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Communication

Synthesis of Novel Azole Fused-Quinazolines *via* One-pot Sequential Ullmann type Coupling and Intramolecular Dehydrogenative C−N Bonding

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An efficient one-pot sequential procedure has been described for the synthesis of novel azole fused quinazolines through Pd/Cu co-catalyzed Ullmann type coupling followed by cross dehydrogenative coupling of various azoles such as 1*H*-imidazole, 1*H*-benzimidazole and 1*H*-1,2,4-triazole with 2-(2-bromophenyl)-1*H*-imidazole/benzimidazoles. The developed strategy has offered good yields (52-81%) of diverse *N*-fused tetra-, penta- and hexa-cyclic frameworks in a single step.

Synthesis of nitrogen containing heterocycles is an everlasting demand in organic chemistry as they are in the core of many natural products and pharmacologically potent molecules.[1] Construction of C−N bond by Ullmann-type reaction or Buchwald coupling is more common procedure to access functionalized azaheterocycles.[2] In recent years, transition metal catalyzed cross dehydrogenative couplings or oxidative cyclizations are emerged as efficient and straightforward methods for the synthesis of these functionalized azaheterocycles from simple and commercially available non-prefunctionalized starting materials.[3] These protocols have received great attention in recent years due to their advantageous features such as atom-economy and reduced by-product generation.[4]

Quinazolines and their analogues are found to have considerable interest because of their wide range of biological properties such as antibacterial, antimalarial, anticonvulsant, antitumor, diuretic and antihypertensive.[5] In addition, quinazolines are the core structures in several pharmacologically potent molecules such as erlotinib, a tyrosine kinase inhibitor used for the treatment of pancreatic cancer (Figure 1). As a consequence several synthetic methods have been developed to fabricate these compounds.[6] Also there are several azole containing drug molecules. For example, omeprazole, a proton pump inhibitor is a benzimidazole derivative (Figure 1). It is believed that fusion of two or more bioactive heterocycles may lead to new hybrid motif with interesting properties. Fused azaheterocycles structures have shown enhanced antimicrobial, antitumor and antipsychotic activities (Figure 1).[8] Also, fused polycyclic structures derived from fusion of quinazolines with azoles have been studied as organic light-emitting devices (OLEDs).[7] Despite their importance in medicinal chemistry and material science, very few synthetic methods are available to access these fused frameworks which might be due to the unavailability of starting materials and complex multistep procedures.

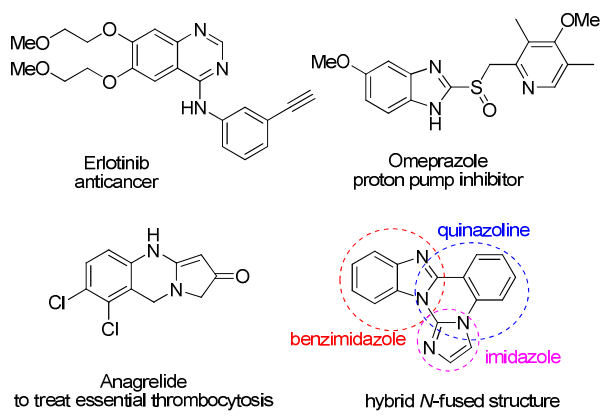

Fig. 1 Pharmacologically active azaheterocycles

Recently, Lv and colleagues reported synthesis of azole fused quinazolines via copper catalyzed domino addition followed by double cyclization (Scheme 1).[7a] In continuation to our interest in the assembly of nitrogen containing polyheterocyclic compounds by employing C−H functionalizations,[9] herein we wish to report our recent results for the synthesis of azole fused quinazolines through a sequential Ullmann type C−N coupling and palladium catalyzed cross dehydrogenative coupling (Scheme 3). The key precursors used for these studies were synthesized by means of well established and economically attractive procedures.[10]

2-(2-Bromophenyl)-4,5-diphenyl-1*H*-imidazole (**1a**) and 1*H*-imidazole (**2a**) were selected as model substrates for the preliminary investigations. On the basis of Mori and Schreiber reports,[11] we envisaged that catalytic amount of copper will enable the dual C−N bonding, Ullmann type coupling and oxidative C−N bonding, between **1a** and **2a** to furnish the targeted fused quinazoline, 2,3-diaryldiimidazo[1,2-*a*:1',2'-*c*]quinazoline (**5a**).

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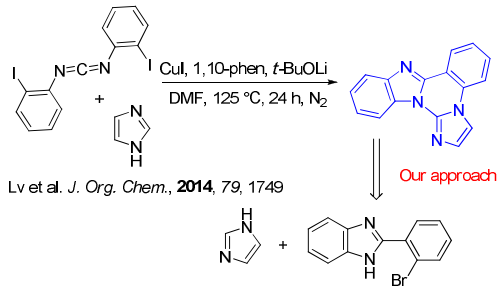
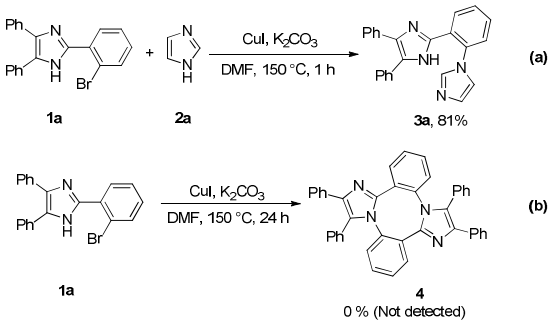


Scheme 1 Retrosynthesis for the novel azole fused quinazolines

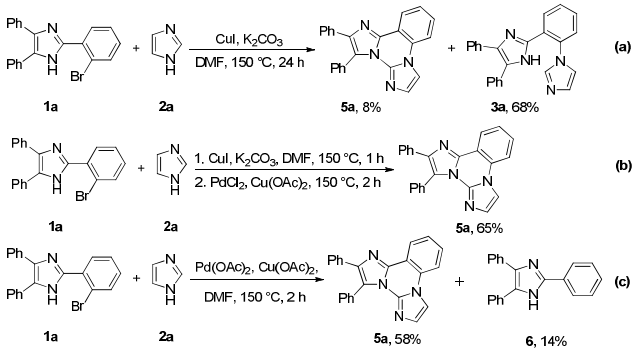
Copper catalyzed Ullmann type coupling of **1a** with imidazole **2a** in the presence of CuI (20 mol %) and K_2CO_3 (2 equiv.) in *N,N*-dimethylformamide after 1 h at 150 °C resulted in formation of 2-(2-(1H-imidazol-1-yl)phenyl)-4,5-diphenyl-1H-imidazole (**3a**) in 81% yield (Scheme 2a). The reaction was clean and no side product was formed in this reaction. Reaction of **1a** was performed in the absence of **2a** under these conditions to examine the selectivity of the reaction (Scheme 2b). Interestingly, formation of 2,3,10,11-tetraphenyldibenzo[*c,g*]diimidazo[1,2-*a*:1',2'-*e*][1,5]diazocine (**4**) was not observed even after longer reaction time and **1a** was recovered in almost quantitative yield.



Scheme 2 Copper catalyzed Ullmann type coupling of **1a**

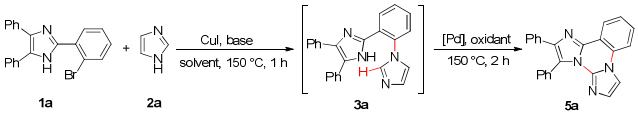
Next to synthesize azole fused quinazolines **5a** under copper catalyzed oxidative C–N coupling reaction; the above reaction was continued for 24 h at 150 °C. As expected, targeted molecule **5a** was detected in the reaction mass albeit in 8% yield (Scheme 3a). The major product isolated from this experiment was Ullmann coupled product, 2-(2-(1*H*-imidazol-1-yl)phenyl)-4,5-diphenyl-1*H*-imid-azole (**3a,** 68%). This might be due to less reactivity of azole N−H toward the oxidative cyclizations. To improve the efficiency of dehydrogenative C−N coupling, catalytic amount of $PdCl_2$ (5 mol %) together with the $Cu(OAc)_2$ (2.0 equiv) was added post Ullmann coupling (Scheme 3b).[9b,12] To our delight Pd/Cu system effectively promoted the oxidative C−N bonding through C−H activation/functionalization to deliver fused quinazoline **5a** in 65% yield (entry 1, Table 1) in a shorter reaction time.

We then screened various palladium catalysts, oxidants, bases, and solvents to obtain the optimum condition for the sequential one-pot two step reaction (Table 1). Among different palladium catalyst such as $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$ and $Pd(PPh_3)_4$ screened for the oxidative C–N coupling, $Pd(OAc)_2$ offered highest yield of **5a** (entries 2-4, Table 1). Diminished yields of **5a** were obtained when K_2CO_3 was replaced with other bases such as Cs_2CO_3, K_3PO_4, Na_2CO_3 and *t*-BuOK (entries 7-10, Table 1). Simultaneously, various solvents were screened and realized that DMF and *N,N*-dimethylacetamide (DMA) are suitable solvents for the sequential process while other solvents, like 1,4-dioxane, toluene and acetonitrile offered low yields of **5a** (entries 11-14, Table 1). Attempts to replace $Cu(OAc)_2$ with other oxidants such as $PhI(OAc)_2$, Ag_2CO_3 $CuCl_2$, Cu_2O and $CuSO_4$ were unsuccessful (entries 15-19, Table 1). Only traces of **5a** were detected when the sequential process was carried out in the absence of palladium catalyst (entry 20, Table 1). When isolated **3a** was allowed to react under optimized conditions of the second step, **5a** was formed in 70% yield. It is also worth to mention that one-step reaction of **1a** and **2a** in the presence of $Pd(OAc)_2$ (5 mol %) and $Cu(OAc)_2$ gave fused quinazolines **5a** in 58% yield along with dehalogenated by-product, 2,4,5-triphenyl-1H-imidazole (**6**), in 14% yield ((Scheme 3c).



Scheme 3 One-pot sequential synthesis of azole fused quinazolines

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Oxidant	Base	Solvent	Yield[b] (%)
1	$PdCl_2$	$Cu(OAc)_2$	K_2CO_3	DMF	65
2	$Pd(PPh_3)_4$	$Cu(OAc)_2$	K_2CO_3	DMF	38
3	$Pd(PPh_3)_2Cl_2$	$Cu(OAc)_2$	K_2CO_3	DMF	45
4	**$Pd(OAc)_2$**	**$Cu(OAc)_2$**	**K_2CO_3**	**DMF**	**71**
5	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	DMF	67[c]
6	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	DMF	63[d]
7	$Pd(OAc)_2$	$Cu(OAc)_2$	Cs_2CO_3	DMF	52
8	$Pd(OAc)_2$	$Cu(OAc)_2$	K_3PO_4	DMF	48
9	$Pd(OAc)_2$	$Cu(OAc)_2$	Na_2CO_3	DMF	28
10	$Pd(OAc)_2$	$Cu(OAc)_2$	*t*-BuOK	DMF	21
11	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	DMA	65
12	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	1,4-dioxane	-[e]
13	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	toluene	20
14	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	CH_3CN	52
15	$Pd(OAc)_2$	$PhI(OAc)_2$	K_2CO_3	DMF	42
16	$Pd(OAc)_2$	Ag_2CO_3	K_2CO_3	DMF	38
17	$Pd(OAc)_2$	$CuCl_2$	K_2CO_3	DMF	64
18	$Pd(OAc)_2$	Cu_2O	K_2CO_3	DMF	-[e]
19	$Pd(OAc)_2$	$CuSO_4$	K_2CO_3	DMF	61
20	-[f]	$Cu(OAc)_2$	K_2CO_3	DMF	traces

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), CuI (20 mol %), base (2.0 mmol), solvent (4 ml), 150 °C, 1 h followed by palladium catalyst (5 mol %), oxidant (2.0 mmol), 150 °C, 2 h. [b]Isolated yield. [c]1.2 mmol of $Cu(OAc)_2$ were used. [d]1.2 mmol of K_2CO_3 were used. [e]Only **3a** was formed. [f]Reaction was performed in the absence of palladium catalyst.

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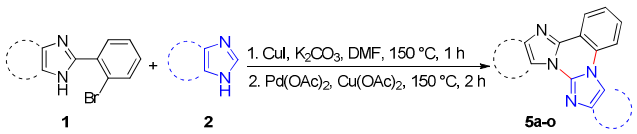
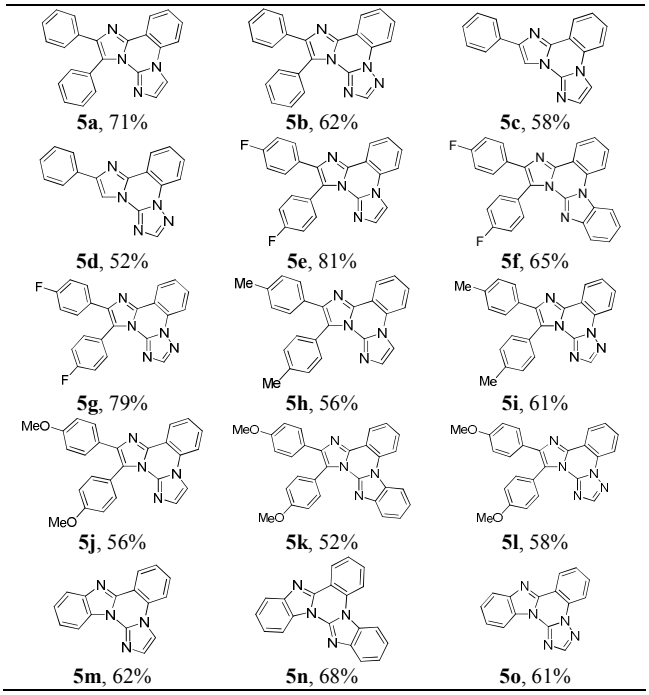
With the established conditions in hand (entry 4, Table 1), we then focussed our attention on evaluating substrate scope for the sequential process and the results were summarized in Table 2. Besides 1*H*-imidazole, 1*H*-benzimidazole and 1*H*-1,2,4-triazole also expediently gave moderate to good yields of *N*-fused structures under these conditions. Diversely substituted 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazoles smoothly participated in one-pot reaction and delivered the corresponding fused structures in good yields (**5a-l**, Table 2). Imidazoles with electron withdrawing group such as fluoro on aryl rings at C_4 and C_5 positions furnished higher yields of fused quinazolines when compared to aryl groups of electron rich groups like methyl and methoxy. Similarly, 2-(2-bromophenyl)-1*H*-benzo[*d*]imidazole also underwent smooth Ullmann type coupling followed by oxidative cyclization and offered polycyclic *N*-fused structures in good yields (**5m-o**, Table 2).

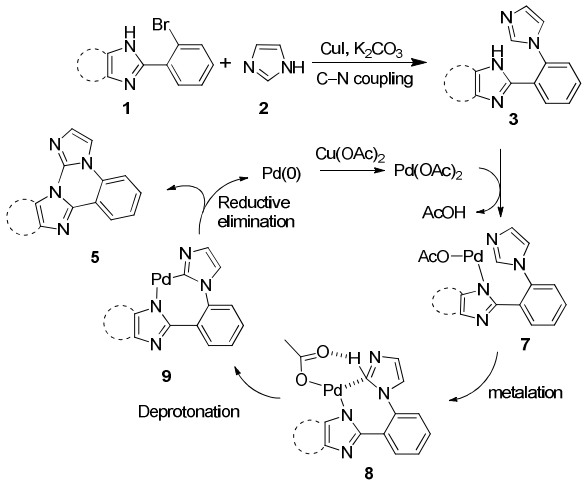
Table 2 Substrate scope for the sequential dual C−N bonding[a, b]





[a] Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), CuI (20 mol %), K_2CO_3 (2.0 mmol), DMF (4 ml), 150 °C, 1 h then $Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (2.0 mmol), 150 °C, 2 h. [b]Isolated yields.

On the basis of literature precedence, the following mechanism has been proposed for the formation of **5** starting from **1** and **2** (Scheme 4). In presence of copper(I), **1** and **2** undergoes Ullmann type C−N coupling to give the intermediate **3**. With the assistance of base, $Pd(OAc)_2$ binds with N−H of **3** and offers **7** which then undergoes intramolecular deprotonation and metallation to give intermediate **9**. Finally, reductive elimination of **9** furnishes desired product **5** and the oxidation of resultant Pd(0) to Pd(II) in presence of $Cu(OAc)_2$ completes the catalytic cycle.



Scheme 4 Plausible mechanism for the formation of **5**.

Conclusions

An expedient and straightforward method has been disclosed to access diversely substituted *N*-fused polycyclic structures by employing C−H functionalization. The designed strategy necessitates simple and easily accessible precursors and builds fused structures with high complexity in a single step. Further applications and mechanism of the reported reaction is under progress in our laboratory.

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Notes and references

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†Electronic Supplementary Information (ESI) available: [General experimental details, copies of ^{1}H and ^{13}C NMR of the synthesized compounds **3a** and **5a-o** are available]. See DOI: 10.1039/b000000x/

1. (a) A. R. Katritzky; C. A. Ramsden; J. A. Joule; V. V. Zhdankin *Handbook of heterocyclic chemistry*; Elsevier, 2010; (b) A. F. Pozharskii; A. T. Soldatenkov; A. R. Katritzky *Heterocycles in life and society. An introduction to heterocyclic chemistry and biochemistry and the role of heterocycles in science, technology, medicine and agriculture*; John Wiley & Sons, 1997.
2. (a) I. P. Beletskaya; A. V. Cheprakov. *Coord. Chem. Rev.* 2004, **248**, 2337; (b) Y. Liu; J.-P. Wan. *Org. Biomol. Chem.* 2011, **9**, 6873; (c) J. Bariwal; E. Van der Eycken. *Chem. Soc. Rev.* 2013, **42**, 9283.
3. (a) C. Liu; H. Zhang; W. Shi; A. Lei. *Chem. Rev.* 2011, **111**, 1780; (b) X. Chen; K. M. Engle; D.-H. Wang; J.-Q. Yu. *Angew. Chem. Int. Ed.* 2009, **48**, 5094.
4. (a) C. S. Yeung; V. M. Dong. *Chem. Rev.* 2011, **111**, 1215; (b) S. E. Allen; R. R. Walvoord; R. Padilla-Salinas; M. C. Kozlowski. *Chem. Rev.* 2013, **113**, 6234; (c) A. Armstrong; J. C. Collins. *Angew. Chem. Int. Ed.* 2010, **49**, 2282; (d) S. H. Cho; J. Y. Kim; J. Kwak; S. Chang. *Chem. Soc. Rev.* 2011, **40**, 5068.
5. (a) J. P. Michael. *Nat. Prod. Rep.* 2005, **22**, 627; (b) A. K. Parhi; Y. Zhang; K. W. Saionz; P. Pradhan; M. Kaul; K. Trivedi; D. S. Pilch;

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DOI: 10.1039/C4OB02375G

E. J. LaVoie. *Biorg. Med. Chem. Lett.* 2013, **23**, 4968; (c) W. T. Ashton; J. B. Hynes. *J. Med. Chem.* 1973, **16**, 1233.
6. (a) D. J. Connolly; D. Cusack; T. P. O'Sullivan; P. J. Guiry. *Tetrahedron.* 2005, **61**, 10153; (b) Y. Ohta; Y. Tokimizu; S. Oishi; N. Fujii; H. Ohno. *Org. Lett.* 2010, **12**, 3963; (c) J. Zhang; D. Zhu; C. Yu; C. Wan; Z. Wang. *Org. Lett.* 2010, **12**, 2841.
7. (a) G. Yuan; H. Liu; J. Gao; K. Yang; Q. Niu; H. Mao; X. Wang; X. Lv. *J. Org. Chem.*. 2014, **79**, 1749; (b) T. Y. Park; J. S. Bae; S. G. Hong; D. H. Lee; D. U. Lee; S. Y. Jeon; S. S. Kim. *Korean patent.* **2010097797**.
8. (a) M. C. Elliott; E. Kruiswijk; M. S. Long. *Tetrahedron.* 2001, **57**, 6651; (b) R. Rohini; K. Shanker; P. M. Reddy; Y.-P. Ho; V. Ravinder. *Eur. J. Med. Chem.* 2009, **44**, 3330; (c) J. Ohmori; M. Shimizu-Sasamata; M. Okada; S. Sakamoto. *J. Med. Chem.* 1997, **40**, 2053.
9. (a) K. Pericherla; A. Jha; B. Khungar; A. Kumar. *Org. Lett.* 2013, **15**, 4304; (b) K. Pericherla; P. Khedar; B. Khungar; A. Kumar. *Chem. Commun.* 2013, **49**, 2924; (c) S. Dhiman; K. Pericherla; N. K. Nandwana; D. Kumar; A. Kumar. *J. Org. Chem.* 2014, **79**, 7399.
10. (a) S. Samai; G. C. Nandi; P. Singh; M. S. Singh. *Tetrahedron.* 2009, **65**, 10155; (b) K. Bahrami; M. M. Khodaei; F. Naali. *J. Org. Chem.* 2008, **73**, 6835.
11. (a) D. Monguchi; T. Fujiwara; H. Furukawa; A. Mori. *Org. Lett.* 2009, **11**, 1607; (b) Q. Wang; S. L. Schreiber. *Org. Lett.* 2009, **11**, 5178.
12. J. A. Jordan-Hore; C. C. C. Johansson; M. Gulias; E. M. Beck; M. J. Gaunt. *J. Am. Chem. Soc.* 2008, **130**, 16184.