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Direct vinylogous oxidative cross-dehydrogenative coupling of 4-nitroisoxazoles with *N*-aryl tetrahydroisoquinolines in water under air conditions†

Yong Zhang,*[a] Biao-Wen Wei,[ab] Wen-Xin Wang,[a] Lei-Ling Deng,[a] Long-Jun Nie,[a] Hai-Qing Luo[a] and Xiao-Lin Fan[a]

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A direct vinylogous cross-dehydrogenative coupling (CDC) reaction of *N*-aryl tetrahydroisoquinolines with 3,5-dialkyl-4-nitroisoxazoles catalysed by CuBr using air as the oxidant in water has been developed. This new strategy provides an efficient and environmentally benign way to access medicinally important isoxazole substituted tetrahydroisoquinoline derivatives under mild conditions.

The development of novel and environmentally benign strategies for constructing C–C bonds is of great significance to organic chemists. In this respect, the direct catalytic oxidative cross-dehydrogenative coupling (CDC)[1] of two C–H bonds, which avoids the prefunctionalization of substrates, is widely recognized as one of the most direct, atom economical and clean methods for the formation of new C–C bonds. Although various oxidants including inorganic metal salts and organic oxidants are applicable, the use of molecular oxygen is quite promising because water may be the only byproduct in these reactions.[2] In particular, when water was used as the only solvent, these aerobic CDC reactions in water processes can completely meet the criteria of green chemistry.[3] However, examples of aerobic CDC reactions in water are quite rare.[4]

On the other hand, selective C–C bond formation at a remote position is a major challenge in modern organic synthesis.[5] With the exploitation of the vinylogy concept,[6] the vinylogous reaction has emerged as an effective strategy to tackle this challenge.[7] However, so far only two examples have recently been disclosed in the literature concerning the application of the vinylogy concept in CDC reaction. In 2011, Carcía Mancheño[8] realised the first example of direct γ-alkylation of α,β-unsaturated aldehydes by isochromans using oxoammonium salt as the oxidant, albeit with poor yields and selectivities. Using silyloxyfurans as the Mukaiyama-type reagents, Doyle[9] found that both rhodium and iron could catalyse the oxidative indirect vinylogous Mannich reaction of tertiary anilines. From the standpoint of atom economy, the development of a novel catalytic direct vinylogous CDC reaction to efficiently synthesise target molecular bearing scaffolds of complexity is still highly desirable.

Both tetrahydroisoquinolines (THIQs)[10] and isoxazoles[11] are heterocyclic privileged scaffolds in pharmaceutical and natural products with a broad spectrum of interesting biological activities respectively. The reasonable assembly of isoxazole and THIQ for the synthesis of isoxazole–THIQ conjugates may provide a new platform for drug discovery. As an extension of our continuous research efforts to develop vinylogous reactions,[12] we described herein the first direct vinylogous CDC reactions of 3,5-dialkyl-4-nitroisoxazoles with *N*-aryl THIQs. This approach provides an easy access to highly functionalized isoxazole substituted *N*-aryl THIQ derivatives (Fig. 1).

To begin our investigation, several copper salts were initially screened to evaluate their abilities to promote the direct vinylogous CDC reaction of *N*-phenyl THIQ **1a** with 3,5-dimethyl-4-nitroisoxazole **2** at 50 °C in THF under air conditions (Table 1, entries 1–6). Among all the copper salts tested, CuBr was proved to be the best catalyst to furnish the desired vinylogous product **3a** in 65% yield. Use of organic solvent other than THF gave diminished yields (entries 7–12). To our delight, a slight improvement of yield was observed when water was used as the solvent. By elevating the reaction temperature to 80 °C, the reaction rate was increased to generate 71% of the desired product after 30 h. Using oxygen as the oxidant resulted in a similar outcome (24 h, 72% yield). Finally, air was selected as the optimal oxidant due to its natural abundance.

Good substrate scope was observed for the copper catalysed direct vinylogous oxidative CDC addition of 3,5-dimethyl-4-nitroisoxazole to *N*-aryl THIQs. Aryl-substituted THIQs with electron-donating substituents in the *para*- and *meta*-positions

[a]*Key Laboratory of Organo-Pharmaceutical Chemistry, Gannan Normal University, Ganzhou 341000, P. R. China. E-mail: yong_zhanggnnu@126.com; Fax: +86 797 8393536; Tel: +86 797 8393536*

[b]*School of Chemistry & Chemical Engineering, South China University of Technology, Guangzhou 510641, P. R. China*

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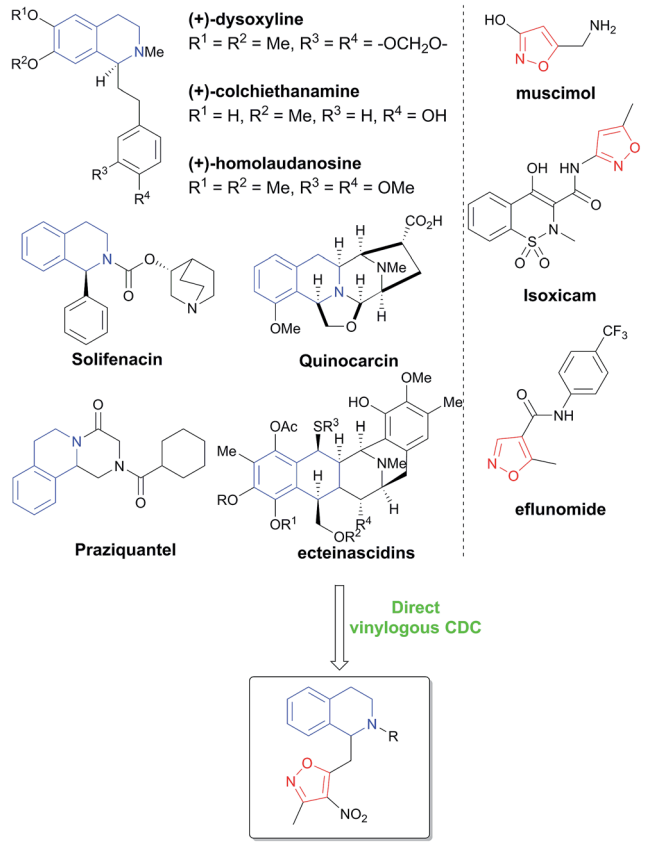
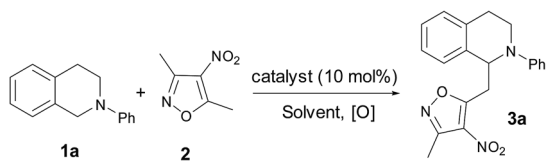


Fig. 1 Selected examples of natural products and pharmaceuticals possessing tetrahydroisoquinoline and isoxazole structural framework.

Table 1 Optimization of reaction conditions[a]



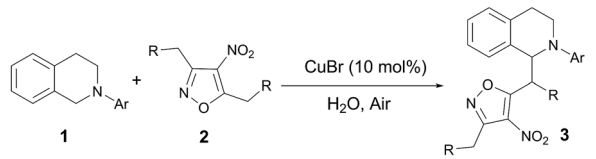
Entry	Catalyst	Solvent	Oxidant	Time (h)	Yield[b] (%)
1	CuCl	THF	Air	30	60
2	CuBr	THF	Air	30	65
3	CuI	THF	Air	30	14
4	CuCN	THF	Air	30	27
5	$Cu(OTf)_2$	THF	Air	30	39
6	$Cu(OAc)_2$	THF	Air	30	14
7	CuBr	DCE	Air	30	56
8	CuBr	Toluene	Air	48	42
9	CuBr	CH_3CN	Air	24	54
10	CuBr	EtOH	Air	36	43
11	CuBr	DMF	Air	36	36
12	CuBr	DMSO	Air	30	60
13	CuBr	H_2O	Air	48	67
14[c]	CuBr	H_2O	Air	30	71
15[c,d]	CuBr	H_2O	Air	48	50
16[c]	CuBr	H_2O	O_2	24	72

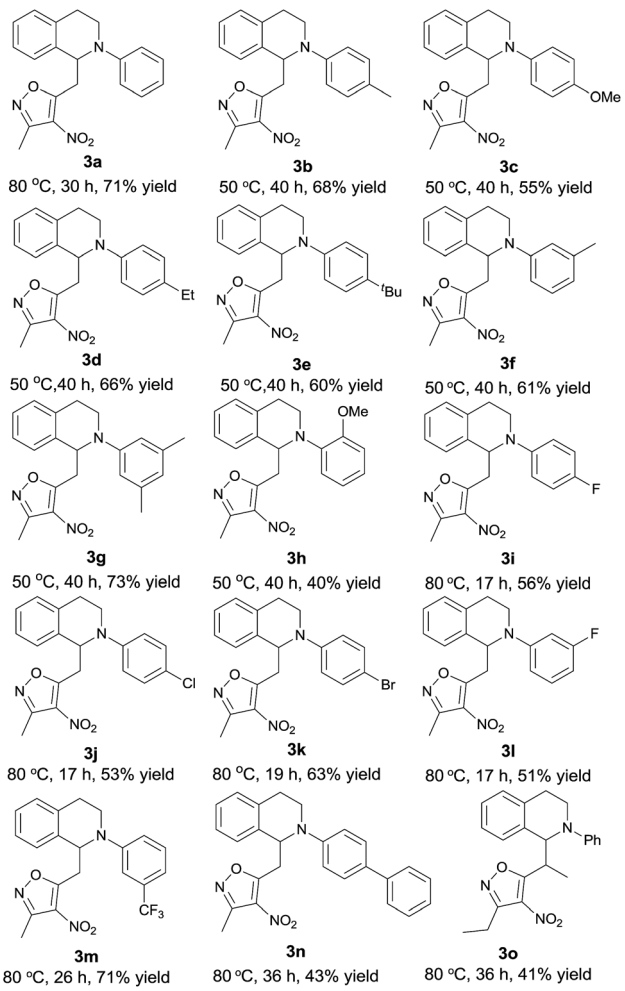
[a] Unless otherwise noted, the reaction was performed with 0.4 mmol of **1a**, 0.2 mmol of **2** and 10 mol% of catalyst in 0.4 mL solvent at 50 °C. [b] Isolated yield. [c] These reactions were performed at 80 °C. [d] 5 mol% of catalyst was used.

of the phenyl ring performed well at 50 °C to give the desired products in satisfactory yields (Table 2, **3b–g**), whist substrate with substituent in the *ortho*-position resulted in an obviously diminished yield (**3h** as an example). Moderate to good yields were also remained when the aryl ring bearing halogen and electron-withdrawing substituents (**3i–n**), albeit with a higher reaction temperature. The use of 3,5-diethyl-4-nitroisoxazole instead of 3,5-dimethyl-4-nitroisoxazole also gave the desired adduct with moderate yield (the ratio of the two diastereoisomers is 1 : 1).

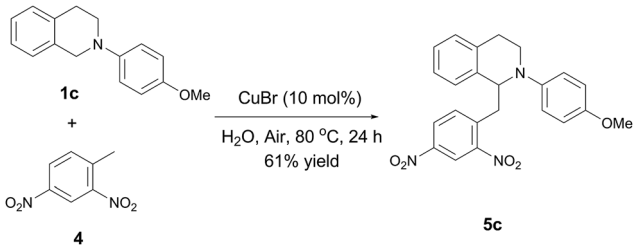
In addition to 4-nitroisoxazole, the direct vinylogous oxidative CDC reaction in water under air condition was also

Table 2 Direct vinylogous CDC reaction of *N*-aryltetrahydroisoquinoline with isoxazole[a]





[a] Unless otherwise noted, the reaction was performed with 0.4 mmol of **1**, 0.2 mmol of **2** and 10 mol% of catalyst in 0.4 mL water. Yield refers to the isolated product.



Scheme 1 The vinylogous CDC reaction of 2,4-dinitro-toluene.

applicable to aryl methane. As shown in Scheme 1, the reaction of 2,4-dinitro-toluene[13] with *N*-aryl THIQ **1c** preceded smoothly under the similar conditions employed in Table 2 to give moderate yield of the vinylogous adduct.

According to the mechanism for the copper catalysed CDC of THIQs clarified by Klussmann,[14] a possible mechanism for the direct vinylogous CDC reaction is given in Fig. 2. The oxidation of **1** was catalysed by copper with oxygen to produce the key iminium ion intermediate **I**, which was trapped by nitronate anion **II** derived from **2**, the formation of which was facilitated by copper. This vinylogous type aza-Henry addition provides the final product **3** along with H_2O as the only by-product.

In order to prove the synthetic potential of the current reaction, we then devoted our efforts to explore some additional transformations of the vinylogous CDC products. As shown in Scheme 2, a partial reduction of the vinylogous CDC adduct **3a** was achieved using $NaBH_4$ as the reducing agent to give isoxazoline **7** in high yield. On the other hand, the 4-nitroisoxazole core can be converted to 4-nitropyrazolyl core by treatment with hydrazine under basic condition, thus affording the pyrazol–THIQ conjugation **6** in high yield, the configuration of which was unambiguously confirmed by X-ray crystallographic analysis.[15] It is noteworthy that pyrazole also represents an important scaffold in pharmaceutical and agrochemical sciences.[16]

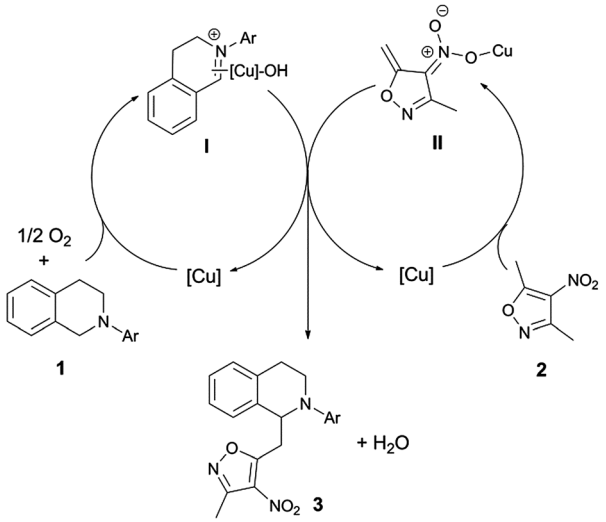
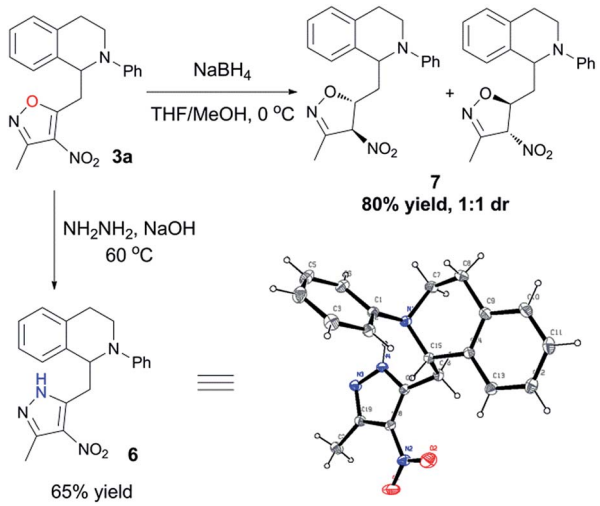


Fig. 2 Possible mechanism.



Scheme 2 Transformations of the corresponding vinylogous CDC products.

Conclusions

In summary, we have developed a direct catalytic vinylogous cross-dehydrogenative coupling (CDC) reaction of *N*-aryl tetrahydroisoquinolines with vinylogous nucleophiles such as 3,5-dialkyl-4-nitroisoxazoles and 2,4-dinitro-toluene. To the best of our knowledge, this is the first example of direct vinylogous CDC reaction in water under air condition. This protocol is direct, environmentally benign and operationally simple for the synthesis of highly functionalized isoxazole substituted tetrahydroisoquinoline derivatives in moderate to good yields.

Acknowledgements

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