Copper-Catalyzed Four-component Synthesis of Imidazo[1,2-*a*]pyridines *via* Sequential Reductive Amination, Condensation, and Cyclization

Emad Allahabadi, Sina Ebrahimi, Mehdi Soheilizad, Mehdi Khoshneviszadeh, Mohammad Mahdavi

PII: S0040-4039(16)31562-3
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.11.081
Reference: TETL 48367

To appear in: *Tetrahedron Letters*

Received Date: 26 August 2016
Revised Date: 4 November 2016
Accepted Date: 18 November 2016

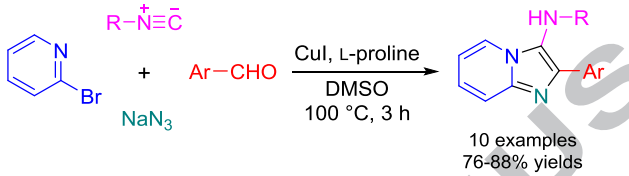
Please cite this article as: Allahabadi, E., Ebrahimi, S., Soheilizad, M., Khoshneviszadeh, M., Mahdavi, M., Copper-Catalyzed Four-component Synthesis of Imidazo[1,2-*a*]pyridines *via* Sequential Reductive Amination, Condensation, and Cyclization, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.11.081

Graphical Abstract

Copper-Catalyzed Four-component Synthesis of Imidazo[1,2-*a*]pyridines *via* Sequential Reductive Amination, Condensation and Cyclization

Leave this area blank for abstract info.

Emad Allahabadi, Sina Ebrahimi, Mehdi Soheilizad, Mehdi Khoshneviszadeh, Mohammad Mahdavi



Copper-Catalyzed Four-component Synthesis of Imidazo[1,2-*a*]pyridines *via* Sequential Reductive Amination, Condensation, and Cyclization

Emad Allahabadi,[a] Sina Ebrahimi,[a] Mehdi Soheilizad,[b] Mehdi Khoshneviszadeh,[c] Mohammad Mahdavi*[a]

[a] *Drug Design and Development Research Center, Tehran University of Medical Science, Tehran, Iran, Tehran 14176, Iran*

[b]*School of Chemistry, College of Science, University of Tehran, PO Box 14155-6455, Tehran, Iran*

[c]*Medicinal & Natural Products Chemistry Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*

Abstract: A novel and efficient four-component approach for the synthesis of 2,3-disubstituted imidazo[1,2-*a*]pyridines is described. The copper-catalyzed reductive amination of 2-bromopyridine by sodium azide followed by sequential condensation and cyclization with aldehydes and isocyanides afforded the corresponding imidazo[1,2-*a*]pyridines in good yields.

Keywords: Copper-catalyzed, Imidazo[1,2-*a*]pyridine, Reductive amination, 2-Bromopyridine, Aldehyde, Isocyanide, Sodium azide.

*Corresponding author: Tel.: +98-21-66954708; fax: +98-21-66461178; e-mail: Mahdavi_chem@yahoo.com

Introduction

The imidazo[1,2-*a*]pyridine core is an important biologically active, nitrogen-containing heterocyclic scaffold due to its extensive applications in medicinal chemistry and material science.[1] Antibacterial,[2] antifungal,[3] antiviral,[4] antineoplastic,[5] antitumor[6] and antiulcer[7] properties have been reported for imidazo[1,2-*a*]pyridine derivatives. Additionally, the imidazo[1,2-*a*]pyridine subunit has been widely used in medicinal chemistry. For example, zolpidem, zolimidine, and alpidem are commercially available drugs based on the imidazo[1,2-*a*]pyridine scaffold for use as sedative, anxiolytic and gastroprotective agents, respectively (Fig. 1).

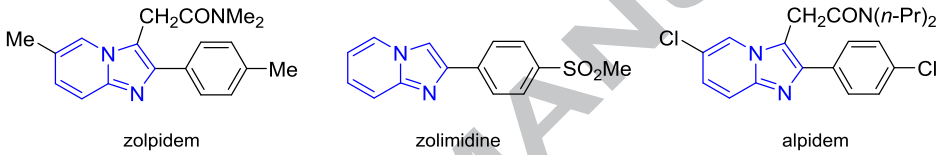
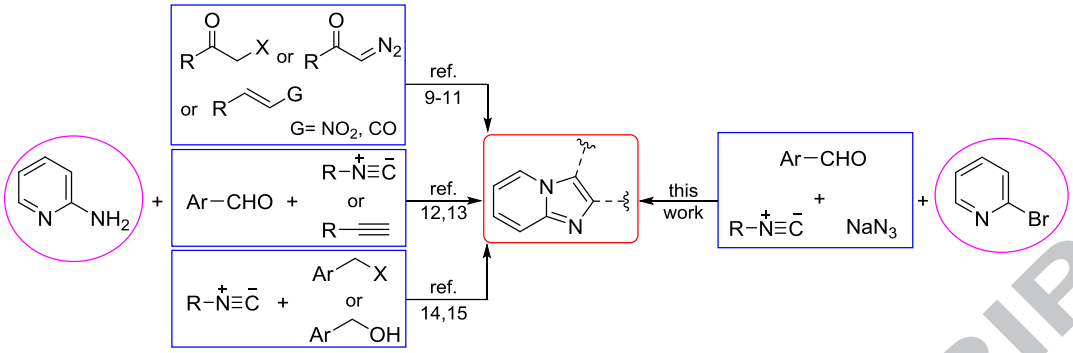


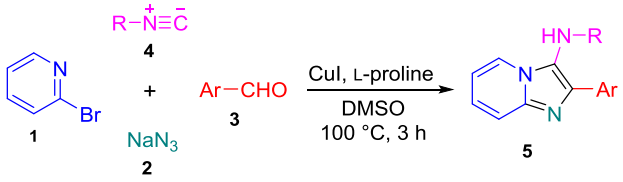
Figure 1. Representative commercially available imidazo[1,2-*a*]pyridine-based drugs

Because of their pharmacological importance, the development of novel synthetic approaches for the preparation of imidazo[1,2-*a*]pyridine derivatives has gained significant attention, and as a result, many synthetic routes for this valuable scaffold have been reported in the literature.[8] Typical approaches include the heterocyclization of 2-aminopyridine with α-haloketones,[9] α,β-unsaturated carbonyl compounds[10] or α-diazoketones.[11] Also, several three-component condensation reactions have been reported including the coupling reaction of 2-aminopyridine and aldehydes with isocyanides[12] or alkynes,[13] and the condensation between 2-aminopyridine, isocyanides, and benzyl halides[14] or benzyl alcohols[15] (Scheme 1).



Scheme 1. General approaches for the synthesis of imidazo[1,2-*a*]pyridines

Recently, the synthesis of fused *N*-heterocycles using the copper-catalyzed reductive amination of aryl halides by sodium azide as a convenient nitrogen source, has been widely applied in organic synthesis.[16] Due to the pharmacological value of imidazo[1,2-*a*]pyridines, and in continuation of our research regarding the preparation of nitrogen-containing compounds,[17] herein, we report a novel and efficient approach for the synthesis of imidazo[1,2-*a*]pyridines **5**, *via* the four-component condensation of 2-bromopyridine **1**, sodium azide **2**, aldehydes **3**, and isocyanides **4**, in the present of CuI as a catalyst and L-proline as a ligand, in DMSO at 100 °C (Scheme 2). To the best of our knowledge, this is the first report on the synthesis of imidazo[1,2-*a*]pyridines using 2-bromopyridine instead of 2-aminopyridine.



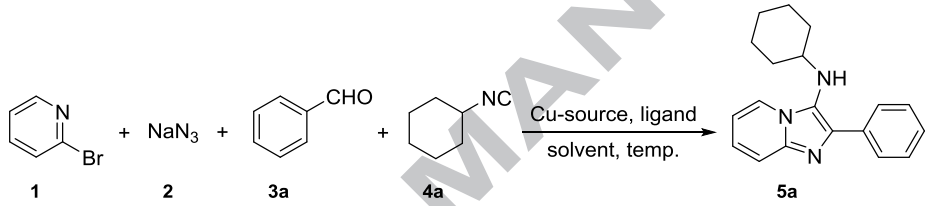
Scheme 2. Four-component synthesis of imidazo[1,2-*a*]pyridines

Result and Discussion

We began with the model reaction of 2-bromopyridine **1**, sodium azide **2**, benzaldehyde **3a**, and cyclohexyl isocyanide **4a**, in the presence of CuI, in dry DMSO at 100 ºC, which led to the isolation of product **5a** in 33% yield (Table 1, entry 1). In order to improve the yield of **5a**,

various experimental conditions were screened by varying the ligands, copper catalysts, solvents and temperatures (Table 1). Firstly, screening the ligands 1,10-phenanthroline, pipecolic acid and L-proline (Entries 2−4), revealed that the yield significantly increased in the presence of a ligand. Among them, L-proline was found to be the most suitable ligand (Entry 4). Various copper salts including CuBr, CuCl, $CuCl_2$ and Cu_2O (Entries 5−8), were screened and the highest yield was obtained with CuI (compare entries 4 and 5−8). Several solvents including DMF, 1,4-dioxane and toluene were tested (Entries 9−11), where DMSO proved to be the most effective (compare entries 4 and 9−11). Finally, decreasing or increasing the reaction temperature did not lead to any further improvement in yield (Entries 12 and 13).

Table 1. Optimization of conditions for the four-component synthesis of **5a**[a]



1 2 3a 4a 5a

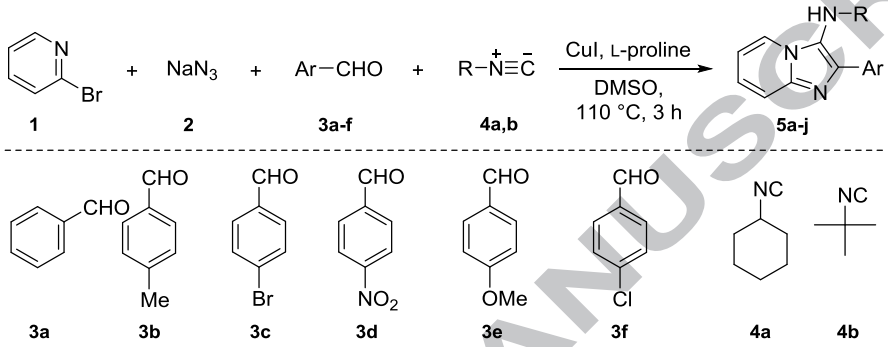
Entry	Catalyst	Ligand	Solvent	Temp. (ºC)	Yield (%)[b]
1	CuI	–	DMSO	100	33
2	CuI	1,10-Phenanthroline	DMSO	100	58
3	CuI	Pipecolic acid	DMSO	100	64
4	**CuI**	**L-proline**	**DMSO**	**100**	**78**
5	CuBr	L-proline	DMSO	100	70
6	CuCl	L-proline	DMSO	100	66
7	$CuCl_2$	L-proline	DMSO	100	62
8	Cu_2O	L-proline	DMSO	100	52
9	CuI	L-proline	DMF	100	60
10	CuI	L-proline	1,4-Dioxane	100	10
11	CuI	L-proline	Toluene	100	5
12	CuI	L-proline	DMSO	80	63
13	CuI	L-proline	DMSO	120	69

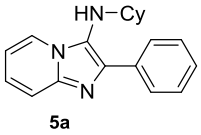
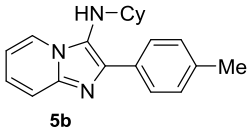
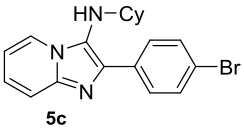
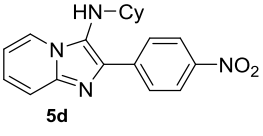
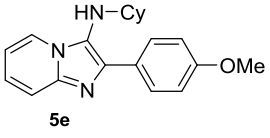
[a] Reagents and conditions: **1** (1 mmol), **2** (2 mmol), **3a** (1 mmol), **4a** (1 mmol), Cu-source (0.05 mmol), ligand (0.1 mmol), solvent (3 mL), 3 h.

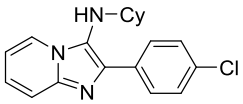
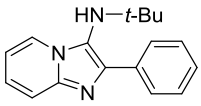
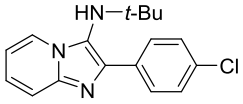
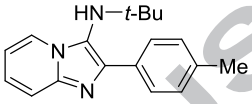
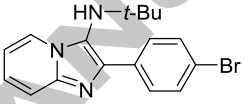
[b] Isolated yield.

With the optimized conditions for the synthesis of imidazo[1,2-*a*]pyridines in hand, we then investigated the substrates scope. Aromatic aldehydes with either electron-withdrawing or electron-donating substituents, regardless of their position on the phenyl ring, provided the corresponding products **5** in good yields (Table 2).[18]

Table 2. Substrate scope for the four-component synthesis of imidazo[1,2-*a*]pyridines[a]



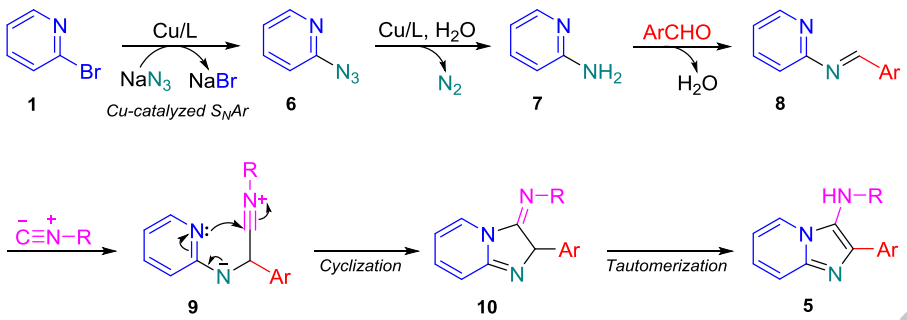
Entry	Aldehyde	Isocyanide	Product	Yield (%)[b]
1	**3a**	**4a**	 **5a**	78
2	**3b**	**4a**	 **5b**	81
3	**3c**	**4a**	 **5c**	79
4	**3d**	**4a**	 **5d**	82
5	**3e**	**4a**	 **5e**	76

6	**3f**	**4a**	 **5f**	81
7	**3a**	**4b**	 **5g**	88
8	**3f**	**4b**	 **5h**	84
9	**3b**	**4b**	 **5i**	84
10	**3c**	**4b**	 **5j**	85

[a] Reagents and conditions: **1** (1 mmol), **2** (2 mmol), **3** (1 mmol), **4** (1 mmol), CuI (0.05 mmol), L-proline (0.1 mmol), DMSO (3 mL), 110 °C, 3 h.

[b] Isolated yield.

A plausible mechanism for the formation of imidazo[1,2-*a*]pyridines **5** is illustrated in Scheme 3. Based on recent reports that sodium azide act as an ammonia surrogate to prepare primary amines in the copper-catalyzed reductive amination of aryl halides,[16] it is reasonable to assume that, initially, reductive amination of 2-bromopyridine **1** using sodium azide in the presence of the copper catalyst produced 2-aminopyridine **7**. Subsequently, condensation of 2-aminopyridine **7** with the aldehyde furnishes imine intermediate **8**. Next, nucleophilic addition of the isocyanide to imine **8**, followed by intramolecular cyclization leads to the formation of intermediate **10** which tautomerizes to afford the desired product **5** (Scheme 3).



Scheme 3. Plausible mechanism for the four-component synthesis of imidazo[1,2-*a*]pyridine **5**.

Conclusion

In summary, we report a new and efficient, one-pot, four-component approach for the synthesis of 2,3-disubstituted imidazo[1,2-*a*]pyridines *via* the copper-catalyzed reductive amination of 2-bromopyridine with sodium azide followed by sequential condensation-cyclization with aldehydes and isocyanides. To date, this is the first report on the synthesis of imidazo[1,2-*a*]pyridine using 2-bromopyridine instead of 2-aminopyridine.

Acknowledgement

This research was supported by a grant from Iran National Science Foundation (INSF).

References:

1. (a) Hanson, S. M.; Morlock, E. V.; Satyshur, K. A.; Czajkowski, C. *J. Med. Chem*. **2008**, *51*, 7243; (b) Wiegand, M. H. *Drugs* **2008**, *68*, 2411; (c) Rupert, K. C.; Henry, J. R.; Dodd, J. H.; Wadsworth, S. A.; Cavender, D. E.; Olini, G. C.; Fahmy, B.; Siekierka. J. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 347; (d) Katsura, Y.; Nishino, S.; Inoue, Y.; Tomoi, M.; Takasugi, H. *Chem. Pharm. Bull*. **1992**, *40*, 371; (e) Smirnova, E. N.; Onschenskaya, T. V.; Zvolinskii, V. P.; Nende, D. L. *Fiz. Khim. Poverkhn*. **1988**, 65.

2. Rival, Y.; Grassy G.; Michel, G. *Chem. Pharm. Bull*. **1992**, *40*, 1170.

3. (a) Fisher, M. H.; Lusi, A. *J. Med. Chem*. **1972**, *15*, 982; (b) Rival, Y.; Grassy, G.; Taudou A.; Ecalle, R. *Eur. J. Med. Chem*. **1991**, *26*, 13.

4. (a) Lhassani, M.; Chavignon, O.; Chezal, J. M.; Teulade, J. C.; Chapat, J. P.; Snoeck, R.; Andrei, G.; Balzarini, J.; Clerc, E. D.; Gueiffier, A. *Eur. J. Med. Chem*. **1999**, *34*, 271; (b) Hamdouchi, C.; de Blas, J.; del Prado, M.; Gruber, J.; Heinz B. A.; Vance, L. *J. Med. Chem*. **1999**, *42*, 50.

5. Badaway E.; Kappe, T. *Eur. J. Med. Chem*. **1995**, *30*, 327.

6. Hranjec, M.; Kralj, M.; Piantanida, I.; Sedi, M.; Suman, L.; Pavel K.; Karminski-Zamola, G. *J. Med. Chem*. **2007**, *50*, 5696.

7. Kaminsky J. J.; Doweyko, A. M. *J. Med. Chem*. **1999**, *40*, 427.

8. Bagdi, A. K.; Santra, S.; Monir, K.; Hajra, A. *Chem. Commun*., **2015**, *51*, 1555

9. (a) Fisher, M. H.; Lusi, A. *J. Med. Chem*. **1972**, *15*, 982; (b) Trapani, G.; Franco, M.; Ricciardi, L.; Latrofa, A.; Genchi, G.; Sanna, E.; Tuveri, F.; Cagetti, E.; Biggio, G.; Liso, G. *J. Med. Chem*. **1997**, *40*, 3109; (c) Ponnala, S.; Kumar, S. T.; Bhat, B. A.; Sahu, D. P. *Synthetic Commun*. **2005**, *35*, 901.

10. (a) Yan, R. L.; Yan, H.; Ma, C.; Ren, Z. Y.; Gao, X. A.; Huang, G. S.; Liang, Y. M. *J. Org. Chem*. **2012**, *77*, 2024; (b) Guetzoyan, L.; Nikbin, N.; Baxendale, I. R.; Ley, S. V. *Chem. Sci*. **2013**, *4*, 764; (c) Monir, K.; Bagdi, A. K.; Mishra, S.; Majee, A.; Hajra, A. *Adv. Synth. Catal*. **2014**, *356*, 1105.

11. Yadav, J. S.; Reddy, B. V. S.; Rao, Y. G.; Srinivas, M.; Narsaiah, A. V. *Tetrahedron Lett*. **2007**, *48*, 7717.

12. (a) Groebke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, *6*, 661; (b) Rousseau, A. L.; Matlaba, P.; Parkinson, C. J. *Tetrahedron Lett*. **2007**, *48*, 4079; (c) Adib, M.; Mahdavi, M.; Noghani, M. A.; Mirzaei, P. *Tetrahedron Lett*. **2007**, *48*, 7263; (d) Shaabani, A.; Soleimani, E.; Maleki, A. Tetrahedron Lett. 2006, 47, 3031.

13. (a) Khan A, T.; Basha R.S.;Lai, M . *Tetrahedron Lett*. **2012**, *53*, 2211; (b) Chernyak, N.; Gevorgyan, V. *Angew. Chem. Int. Ed*. **2010**, *49*, 2743; (c) Rassokhina, I. V.; Shirinian, V. Z.; Zavarzin, I. V.; Gevorgyan, V.; Volkova Y. A. *J. Org. Chem*. **2015**, *80*, 11212.

14. Adib, M.; Sheikhi E.; Rezaei, N. *Tetrahedron Lett*. **2011**, *52*, 3191.

15. Ramesha, A. B.; Raghavendra, G. M.; Nandeesh, K. N.; Rangappa, K. S.; Mantelingu, K. *Tetrahedron Lett*. **2013**, *54*, 95.

16. (a) Jia, F. C.; Xu, C.; Zhou, Z. W.; Cai, Q.; Li, D. K.; Wu A. X. *Org. Lett*., **2015**, *17*, 2820; (b) Jia, F.C.; Zhou, Z. W.; Xu, C.; Cai, Q.; Li, D. K.; Wu, A. X. *Org. Lett*., **2015**, *17*,4236; (c) Shindea, M. H.; Kshirsagar, U. A. *RSC Adv*., **2016**, *6*, 52884; (d) Dhiman, S.; Saini, H. K.; Nandwana, N. K.; Kumar, D.; Kumar, A. *RSC Adv*., **2016**, *6*, 23987; (e) Goriya, Y.; Ramana, C. V. *Chem. Commun*. **2014**, *50*, 7790; (f) Goriya, Y.; Ramana, C. V. *Chem. Commun*. **2013**, 49, 6376.

17. (a) Noushini, S.; Mahdavi, M.; Firoozpour, L.; Moghimi, S.; Shafiee, A.; Foroumadi, A. *Tetrahedron*, **2015**, *71*, 6272; (b) Goli-Garmroodi, F.; Omidi, M.; Saeedi, M.; Sarrafzadeh, F.; Rafinejad, A.; Mahdavi, M.; Bardajee, G. R.; Akbarzadeh, T.; Firoozpour, L.; Shafiee, A.; Foroumadi, A. *Tet. Lett*., **2015**, *56*, 743; (c) Rahmani-Nezhad, S.; Safavi, M.; Pordeli, M.; Ardestani, S. K; Khosravani, L.; Pourshojaei, Y.; Mahdavi, M.; Emami, S.; Foroumadi, A.; Shafiee, A. *Eur. J. Med. Chem*. **2014**, *86*, 562; (d) Saeedi, M.; Mahdavi, M.; Foroumadi, A.; Shafiee, A. *Tetrahedron*, **2013**, *69*, 3506; (e) Hosseini-Zare, M. S.; Mahdavi, M.; Saeedi, M.; Asadi, M.; Javanshir, S.; Shafiee, A.; Foroumadi, A. *Tet. Lett*., **2012**, *53*, 3448; (f) Tahghighi, A.; Razmi, S.; Mahdavi. M.; Foroumadi, P.; Ardestani, S. K.; Emami, S.; Kobarfard, F.; Dastmalchi, S.; Shafiee, A.; Foroumadi, A. *Eur. J. Med. Chem*. **2012**, *50*, 124.

18. *General procedure for the preparation of compounds **5a–j**, exemplified with **5a***: A mixture of 2-bromopyridine (1 mmol), NaN_3 (1 mmol), benzaldehyde (1 mmol), cyclohexyl isocyanide (1 mmol), CuI (0.05 mmol) and L-proline (0.1 mmol), in dry DMSO (3 mL) was stirred in a sealed vessel under air for 3 hours at 100 °C. After reaction completion (TLC), the reaction mixture was cooled, quenched with water (20 mL), and extracted with EtOAc (3 × 20 mL). The extract was washed with 30% NaCl solution (V/V), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography using

petroleum ether/ethyl acetate (3:1) as eluent to afford the pure product **5a**. *N-cyclohexyl-2-phenylimidazo[1,2-a]pyridin-3-amine (**5a**)*: m.p. 198–200 °C (lit.[14] 195–197 °C); ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 1.05-1.71 (10H, m), 2.82-2.87 (1H, m), 4.80 (1H, d, *J* = 6.0 Hz), 7.15 (3H, m), 7.20 (2H, d, *J* = 8.0 Hz), 7.44 (3H, m), 8.38 (1H, d, *J* = 7.0 Hz) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 20.8, 28.36, 30.0, 55.6, 110.7, 116.3, 123.6, 123.8, 127.5,128.5, 129.2, 132.5, 136.0, 137.9, 140.9.

Highlights

- A four component has been used to synthesis imidazo[1,2-*a*]pyridines
- The mechanism relies on sequential reductive amination, condensation, and cyclization
- Sodium azide acts as an ammonia surrogate to primary amines in a copper-catalyzed reductive amination of aryl halides