]pyridine at C-3 position to give aryl alcohol intermediate **6**. Apparently, the C-3 position is the most electron-rich position in imidazo[1,2-*a*]pyridine nucleus and thus electrophilic substitution reaction takes place at this position selectively. This intermediate **6** then generates an ion **7** by losing OH in presence of $Yb(OTf)_3$ which is then attacked by the nitrogen of acetamide to give the desired product **4**. However, if the intermediate **7** is attacked by another molecule of imidazo[1,2-*a*]pyridine then it leads to *bis*(imidazo[1,2-*a*]pyridine) derivative **5**. To further confirm the structure of **5** we reacted imidazo[1,2-*a*]pyridine (**1a**) and aldehyde (**2a′**) in the absence of acetamide under similar condition and as expected we got the compound **5aa′**.

We subsequently investigated the possibility of recycling of the catalyst. After first cycle for model reaction, the product was extracted by ethyl acetate and $Yb(OTf)_3$ was dried on rotatory evaporator under vacuum for subsequent reactions. The recovered $Yb(OTf)_3$ was charged with fresh lot of aldehyde, acetamide, imidazopyridine, and the reaction was performed under same conditions. After completion of reaction the product was extracted. The above sequence was repeated four times to give **4a** in good yields (72%, 69%, 68% & 66%) without much loss in catalytic activity of $Yb(OTf)_3$.

In summary, we have developed a straightforward method for the synthesis of 1-amidomethyl-imidazo[1,2-*a*]pyridines by $Yb(OTf)_3$ catalyzed three-component reaction of aldehydes, acetamide, imidazopyridine. A series of 3-substituted imidazo[1,2-*a*]pyridines have been synthesized in excellent yield (21–74%). The catalyst can be recycled upto four cycles without much decrease in catalytic activity. Environment friendly catalyst and good yield are the advantages of the method. To the best of our knowledge this is the first report on synthesis of 1-amidomethyl-imidazo[1,2-*a*]pyridines. We are evaluating c-Src kinase inhibition and anticancer activity of **4**, which will be published elsewhere.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.121.

References and notes

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16. *General procedure for the synthesis of* ***4****:* Ytterbium triflate (78 mg, 0.125 mmol, 20 mol %) was added to a 10 mL round bottom flask containing imidazo[1,2-*a*]pyridine (**1**) (0.627 mmol, 1.0 equiv), aldehyde (**2**) (0.627 mmol, 1.0 equiv) and acetamide (**3**) (56 mg, 0.940 mmol, 1.5 equiv) in 1,4-dioxane (3 mL). The reaction mixture was stirred at 120 °C for 12 h. After completion of the reaction, the reaction mixture was allowed to cool to room temperature and the volatiles were evaporated. The residue was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. Crude compound was purified by column chromatography using dichloromethane/methanol (96:4 v/v) as eluent to get compound **4**.