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Efficient one-pot room-temperature synthesis of 2-imidazolines from aldehydes

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The reactions of various aromatic and aliphatic aldehydes with ethylenediamine followed by *N*-iodosaccharin treatment proceed at room temperature to give the corresponding dihydroimidazoles in high yields. The process is simple, fast and convenient.

Key words: Imidazoline, Aldehyde, Ethylenediamine, *N*-Iodosaccharin.

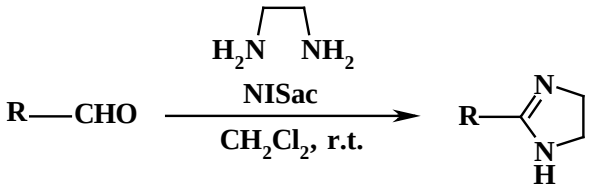
INTRODUCTION

Imidazoline derivatives exhibit significant biological and pharmacological properties including antihypertension, antihistamine, antihyperglycemia, antiinflammation, antidepression and antitumor activities [1]. They are also used as synthetic intermediates [2], chiral catalysts [3] and ligands for asymmetric catalysis [4] in organic synthesis.

Many methodologies for the synthesis of 2-imidazolines from nitriles [1], esters [5], carboxylic acids [6], aldehydes [7], hydroxy amides [8] and benzimidate [9] as starting materials have been developed. Recently, several protocols for the synthesis of imidazoline derivatives have been reported by condensation of aldehydes with ethylenediamine using various oxidants and catalysts such as NBS [10], ceric ammonium nitrate (CAN) [11], I_2 [12,13], H_2O_2 [14], $K_4[Fe(CN)_6]$ [15], and Al_2O_3-OK [16], etc. Some of these procedures suffer from limitations including long reaction time, high temperature, N_2 atmosphere, use of strong oxidizing agent, difficult work-up and limitation in the use of aliphatic and heteroaromatic aldehydes as a substrate.

N-Halosaccharins (NXSac, X = Cl, Br, I) are stable crystalline compounds, soluble in most common organic solvents, insoluble in water [17, 18] and more electrophilic than their analogues such as *N*-haloamides. *N*-halosaccharins are oxidizing [19] and halogenating agents which are often employed for the halogenation of alkenes, activated aromatic compounds, enol acetates, 1,3-diones, etc. [18, 20].

Herein, we report an efficient one-pot method for the synthesis of 2-imidazolines from various aldehydes and ethylenediamine using *N*-iodosaccharin at room temperature (Scheme 1).



R :aryl,alkyl

Scheme 1

EXPERIMENTAL

Materials were purchased from Fluka and Merck companies. NISac was prepared according to the reported procedure [17b]. Products were characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR and FT-IR) and physical properties and comparison with authentic samples.

General procedure for the synthesis of imidazoline

A mixture of aldehyde (1 mmol), ethylenediamine (2 mmol) and *N*-iodosaccharin (2 mmol) in CH_2Cl_2 was stirred at room temperature for the appropriate time according to Table 1. After completion of the reaction, NaOH (10%) aq or sat. $NaHCO_3$ was added to the reaction mixture and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure and the corresponding 2-imidazoline was obtained in 90-95% yield.

Some Product Characterization Data

2-(4-Bromophenyl)imidazoline (Table 2, entry 10): IR (KBr): 3150, 2930, 2870, 1625, 1475, 1290, 820 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$): δ=7.66 (d, *J*=8.4 Hz, 2H), 7.56 (d, *J*=8.4 Hz, 2H), 3.811(s,

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4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 161.8, 131.6, 130.6, 128.0, 124.0.

2-(4-Cyanophenyl)imidazoline (Table 2, entry 12): IR (KBr): 3150, 2930, 2200, 1590, 1270, 840 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$): δ=7.9 (d, *J*=8.4 Hz, 2H), 7.6 (d, *J*=8.4 Hz, 2H), 3.729 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 164.0, 135.5, 131.2, 125.7, 119.1, 114.0.

2-(2-Furyl)imidazoline (Table 2, entry 15): IR (KBr): 3125, 2925, 2860, 1640, 1505, 1170, 975 cm^{-1}, ^{1}H NMR (400MHz, $CDCl_3$): δ=7.49 (d, *J*=4, 1H), 7.02 (d, *J*=4 Hz, 1H), 6.5 (q, *J*=4 Hz, 1H), 3.79 (s, 4H).

RESULTS AND DISCUSSION

The reaction conditions were optimized using ethylenediamine and benzaldehyde as model substrates. Therefore, benzaldehyde (1 mmol) was treated with ethylenediamine (2 mmol) in the presence of different amounts of *N*-iodosaccharin in various solvents at room temperature. It was observed that this reaction goes well in dichloromethane among the commonly used organic solvents such as dichloroethane, ethanol and acetonitrile (Table 1, entries 1–4).

After choosing the solvent, we changed the amount of NISac to 1, 1.5 and 2.5 mmol and the product was obtained in 50–93% yields (Table 1 entries 5-7). Using higher amounts of NISac did not affect the yield and reaction time (Table 1, entry 7). Also, we decreased the amount of ethylenediamine from 2 to 1.5 mmol and the yield of the reaction decreased, while the reaction time increased (Table 1, entry 8).

After optimization of the reaction conditions, the reaction of other aldehydes with ethylenediamine was carried out in the presence of NISac and the results are presented in Table 2. As shown in Table 2, several substituted aromatic, heteroaromatic and aliphatic aldehydes were used successfully in this procedure.

Aromatic aldehydes having electron donating groups such as methoxy and methyl (Table 2, entries 2-7) or electron withdrawing groups such as chloro, bromo and nitro (Table 2, entries 8-12) were converted to the corresponding imidazolines in excellent yields. Similarly, heteroaromatic aldehydes such as pyridine, furan and thiophen carbaldehyde reacted with ethylenediamine to give the desired compounds without any problem in 93-95% yields (Table 2, entries 13-16). Finally, butanal as an aliphatic aldehyde (Table 2, entry 17) successfully afforded 2-propylimidazoline in excellent yield under the optimal reaction conditions. It is important to note that no iodinated or over-oxidized products (i.e. imidazole) were found in the reaction mixtures. The yields of the reactions were dependent on the substituents present on the substrates. Reactions with substrates having electron-withdrawing groups proceeded at faster rates than those with electron-donating groups.

In Table 3, we compared our results with those obtained by a reported procedure for the synthesis of 2-(2-pyridyl)imidazoline. The data presented in this table show the promising feature of this method in terms of reaction rate and the yield of product compared with that reported in the literature.

Table 1: Optimization of reaction conditions.

Entry	Solvent	NISac (mmol)	Ethylenediamine (mmol)	Time (h)	Yield (%)[a]
1	MeOH	2	2	5	70
2	CH_3CN	2	2	5	73
3	$ClCH_2CH_2Cl$	2	2	5	75
4	CH_2Cl_2	2	2	2	93
5	CH_2Cl_2	1	2	4	65
6	CH_2Cl_2	1.5	2	4	75
7	CH_2Cl_2	2.5	2	2	93
8	CH_2Cl_2	2	1.5	5	70

[a]Yields refer to isolated products.

Table 2. Reaction of aldehydes with ethylenediamine in the presence of NISac [a]

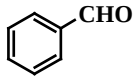
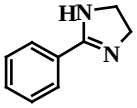
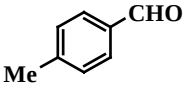
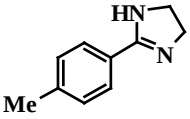
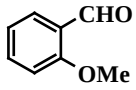
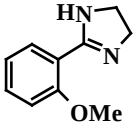
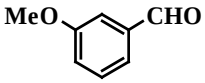
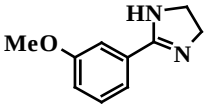
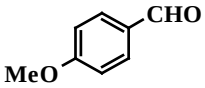
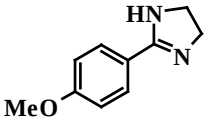
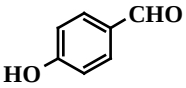
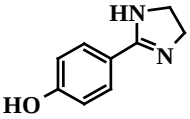
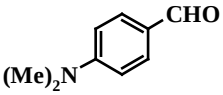
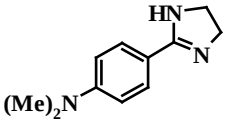
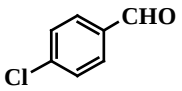
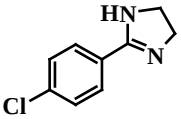
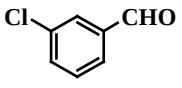
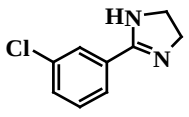
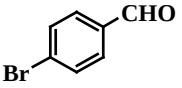
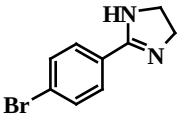
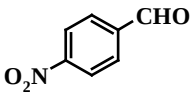
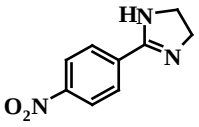
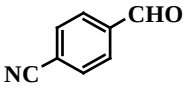
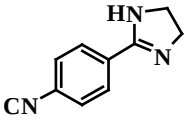
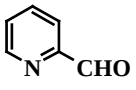
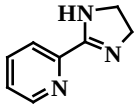
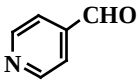
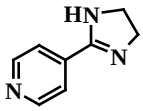
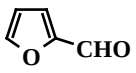
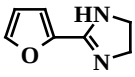
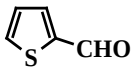
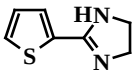
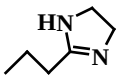
Entry	Substrate	Product	Time (h)	Yield (%)	M.p. (°C) [Ref.]
1			2	93	100-102 [10a]
2			3.5	92	181-182 [13]
3			0.2	90	72-74 [10a]
4			1.5	90	100-102 [10a]
5			4	90	135-137 [10a]
6			2.5	90	299-301 [1a]
7			2	93	255–257 [13]
8			2.5	92	183-185 [10a]
9			2.5	90	134-136 [21]
10			1.5	90	239–241 [7a]

Table 2 continued

Entry	Substrate	Product	Time (h)	Yield (%)	M.p. (°C) [Ref.]
11			1	95	232-233 [7a]
12			1	90	196–198 [7a]
13			0.25	95	99–100 [22]
14			0.25	93	135-136 [22]
15			3	93	180-181 [22]
16			3	94	175-176 [22]
17	$CH_3(CH_2)_2CHO$		1	90	43-45 [23]

[a]The reaction was carried out at room temperature using aldehyde (1 mmol), ethylenediamine (2 mmol), NISac (2 mmol) and CH_2Cl_2 (5 mL).

Table 3. Comparison of some other procedures with the present method for synthesis of 2-(2-pyridyl)imidazoline from 2-pyridine carbaldehyde.

Entry	Oxidant	Reaction conditions	Time	Yield(%) [Ref]
1	NISac	rt	15 min	95
2	I_2	70^0C (under Ar)	3 h	97 [12]
3	NBS	0^0C-rt	overnight	100 [10]
4	CAN	reflux	50 min	65 [11]

CONCLUSION

We have developed a mild, simple one-pot method for the synthesis of 2-imidazoline from aldehydes and ethylenediamine using an efficient oxidizing agent (NISac). This method is performed at room temperature and many functional groups such as halogen, amine and nitrile can be introduced without any problem. It needs no heat or inert atmosphere and has high product yields and short reaction time.

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REFERENCES

1. (a) M. Sun, H. D. Wei. Li, Y. Zheng, J. Cai, M. Ji, *Synthetic Commun.*, **38**, 3151 (2008). (b) T. Shalina Begum, U.C.A. Jaleel and P.M. Shafi, *Int. J. Pharm. Biomed. Sci*, **4(1)**, 40 (2013).
2. (a) R. C. F. Jones, J. R. Nichols, *Tetrahedron Lett.*, **31**, 1771 (1990). (b) M. E. Jung, A. Huang, *Org. Lett.*, **2**, 2659 (2000).
3. E. J. Corey, M. J. Grogan, *Org. Lett.*, **1**, 157 (1999).
4. Bastero, C. Claver, A. Ruiz, S. Castillon, E. Daura, C. Bo, *Chem. Eur. J.*, **10**, 3747 (2004).
5. G. Neef, U. Eder, G. Sauer, *J. Org. Chem.*, ***46***, 2824 (1981).
6. H. Vorbruggen, K. A. Krolikiewicz, *Tetrahedron Lett.*, **22**, 4471 (1981).
7. (a) M. Ishihara, H. Togo, *Tetrahedron*, **63**, 1474 (2007). (b) H. Fujioka, K. Murai, O. Kubo, Y. Ohla, Y. Kita, *Tetrahedron*, **63**, 638 (2007).

8. N. A. Boland, M. Casey, S. J. Hynes, J. W. Matthews, M. P. A. Smyth, *J. Org. Chem*., **67**, 3919 (2002).
9. (a) J. Spychala, *Synthetic Commun*., **30**, 1083 (2000).
10. H. Fujioka, K. Murai, Y. Ohba, *Tetrahedron Lett.*, **46**, 2197 (2005) (b) G. S.Sant'Anna, P. Machado, P. D. Sauzem, F. A. Rosa, M. A. Rubin, J. Ferreira, H. G. Bonacorso, N. Zanatta, M. A. P. Martins, *Bioorg. Med. Chem. Lett.*, **19**, 546 (2009).
11. R. Kumar, Y. C. Joshi, *E. J. Chem*., **4**, 606 (2007).
12. M. Ishihara and H. Togo, *Tetrahedron*, **63** 1474 (2007).
13. P. Gogoi, D. Konwar, *Tetrahedron Lett.*, **47**, 79 (2006).
14. G. Bai, K. Xu, G. Chen, Y. Yang, T. Li, *Synthesis*, 1599 (2011).
15. Kabeer Shaikh, A.Vishal Patil, *Org. Commun*., **5:1**, 12 (2012).
16. P. J. Das, A. Baruah, *Indian J. Chem.* **51**, 752 (2012).
17. (a) D. Dolenc, *Synlett*, **4**, 544 (2000). (b) S. Soraia, S. Jaoquim and D. Marco, *Synth. Commun.*, **33**, 935 (2003).
18. D. Dolene, B. Sket, *Synlett*, 327 (1995).
19. V. Manoharan, N. Venkatasubramanian, *Indian Chem. Soc*., **63**, 613 (1986).
20. (a) I. Mozek, B. Sket, *Synthetic Commun.*, **22**, 2513 (1992). (b) D. Dolenc, *Synth. Commun.*, **33**, 2917 (2003).
21. S. Haneda, A. Okui, C. Ueba, M. Hayashi, *Tetrahedron*, **63**, 2414 (2007).
22. M. Anastassiadou, S. Danoum, L. Crane, G. Baziard-mouysset, M. Payard, D. H. Caignard, M. C. Rettori, P. Renard, *Bioorg. Med. Chem*., **9**, 585 (2001).
23. A. Grigorev, G. I. Shchukin, L. B. Volodarskii, *Izv. Akad. Nauk SSSR. Ser. Khim.*, **5**, 1140 (1983).

ЕФЕКТИВНА ЕДНОСТАДИЙНА СИНТЕЗА ПРИ СТАЙНА ТЕМПЕРАТУРА НА 2-ИМИДАЗОЛИНИ ОТ АЛДЕХИДИ

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Реакциите на различни ароматни и алифатни алдехиди с етилендиамин, последвано от третиране с N-йодозахарин, проведено при стайна температура, за да се получат съответните дихидроимидазоли с високи добиви. Процесът е прост, бърз и удобен.