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A mild and efficient one-pot synthesis of 2-dihydroimidazoles from aldehydes

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Abstract—The reactions of various aldehydes and 1,2-diamines followed by NXS treatment proceed at 0 °C–rt to give the corresponding dihydroimidazoles in high yields. The reaction is mild, and many functional groups such as halogens, nitriles, and esters can exist.

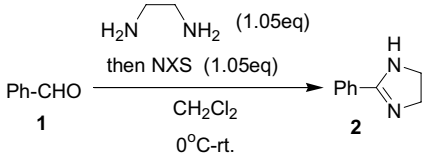
The importance of dihydroimidazole units especially in biochemistry is recently increasing, since they are found in many biologically active compounds.[1] They are also used in organic synthesis as synthetic intermediates,[2] chiral auxiliaries,[3] and chiral ligands.[4] Therefore, several methodologies for synthesizing them have already been developed, mainly using nitriles[5] and esters[6] as the starting substrates. However, these previous methods have several drawbacks, namely the need for a high reaction temperature, acidic conditions, and the use of metal cyanide for preparation of the nitrile compounds that limit their uses. Although several new methods have been recently developed,[7] they need rather special starting materials such as azalactones,[7a] 2-aryl-1,1-dibromoethanes,[7b] and amino amides.[7c] The development of mild and efficient methods is still strongly desirable. We present here a novel mild and efficient method, which overcomes the drawbacks of the previous reactions.

N-Iodosuccinimide (NIS) treatment of the mixture of benzaldehyde **1** and ethylenediamine in CH_2Cl_2[8] afforded the dihydroimidazole **2** in excellent yield at 0 °C–rt. Other halogenating reagents, *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS), gave the same results (Table 1). The following experiments were then done using the cheapest NBS.

General procedure is as follows. Namely, a solution of **1** (1.0 mmol) in CH_2Cl_2 (10 mL) and ethylenediamine (1.05 mmol) were mixed and stirred at 0 °C for 20 min, and NBS (1.05 mmol) was added to the mixture and the resulting solution was allowed to warm to rt and stirred overnight. NaOH (10%) aq or sat $NaHCO_3$ was added to the reaction mixture to make sure the solution is alkaline. The mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography[9] to give **2**.

This reaction is rationalized as follows (Scheme 1). First, imidazolidine **i** is formed by the condensation of **1** and ethylenediamine without any catalysts. Its formation was confirmed by a ^1H NMR experiment. Second, the reaction of **i** and *N*-halosuccinimide afforded the haloamine **ii**. Third, the elimination of HX then afforded the salt **2**·HX.[10] Alkaline work-up afforded the dihydroimidazole **2**. In the reaction, the succinimide anion formed by the loss of the halonium ion would assist in

Table 1.



Entry	NXS	Yield (%)
1	NIS	99
2	NBS	99
3	NCS	99

Keywords: Dihydroimidazole; Aldehyde; 1,2-Diamine; *N*,*N*-Acetal; *N*-Halosuccinimide; Mild reaction.
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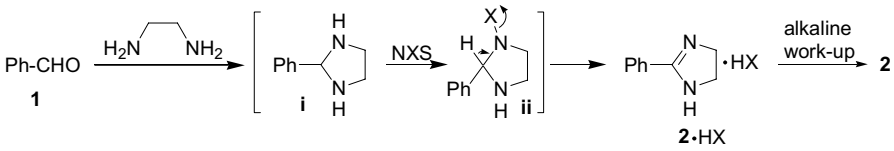
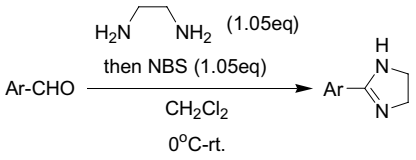
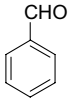
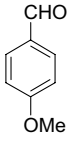
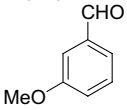
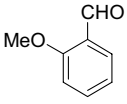
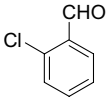
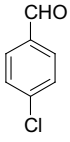
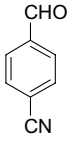
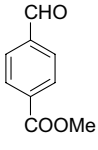
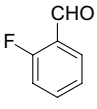
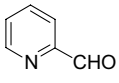


Scheme 1.

the elimination, because the use of bromine only in place of NBS did not give **2**.

Table 2.



Entry	Ar–CHO	Yield (%)
1		99
2		94
3		96
4		69
5		83
6		99
7		95
8		94
9		96
10		100

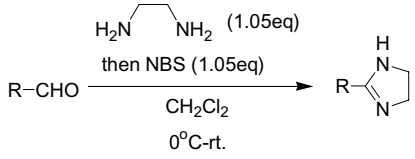
The generality of the reaction was next examined. Table 2 shows the results using aromatic aldehydes. The result of benzaldehyde is shown for comparison (entry 1). The reactions well proceed in spite of an electron-donating substituents, a methoxy group (entries 2–4), and electron-withdrawing substituents such as chloro, nitrile, ester, and fluoro groups (entries 5–9), whereas the *o*-substituted ones gave products in rather lower yields than those of the *m*- and *p*-substituted ones (entries 4, 5). These facts suggest that the steric factor is more important than the electronic factor in this reaction. It is noteworthy that the nitrile and ester groups remain intact under this reaction condition, although they were used for the formation of dihydroimidazole compounds in the previous reports. The pyridine aldehyde also gives the desired compound in a quantitative yield without any problem (entry 10).

Table 3 shows the results of the aliphatic aldehydes. The method works well not only for simple primary aldehydes (entry 1) but also for unsaturated aldehydes and secondary aldehydes (entries 2–4). The method is also available for aldehyde having an ester (entry 5).

The use of a chiral diphenylethyldiamine in place of ethylenediamine was next studied (Table 4), since the application of chiral dihydroimidazoles as chiral ligands has been recently increasing. The aromatic aldehyde (entry 1), pyridine aldehyde (entry 2), and aliphatic aldehydes (entries 3, 4) afforded the corresponding chiral dihydroimidazole in high yields.

In conclusion, we have developed a mild and effective method for producing dihydroimidazoles from alde-

Table 3.



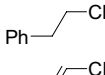
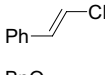
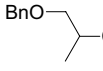
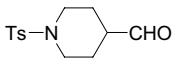
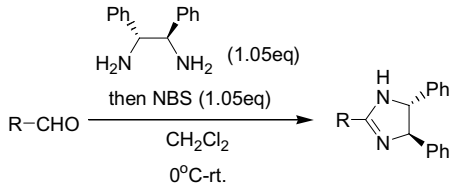
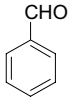
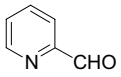
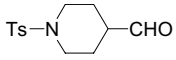
Entry	R–CHO	Yield (%)
1		96
2		87
3		94
4		85
5	$BzO(CH_2)_8CHO$	98

Table 4.



Entry	R–CHO	Yield (%)
1		92
2		96
3		87
4		95

hydes and 1,2-diamines. This method works at low temperature, 0 °C–rt, and many functional groups such as halogens, esters, and nitriles can exist without any problem. Furthermore, since the aldehyde is a popular functional group, the method here is considered useful in organic synthesis.

References and notes

1. For examples, see: (a) Greenhill, J. V.; Lue, L. In *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Eds.; Elsevier: New York, 1993; Vol. 3; (b) Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Sciven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 3, pp 77–220; (c) Prisinzano, T.; Law, H.; Dukat, M.; Slassi, A.; MaClean, N.; Demchyshyn, L.; Glennon, R. A. *Bioorg. Med. Chem.* **2001**, *9*, 613–619; (d) Gilman, A. G.; Goodman, L. S. *The Pharmacological Basic of Therapeutics*, 10th ed.; Macmillan & Co: New York, 2001; (e) Anasatassiadou, M.; Danoun, S.; Crane, L.; Baziard-Mouysset, G.; Payard, M.; Caignard, D. H.; Rettori, M. C.; Renard, P. *Bioorg. Med. Chem.* **2001**, *9*, 585–592.
2. For examples, see: (a) Jones, R. C. F.; Nichols, J. R. *Tetrahedron Lett.* **1990**, *31*, 1771–1774; (b) Jung, M. E.; Huang, A. *Org. Lett.* **2000**, *2*, 2659–2661.
3. For examples, see: (a) Jones, R. C. F.; Turner, I.; Howard, K. J. *Tetrahedron Lett.* **1993**, *34*, 6329–6332; (b) Langlois, Y.; Dalko, P. I. *J. Org. Chem.* **1998**, *63*, 8107–8117.
4. For examples, see: (a) Morimoto, T.; Tachibana, K.; Achiwa, K. *Synlett* **1997**, 783–785; (b) Davinport, A. J.; Davies, D. L.; Fawcett, J.; Russell, D. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1500; (c) Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713–4716.
5. For the examples, see: (a) Ferm, R. J.; Riebsomer, J. L. *Chem. Rev.* **1954**, *54*, 593–613; (b) Botteghi, C.; Schionato, A. *J. Organomet. Chem.* **1989**, *370*, 17–31; (c) Corbel, J. C.; Uriac, P.; Huet, J.; Martin, C. A. E.; Advenier, C. *Eur. J. Med. Chem.* **1995**, *30*, 3–13; (d) Pigini, M.; Bousquet, P.; Carotti, A.; Dontenwill, M.; Giannella, M.; Moriconi, R.; Piergentili, A.; Quaglia, W.; Tayebati, S. K.; Brasili, L. *Bioorg. Med. Chem.* **1997**, *5*, 833–841; (e) Mitchell, J. M.; Finney, N. S. *Tetrahedron Lett.* **2000**, *41*, 8431–8434.
6. For examples, see: (a) Neef, G.; Eder, U.; Sauer, G. *J. Org. Chem.* **1981**, *46*, 2824–2826; (b) Rondu, F.; Bihan, G. L.; Wang, X.; Lamouri, A.; Toubou, E.; Dive, G.; Bellahsene, T.; Pfeiffer, B.; Renard, P.; Guardiola-Lemaitre, B.; Manechez, D.; Penicaud, L.; Ktorza, A.; Godfroid, J.-J. *J. Med. Chem.* **1997**, *40*, 3793–3803; (c) Touzeau, F.; Arrault, A.; Guillaumet, G.; Scalbert, E.; Pfeiffer, B.; Rettori, M.-C.; Renard, P.; Mérour, J.-Y. *J. Med. Chem.* **2003**, *46*, 1962–1979.
7. For examples, see: (a) Peddibhotla, S.; Tepe, J. J. *Synthesis* **2003**, 1433–1440; (b) Huh, D. H.; Ryu, H.; Kim, Y. G. *Tetrahedron* **2004**, *60*, 9857–9862; (c) You, S.-L.; Kelly, J. W. *Org. Lett.* **2004**, *6*, 1681–1683.
8. Among the examined reaction solvents, toluene, CH_2Cl_2, AcOEt, and THF, CH_2Cl_2 gave the best results (99% yield of **2**), whereas other three solvents afforded **2** in decreased yields (toluene, 75% of **2**; AcOEt, 73% of **2**; THF, 76% yield of **2**).
9. Eluent for the compounds in entries 1, 3, 5–9 in Table 2: AcOEt/Et_3N system; eluent for the compounds in entries 2, 4, 10 in Table 2 and entries 1, 2 in Table 3: CH_2Cl_2/MeOH/Et_3N system; eluent for the compounds in entries 3–5 in Table 3: CH_2Cl_2/MeOH/Et_3N system; eluent for the compounds in Table 4: hexane/AcOEt/Et_3N system.
10. Transformation of C–N single bond to C–N double bond from N-chloroamine, see: Scully, F. E., Jr.; Davis, R. C. *J. Org. Chem.* **1978**, *43*, 1467–1468.