A one-pot stereoselective synthesis of novel polyfunctionalized imidazolidines

Abolfazl Olyaei, Mohsen Karbalaei Karimi, Reza Razeghi

PII: S0040-4039(13)01382-8
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.08.029
Reference: TETL 43391

To appear in: *Tetrahedron Letters*

Received Date: 19 June 2013
Revised Date: 20 July 2013
Accepted Date: 7 August 2013

Please cite this article as: Olyaei, A., Karimi, M.K., Razeghi, R., A one-pot stereoselective synthesis of novel polyfunctionalized imidazolidines, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.08.029

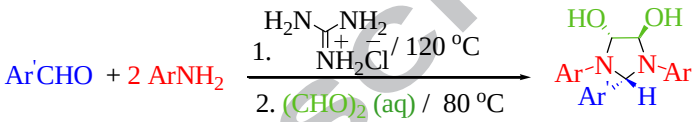
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

A one-pot stereoselective synthesis of novel polyfunctionalized imidazolidines

Abolfazl Olyaei, Mohsen Karbalaei Karimi, Reza Razeghi

Leave this area blank for abstract info.



Tetrahedron Letters
journal homepage: www.elsevier.com

A one-pot stereoselective synthesis of novel polyfunctionalized imidazolidines

Abolfazl Olyaei ∗, Mohsen Karbalaei Karimi, Reza Razeghi

Department of Chemistry, Payame Noor University, PO BOX 19395-3697, Tehran, Iran

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Heteroarylamine
Aldehyde
Imidazolidine
Glyoxal

ABSTRACT

A facile, one-pot stereoselective synthesis of novel *trans*-4,5-dihydroxy-2-aryl-1,3-bis(heteroaryl)imidazolidines is achieved by a cyclocondensation reaction of two equivalents of heteroarylamines with benzaldehyde derivatives, in the presence of guanidinium chloride as a polyfunctional organocatalyst, with aqueous glyoxal to afford the title products. This general protocol provides a wide range of new polyfunctionalized imidazolidines in good to high yields.

The synthesis of imidazolidines through the cyclocondensation of diamines, bisamides and urea derivatives with aqueous glyoxal and other appropriate carbonyl compounds has been the subject of numerous investigations.[1-11] In 1962, Vail and co-workers reported the reaction of various bisamides of the type RCONH-XNHCOR (X = alkylene or substituted alkylene) with glyoxal to produce the desired cyclic compounds.[1] In the case of diamines, most of the reports are limited to ethylenediamine and its derivatives.[2,3] Koppes described the reaction of hexafluorodiaminopropane with glyoxal which led to the formation of 3,3,7,7-tetrakis(trifluoromethyl)-2,4,6,8-tetraazabicyclo[3.3.0]octane. In this reaction, 4,5-dihydroxy-2,2-bis(trifluoromethyl)imidazolidine could not be isolated.[4]

We have previously reported the synthesis of imidazolidines by employing a one-pot reaction using 2-aminopyrimidine or 2-aminopyrazine, aqueous formaldehyde and glyoxal in alcohols, acetonitrile and acetic anhydride under reflux conditions (Figure 1).[12-14] Based on ^{1}H NMR analysis, it was found that *trans*-imidazolidines were obtained selectively in these cyclocondensation reactions.

Imidazolidines, cyclic aminals of pharmacological interest, as well as *N,N′*-dibenzyl-2-arylimidazolidines, *N,N′*-bisaminoalkylimidazolidines, and *N,N′*-dihydroxyphenylimidazolidines have shown fungicidal, antiparasitic, antibacterial, anti-amebic, and antiviral activities.[15,16] They are important building blocks in biologically active compounds, and are carriers of pharmacologically active carbonyl compounds.[17-19] To the best of our knowledge, there are no reports in the literature on the synthesis of these heterocycles.

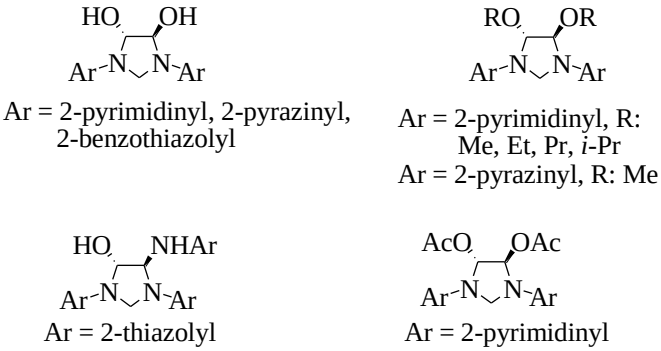
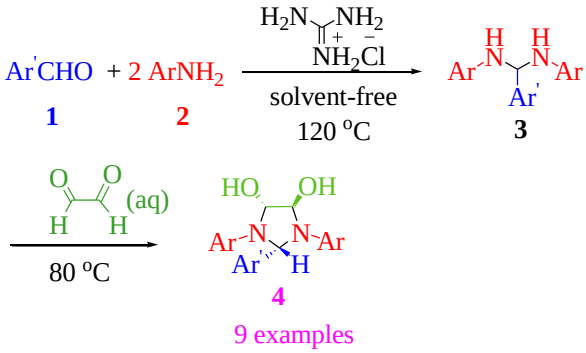


Figure 1. Examples of imidazolidines

In continuation of our research aimed at developing reactions under solvent-free conditions,[20] we report herein an efficient and simple process for the stereoselective synthesis of novel polyfunctionalized imidazolidines via the one-pot reaction of aryl aldehydes **1**, heteroaryl amines **2** and aqueous glyoxal in the presence of guanidine hydrochloride as the catalyst (Scheme 1).

To achieve suitable conditions for the synthesis of the imidazolidines for the first step, the reaction of benzaldehyde (1 mmol), 2-aminopyrimidine (2 mmol) and guanidine hydrochloride (0.1 mmol) was selected as a model system. In the second step, the reaction of the obtained *gem*-diamine (intermediate **3**) with aqueous glyoxal (1 mmol) was investigated. The results indicated that in the first step a temperature of 120 °C, and in the second reaction step a temperature of 80 °C, were effective in terms of the reaction time

∗ Corresponding author. Tel.: +0098-281-2224024; fax: +0098-281-2226400; e-mail: olyaei_a@pnu.ac.ir



Scheme 1. A one-pot, two-step approach for the synthesis of polyfunctionalized imidazolidines **4**

and yield obtained. We also varied the amount of catalyst (5, 7, 10, 12, 15 mol%) and the results revealed that 10 mol% gave a high yield of the product. After optimization, we investigated the use of other aryl aldehydes (4-fluorobenzaldehyde, 4-chlorobenzaldehyde, 2-nitrobenzaldehyde, 3-nitrobenzaldehyde, and 2,4-dichlorobenzaldehyde) (**1b-f**), heteroaryl amines (2-amino-4,6-dimethylpyrimidine and 2-amino-4-methylpyrimidine) (**2b,c**) and glyoxal in this reaction, and obtained a library of imidazolidines **4b-i** in good to high yields.[21] The results are shown in Table 1. To the best of our knowledge, this new procedure represents the first example of an efficient and one-pot reaction for the stereoselective synthesis of novel *trans*-4,5-dihydroxy-2-aryl-1,3- bis(heteroaryl)imidazolidines.

Table 1. Synthesis of imidazolidine derivatives **4**

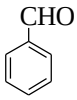
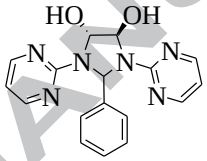
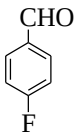
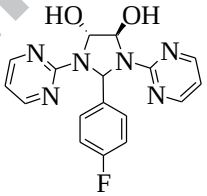
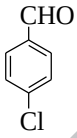
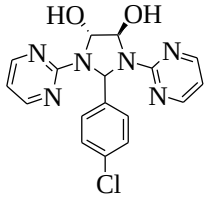
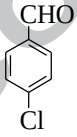
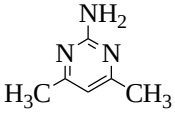
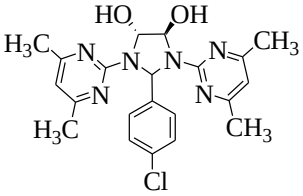
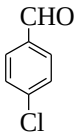
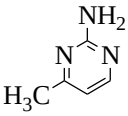
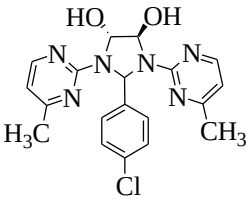
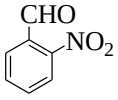
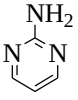
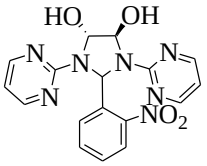
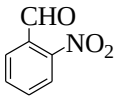
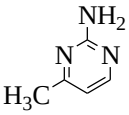
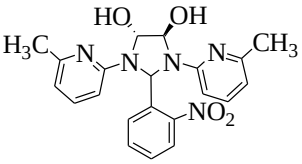
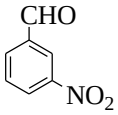
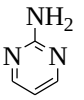
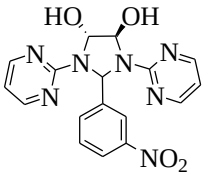
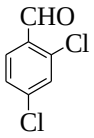
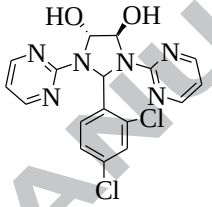
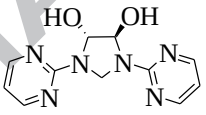
Entry	Aldehyde	Amine	Product	Time (min)		Yield (%)
				Step 1	Step 2	
1			 **4a**	60	15	80
2			 **4b**	60	10	75
3			 **4c**	20	15	85
4			 **4d**	60	10	80
5			 **4e**	70	6	83
6			 **4f**	45	5	84

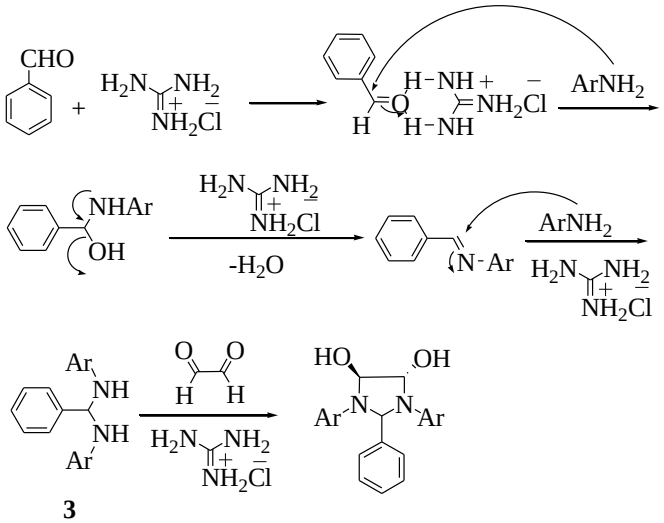
Table 1. (Continued)

Entry	Aldehyde	Amine	Product	Time (min) Step 1	Time (min) Step 2	Yield (%)
7			 **4g**	30	5	79
8			 **4h**	15	8	86
9			 **4i**	40	12	77
10			 **4j**	40	5	88

Aldehydes containing electron-withdrawing functional groups at various positions required different reaction times, but the yields of products were similar. However, in the case of aryl aldehydes bearing an electron-donating group, the reaction did take place, but lower yields were obtained.

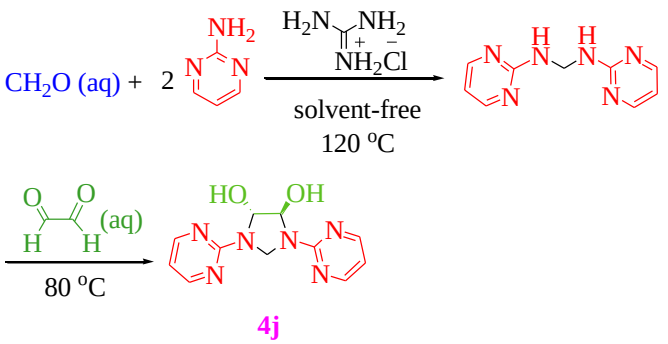
The stereochemistry of the products was assigned based on ^{1}H NMR and ^{13}C NMR spectroscopy. It was found that compounds **4a-i** had unsymmetric structures. The ^{1}H NMR spectra of compounds **4a-i** showed two signals for the hydroxyl groups, in agreement with a *trans* configuration. The IR spectra of compounds **4** showed broad OH stretching absorptions at about 3180 cm^{-1} in agreement with intramolecular hydrogen bonding between the OH and nitrogen of the heteroaryl amines.

The formation of the product in the present reaction is expected to involve the following tandem reaction mechanism. We propose that guanidine hydrochloride acts as a polyfunctional organocatalyst. It is clear from the sequence of steps that guanidine hydrochloride initially acts as a hydrogen-bond donor to activate the aldehyde by formation of a six-membered ring with the aldehyde oxygen. Subsequently, a Schiff base was formed by nucleophilic addition of the amine to the aldehyde and dehydration in the presence of the catalyst acting as an acid. Next, the Schiff base is further attacked by a second amine to give *gem*-diamine as intermediate **3**. Finally, nucleophilic addition of intermediate **3** to the carbonyls of glyoxal gave the final product (Scheme 2).



Scheme 2. Proposed mechanism for the formation of imidazolidines **4**

In an attempt to expand the scope of this method, we employed formaldehyde instead of aryl aldehydes (entry 10), and obtained compound **4j**, being consistent with the expected structure (Scheme 3).[12] The ^{1}H NMR spectrum of compound **4j** indicated that a symmetrical structure had been formed.



4j

Scheme 3. One-pot synthesis of imidazolidine **4j**

In summary, to the best of our knowledge, this Letter describes the first report on the stereoselective synthesis of novel *trans*-4,5-dihydroxy-2-aryl-1,3-bis(heteroaryl)imidazolidines via the reaction of heteroaryl amines, aryl aldehydes and glyoxal. The advantages of the present method are high efficiency and generality, clean reaction profiles and the two-step synthetic sequence can be carried out without isolation of the intermediate. This leads to a reduction in the overall reaction time and energy requirements, and constitutes an economical method for preparing new imidazolidine compounds.

Acknowledgments

The authors thank the Research Council of Payame Noor University for financial support.

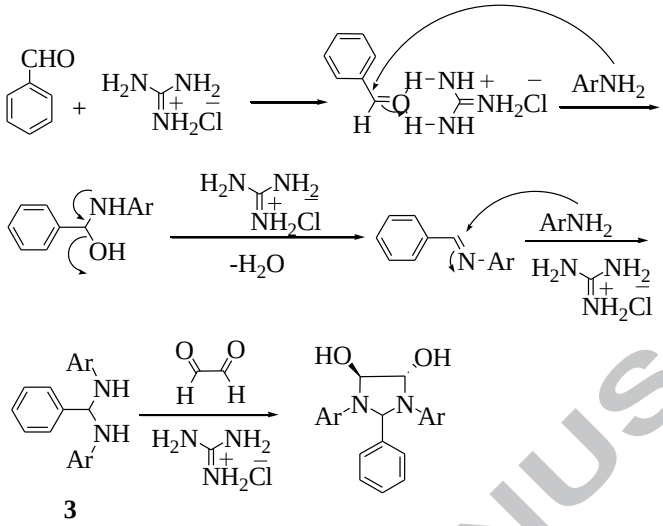
Supplementary data

Supplementary data (^{1}H and ^{13}C NMR, MS, CHN and IR) associated with this article can be found, in the online version.

References and notes

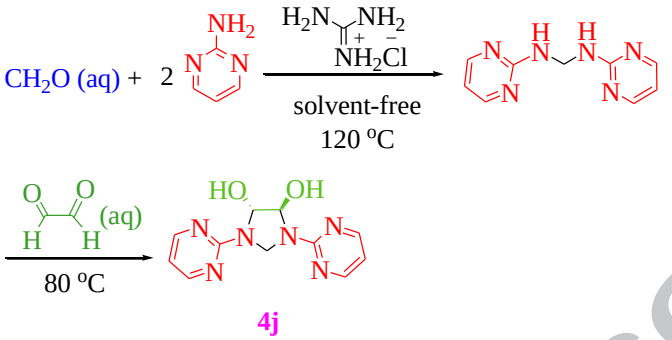
1. Vail, S. L.; Moran, C. M.; Moor, H. B.; Kullman, R. M. H. *J. Org. Chem*. **1962**, *27*, 2071.
2. Alexakis, A.; Tranchier, J. P.; Lensen, N.; Mangeney, P. *J. Am. Chem. Soc*. **1995**, *117*, 10767.
3. Willer, R. L.; Moore, D. W.; Vanderah, D. J. *J. Org. Chem*. **1985**, *50*, 2365.
4. Koppes, W. M.; Chaykovsky, M.; Adolph, H. J.; Gilardi, R. D.; George, C. F. *J. Org. Chem*. **1987**, *52*, 1113.
5. Ferguson, I. J.; Katritzky, A. R.; Patel, R. *J. Chem. Soc., Perkin Trans. 2*, **1976**, 1564.
6. Dunnavant, W. R.; James, F. L. *J. Am. Chem. Soc*. **1956**, *78*, 2740.
7. Nematollah, J.; Ketcham, R. *J. Org. Chem*. **1963**, *28*, 2378.
8. Frick, J. G.; Harper, R. G. *Ind. Eng. Chem. Prod. Res. Dev*. **1982**, *21*, 599.
9. Cort, L. A.; Francis, N. R. *J. Chem. Soc*. **1964**, 2799.
10. Willer, R. L.; Moore, D. W.; Lowe-Ma, C. K.; Vanderah, D. J. *J. Org. Chem*. **1985**, *50*, 2368.
11. Nielsen, A. T.; Nissan, R. A.; Chafin, A. P.; Gilardi, R. D.; George, C. F. *J. Org. Chem*. **1992**, *57*, 6756.
12. Ghandi, M.; Olyaei, A.; Salimi, F. *Synth. Commun*. **2007**, *37*, 247.
13. Ghandi, M.; Olyaei, A. *J. Heterocycl. Chem.* **2007**, *44*, 323.
14. Ghandi, M.; Salimi, F.; Olyaei, A. *J. Heterocycl. Chem*, **2006**, *43*, 791.
15. Caterina, M. C.; Perillo, I. A.; Boiani, L.; Pezaroglo, H.; Cerecetto, H.; González, M.; Salerno, A. *Bioorg. Med. Chem*. **2008**, *16*, 2226.
16. Sharma, V.; Khan, M. S. *Eur. J. Med. Chem.* **2001**, *36*, 651.
17. Sharma, V.; Crankshaw, C. L.; Piwnica-Worms, D. *J. Med. Chem.* **1996**, *39*, 3483.
18. Sage, C. R.; Michelitsch, M. D.; Stout, T. J.; Biermann, D.; Nissen, R.; Finer-Moore, J.; Stroud, R. M. *Biochemistry* **1998**, *37*, 13893.
19. Crank, G.; Harding, D. R. K.; Szinai, S. S. *J. Med. Chem.* **1970**, *13*, 1212.
20. (a) Shockravi, A.; Sadeghpour, M. Olyaei, A. *J. Chem. Res.* **2009**, 656; (b) Shockravi, A.; Sadeghpour, M.; Olyaei, A. *Synth. Commun.* **2010**, *40*, 2531; (c) Olyaei, A.; Raufmoghaddam, S.; Sadeghpour, M.; Ebadzadeh, B. *Chin. J. Chem.* **2010**, *28*, 825; (d) Olyaei, A.; Shams, B.; Sadeghpour, M.; Gesmati, F.; Razaziane, Z. *Tetrahedron Lett.* **2010**, *51*, 6086; (e) Olyaei, A.; Zarnegar, M.; Sadeghpour, M.; Rezaei, M. *Lett. Org. Chem.* **2012**, *9*, 451; (f) Olyaei, A.; Vaziri M.; Razeghi, R. *Tetrahedron Lett.* **2013**, *54*, 1963.
21. *General procedure for the synthesis of imidazolidines (**4**):* A mixture of heteroarylamine (2 mmol), aldehyde (1 mmol) and guanidinium chloride (0.1 mmol) was heated at 120 °C for 15-70 min (Table 1), in an oil-bath under solvent-free conditions. Upon completion, as monitored by TLC, the mixture was cooled to 80 °C, then glyoxal (40% aqueous solution, 1 mmol) was added and the mixture stirred at the same temperature for 5-15 min as indicated in Table 1. After completion, the mixture was cooled to room temperature and EtOH (5 mL) was added until solid products precipitated. The precipitate was filtered, washed with EtOH and dried. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 30/70) to afford the corresponding pure white products **4**. *4,5-Dihydroxy-2-phenyl-1,3-bis(2-pyrimidinyl)imidazolidine (**4a**):* m.p. = 201-202 °C; IR (KBr): 3120, 2946, 1585, 1454, 1319, 1272, 1041 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ: 5.93 (m, 2H, *CH*-OH), 6.23 (d, 1H, *J* = 6.0 Hz, OH), 6.52 (d, 1H, *J* = 3.6 Hz, *OH*), 6.71 (s, 1H, *CH*), 6.74 (t, 1H, *J* = 4.8 Hz, *pyrimidinyl-H5*), 6.77 (t, 1H, *J* = 4.8 Hz, *pyrimidinyl-H5'*), 7.11-7.82 (m, 5H, *phenyl-H*), 8.35 (d, 2H, *J* = 4.8 Hz, *pyrimidinyl-H4,6*), 8.42 (d, 2H, *J* = 4.8 Hz, *pyrimidinyl-H4',6'*) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ: 74.35, 85.63, 85.93, 112.36, 112.65, 127.42, 127.50, 129.62, 141.71, 158.13, 158.37, 158.83, 159.34 ppm; MS (EI): *m/z* 336 (M^{+}), 319, 277, 213, 201, 184, 124, 106, 96, 79; Anal. calcd. for $C_{17}H_{16}N_6O_2$: C, 60.71; H, 4.76; N, 25.00. Found: C, 60.80; H, 4.70; N, 25.09. *4,5-Dihydroxy-2-(4-chlorophenyl)-1,3-bis(4-methyl-2-pyrimidinyl) imidazolidine (**4e**):* m.p. = 194-196 °C; IR (KBr): 3178, 2962, 1569, 1450, 1253, 1041 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ: 2.25 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 5.88 (m, 2H, *CH*-OH), 6.17 (br s, 1H, *OH*), 6.51 (br s, 1H, *OH*), 6.62 (s, 1H, *CH*), 6.64 (d, 1H, *J* = 5.2 Hz, *pyrimidinyl-H5*), 6.66 (d, 1H, *J* = 5.2 Hz, *pyrimidinyl-H5'*), 7.27 (d, 2H, *J* = 8.4 Hz, *phenyl-H*), 7.82 (d, 2H, *J* = 8.4 Hz, *phenyl-H*), 8.25 (m, 2H, *pyrimidinyl-H6,6'*) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ: 24.05, 24.20, 73.84, 85.47, 85.62, 111.80, 112.21, 127.34, 131.73, 141.18, 157.55, 157.94, 158.56, 159.11 ppm; MS (EI): *m/z* 400 (M+2)$^{+}$, 398 (M^{+}), 341, 339, 234, 232, 138, 110, 93, 66; Anal. calcd. For $C_{19}H_{19}ClN_6O_2$: C, 57.28; H, 4.77; N, 21.10. Found: C, 57.34; H, 4.79; N, 21.14.

Scheme 2. Proposed mechanism for the formation of imidazolidines **4**



3

Scheme 3. One-pot synthesis of imidazolidine **4j**



Scheme 1. A one-pot, two-step approach for the synthesis of polyfunctionalized imidazolidines **4**

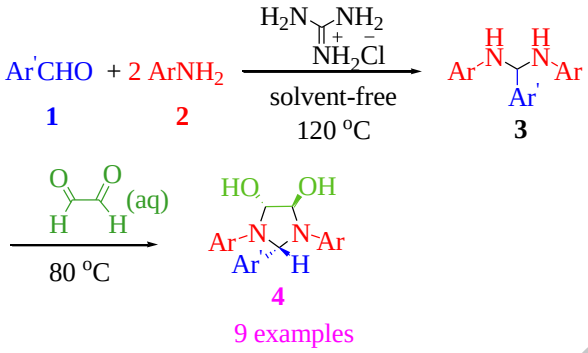


Table 1. Synthesis of imidazolidine derivatives **4**

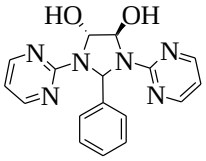
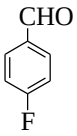
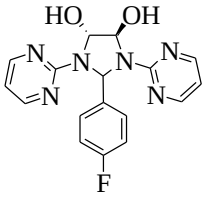
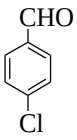
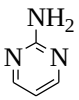
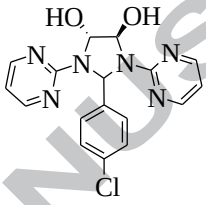
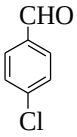
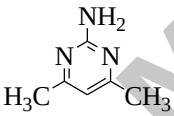
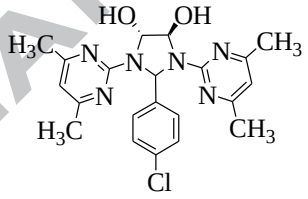
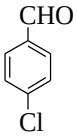
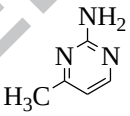
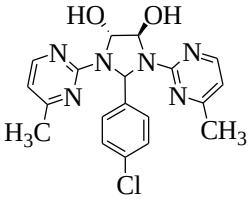
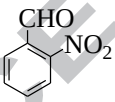
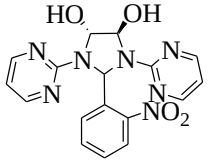
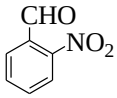
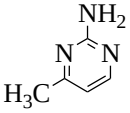
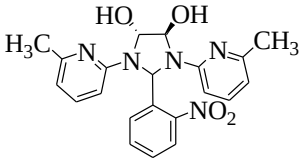
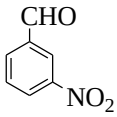
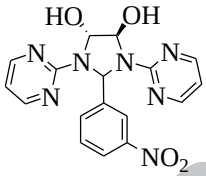
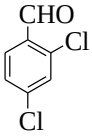
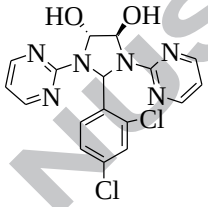
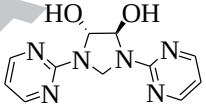
Entry	Aldehyde	Amine	Product	Time (min)		Yield (%)
				Step 1	Step 2	
1			 **4a**	60	15	80
2			 **4b**	60	10	75
3			 **4c**	20	15	85
4			 **4d**	60	10	80
5			 **4e**	70	6	83
6			 **4f**	45	5	84

Table 1. (Continued)

Entry	Aldehyde	Amine	Product	Time (min)		Yield (%)
				Step 1	Step 2	
7			 **4g**	30	5	79
8			 **4h**	15	8	86
9			 **4i**	40	12	77
10			 **4j**	40	5	88