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Microwave assisted synthesis of 2-aminooxazolo [4,5-*b*] pyridine derivatives via intramolecular C–O bond formation in aqueous medium

Umesh B. Kosurkar [a], Tulshiram L. Dadmal [a], K. Appalanaidu [a], Y. Khageswara Rao [a], Jagadeesh B. Nanubolu [b], Ravindra M. Kumbhare [a,*]

[a] *Fluoroorganic Division, Indian Institute of Chemical Technology, CSIR, Hyderabad 500 007, India*
[b] *Laboratory of X-ray Crystallography, Indian Institute of Chemical Technology, CSIR, Hyderabad 500 007, India*

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ABSTRACT

A highly, efficient synthetic protocol for the synthesis of 2-aminooxazolo[4,5-*b*]pyridine derivatives is established via intramolecular C–O bond coupling using copper iodide as a catalyst and water as solvent. A variety of functionalized substrates were found to react under this reaction conditions to provide products in good to excellent yields.

In recent years, an intramolecular carbon–oxygen cross coupling chemistry for the synthesis of benzoxazole employing copper catalysis is reported.[1] Pyridine nucleus found in many alkaloids such as Ricicine, Nicotine, Anabasine, Myosmin, etc. is considered as valued biological active compounds. Heterocycles fused with pyridine nucleus resulted in anticancer,[2] antipyretic,[3] and anticonvulsant activities.[4] The recent literature[5] showed that pyridine derivatives worked well on breast cancer cell line MDA-MB-231, MCF-7. Oxazole containing compounds possess anticancer and anti-HIV-1 properties,[6,7] leukemia and potent selective 5-HT1A serotonin receptor ligands,[8] and some other useful activities.[9–12] Pyridine analog of benzoxazole possess biological activity[13] and fluorinated analog of 2-aminooxazolo[5,4-*b*] pyridine derivatives is an important candidate for the treatment of Alzheimer disease.[14]

Classical method[15] for the synthesis of 2-aminooxazolo[4,5-*b*] pyridine involves the use of silver nitrate which is toxic, corrosive and requires harsh reaction condition. Other methods[16] by use of volatile solvents take more time. To the best of our knowledge there is no report for the synthesis of 2-aminooxazolo[4,5-*b*] pyridine derivatives from the 2-amino-3-hydroxypyridine in aqueous medium. Therefore the development of an efficient method for its construction is highly desirable for drug discovery. Hence in continuation of our efforts to develop the efficient procedure for the preparation of heterocyclic entities,[17] herein we describe the microwave assisted synthesis of 2-aminooxazolo[4,5-*b*] pyridine derivatives with more yield in less time using inexpensive and non-toxic copper iodide which provides the efficient strategy for the C–O cross coupling.

Microwave technology shortens the reaction time, provides better yield and high purity in chemical transformation. Microwave accelerated one pot reactions have been applied recently.[18] In recent years, use of water as reaction media has gained much interest. In industries around 80% of the waste are produced by the use of organic solvents.[19,20] Water is abundant, cheap, nonflammable, nontoxic, and green solvent. Selectivity and reactivity in reaction carried out in aqueous media can be achieved due to chemical and physical properties of water which cannot be possible using organic solvents (Scheme 1).[21–23]

In order to optimize the reaction condition, we have selected the synthesis of 2-aminooxazolo [4,5-*b*] pyridine as a model reaction (Table 1). Initially, we carried out the reaction in water with and without catalysts at room temperature but there is no progress of reaction. Later on heating in water without catalyst using triethylamine as base for 5 h, we observed less yield (21%). Reaction resulted into good yield (85%) on conventional heating

* Corresponding author. Tel.: +91 40 27191776; fax: +91 40 27193185.
E-mail address: rakumbhare@yahoo.com (R.M. Kumbhare).

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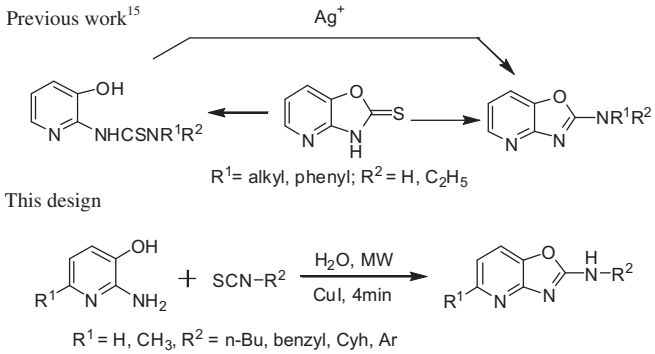
0040-4039/



Scheme 1. Comparison of previous work with our design.

Table 1
Catalyst optimization

Entry	Cu catalyst (5 mol %)	Power (W)	Time (min)	Yield[a] (%)
1	CuCl	540	6	70
2	CuBr	540	6	72
3	**CuI**	**360**	**4**	**88**
4	Cu_2O	540	5	53
5	$Cu(SO_4)_2$	540	6	58
6	$Cu(OAC)_2$	540	7	66

Note: Bold value indicate the reaction condition.
Reaction condition: 2-amino-3-hydroxy pyridine (1 mmol), Phenyl isothiocyanate (1 mmol), Et_3N (4 mmol), CuI, 360 W at 100 °C and water as solvent.
[a] Isolated yield.

at 90 °C using CuI as catalyst in water solvent for 3 h. But when reaction was carried out under microwave irradiation using different catalysts (Table 1), CuI showed better yield in shorter time. So we selected microwave method for the reaction. Copper iodide is responsible for cyclodesulfurization by removing sulfur from 1-(3-hydroxypyridin-2-yl)-3-phenylthiourea in the form of Cu_2S as black precipitate and develops the intramolecular C–O cross coupling. Further product of the reaction **3o** was confirmed by X-ray crystallography[24] (Fig. 1).

Our observation in the change of yield concludes that yield depends on the electrophilicity of isothiocyanate and nucleophilicity of 2-amino-3-hydroxy pyridine. Now, to study the viability of reaction, a series of substrates were studied (Table 2).[25] The 3-hydroxy-2-amino pyridine and its 6-methyl analog do not show a significant change in the yield of the products. Electron withdrawing substituent on phenyl isothiocyanate increases the yield of product while electron donating substituent decreases the yield, giving **3r** in high

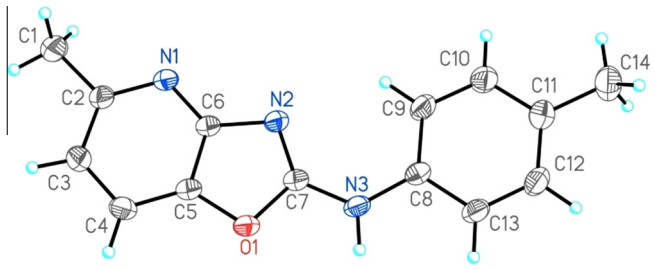
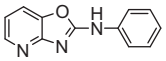
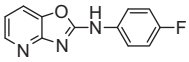
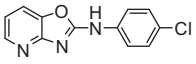
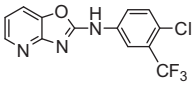
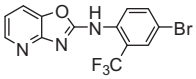
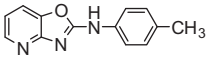
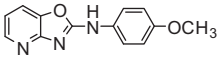
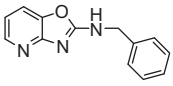
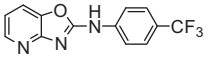
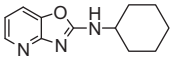
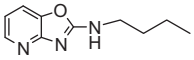
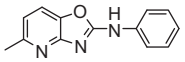
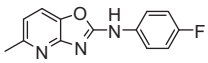
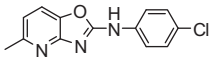
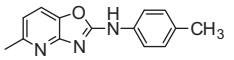
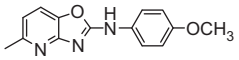
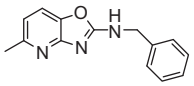
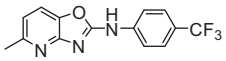
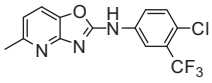
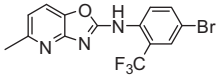
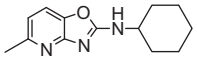
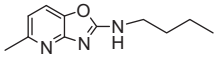


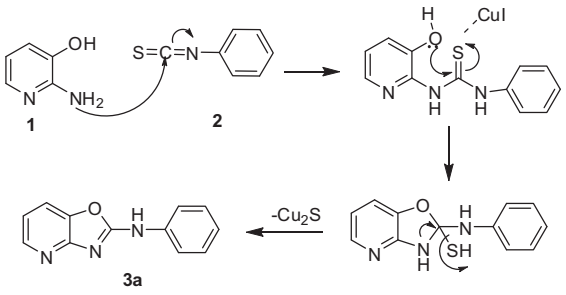
Figure 1. ORTEP molecular diagram of **3o**.

Table 2
Copper iodide catalyzed C–O bond formation

Entry	Product	Time (min)	Yield[a] (%)
3a		4	88
3b		5	84
3c		5	83
3d		4	84
3e		4	86
3f		4	83
3g		5	81
3h		5	80
3i		3	90
3j		5	78
3k		5	76
3l		4	90
3m		4	85
3n		4	84
3o		4	83
3p		5	82
3q		5	81
3r		3	92
3s		3	88
3t		3	91
3u		5	79
3v		5	78

[a] Isolated yields.

yield. When pyridine substrate was treated with cyclohexyl and *n*-butyl isothiocyanate, the reaction results in less yield of the products compared to aromatic isothiocyanate. This is attributed to the decrease in electrophilicity of isothiocyanate carbon.



Scheme 2. A plausible mechanism for the synthesis of **3a**.

A plausible mechanism for the synthesis of **3a** is depicted below (Scheme 2).

In summary, we have developed a novel, one pot, and versatile method for the synthesis of 2-aminooxazole[4,5-*b*]pyridine via intramolecular C–O bond coupling using copper iodide as a catalyst in aqueous solvent using microwave technology. Starting materials used are readily available, inexpensive, and harmless. The procedure is extremely useful in synthetic and medicinal chemistry. As this method is conducted in aqueous solvent which is economically and environmentally benign solvent, it can be applicable in industry.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.090.

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24. CCDC 964599 contains the supplementary crystallographic data for this paper. Crystal data for **3o**: $C_{14}H_{13}N_3O$, $M = 239.27$, colourless block, $0.39 \times 0.24 \times 0.18$ mm^3, monoclinic, space group $P2_1/c$ (No. 14), $a = 6.1565(6)$, $b = 17.7411(16)$, $c = 12.1353(9)$ Å, $\beta = 15.779(4)°$, $V = 1193.54(18)$ Å^3, $Z = 4$, $D_c = 1.332$ g/cm^3, $F_{000} = 504$, CCD area detector, Mo-Kα radiation, $\lambda = 0.71073$ Å, $T = 293(2)$ K, $2\theta_{max} = 50.0°$, 11,333 reflections collected, 2105 unique ($R_{int} = 0.0258$), Final *GooF* = 0.898, *R1* = 0.0430, *wR2* = 0.1169, *R* indices based on 1916 reflections with $I > 2\sigma(I)$ (refinement on F^2), 169 parameters, $\mu = 0.087$ mm^{-1}.
25. *Typical experimental procedure*: In seal tube, the mixture of 2-amino-3-hydroxy pyridine (0.1 g, 1 mmol), Phenyl isothiocyanate (1 mmol), Triethylamine (4 mmol) and CuI (5 mol %) were added in water (2 mL) and the reaction mixture was microwave irradiated at 360 W for 4 min at 100 °C. After the completion of reaction (monitored by TLC), water added to the reaction mixture and extracted with ethyl acetate. Organic layer washed with brine solution (2 × 20 mL) and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure to give crude product which was further purified by Silica gel column chromatography (20% EtOAc/*n*-Hexane) to give **3a** (0.17 g, 88%).
*Spectral data for N-phenyloxazolo[4,5-b]pyridin-2-amine (**3a**)*: White solid; mp 261–263 °C; IR (KBr): 3374, 2875, 1651, 1548, 1423, 1221 cm^{-1}; ^{1}H NMR (300 MHz, DMSO) δ_H: 10.61 (1H, s, NH), 8.34–8.19 (1H, m, ArH), 7.92–7.54 (3H, m, ArH), 7.47–7.28 (2H, m, ArH), 7.18–6.98 (2H, m, ArH); ^{13}C NMR (300 MHz, DMSO) δ_C : 158.8, 155.9, 142.7, 138.4, 136.6, 127.4, 121.4, 116.9, 115.3, 113.9; HRMS: *m/z* calcd for $C_{12}H_{10}ON_3$ $(M+H)^+$: 212.0818; found 212.0813.