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PII: S0040-4039(14)01963-7
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.11.070
Reference: TETL 45454

To appear in: *Tetrahedron Letters*

Received Date: 27 August 2014
Revised Date: 13 November 2014
Accepted Date: 14 November 2014

Please cite this article as: Munusamy, S., Venkatesan, S., Sathiyanarayanan, K.I., Copper catalyzed C-N bond formation / C-H activation: Synthesis of aryl 4H-3,1-benzoxazin-4-ones, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.11.070

Graphical Abstract

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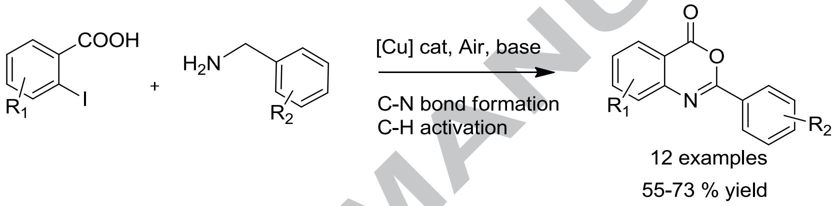

Tetrahedron Letters
journal homepage: www.elsevier.com

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

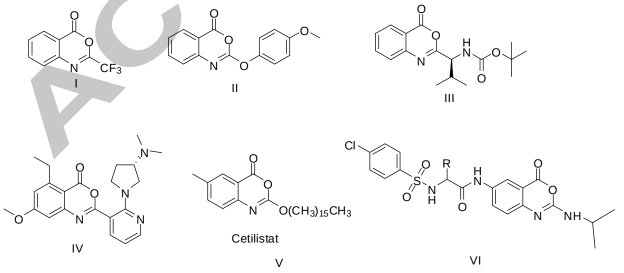
Keywords:
heterogeneous catalysis
C-N bond formation
aerobic oxidation
domino reaction
heterocycle

ABSTRACT

We have developed a practical and efficient synthesis of 2-phenyl-4H-benzo[d][1,3]oxazine-4-one derivatives through copper catalyzed tandem reaction of 2-iodobenzoic acid with arylmethanamines under aerobic conditions. Compared to the literature methods towards the synthesis of 2-phenyl-4H-benzo[d][1,3]oxazine-4-one, the synthetic method reported in this paper has broad substrate scope, mild reaction condition and uses an inexpensive catalyst.

The development of simple synthetic methods for the rapid access to *N*-heterocycles with complexity and diversity has broad applications in chemistry, biology and material sciences. This has attracted considerable attention in synthetic organic chemistry.[1] In this respect, benzoxazinones are among the most important *N*-heterocycles in many biological compounds and pharmaceutical drugs (Fig. 1).[2] They exhibit a variety of bioactivities such as antibacterial, antifungal, HSV-1 protease inhibition, serine proteases inhibition, and others.[3] Along similar lines, the key pharmacophore in cetilisate, which showed promising market prospect as an antiobesity remedy, contains benzoxazinone unit.[4]

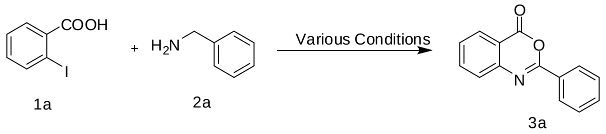
Figure 1
Structure of some of the bioactive 4H-3,1-benzoxazin-4-one derivatives



Considering the importance of these heterocyclic compounds, many synthetic routes have been developed for the synthesis of benzoxazinone derivatives.[5] Conventional methods for the synthesis of benzoxazinones are the cyclization of anthranilic acid or *N*-acylanthranilic acid[6] and palladium catalyzed carbonylation reactions of *o*-iodoanilines with unsaturated halides,[7] triflates[8] and acid chlorides[9] which have been developed by many groups recently. Other notable synthetic methods include solvent-free synthesis from isatoic anhydride[5] and orthoester with primary amine employing silica-sulphuric acid (SSA)[10] and a solid phase traceless synthesis.[11] Recently, Rajendar Reddy and co-workers reported the synthesis of benzoxazinones through benzylic oxidation and oxidative dehydrogenation using potassium iodide-tert-butylhydroperoxide(KI-TBHP).[12] Zheng-Hui Guan and coworkers have reported the synthesis of 2-arylbenzoxazinones from the oxidation of 2-arylindoles using oxone as the sole oxidizing agent.[13] Another notable method has been developed by Liu and coworkers. This method involves palladium catalyzed C≡C triple bond cleavage of 2-azidoalkynylbenzenes for the synthesis of benzoxazinones.[14] However, in terms of substrate scope, yields and reaction conditions, these methods suffer from one or more drawbacks. These methods use carbon monoxide gas or heavy metals or rely on the involvement of multi-step process for the synthesis of substrate. Herein, we report a simple, efficient and economical copper catalyzed strategy for the synthesis of benzoxazinones derivatives through cascade reaction of 2-iodobenzoic acid and (aryl) methanamines with air as the sole oxidizing agent without the addition of any ligand. Oxidation reactions that utilize environmentally benign oxidizing agents such as peroxides or O_2 are preferable according to the principles of green chemistry.[15]

Initial experiments were carried out with 2-iodobenzoic acid and benzylamine as the model substrates to optimize the reaction conditions including catalaysts, bases and reaction temperature under air (1atm). Various copper catalysts were tested (0.2 equivalents) with 2 equivof K_2CO_3 (with respect to 2-Iodobenzoic acid) as a base and DMSO as a solvent at 90 °C. Among the various copper catalysts used, CuI provided the expected product with high yield (Table 1, entry). During optimization of the catalyst, it was noted that this CuI catalyzed tandem reaction could be realized without the addition of any ligand. Effects of bases, including organic and inorganic bases, was screened, and K_2CO_3 showed the best activity. Then the effects of solvent on this tandem reaction were also investigated using CuI as the catalyst, and the highest yield was observed in the case of DMSO as the reaction medium. When we carried out the reaction in nitrogen atmosphere (exclusion of air), an Ullmann type *N*-arylated product, 2-(benzylamino) benzoic acid was observed.

Table 1
Optimization of the reaction condition for the synthesis of **3a**[a]



Entry	Catalyst	Base	Solvent	Yield(%)[b]
1	CuI	K_2CO_3	DMSO	70
2	CuBr	K_2CO_3	DMSO	58
3	CuCl	K_2CO_3	DMSO	42
4	$Cu(OAc)_2$	K_2CO_3	DMSO	35
5	$CuSO_4$	K_2CO_3	DMSO	Trace
6	$CuCl_2$	K_2CO_3	DMSO	Trace
7	CuI	Na_2CO_3	DMSO	45
8	CuI	TEA	DMSO	42
9	CuI	Pyridine	DMSO	30
10	CuI	K_2CO_3	DMF	40
11	CuI	K_2CO_3	Acetonitrile	33
12[c]	CuI	K_2CO_3	Solvent free	---

[a]Unless otherwise noted, the reactions were carried out with 2 mmol of 1a and 4 mmol of 2a, 0.4 mmol of catalyst and 4mmol of base under aerobic condition. [b]Isolated yield [c]reaction was carried out under solvent-free condition.

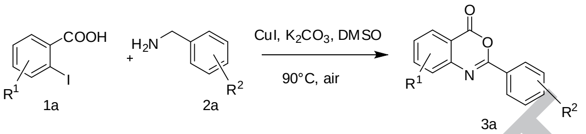
With the optimized reaction condition in hand, the scope and the generality of this CuI catalyzed tandem reaction leading to 2-arylbenzoxazinones were investigated. First, it was observed that aryl- and heteroaryl- substituted benzyl amines were compatible with the reaction conditions to provide the desired product in moderate to good yields (Table 2).

It was also found that various aryl substituted benzylamines underwent this tandem reaction smoothly irrespective of the substituents present in the aromatic ring. In addition to this, we tried the same reaction in alkyl methanamines but the results were negative. This copper catalyzed domino reaction could tolerate many functional groups such as C-Cl bond, a C-Br bond, a nitro group and heterocycles containing nitrogen in aryl methanamines.

In order to explore the reaction mechanism, we carried out the reaction in nitrogen atmosphere (exclusion of air) to avoid the oxidation process. As expected, we got the Ullmann coupled product without cyclization, and we got only trace amount of 2-arylbenzoxazinones. The isolated Ullmann product was again treated with our standard reaction condition (Scheme 1) under air, and we got the 2-arylbenzoxazinones in good yield. A possible mechanism has been proposed based on the results derived from the experiments carried out. In the first step, copper catalyzed Ullmann coupling afforded 2-(benzylamino) benzoic acid (4). Subsequent aerobic oxidation of **4** afforded intermediate I containing C=N bond and nucleophilic addition of carboxylic acid group to the C=N bond in I gave II. Intermediate **4** was isolated and characterized (see supporting information). Further aerobic oxidation of II affords the target product (**3**).

Table 2

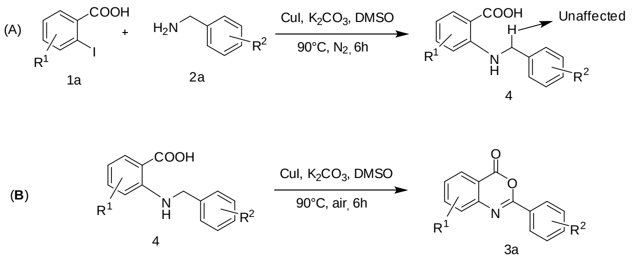
Copper catalyzed domino condensation for the synthesis of 4H-3,1-benzoxazin-4-ones[a]



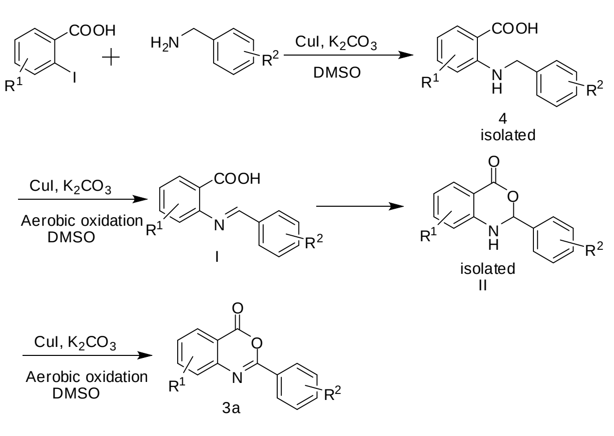
Entry[a]	3	Yield [%][b]	Time (h)
1	**3a**: R^1 = H, R^2= H	70	12
2	**3b**: R^1 = H, R^2= 2-Cl	65	13
3	**3c**: R^1 = H, R^2= 3-Cl	68	12
4	**3d**: R^1 = H, R^2= 4-Cl	72	14
5	**3e**: R^1 = H, R^2= 4-Br	73	12
6	**3f**: R^1 = H, R^2= 4-NO_2	63	11
7	**3g**: R^1 = H, R^2= 3-CH_2NH_2	58	14
8	**3h**: R^1 = H, R^2 = 4-CH_2CH_3	55	15
9	**3i**: R^1 = H, R^2=3- picolylamine	68	12
10	**3j**: R^1 = 4-Cl, R^2= H	60	11
11	**3h**: R^1 = 4-Cl, R^2= 3-F	62	11
12	**3i**: R^1 = 4-Cl, R^2= 4-Cl	65	11

[a]Unless otherwise noted, the reactions were carried out with 2 mmol of 1a and 4 mmol of 2a, 0.4 mmol of catalyst and 4 mmol of base under aerobic condition. The samples are characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by reported methods. [b]Isolated yield.

Scheme 1.
(A) Reaction between **1a** and **2a** under nitrogen atmosphere affords Ullmann product (B) Aerobic oxidation of isolated Ullmann product under air atmosphere



Scheme 2.
Possible mechanism for the Copper catalyzed domino synthesis of 2-arylbenzoxazinanes



In summary, we report that we have developed a simple and efficient copper catalyzed domino synthesis of 2-arylbenzoxazinones using 2-iodobenzoic acid and substituted benzylamine under air.[16] This synthetic methodology has many advantages such as 1) easily available starting material 2) use of air as an oxidizing agent 3) ligand-free condition.

Acknowledgment

S. M and S. V thank VIT University, Tamil Nadu, India, for providing Research Associateship. The DST-FIST NMR facility at VIT University is greatly acknowledged.

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16. *General procedure for the synthesis of 2-phenyl-4H-benzo[d][1,3]oxazine-4-one:* To an oven dried three necked RB flask containing 2-iodobenzoic acid (**1**) (2 mmol), benzyl amine (**2**) (4 mmol) and CuI (0.4 mmol) in DMSO (3ml) 0.55 g of K_2CO_3 was added. Then, the reaction mixture was stirred at 90 °C under air atmosphere for 12h. The completion of the reaction was monitored by TLC. After being cooled at room temperature the reaction mixture was poured into ice cooled water and extracted with ethyl acetate two times. The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography (hexane(80) / ethyl acetate (20)) on silica gel to afford 2-phenyl-4H-benzo[d][1,3]oxazine-4-one.


COOH
I
R1
H2N
R2
[Cu] cat, Air, base
C-N bond formation
C-H activation
O
O
N
R1
R2
12 examples
55-73 % yield