Water mediated deprotective intramolecular hydroamination of N-propargylaminopyridines: synthesis of imidazo[1,2-a]pyridines

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PII: S0040-4039(13)01510-4
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.08.112
Reference: TETL 43475

To appear in: *Tetrahedron Letters*

Received Date: 16 July 2013
Revised Date: 23 August 2013
Accepted Date: 27 August 2013

Please cite this article as: Mohan, D.C., Sarang, N.B., Adimurthy, S., Water mediated deprotective intramolecular hydroamination of N-propargylaminopyridines: synthesis of imidazo[1,2-a]pyridines, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.08.112

Water mediated deprotective intramolecular hydroamination of N-propargylaminopyridines: synthesis of imidazo[1,2-a]pyridines

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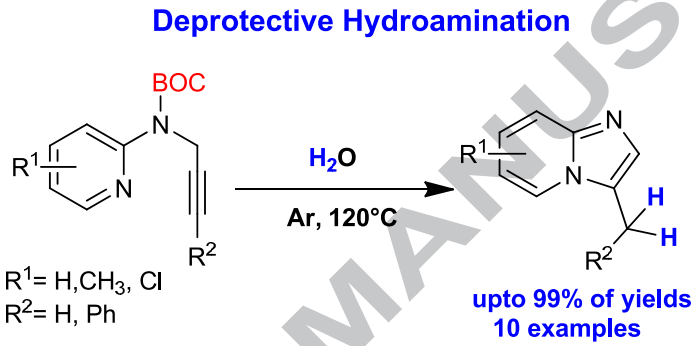


Abstract: Metal-free synthesis of substituted imidazole [1,2-a]pyridines from deprotective N-(prop-2-yn-1-yl)pyridin-2-amines in water is elucidated. Electron releasing substituents on pyridine ring provided pure products in quantitative yields without separation by column chromatography.

***Keywords*:** N-Propargylaminopyridines, imidazo [1,2-a]pyridine, hydroamination, synthesis, water.

Bridged nitrogen heterocyclic compounds are widely found in many biologically active compounds.[1] Among them imidazo-[1,2-a]pyridine scaffolds represent an important class of organic moieties and are attractive for both synthetic and medicinal chemists due to their antibacterial,[2] antifungal,[3] antiviral,[4] and anti-inflammatory properties.[5] Recently a numerous imidazo-[1,2-a]pyridine based drugs have been developed such as alpidem,[6] olprinone,[7]

minodronic acid[8] (to treat anxiety, heart failure and osteoporosis), zolimidine (peptic ulcer),[9] necopidem, saripidem[10] (sedative and anxiolytic) and optically active GSK812397 candidate (HIV Infection)[11]are derived (Figure 1). In addition, imidazo-[1,2-a]pyridine derivatives received considerable attention in the field of material chemistry as sensor devises.[12] Because of such appealing applications of imidazo-[1,2-a]pyridines recently a variety of synthetic methods have been developed including intermolecular diamination of alkynes,[13] oxidative cross-coupling/cyclization,[14] three-component coupling reaction of alkynes,[15] Cu(I)-catalyzed method,[16] tetrabutylammonium iodide oxidative coupling,[17] Morita-Baylis -Hillman(MBH) reaction[18] and other methods.[19]

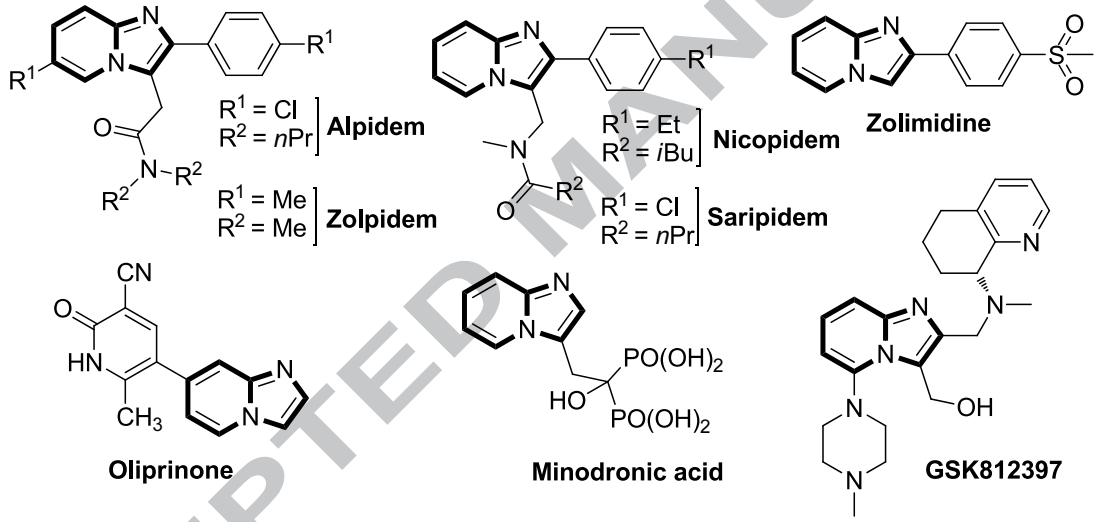
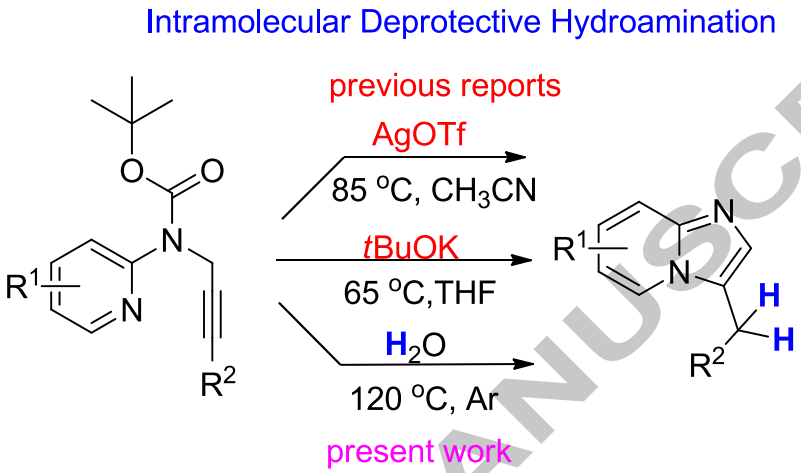


Figure 1. Imidazo[1,2-a]pyridine derived drugs

Since the last two decades the development of synthetic methodologies using benign solvents/neat and metal-free conditions are encouraged. However, many organic reactions require a solvent; consequently performing such reactions in water is more attractive and find merits over volatile organic solvents.[20] Moreover, water also exhibits unique reactivity and selectivity that cannot be attained in conventional organic solvents.[21] Additionally, due to hydrophobic effects using water as a solvent not only accelerates reaction rate but also enhances selectivity even when the reactants are sparingly soluble or insoluble in this

medium.[22] In continuation of our studies on the development of green and sustainable methods,[23] we report herein a metal-free water mediated synthesis of substituted imidazo[1,2-a]pyridines from deprotective *tert*-butyl prop-2-yn-1-yl(pyridin-2-yl)carbamates (Scheme 1).[24]

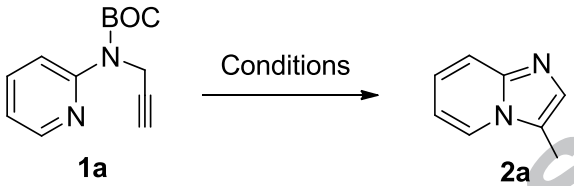


Scheme 1

We are interested in transforming BOC-protected aminopyridines, such as **1a**, into imidazo [1,2-a]pyridines without the need for any extra deprotection step; therefore we explored various conditions to accomplish this reaction in one step. We initiated our studies with *tert*-butyl prop-2-yn-1-yl (pyridin-2-yl) carbamate **1a** as a substrate to optimize the reaction conditions (Table 1). Initially, the reaction was performed in water at room temperature; no product formation was observed (Table 1, entry 1). When the reaction carried out at 60 °C, the desired product **2a** was isolated in 35% yield in 24 h (Table 1, entry 2). A clear improvement of the yield was observed when the reaction temperature was raised from 60 °C to 120 °C (Table 1, entries 3–6). Performing the reaction under argon atmosphere instead of open air at 120 °C, 98% yield of **2a** was isolated (Table 1, entry 7). Though organic substrates are insoluble in water at room temperature, at high temperature water may exhibit acidic character and reaction proceeds at that temperature. When the reaction performed under open

atmosphere at 120 °C, some amount of substrate charring was observed (Table 1, entry 6). Reactions in other solvents were either poorly effective or entirely ineffective (Table 1, entry 8-12). To the best of our knowledge, this is the first report on water mediated deprotective intramolecular hydroamination in the absence of metal and organic solvent.

Table 1 Optimization of reaction conditions[a]



1a **2a**

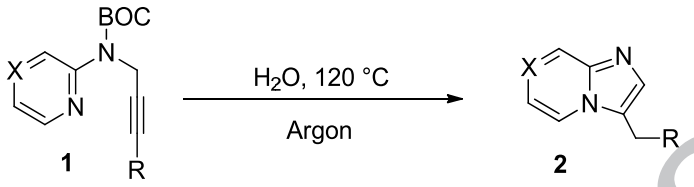
Entry	Solvent	Temp (°C)	Time (h)	Atms	Yield (%)
1	H_2O	rt	4	Air	nr
2	H_2O	60	24	Air	35
3	H_2O	80	5	Air	46
4	H_2O	100	1	Air	62
5	H_2O	100	1.5	Air	70
6	H_2O	120	1	Air	76
7	**H_2O**	**120**	**1**	**Ar**	**98**
8	DMSO	100	4	Ar	nr
9	DMF	100	4	Ar	nr
10	toluene	100	3	Ar	nr
11	EtOH	80	4	Ar	30
12	CH_3CN	80	4	Ar	trace

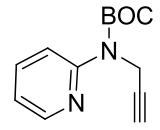
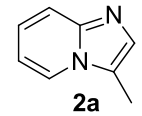
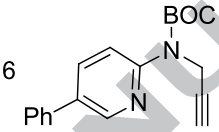
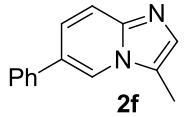
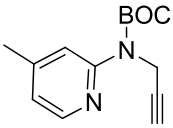
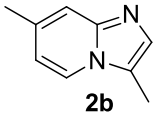
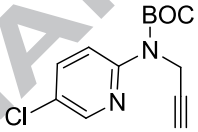
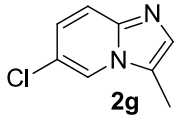
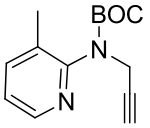
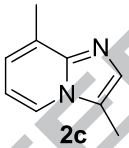
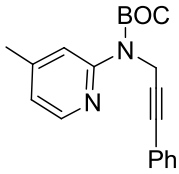
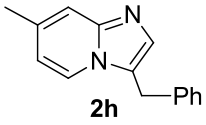
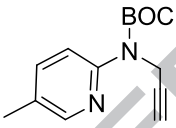
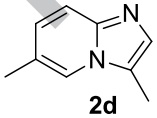
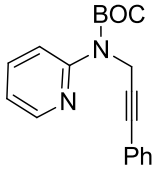
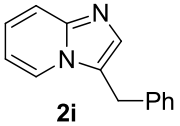
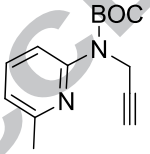
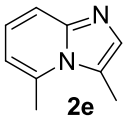
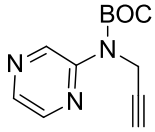
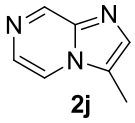
[a]Reaction conditions: **1a** (1 mmol), solvent (4 mL), in a sealed tube; isolated yield.

The scope of this methodology was then extended for the synthesis of a variety of substituted imidazo[1,2-a]pyridines **2**[25] (Table 2). The substituted *tert*-butyl prop-2-yn-1- yl (pyridin-2-yl)carbamate starting materials **1** were readily prepared by following literature procedure.[24b] Notably, the products **2a**-**2e** were obtained in quantitative yields without subjecting to column chromatography. The presence of a variety of electron-withdrawing groups (Ph and Cl)

provided the corresponding methyl imidazo[1,2-a]pyridines **2f** and **2g** in moderate to good yields. These moderate yields may be due to lowering of electron density on pyridine ring. In addition, phenyl substituted at terminal alkynes also underwent this transformation and

Table 2 Scope for syntheses of **2**[a]

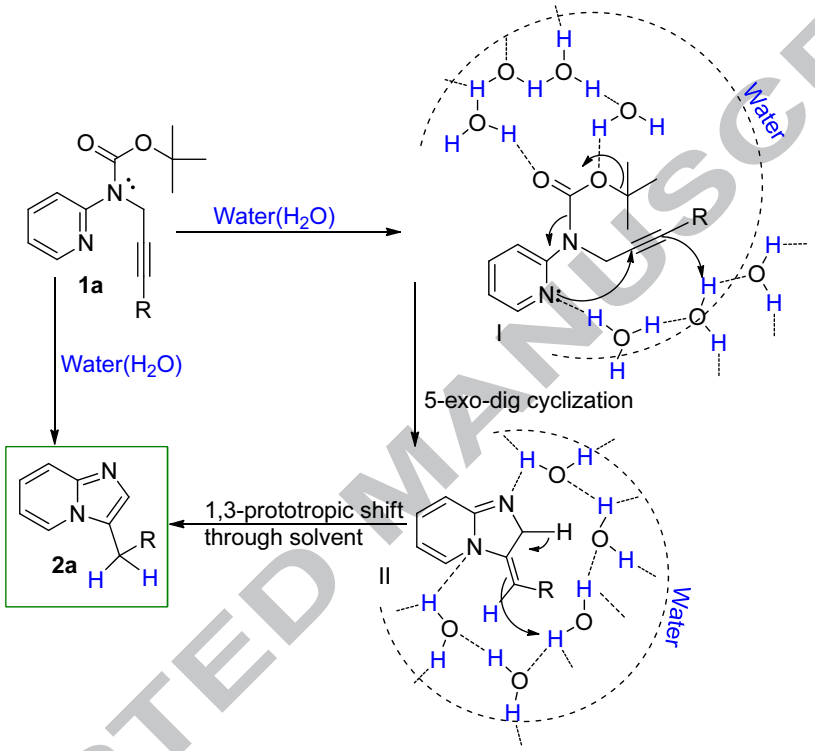


Entry	Substrate	Time (h)	Product **2**	Yield (%)[b]	Entry	Substrate	Time (h)	Product **2**	Yield (%)[b]
1.		1	 **2a**	98	6		3	 **2f**	72
2.		1.5	 **2b**	99	7		6	 **2g**	67
3		1.5	 **2c**	95	8		12	 **2h**	95
4		1.5	 **2d**	97	9		12	 **2i**	62
5		1.5	 **2e**	90	10		4	 **2j**	54

[a]Reaction conditions; **1a** (0.1 mmol), H_2O (4 mL), oil bath in a sealed tube. [b]Isolated yield.

generated corresponding imidazo[1,2-a]pyridine **2h** and **2i** in 95% and 62% yields respectively. Interestingly, *tert*-butylprop-2-yn-1-yl(pyrazin-2-yl)carbamate also displayed a good reactivity and yield the product 3-methylimidazo[1,2-a]pyrazine **2j** in 54% yield. Based on the above observations and literature reports[23a] a probable mechanism is proposed

(Scheme 2). Initially, *tert*-butylprop-2-yn-1-yl-(pyridin-2-yl)carbamate **1a** in presence of water form hydrogen bonds (intermediate I) and undergo intramolecular hydroamination through *5-exo-dig* cyclization[23a] yield the intermediate **II**. Subsequently, **II** abstracts proton from water through 1, 3 prototrophic shifts provide the final product **2a**.



Scheme 2. Probable mechanism for synthesis of **2a.**

In summary, we reported the synthesis of imidazo[1,2-a]pyridine from deprotective N-(prop-2-yn-1-yl)pyridin-2-amines through intramolecular hydroamination using water as a solvent and catalyst. Through this method moderate to excellent yields of desired products could be obtained. The method is also applicable for the synthesis of 3-methylimidazo[1,2-a]pyrazine.

Acknowledgments

We thank Dr. A.V. Boricha/Mr B. M. Bhil, and Mr. Arun K Das of this institute for recording NMR and mass respectively. D.C.M is thankful to UGC New Delhi, India for his fellowship.

DST, Govt. India (SR/S1/OC-13/2011) and CSIR (CSC-0123) are acknowledged for the financial support.

Supporting information available: Characterization data and copies of NMR spectra for all compounds.

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25. Synthesis of imidazo[1,2-]pyridines **2**: In a 10 mL round bottomed flask, 1.0 mmol of **1** and 4 mL of water were placed. The flask was purged with argon gas and tightly sealed. The reaction flask was then heated to 120°C for specified period of time (Table 2) in an oil bath. After room temperature, the mixture was poured into 20 mL of saturated $NaHCO_3$ solution, the product was extracted with dichloromethane (DCM) (20 mL × 3), followed by drying with anhydrous Na_2SO_4. The left out residue after the removal of organic solvent under reduced pressure was purified by column chromatography using silica gel to obtain the desired product **2**. [Note: The products **2a-2e** were obtained pure (by NMR) without separation by column chromatography, but by simple extraction and removal of DCM].

Graphical Abstract

Water mediated deprotective intramolecular hydroamination of N-propargylaminopyridines: synthesis of imidazo[1,2-a]pyridines

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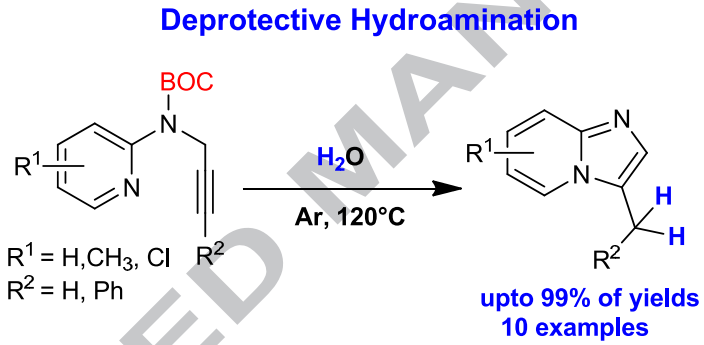

Abstract: Metal-free synthesis of substituted imidazole[1,2-a]pyridines from deprotective N-(prop-2-yn-1-yl)pyridin-2-amines in water. Electron releasing substituents on pyridine ring provided pure products in quantitative yields without separation by column chromatography.

Keywords: N-Propargylaminopyridines, imidazo[1,2-a]pyridine, hydroamination, synthesis, water.