Aluminium Mediated Isocyanide Insertion and Sequential Ring Opening Cyclization (SROC) Strategy: Synthesis of Azole Fused Benzimidazoquinazoline Skeletons

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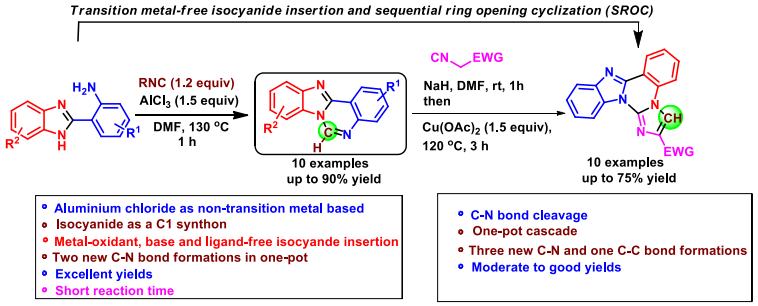
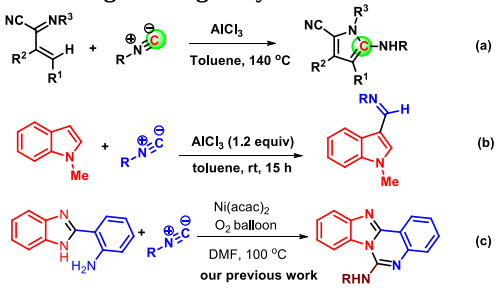
Supporting Information Placeholder



ABSTRACT: A first report on transition-metal-free aluminium chloride mediated isocyanide insertion between two amine nucleophiles have been presented. Also, an unusual C-N bond cleavage allow for the further development of copper mediated ring opening cyclization (SROC) strategy for the synthesis of azole fused benzimidazoquinazoline scaffolds. The key features of this protocol are aluminium chloride as non-transition-metal based mediator, oxidant/base/ligand free isocyanide insertion, three new C-N and one C-C bond formations and simultaneous construction of multiprivileged azole fused benzimidazoquinazoline in good yields.

The C1 insertions leading to C-C/C-X for the synthesis of annulated heterocycles have been explored *via* transition metal catalysis by using various reagents such as DMF, [1a] MeOH,[1b] DMSO, [1a] NMP, [1a] TMEDA, [1a] CO[1c] and isocyanides.[2] Among which isocyanide due to its peculiar intrinsic ambiphilic property and its affinity towards metal has been widely explored as C1 synthon in the synthesis of nitrogen heterocycles. The ambiphilic nature of isocyanide have been widely used for the synthesis of medicinally and biologically important diverse heterocycles.[2] Further, isocyanides have been successfully employed as C1 synthon in cycloaddition reactions[3] (Scheme 1a and Ref. 2). Moreover, recently Chatani et al.[4] have explored ambiphilic nature of isocyanide by $AlCl_3$ mediated insertion between aromatic CH-bond of comparatively weak nucleophilic indole (Scheme 1b). On the other hand, the unique affinity of isocyanide towards metals has been explored with transition metals such as palladium, cobalt and nickel catalyzed insertions between various bisnucleophiles in recent times.[5] However, non-transition metal based/transition metal-free isocyanide insertion between two nucleophiles is unprecedented till date. Moreover, recently we reported the nickel catalyzed a base/oxidant free isocyanide insertion in 2-aminobenzimidazole[6] (Scheme 1c) which intrigued us to develop a transition metal free isocyanide insertion. However, while working on the idea we observed the formation of benzimidazoquinazoline (BzQ) via deaminated isocyanide insertion between two amine nucleophiles by using aluminium

Scheme 1 Strategies using isocyanide as C1 source



chloride as mediator. The BzQ framework is common among the privileged heterocycles possessing good spectrum of activities such as antimalarial,[7a] anti-inflammatory,[7b] anticonvulsant, [7c] antidiabetic,[7d] and antitumor[7e] activities. Among them benzimidazo[1,2-c]quinazolines such as Erlotinib alkaloid (Figure 1, **I**) and its analogues (Figure 1, **II**) showed a good anticancer activity.[8] Similarly, imidazole based skeletons are highly privileged in nature which show several bioactivities which includes drug molecule Omeprazole (Figure 1, **III**) (a good proton pump inhibitor) and Ondansetron (Figure 1, **IV**) (used to suppress the nausea caused by cancer chemotherapy). Owing to the importance of BzQs, several methodologies were reported for its synthesis.[9] We envisioned to use this interesting amidine containing BzQ product in Van-Leusen reaction for the synthesis of azole fused BzQ. However, we observed

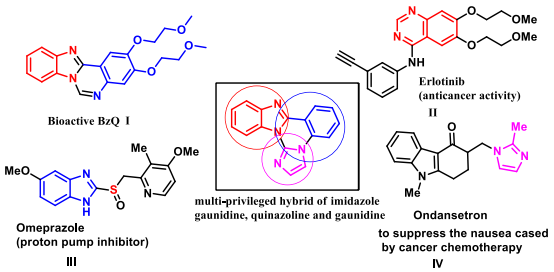
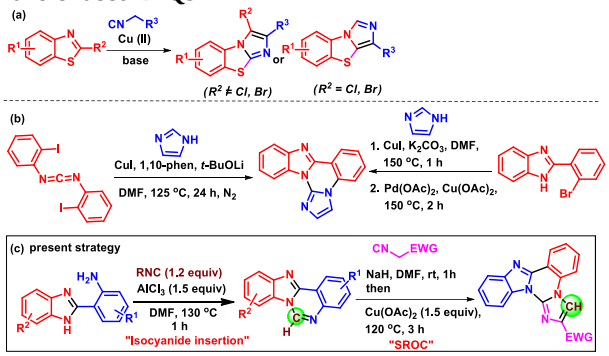


Figure 1 Representative privileged bioactive molecules

an interesting and unusual ring opened Van-Leusen type product. We hypothesized to use this ring opened product for the synthesis of regiodivergent azole fused BzQ through an overall ring-opening cyclization sequence from BzQ. Recently, ring opening cyclization reactions[10] for the synthesis of various heterocycles have gained importance due to its domino and sustainable nature to transform one heterocycle into other privileged heterocycle (Scheme 2a). There are only couple of reports for the synthesis of azole fused BzQ *viz.* copper-catalyzed cascade of diimide[11a] and palladium catalyzed Ullmann-CDC sequence[11b] (Scheme 2b). In continuation of our research interests in isocyanide insertions[12a,6] and annulation strategies,[12b,12c] herein, we have demonstrated for the first time a non-transition metal mediated isocyanide insertion followed by ROC sequence for the synthesis of privileged azole fused BzQs as shown in Scheme 2c.

Scheme 2 Previously reported ROC strategy and synthesis of azole fused BzQs



Our initial attempts were directed towards the optimization of isocyanide insertion strategy (Table 1). It is to be noted that there were only traces of product in absence of mediator (Entry 1). When we performed the reaction of amine **3a** with cyclohexylisocyanide **4a** in toluene solvent using $AlCl_3$ as promoter at 110 °C, pleasingly afforded the deaminative product BzQ **5aa** compound in 62% yield (Entry 2). Later we have screened various solvents such as chlorobenzene, *p*-xylene, DMSO, DCE and DMF (Entries 3-8) which gave up to 90% of yield in DMF as solvent with increased equivalents of $AlCl_3$ and isocyanide (Entry 8). There was no further increment in the yield by increasing equivalents of either $AlCl_3$ or isocyanide (Entries 9 and 10). The reaction with other isocyanides was unsatisfactory (see SI for isocyanide screening and detailed optimization). So, finally we chose 1.5 equivalents of aluminium chloride, 1.2 equivalents of isocyanide and DMF as solvent at 130 °C as satisfactory optimized condition (Entry 8).

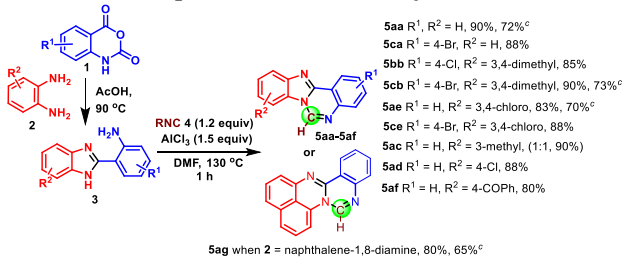
Table 1. Optimization for deaminative isocyanide insertion strategy[a,b]

Entry	Reagent/CyNC (equiv)	Solvent	Temp	Yield
1	-	Toluene	110	trace
2	$AlCl_3$ (1.2)/CyNC (1)	Toluene	110	62
3	$AlCl_3$ (1.5)/CyNC (1)	Chlorobenzene	130	80
4	$AlCl_3$ (1.5)/CyNC (1.2)	*P*-Xylene	130	70
5	$AlCl_3$ (1.5)/CyNC (1.2)	Chlorobenzene	130	88
6	$AlCl_3$ (1.5)/CyNC (1.2)	DMSO	130	40
7	AlCl3 (1.5)/CyNC (1.2)	DCE	100	82
8	**$AlCl_3$ (1.5)/CyNC (1.2)**	**DMF**	**130**	**90**
9	$AlCl_3$ (2)/CyNC (1.2)	DMF	130	88
10	$AlCl_3$ (1.5)/CyNC (2)	DMF	130	89

[a] Reaction conditions: Amine **3a** (0.5 mmol), CyNC **4a** (0.5 mmol) and solvent 2 mL. [b] Yield of isolated product after column chromatography.

With this optimized conditions, we have checked the scope of various 2-aminophenylbenzimidazoles, which provided the products in high to excellent yields (**5aa-5af**, Scheme 3). We have also checked the feasibility of one-pot synthesis of **5** directly from isatoic anhydride **1** in sequential manner which also provided the products however with comparatively less yields (**5aa**, **5cb-5ae**, **5ag**, Scheme 3).

Scheme 3 Scope of deaminative isocyanide insertion

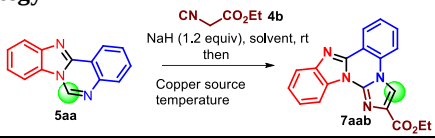


[a] General conditions: Amine **3aa** (0.5 mmol), cyclohexyl isocyanide **4a** (0.6 mmol), aluminium chloride (0.75 mmol) and DMF (2 mL); [b] Isolated yields after column chromatography. [c] One-pot yield from **1a**

After having developed the isocyanide insertion strategy we started to optimize the SROC strategy (Table 2). We found the NaH as the best base for ring opening (see SI for screening of base and detailed optimization). By keeping these ring opening conditions constant, we screened various conditions for further cyclization and it is to be noted that the reaction in absence of any copper source did not provided even traces of the cyclized product (Entry 1). Later, we screened various copper sources such as $CuCl_2$, CuI, CuBr, $CuBr_2$ and $Cu(OAc)_2.H_2O$ in DMF under reflux conditions (Entries 2-6) which pleasingly provided the product **7aac** albeit in 50% yield in case of $Cu(OAc)_2.H_2O$ as copper source (Entry 6). When we used anhydrous copper acetate at various temperatures (Entries 7-8) it resulted in the product up to 69% yield at 120 °C (Entry 8). Significantly, the increase in amount of copper source up to 1.5 equiv could able to improve the yield up to 75% yield (Entry 9), however our attempts of further increase or decrease in the amount of copper source were not fruitful (Entries 10 and 11). Our attempts to check the progress

of reaction under catalytic version led to trace amount of the product (Entry 12). Hence, we chose the reaction with 1.5 equiv of copper acetate at 120 °C under DMF solvent as the optimized reaction condition (Entry 9) for checking scope of the SROC strategy.

Table 2 Optimization for ring opening cyclization (ROC) strategy[a,b]



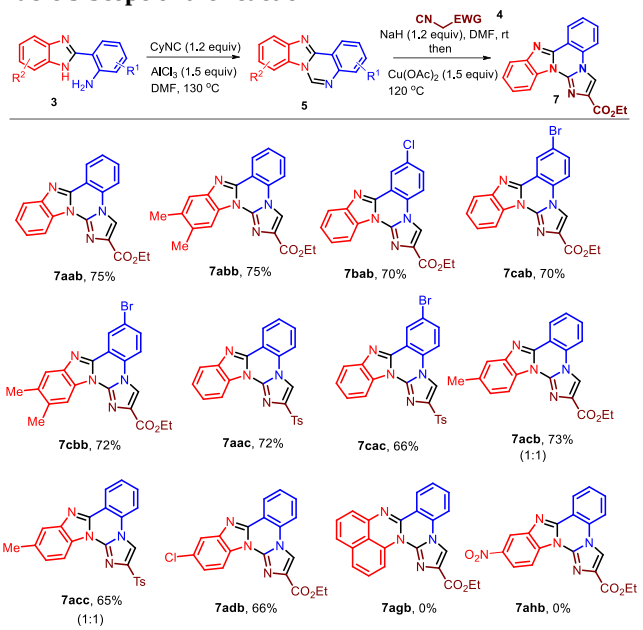
Entry	Copper source/Ligand	Solvent	Temp	Yield (%)
1	-	DMF	reflux	0
2	$CuCl_2$ (1)	DMF	reflux	20
3	CuI(1)	DMF	reflux	10
4	CuBr (1)	DMF	reflux	15
5	$CuBr_2$ (1)	DMF	reflux	30
6	$Cu(OAc)_2$. H_2O (1)	DMF	reflux	50
7	$Cu(OAc)_2$ (1)	DMF	reflux	55
8	$Cu(OAc)_2$ (1)	DMF	140	60, 69,[c] 20[d]
9	**$Cu(OAc)_2$ (1.5)**	**DMF**	**120**	**75**
10	$Cu(OAc)_2$ (2)	DMF	120	76
11	$Cu(OAc)_2$ (0.5)	DMF	120	30
12	$Cu(OAc)_2$ (0.2)/PPh_3 (0.4)	DMF	120	trace

[a] Reaction conditions: **5aa** (0.5 mmol), ethylisocyanoacetate **4b** (0.6 mmol), NaH (0.6 mmol), copper source and DMF 2 mL. [b] Yield of isolated product after column chromatography. [b] Reaction temp 120 °C. [c] Reaction temp 100 °C.

With this optimized condition in hand, further we envisaged to examine the scope of the reaction with respect to various 2-aminophenylbenzimidazole **3** by following two step sustainable approach *viz*. aluminium chloride mediated deaminative isocyanide insertion and SROC strategy involving a simple work-up and avoiding column chromatography of intermediate **5**. When we used various electron donating as well as electron-withdrawing 2-aminophenylbenzimizole **3** and isocyanides **4** such as ethylisocyanoacetate **4b** and TOSMIC **4c** it afforded the desired products **7aab**-**7acb** in moderate to good yields (65-75%, Table 3).

Initially when we used unsubstituted 2-aminophenylbenzimidazole **3aa** it gave the desired product in 75% yield (**7aab**). Also, the electron donating dimethyl substitution over benzimidazole such as **3ab** gave the product **7abb** in 75% yield. When we used the electron withdrawing benzimidazoles such as **3ba** and **3ca** also worked well in the reaction which gave the desired product in 70% yields (**7bab** and **7cab**). Later we tested the benzimidazoquinazoline with electron donating methyl substitution over benzimidazole part and electron withdrawing bromo substitution over quinazoline part such as **5cb** which is tolerated well in the reaction giving the product **7cbb** in 72% yield. Delightfully employing TOSMIC **4c** in the reaction worked smoothly to give the products in **7aac** and **7cac** in 72% and 66% yields respectively. The unsymmetrical benzimidazole such as **3ac** gave the products in good to moderate yields (73-65%) however, with 1:1 mixture of regioisomers (**7acb** and **7acc**). However, the unsymmetrical benzimidazole such as **3ad** with chloro substitution led to the single regioisomer in 66% yield (**7adb**). Further the substrates with napthyl substitution and strong electron withdrawing nitro substituted compounds failed to give the expected products (**7aeb** and **7ahb**).

Table 3 Scope of the reaction [a,b]



[a] Reaction conditions: **3** (0.2 mmol), CyNC **4a** (0.24 mmol), $AlCl_3$ (0.3 mmol) and DMF (1.5 mL); isocyanide **4** (0.24 mmol), NaH (0.24 mmol), DMF (1.5 mL) and Cu(OAc)2 (0.3 mmol); [b]Isolated yields after column chromatography.

Based on the literature study,[4,10a] and the isolated intermediate acyclic imidazole product **6aac** (CCDC-1532830, see SI for X-ray data of intermediate **6aac**), we proposed a plausible mechanism as depicted in Figure 2. Initially, there is formation of isocyanide-aluminium chloride complex **A** which on further attack of **3aa** results in intermediate **B**. The intermediate **B** rearranges *via* proton shift to afford intermediate **C** which on intramolecular nucleophilic attack of imidazolium nitrogen gives the intermediate **D**. Further, demetallation followed by deamination affords the compound **5aa**. The attack of anion **F** on the imine **5aa** generates intermediate **G** which on annulation and C-N bond cleavage gives ring opened product **6**. The compound **6**, forms the copper (II) complex **I** which cyclizes to copper (II) complex **J** followed by subsequent reductive elimination affords the desired product **7**.

In conclusion, we have developed a distinct two-step strategy involving a novel aluminium chloride mediated non-transition metal based isocyanide insertion and SROC strategy involving copper mediated regio divergent synthesis of azole fused BzQs. An interesting ROC sequence on cyclic amidines via unusual Van-Leusen reaction leading to regiodivergent azole-fused BzQs is noteworthy. The present unprecedented metal-oxidant, ligand and base free deaminative isocyanide insertion make the strategy unique. The salient features of this method are formation of three new C-N bonds, rapid access to biologically relevant heterocyclic scaffolds, short reaction time, high bond forming index (BFI), and the use of inexpensive, readily available starting materials. The diverse potential of the present SROC strategy has been demonstrated by synthesizing naphthalene fused quinazoline compounds. Further

studies on aluminium mediated isocyanide insertions and exploration of ROC strategy are currently underway.

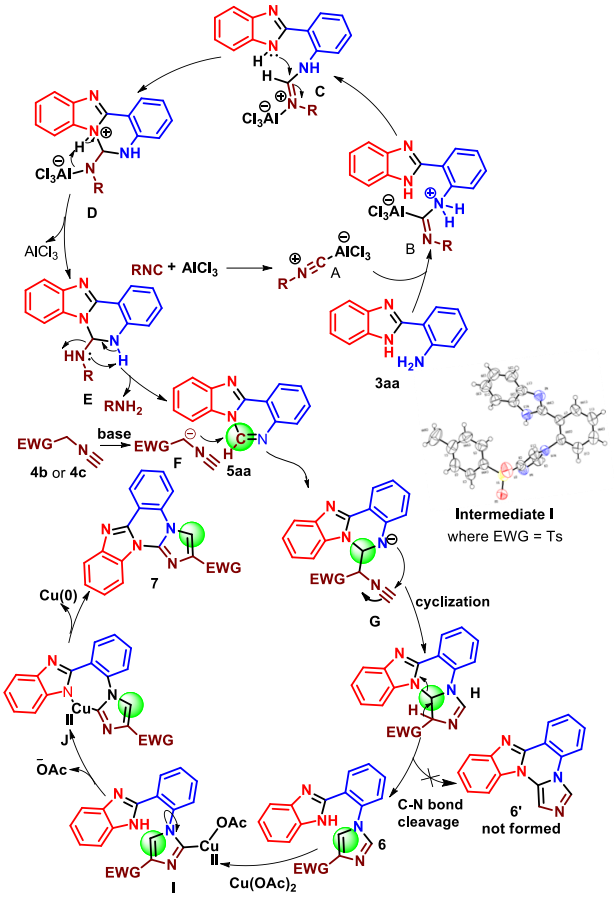


Figure 2 Plausible reaction mechanism for deaminative isocyanide insertion and SROC strategy for the synthesis of **7**.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, characterization data, and copies of NMR (PDF).
Crystallographic data for compound **6aac** (CIF).

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