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Transition-metal and oxidant-free approach for the synthesis of diverse N-heterocycles by TMSCl activation of isocyanides†

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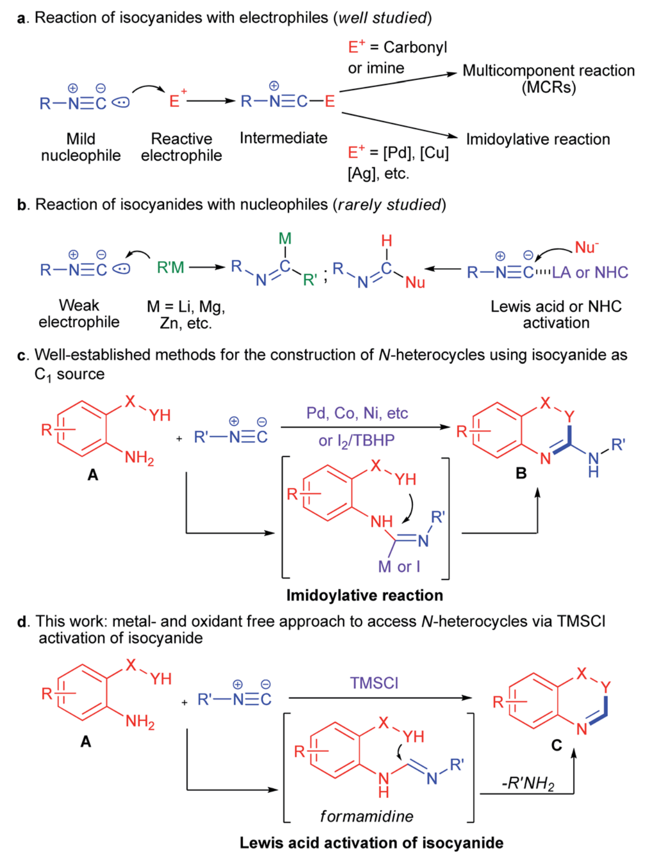
A highly efficient TMSCl-mediated addition of N-nucleophiles to isocyanides has been achieved. This transition-metal and oxidant-free strategy has been applied to the construction of various N-heterocycles such as quinazolinone, benzimidazole and benzothiazole derivatives by the use of distinct amino-based binucleophiles. The notable feature of this protocol includes its mild reaction condition, broad functional group tolerance and excellent yield.

In the past decades, isocyanides have proved themselves to be irreplaceable structural scaffolds in organic synthesis.[1] The chemistry of isocyanides is characterized by the great diversity of transformations that includes multicomponent reactions (MCRs, such as Passerini and Ugi reaction),[2] transition metal-catalyzed insertions (also called imidoylative reaction),[3] as well as isocyanide-mediated radical cascade reactions.[4] Generally, the isocyanide group can act as a mild nucleophile by electrophilic activation in the presence of carbonyl, imine or transition-metal catalysts, which allow further transformations after the incorporation of isocyanide core into starting material (Scheme 1a). In contrast, the reactions of isocyanides with external nucleophiles are particularly challenging because of the poor electrophilicity of isocyanides, and most of these reactions require highly reactive organometallic nucleophiles (Scheme 1b).[5] Only a few reports achieved the direct additions of weak nucleophiles to isocyanides by Lewis acid complexation[6] or NHC catalyst (Scheme 1b).[7] Therefore, the development of new catalyst system for the activation of isocyanide as electrophilic reagent would be highly desirable.

On the other hand, nitrogen-containing heterocycles are invaluable building blocks in organic chemistry and are considered to be "privileged" structure in medicinal chemistry.[8] In this context, the construction of N-heterocycles has been a major research topic in synthetic chemistry.[9] Among these reports, isocyanides have emerged as C_1 synthons for the synthesis of various N-heterocycles *via* isocyanide insertion reactions[10] (similar to carbon monoxide[11]). For example,



Scheme 1 Strategies for isocyanide activation.

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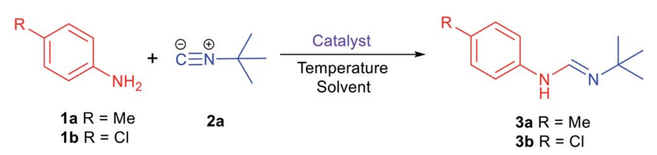
bisnucleophile agents **A** could be applied to the synthesis of N-heterocycles **B** through isocyanide insertion-cyclizations by the use of transition metals (such as Pd, Co, Ni, *etc.*)[12] or I_2/TBHP catalytic system[13] (Scheme 1c). However, these reports suffer from the use of expensive transition metals or peroxide reagents. Meanwhile, in light of the success of Lewis acid promoted nucleophilic additions to isocyanides. We envisaged that the use of Lewis acid might catalyse the nucleophilic addition of **A** to isocynide,[14] and subsequent cyclization of the formamidine intermediate could deliver the corresponding N-heterocycles **C** (Scheme 1d). Thus, an unprecedented transition-metal and oxidant-free approach to access various N-heterocycles using isocynide as C_1 source could be achieved.

Our study commenced with the reaction between 4-methylaniline (**1a**) and *tert*-butyl isocyanide (**2a**) in acetonitrile at 70 °C. A survey of reaction parameters was summarized in Table 1. First, no desired product was observed in the absence of Lewis acid catalyst (Table 1, entries 1). Then, 1.0 equivalent of CuCl was selected as the Lewis acid based on the literature report,[14] formamidine product **3a** could be obtained in 50% yield after stirring for 24 h (entry 2). Then, a series of transition metal-based Lewis acids such as AgCl, $FeCl_3$ and $ZnCl_2$ were also evaluated in the same reaction condition, and the results were still unsatisfactory (entries 3–5). Next, we chose Brønsted acids[15] such as CF_3COOH, and TfOH as the activation reagents for this reaction (entries 5–7). Only a trace mount of formamidine **3a** was detected along with unreacted starting material. Fortunately, in the presence of $BF_3 \cdot Et_2O$, the reaction could afford the corresponding product **3a** in 55% yield (entry 8). Surprisingly, further optimization of the reaction conditions revealed silicon-based Lewis acid TMSCl could catalyse the reaction with 85% yield (entry 9).[16] To the best of our knowledge, the nucleophilic activation of isocyanides using silicon-based Lewis acid has not yet been reported.[17] Meanwhile, catalyst loading had obvious effects on the reaction yields. A slightly increased yield was observed with 1.5 equiv. of TMSCl, while decreasing the amount of TMSCl to 0.5 equiv. resulted in a lower yield of **3a** (entries 10 and 11). A survey of other reaction media revealed that the overall results could not be improved (entries 12–14). In addition, a lower yield was obtained when the reaction was performed at room temperature (entry 15). Finally, formamidine **3b** could also be obtained in high yield using 4-chloroaniline **1b** as nucleophile (entry 16).

With the optimal conditions in hand, we applied this strategy to the synthesis of various quinazolinones[18] by employing 2-aminobenzamides **4** as bisnucleophile agents (Table 2). In general, the reaction works well when R^1 was an aromatic group. Substituents at *para*-positions bearing either electron-donating or electron-withdrawing groups can afford the desired products in good to excellent yields (**5a–5f**). The cyclization products with substituents at *meta*-positions were also obtained in good yields (**5g**, **5h**), while lower yield was observed with substituent at *ortho*-position (**5i**). Then, substrates with aliphatic groups, such as methyl, *n*-propyl, benzyl, propargyl, *etc.*, were also employed in this reaction to give the corresponding products in 84–90% yields (**5j–5o**). Next, 2-aminobenzamides with various R^2 groups were evaluated in

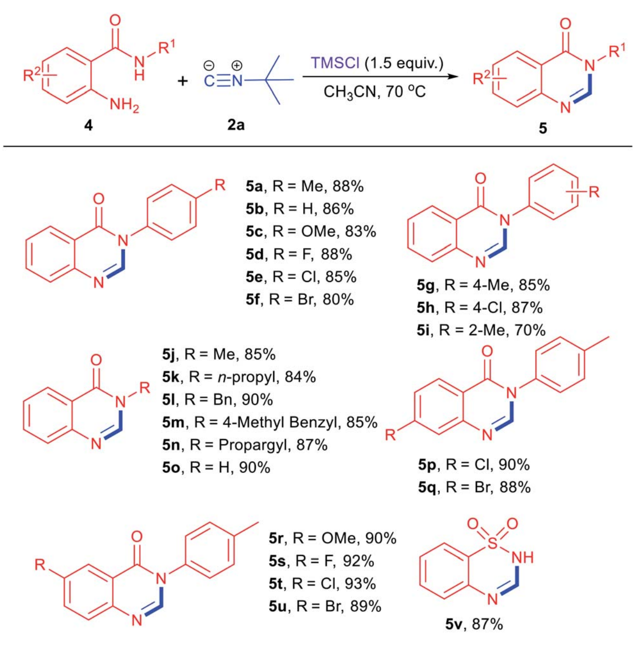
Table 1 Optimization of the reaction conditions[b]



Entry	Catalyst (equiv.)	Temperature (°C)	Solvent	Product	Yield[b] (%)
1	—	70	CH_3CN	**3a**	0
2	CuCl (1.0)	70	CH_3CN	**3a**	50
3	AgCl (1.0)	70	CH_3CN	**3a**	Trace
4	$FeCl_3$ (1.0)	70	CH_3CN	**3a**	Trace
5	$ZnCl_2$ (1.0)	70	CH_3CN	**3a**	55
6	CF_3COOH (1.0)	70	CH_3CN	**3a**	0
7	TfOH (1.0)	70	CH_3CN	**3a**	10
8	$BF_3 \cdot Et_2O$ (1.0)	70	CH_3CN	**3a**	55
9	TMSCl (1.0)	70	CH_3CN	**3a**	85
10	**TMSCl (1.5)**	**70**	**CH_3CN**	**3a**	**90**
11	TMSCl (0.5)	70	CH_3CN	**3a**	71
12	TMSCl (1.5)	70	DCE	**3a**	79
13	TMSCl (1.5)	70	THF	**3a**	59
14	TMSCl (1.5)	70	Toluene	**3a**	80
15	TMSCl (1.5)	rt	CH_3CN	**3a**	52
16	TMSCl (1.5)	70	CH_3CN	**3b**	92

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), catalyst (0.5–1.5 equiv.), solvent (2 mL), 24 h. [b] Isolated yields.

Table 2 Substrate scope for the synthesis of various quinazolinones[a]



[a] Reaction conditions: **4** (0.2 mmol), **2a** (0.3 mmol), TMSCl (1.5 equiv.), CH_3CN (2 mL), 70 °C, 24 h. Isolated yields.

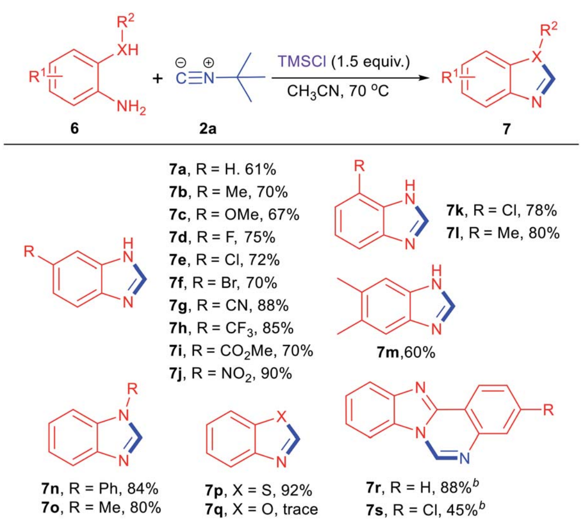
the standard condition, and functionalized quinazolinones were generated in 88–93% yields (**5p–5u**). It is worth noting that 2-aminobenzene sulfonamide could also be tolerated in this reaction, affording the cyclization products **5v** in 87% yield.

The scope of this methodology has been also extended to the synthesis of other N-heterocycles by simply changing the amino-based binucleophiles (Table 3). First, diverse *o*-phenylenediamines were subjected to the same reaction conditions. To our delight, the reaction proceed smoothly in all cases regardless of the electronic and steric properties of the substituents, giving the corresponding 1*H*-benzo[*d*]imidazole derivatives[19] in moderate to good yields (**7a–7m**). Furthermore, *N*-methyl and *N*-phenyl-*o*-phenylenediamine were also tolerated in this reaction, delivering 2-aminobenzimidazole **7n** and **7o** in 84% and 80% yields respectively. It is worth noting 2-amino-benzenethiol could undergo the same transformation to furnish benzo[*d*]thiazole product **7p** in 92% yield. However, the reaction failed to generate benzo[*d*]oxazole **7q** with *o*-aminophenol under identical condition. Finally, diversified facile synthesis of benzimidazo[1,2-*c*]quinazolines **7r** and **7s** could be achieved in reasonable yields.

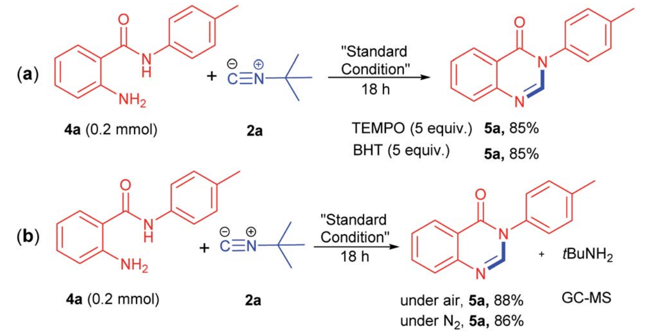
To gain an insight into the reaction mechanism, several control experiments were performed as presented in Scheme 2. Initial radical inhibition studies using TEMPO and BHT indicated that the reaction does not proceed through a radical pathway (Scheme 2a). The reaction of 2-aminobenzamides **4a** with **2a** by the standard condition under N_2 provided **5a** in 86% yield, revealing that oxygen is not participated in this reaction (Scheme 2b). In the meantime, the generation of $^tBuNH_2$ as byproduct was confirmed by GC-MS.[20]

The following reaction mechanism is proposed based on our experimental observations and previous literature reports.[20] First, nucleophilic addition of bisnucleophile agents **A** to *tert*-butyl isocyanide **2a** *via* TMSCl activation could generate

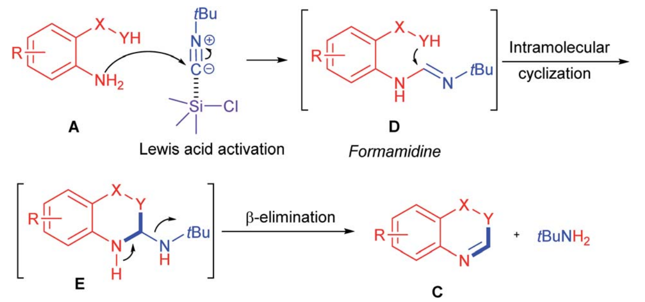
Table 3 Substrate scope for the synthesis of other N-heterocycles[a]



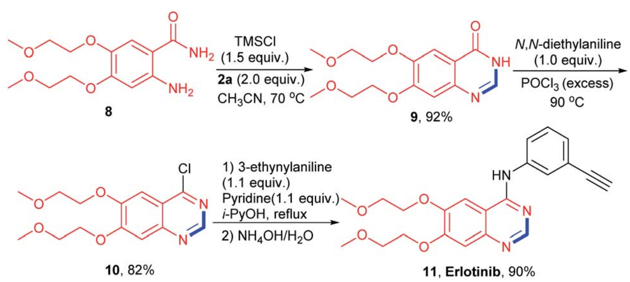
[a] Reaction conditions: **6** (0.2 mmol), **2a** (0.3 mmol), TMSCl (1.5 equiv.), CH_3CN (2 mL), 70 °C, 24 h. Isolated yield. [b] 2.0 equiv. of TMSBr in 2 mL C_2H_5OH was used.



Scheme 2 Control experiments. (a) Radical inhibiton studies. (b) Standard conditon under N_2 conditions.



Scheme 3 Plausible reaction mechanism.



Scheme 4 Synthesis of biologically active compounds.

formamidine intermediate **D.** Then intramolecular nucleophilic addition of formamidine **D** could deliver the cylization intermediate **E.** Finally, β-elimination of intermediate **E** could afford the desired product **C** along with byproduct $^tBuNH_2$ (Scheme 3).

The present activating strategy was also applied to the synthesis of a biologically active molecule Erlotinib (FDA-approved tyrosine kinase inhibitor).[21] The reaction of starting material **8** with isocyanide **2a** was performed under the standard condition, affording the key intermediate **9** in 92% yield. Subsequent chlorination and amination reactions could afford Erlotinib in 74% yield over two steps (Scheme 4).

Conclusions

In conclusion, we have developed an efficient silicon-based Lewis acid system for the activation of isocyanides. Based on this strategy, a new robust transition-metal and oxidant free method for the construction of various N-heterocycles could be realized using isocyanide as methine source. Quinazolinone, benzoimidazole, and benzothiazole derivatives could be obtained in good to excellent yields under mild conditions. The present strategy opens a powerful pathway for the activation of isocyanides, and further studies on the application of this methodology are currently underway.

Conflicts of interest

There are no conflicts to declare.

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