Copper(II)-catalyzed-α-C(sp^3)-H activation of cyclic amines: a simple and efficient strategy for the synthesis of fused pyrazole derivatives

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Graphical Abstract

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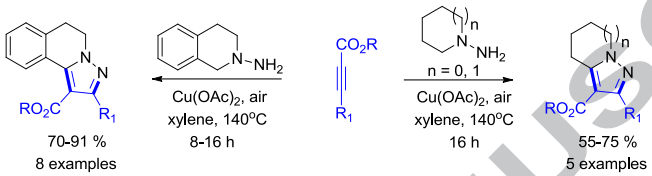

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Copper(II)-catalyzed-α-C(sp^3)-H activation of cyclic amines: a simple and efficient strategy for the synthesis of fused pyrazole derivatives

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ABSTRACT

In this paper, we have described a simple and efficient strategy for the synthesis of fused pyrazole derivatives. The key steps of our strategy involves hydroamination, copper-catalyzed cross dehydrogenative coupling (CDC) followed by aromatization (aerial oxidation) in one-pot. Our strategy offers a valuable alternative to known methods for synthesis of fused pyrazole derivatives. Overall, we have synthesized 13 diverse fused pyrazole derivatives in moderate to excellent yields.

The activation of Carbon-Hydrogen (C-H) bond for coupling reactions is economic, sustainable and environmentally benign; as these reactions bypass the pre-functionalization or de-functionalization step. The C-H activation method enables direct synthesis of complex molecules from simple starting materials and have been extensively employed in the construction of Carbon-Carbon and Carbon-heteroatom bonds.[1] In particular, the C-H activation through cross dehydrogenative coupling (CDC)/oxidative coupling reactions can meet the criterion of green chemistry and are atom economic as these reactions produce only water as the byproducts. In recent times, among CDC reactions, α-C(sp^3)-H functionalization of tertiary amines gained greater importance due to direct access of *N*-containing heterocyclic compounds.[2] Furthermore, copper-catalyzed aerobic CDC reaction *via* α-C(sp^3)-H functionalization of *N*-aryl-substituted tetrahydroisoquinoline with various reaction partners, especially electron rich counterparts (Nucleophiles) have been well established in the literature (Figure 1).[3]

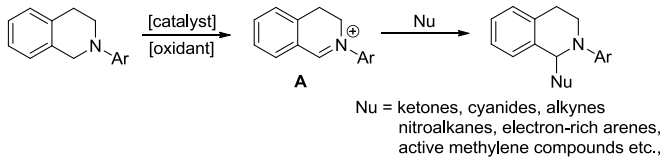

Figure 1. CDC reaction of *N*- aryl substituted tetrahydro-isoquinoline with nucleophile *via* iminium ion.

A large number of catalysts (Ag, Cu, Ru, Rh, Co, Pd, I_2 *etc*.,) oxidants, and nucleophiles have been reported for this reaction and are compatible under aerobic oxidative condition.[4] Mechanistically, an iminium ion intermediate (**A**) is generated *in situ* on oxidation of the corresponding amine and serves as an active electrophile for subsequent nucleophilic addition reaction (Figure 1).

Despite the significant potential of α-C(sp^3)-H functionalization of tertiary amines, CDC reaction suffers from limited substrate scope because *N*-arylsubstituted-1,2,3,4-tetrahydroisoquinoline and *N, N*-dimethyl aniline (tertiary amine) derivatives have been reported as suitable substrates.[5] And also, aryl or benzyl substitution on tertiary amine is required to induce CDC reaction at α-position to nitrogen. However, Xu and Li reported copper-catalyzed CDC reaction of aliphatic tertiary amines with terminal alkynes but additive is necessary to carry out the transformation.[6] To the best of our knowledge, the direct oxidative functionalization of both aryl-substituted and aliphatic-substituted tertiary amines under simple and mild aerobic conditions using internal/electron deficient alkynes as reaction partners have not been well investigated.

Dinitrogen-fused heterocyclic frameworks are present in many pharmaceutical, agrochemical, and biologically active compounds, and are prominent candidates for new drugs and functional materials. Especially the molecules containing pyrazolo[5,1-*a*]isoquinoline (PIQ) framework shows remarkable biological activities due to the PIQ hybrid structure (isoquinoline and pyrazolo[1,5-*a*]pyridine).[7] To mention a few, PIQ derivatives show activities for inhibition of CDC25B, TC-PTP, and PTP1B.[8]

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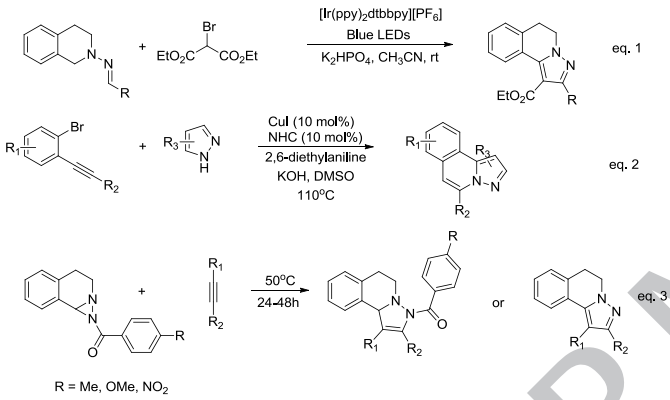
The another important class of dinitrogen-fused heterocyclic frameworks, fused-pyrazoles derivatives display a broad spectrum of biological activities including antibiotic, kinase inhibitor, and anticonvulsant activities.

Recently, Zhu and coworkers described an interesting Iridium-catalyzed [4+1] annulation of hydrazone with diethyl 2-bromomalonate under the influence of visible light (Scheme 1, eq. 1). Unfortunately, this method demonstrated a rather narrow substrate scope.[9a] A Copper-catalyzed tandem reaction of 2-alkynylbromobenzene with pyrazole provides a facile route to pyrazole[5,1-*a*]isoquinolines. This method involves hydroamination followed by C-H activation to provide desired products in low to moderate yields (Scheme 1, eq. 2).[9b] In 2007, Alper and co-workers reported the synthesis of pyrazolo[5,1-*a*]isoquinolines through regioselective cycloaddition of stable aroyldiaziridines of 3,4-tetrahydroisoquinolines with both mono and disubstituted alkynes (Scheme 1, eq. 3).[9c] But the difficulty in preparation of diaziridine compounds and handling reactive 1,3-dipolar intermediates often limits their synthetic application.

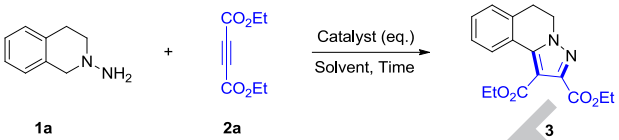


Scheme 1. Selected literature approaches to fused pyrazoles.

Numerous metal-catalyzed and organo-catalyzed cycloaddition of azomethine imines have been reported for the synthesis of diverse dinitrogen-fused heterocycles and these literature procedures are generally efficient and reliable, often involve preformed azomethine imines.[10] However, the direct oxidative α-functionalization of tertiary amines with various reaction partners provides a sustainable alternate route for the synthesis of nitrogen-fused heterocycles. Considering the above-mentioned factors, we envisioned a novel synthesis of dinitrogen-fused heterocycles *via* tandem/cascade hydroamination, CDC reaction followed by aerial oxidation approach from commercially available starting materials under simple, mild and facile operational condition.

For our initial studies, we have selected commercially available 3,4-dihydroisoquinolin-2(*1H*)-amine (**1a**) and diethyl acetylenedicarboxylate (**2a**) as model substrates. Treatment of **1a** with **2a** in presence of catalytic amount of AgOAc in DCE at 110°C for 16h (Table 1, entry 1), did not result in the formation of any detectable product (**3**). The subsequent increase in both catalyst loading and temperature (Table 1, entry 2) led to 10% formation of desired product and the further change of the solvent to xylene enhanced the product formation to 48% yield (Table 1, entry 3). Experimentation with various Ag-catalysts (Table 1, entry 4 & 5) and Cu-catalysts (Table 1, entry 6 & 7) revealed that the choice of $Cu(OAc)_2$ could dramatically improve the yield to 91% and shortens the reaction time to 8h (Table 1, entry 7). Attempts to further improve the efficiency of product formation by screening different solvents and catalysts were unsuccessful (Table 1, entry 8-10). Therefore, the optimum reaction condition comprised of 1 equiv. of **1a** with 1.1 equiv. of **2a** in the presence of 1 equiv. of $Cu(OAc)_2$ in xylene at 140°C for 8h, provided diethyl 5,6-dihydropyrazolo[5,1-*a*]isoquinolines-1,2-dicarboxylate (**3**) in 91% isolated yield.

Table 1. The Screening of reaction conditions[a]



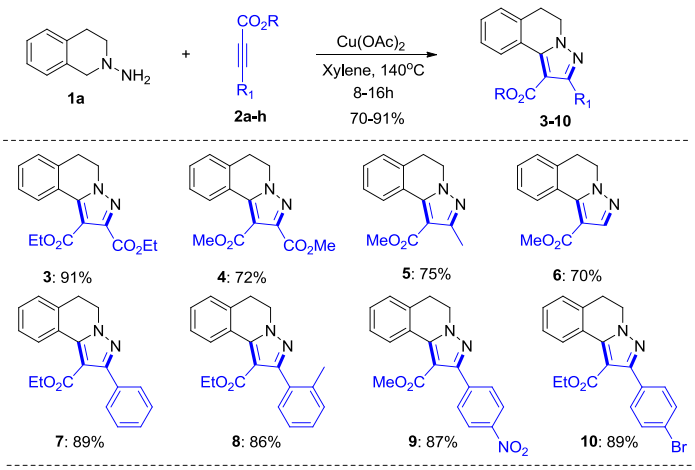
1a 2a 3

Entry	Catalyst (equiv)	Solvent	Time (h)	Yield (%)[b]
1	AgOAc (0.5)	DCE[c]	16	--[d]
2	AgOAc (1.0)	DCE[c]	16	10
3	AgOAc (1.0)	xylene	8	48
4	Ag_2CO_3(1.0)	xylene	16	19
5	Ag_2O (1.0)	xylene	16	trace
6	CuBr (1.0)	xylene	16	trace
7	$Cu(OAc)_2$	xylene	8	91
8	--	xylene	16	--[d]
9	--	AcOH	16	31
10	AcOH	xylene	16	trace

[a]All reactions were carried out on 1 mmol scale.
[b]Isolated yields.
[c]Reactions were performed in a sealed tube.
[d]Starting material was recovered.

With the optimized condition established (Table 1, entry 7), we examined the scope of substrate **1a** with various alkynes (Scheme 2). The results listed in Scheme 2 show that various internal / electron deficient alkynes (**2a-h**) bearing different substituents underwent this cascade reaction smoothly to afford the corresponding products (**3-10**) in good to excellent yield. The various internal / electron deficient alkynes, from aryl or alkyl substitution to electron withdrawing substitution, were very compatible under the reaction condition. Even though the electronic nature of alkynes did have an influence on reaction time but could not show the significant effect on the yield of respective PIQ derivatives.

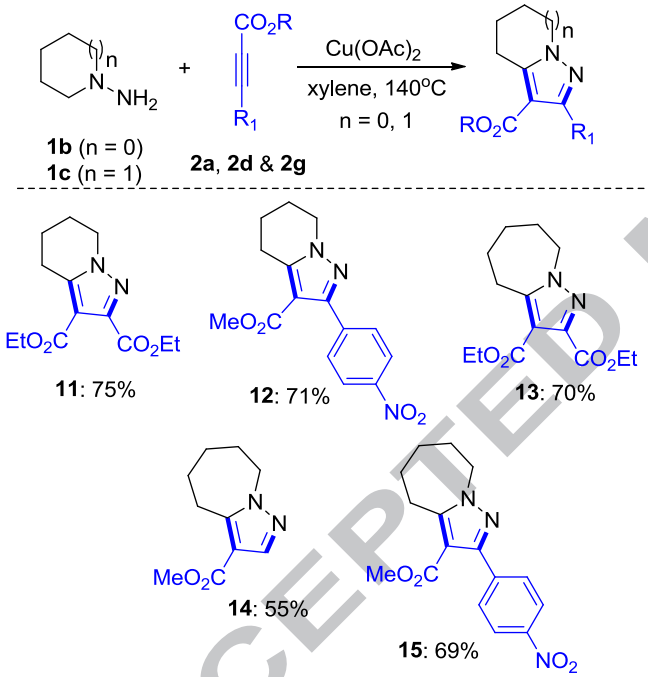
Scheme 2. Scope for synthesis of 5,6-dihydropyrazolo[5,1-*a*]iso-quinolines-1,2-dicarboxylate derivative[a]



[a]Reaction condition: **1a** (5 mmol), **2a-h** (5.5 mmol), $Cu(OAc)_2$ (5 mmol), xylene (25 mL) at 140°C. The reaction time varied from 8-16h.

In order to explore the scope and limitations of our methodology, we have next selected aliphatic cyclic tertiary amine, piperidin-1-amine (**1b**) and conducted the experiment with diethyl acetylenedicarboxylate (**2a**) under optimized reaction condition (Table 1, entry 7). To our delight fused-pyrazole (**11**) was obtained in 75% isolated yield, indicating that cross dehydrogenative coupling of unactivated/inactivated aliphatic tertiary amines could be possible under this aerobic oxidative condition. Then another alkyne **2g** was treated with **1b** under the same reaction condition and the corresponding fused-pyrazole **12** was obtained in 71% isolated yield (Scheme 3). Encouraged by these results, we have further determined the scope of a substrate, azepan-1-amine (**1c**) as reaction partner with various alkynes (**2a**, **2d** & **2g**). The fused-pyrazole **13-15** were obtained in 70%, 55% & 69% isolated yield respectively (Scheme 3). The results in Scheme 3 demonstrates that the electronic and steric nature of substrate did not have an obvious effect on yield of **11-15** and are very tolerable under tandem aerobic oxidative condition.

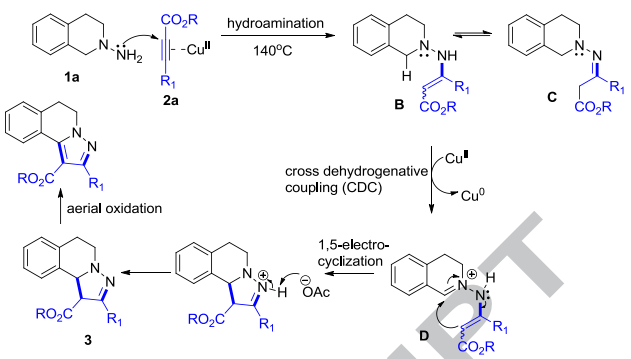
Scheme 3. Scope for synthesis of tetrahydropyrazolo[1,5-*a*]pyridine or azepine-2,3-dicarboxylate derivative[a]



[a]Reaction condition: **1b** or **1c** (5 mmol), **2a, 2c-e** or **2g** (5.5 mmol), $Cu(OAc)_2$ (5 mmol), xylene (25 mL) at 140°C for 16h.

Here in, we are not exploring the mechanism, but assume that the reaction proceeds analogous to that reported in the literature,[9c,11] accordingly a plausible mechanism was proposed in Scheme 4. Initially, 3,4-dihydroisoquinolin-2(*1H*)-amine (**1a**) on hydroamination with diethyl acetylenedicarboxylate (**2a**) under the enhanced temperature/Cu(II) generates enamine (**B**) which is in equilibrium with imine (**C**). The enamine (**B**) on α-C(sp^3)-H activation gives azomethine iminium ion (**D**), which on 1,5-electrocyclization followed by aerial oxidation provides the required product pyrazolo[5,1-*a*]isoquinoline (**3**).

In conclusion, we have developed a synthetic strategy for the synthesis of fused pyrazole derivatives from easily accessible or commercially available starting materials. Our method also demonstrates the importance of α-C(sp^3)-H functionalization of tertiary amines for the synthesis of biologically important dinitrogen-fused heterocyclic frameworks.



Scheme 4. Plausible mechanism.

Acknowledgments

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Supplementary Material

All the experimental details, spectral data, ^1H and ^{13}C NMR spectra for the compounds **3-15** are available in the Supporting Information.

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Highlights

- Simple and efficient strategy for synthesis of fused pyrazole derivatives
- Our strategy demonstrates various aspects of α-C(sp^3)-H functionalization of tertiary amines which have not been explored earlier
- Our strategy open the possibility to design coupling reactions with suitable substrates towards targeted products