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GRAPHICAL ABSTRACT

Transition metal and base free synthesis of 2-aryl-2-oxazolines from aldehydes and β-amino alcohols catalyzed by Potassium Iodide

C. Uma Maheswari,*[1] G. Sathish Kumar, [2] and M. Venkateshwar.[2]

[1] Department of Chemistry, Center for Nanotechnology and advanced Biomaterials (CeNTAB), School of Chemical and Biotechnology, SASTRA University, Thanjavur-613401, India

[2] Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500607, India

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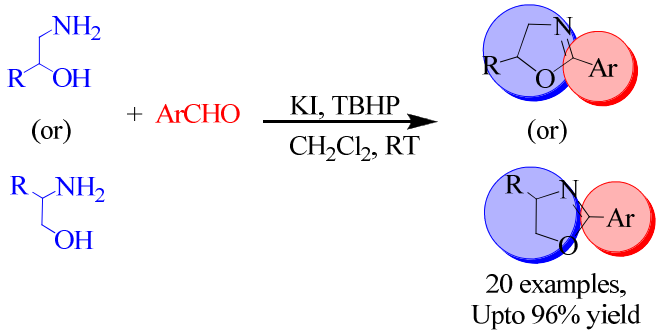

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Transition metal and base free synthesis of 2-Aryl-2-oxazolines from aldehydes and β-amino alcohols catalysed by Potassium Iodide

Cite this: DOI: 10.1039/xoxxoooooox

C. Uma Maheswari,* [a] G. Sathish Kumar [b] and M. Venkateshwar. [b]

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

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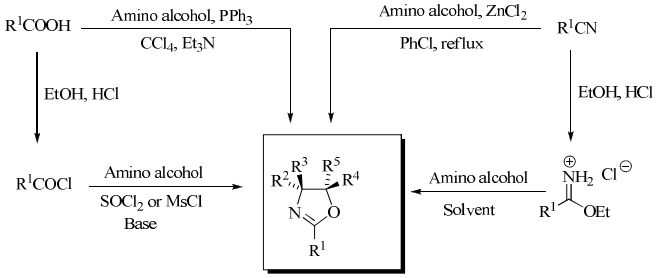
Synthesis of 2-aryl-2-oxazolines from *β*-amino alcohols and aldehydes was achieved in good to excellent yields by employing Potassium Iodide (KI)-*tert*- Butyl hydroperoxide (TBHP) catalytic system. This protocol is very mild, metal and base free and can be performed under ambient reaction conditions. This oxidative cyclization strategy was further extended for the synthesis of optically active 2-oxazolines, which can act as very useful chiral auxiliaries and as ligands.

Construction of nitrogen containing five-member heterocycles is an important synthetic strategy for organic chemists due to their wide range of applicability in synthesis of various biologically active compounds and their scope as ligands in homogeneous asymmetric catalysis. Among them, 2-oxazolines (4,5-dihydrooxazoles) exist in a variety of natural products, bio-active compounds and also as enzyme inhibitors.[1] Oxazoline derivatives exhibit various pharmaceutical activities such as anti-diabetic,[2] antihypertensive,[3] anti-depressive,[4] anticancer,[5] anti-HIV-1[6] and antitumor[7] activities to name a few. Chiral mono-and bis-oxazolines are used as chiral auxiliaries and as ligands in asymmetric synthesis.[8] Achiral oxazolines finds their use as an important protecting group and as a valuable intermediate in organic synthesis.[9] Numerous methods for the construction of 2-oxazolines have been reported (Scheme 1), from carboxylic acids,[10] esters,[11] nitriles,[12] aldehydes,[13] and olefins.[14]

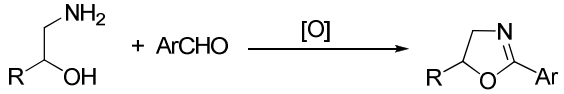
Despite certain degree of success in the above mentioned methods, they have several limitations like multi-step synthesis and significant amount of by-product formation. Moreover, some of these methods require elaborate purification process and harsh reaction conditions. Oxidative methods for the formation of heterocyclic compounds are quite attractive and several methods were already reported for the formation of benzoxazoles, benzimidazoles and imidazolines from aldehydes.[15]

[a] Department of Chemistry, School of Chemical and Biotechnology, SASTRA University, Thanjavur-613401, India, Tel.: +91 -(4362) 304346; Fax: +91-(4362)-264111.
[b] Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500607, India.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/



Scheme 1: Common routes for the construction of 2-oxazolines.

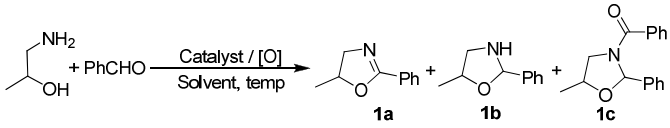
However, synthesis of oxazolines by oxidative strategy from aldehydes was little explored and was performed using pyridinium hydrobromide perbromide (PHPB),[16] N-Bromosuccinimide (NBS),[17] and 1,3-Diiodo-5,5-dimethylhydantoin (DIH).[18] The main drawbacks of these procedures are: they use stoichiometric amount of reagents to facilitate the conversion in the presence of excess base. This in turn leads to excess amount of inorganic salts as by-product. To circumvent this problem associated with stoichiometric process, they can be replaced by environmentally friendly catalytic oxidative methods which comes under the well-known term "green chemistry" as proposed by Anastas and Warner.[19] In catalytic oxidation, the stoichiometric oxidants used for synthesis of fine chemicals are molecular oxygen, hydrogen peroxide, alkyl hydroperoxides especially *tert*- Butyl hydroperoxide (TBHP), persulfate, percarbonate, hypochlorite and hypochlorates to name a few.[20] In similar lines, there are few reports on TBHP mediated oxidative cyclization for the synthesis of heterocycles. For eg. for the synthesis of benzothiazoles,[21] pyrazoles,[22] oxazoles,[23] 2-phenylquinazolines,[24] in the presence of iodine or transition metals like Cu or Fe. But there are no reported literatures for the synthesis of 2-oxazolines. Thus formation of 2-aryl-2-oxazolines by oxidative cyclization starting from readily available aldehydes and *β*-amino alcohols prove to be an important strategy (Scheme 2).



Scheme 2: Formation of 2-aryl-2-oxazolines by Oxidative Cyclization.

We have successfully demonstrated the catalytic oxidative transformations *viz.*, synthesis of 3*H*-Quinazolin-4-ones and 4*H*-3,1-Benzoxazin-4-ones,[25] amidation of aldehydes and alcohols,[26] selective oxidation of aromatic amines to nitro compounds [27] using catalytic amount potassium iodide in the presence of TBHP as the external oxidant. As part of our ongoing study on iodine/iodide mediated catalytic oxidative functionalization, herein, we would like to present a mild and selective synthesis of 2-aryl-2-oxazolines using KI-TBHP catalytic system.

Table 1: Optimization of reaction conditions [a,b]



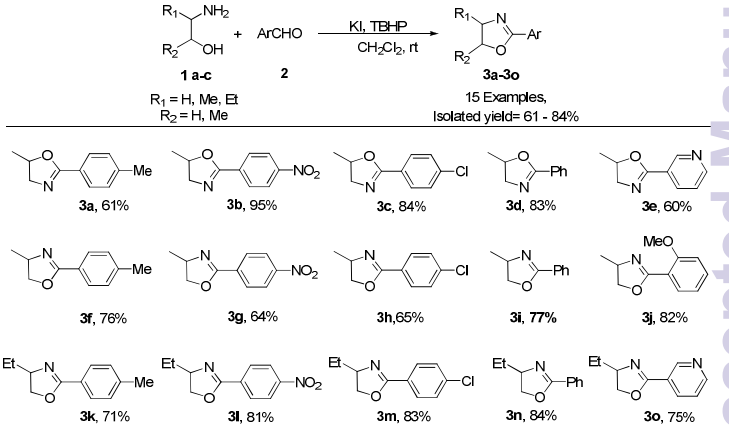
S.No	Catalyst (mmol)	[O]	Solvent	Conversion (%)[b]	Selectivity[b]		
					1a	1b	1c
1.	--	--	AcOH	58	--	100	--
2.	--	TBHP	AcOH	60	06	83	--
3.	KI	--	AcOH	64	--	100	--
4.	KI	TBHP	AcOH	95	45	--	27
5.	KI	TBHP	H_2O	93	42	--	19
6.	KI	TBHP	CH_3CN	67	54	18	16
7.	KI	TBHP	CH_3CN[c,d]	63	40	16	--
8.	KI	TBHP	THF	48	05	85	--
9.	KI	TBHP	CH_2Cl_2	92	88	--	--
10.	KI	TBHP	Toluene	75	55	06	--
11.	KI	NaOCl	CH_2Cl_2[d]	84	03	46	--
12.	KI (0.1)	TBHP	CH_2Cl_2	64	55	33	--
13	KI (0.1)	TBHP	CH_2Cl_2[e]	89	86	--	--

[a] Reaction conditions: 1-amino-2-propanol (1.2 mmol), benzaldehyde (1 mmol), KI (0.2 mmol), 70% aq. TBHP (3.0 mmol), Solvent (3ml), rt, 6h. [b] Conversion and selectivity based on GC. [c] Reaction at 80 °C. [d] Simple amide (N-(2-hydroxypropyl)benzamide) was observed as the major product. [e] Reaction time = 12h

For our initial optimization studies, benzaldehyde and 1-amino-2-propanol was taken as the model substrates (Table 1). Blank reactions without oxidant and catalyst (KI or I_2) proved to be futile and yielded only oxazolidine (**1b**) as the major product (entries 1-3). When KI in combination with TBHP in dil. AcOH was taken, the required 2-oxazoline (**1a**) was formed along with an amide (**1c**) (entry 4). Similar observation was made using water as the solvent (entry 5). However, drastic improvement in product selectivity was observed shifting from aqueous to organic solvents. Among different organic solvents screened, CH_2Cl_2 proved to be the best solvent in terms of conversion and selectivity (entry 8). Either the change of oxidant (from TBHP to NaOCl) or decrease in catalyst loading (from 20 mol% to 10 mol%) could not improve the product conversion or selectivity (entries 10-12). But when 10 mol% of KI was used and the reaction time was prolonged for 12 h, we could observe comparable yields as 20 mol% catalyst loading with 6 h reaction time (entry 13). Thus KI in conjunction with TBHP as the oxidant in CH_2Cl_2 at room temperature was taken as the optimized reaction condition for oxidative cyclization (entry 13).

The general applicability of this reaction was evaluated with structurally diverse aldehydes and amino alcohols (Table 2). In general the yields are moderate to good with different amino alcohols and aldehydes. However, there was a slight variation in the product yields depending on the position of the substitution on the amino alcohol as well as aldehydes. For example, in case of 1-amino-2-propanol, electron withdrawing groups on aldehydes gave better yields compared to the electron donating substrates (entries 1-5). In case of 2-amino-1-propanol, yields are better with electron donating substrates (entries 6-10). No such trend was observed when 2-amino-1-butanol was taken as the amino alcohol variant. The yields are generally good with both electron withdrawing and electron donating aldehydes (entries 11-15). When we employed aliphatic aldehyde, butyraldehyde as aldehyde source with **1a** for this reaction, the yield decreased considerably (<20%). Thus this methodology was best suited for the synthesis of 2-aryl-2-oxazolines.

Table 2 Synthesis of 2-oxazolines from aldehydes catalyzed by KI-TBHP.[a,b]

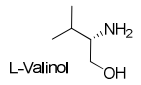
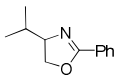
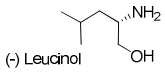
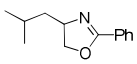
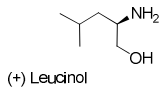
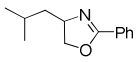
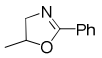
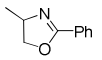


[a] Reaction Conditions: KI (0.1 mmol), 70% aq. TBHP (3.0 mmol), β-amino-alcohol (1.2 mmol), aldehyde (1 mmol), CH_2Cl_2 (3 mL), 12 h. [b] Isolated yield.

This oxidative cyclization strategy was applied for the synthesis of optically active 2-oxazolines, which are very useful as chiral auxiliaries and as ligands (Table 3). The reaction with benzaldehyde and various chiral amino alcohols (>98% *ee*) provided the product with good yields and good optical purity (entries 16-20). There is no improvement in optical purity of the product, even when the reactions were carried out at lower temperature (0 °C). The slight drop in optical purity may be explained on the basis of imine-enamine tautomerism, which accounts for partial racemization.

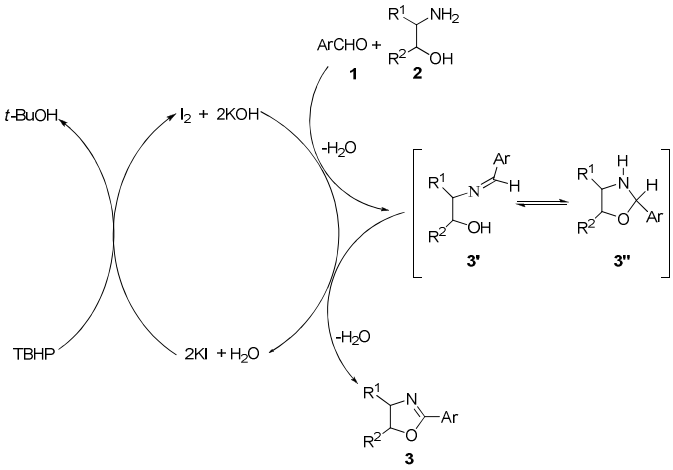
Since chiral Oxazolines are very useful chiral auxiliaries and important class of ligands, the feasibility of the present catalytic system on multi-gram scale was examined for the synthesis of **3p** [(*S*)-4-isopropyl-2-phenyl-4,5-dihydrooxazole]. Reaction of commercially available chiral amino alcohol, L-Valinol (5g, 48.5 mmol, 1.2 equiv.) with benzaldehyde (1 equiv.), KI (0.1 equiv.) and 3.0 equiv. of TBHP at room temperature in 40 mL of CH_2Cl_2 provided **3p** in 80% (6.12 g) isolated yield after 12h with good *ee* of 90.6%.

Table 3. Synthesis of chiral 2-phenyl-2-oxazolines from benzaldehyde with chiral amino-alcohols.[a]

Entry	Amino-alcohol	Product	Yield(%)[b]	Optical Purity (%)[c]
1	 L-Valinol		81	92, 96[d]
2	 (-) Leucinol		68	86
3	 (+) Leucinol		67	93
4	 (-) 1-amino-propan-2-ol		78	90
5	 (-) 2-amino-propan-1-ol		74	93

[a] Reaction Conditions: amino-alcohol (1.2 mmol), aldehyde (1 mmol), CH_2Cl_2 (3 mL), KI (0.1 mmol), TBHP (3.0 mmol), 10 h. [b] Isolated yield. [c] Optical purity based on optical rotation. [d] TBHP in decane was used.

A plausible mechanism for the formation of 2-aryl-2-oxazolines was described as in Scheme 3. The initial step could be the formation of imine **3'**. Iodine acts as a mild lewis acid, thus facilitating the intra-molecular cyclization of **3'** to give oxazolidine **3"**. Oxazolidine in presence of oxidant undergoes oxidative dehydrogenation to yield the desired 2-aryl-2-oxazolines under the present reaction condition.



Scheme 3: Plausible mechanism for the formation of 2-aryl-2-Oxazolines.

Conclusions

In summary, we have developed a simple and straightforward method for the synthesis of the 2-aryl-2-oxazolines by oxidative cyclization of aldehydes and an amino-alcohol using KI-TBHP. This method eliminates the use of transition metal, stoichiometric reagents and base for the formation of 2-aryl-2-oxazolines, a biologically active heterocyclic compound. Moreover, the reaction was carried out at ambient conditions and no other side products are obtained. The present methodology was also extended to chiral amino alcohol derivatives to yield chiral oxazolines, which are important as ligands and auxiliaries. In addition, the present non-transition metal-oxidant catalytic system also provides an easy scale-up and separation protocol.

Acknowledgements: CUM thanks SASTRA University's in house T.R. Rajagopalan funding program. She thanks Dr. K. Rajender Reddy, Senior Scientist, I&PC Division, Indian Institute of Chemical Technology (IICT), Hyderabad, India for his constant motivation and Suggestions.

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