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# Copper(I)-Catalyzed [3+2] Cycloaddition/Ring-Opening Rearrangement/[4+2] Cycloaddition/Aromatization Cascade: An Unprecedented Chemo- and Stereoselective Three Component Coupling of Sulfonyl Azide, Alkyne and *N*-Arylidenepyridin-2-amine to Pyrido[1,2-*a*]pyrimidin-4-imine

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**Abstract:** A novel synthetic protocol for the one-pot chemo- and stereoselective construction of diversely functionalized pyrido[1,2-*a*]pyrimidin-4-imines *via* copper(I)-catalyzed [3+2] cycloaddition/ring-opening rearrangement/[4+2] cycloaddition/aromatization cascade of sulfonyl azides, alkynes and *N*-arylidenepyridin-2-amines under mild reaction conditions is reported. In addition, the catalytic activity of copper(I)-modified zeolite, a recyclable, heterogeneous catalyst is also investigated, which gives improved yield compared to its homogeneous equivalents.

**Keywords:** fused-ring systems; heterogeneous catalysis; multicomponent reactions; stereoselectivity

The pyrido[1,2-*a*]pyrimidine skeleton is a privileged scaffold in medicinal chemistry for facile access to "drug-like" small molecules.[1–5] Notably, the pyrido-[1,2-*a*]pyrimidin-4-one pharmacophore displays diverse biological activities and considerable progress has been made in the synthesis and expanding the scope of pyrido[1,2-*a*]pyrimidin-4-ones in the field of medicinal chemistry. Some outstanding representatives have been introduced into human therapy as a neuroleptic (risperidone),[6] a tranquilizer (pirenperone),[7] an antiallergic (ramastine),[8] an antidepressant (lusaperidone)[9] and a non-narcotic analgesic (rimazolium)[10] agents. Wu et al., synthesized a pyrido[1,2-*a*]pyrimidin-4-imine, namely (*E*)-3-(benzenesulfonyl)-2-(methylsulfanyl)pyrido[1,2-*a*]pyrimidin-4-ylidenamine, and screened it as a potent and selective 5-$HT_6$ antagonist.[11] To the best of our knowledge, there is no report on the direct synthesis of *N*-substituted pyrido[1,2-*a*]pyrimidin-4-imines. Consequently, new synthetic methods that allow an efficient and easy access to more structurally diverse new derivatives of this fused heterocyclic system are highly warranted, especially in the early stages of drug discovery.

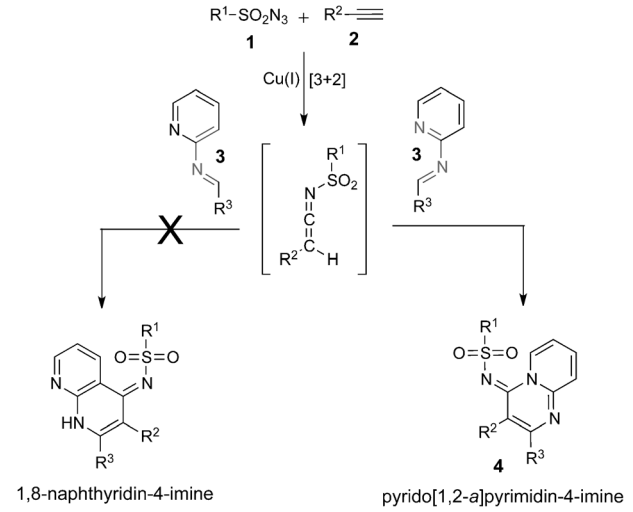
Cascade multicomponent reactions (MCRs),[12] enabling multiple carbon-carbon and carbon-heteroatom bond formations in one pot have become increasingly popular as attractive tools for the rapid generation of complex molecular scaffolds. These reactions can serve as the basis for both targeted organic synthesis and combinatorial chemistry, which allows one to synthesize simultaneously several hundred samples for biological screening with the use of automated efficient approaches. It has been recognized that MCRs have not only been sought after for their academic interest but also for their industrial relevance, especially owing to the presence of many elements of an ideal synthesis, such as operational simplicity, atom economy, bond-forming efficiency, access to molecular complexity from simple starting materials, and low levels of by-product generation. Such reactions are thus economically and environmentally attractive and have become an important area of research in synthetic organic chemistry. However, to ensure sufficient molecular diversity and complexity, there is a continuous need for novel reactions with rational design.

Recently, copper-catalyzed MCRs involving the cycloaddition of sulfonyl azides and terminal alkynes have attracted enormous attention from various research groups.[13] This copper-catalyzed MCR has been utilized for the synthesis of variety of heterocyclic systems.[14] Despite the significant advances made in this area, there still exists ample scope for exploring this reaction towards fine molecules synthesis. Re-

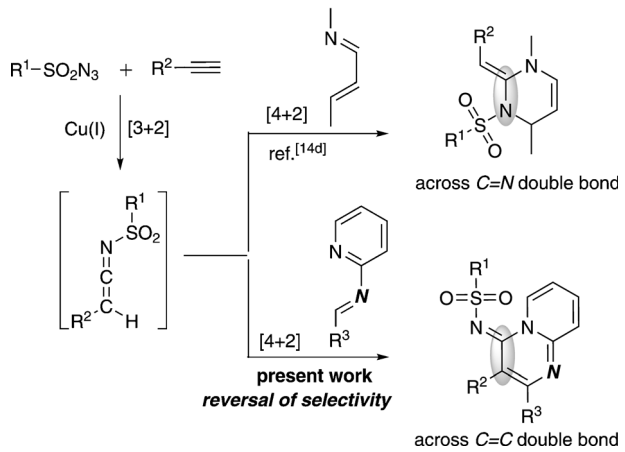
cently, we have developed cascade syntheses of imidazolidin-4-ones[15] and bis-*N*-sulfonylcyclobutenes[16] from *N*-sulfonylketenimine, generated *in situ* from copper-catalyzed cycloaddition of sulfonyl azides and terminal alkynes. Encouraged by this straightforward access to valuable chemical motifs, we became interested in exploiting the synthetic potential offered by this unique intermediate towards the synthesis of other novel and pharmacologically relevant heterocyclic systems.

In the present study, we have utilized a 1,3-diazadiene skeleton, namely, *N*-arylidenepyridin-2-amine for a facile [4+2] cycloaddition with *N*-sulfonylketenimine, generated *in situ* from the copper(I)-catalyzed [3+2] cycloaddition of sulfonyl azides and terminal alkynes. To our surprise, the cycloaddition proceeds exclusively across the C=C double bond of *N*-sulfonylketenimine and subsequent aromatization leading to pyrido[1,2-*a*]pyrimidin-4-imines (Scheme 1), in contrast to the previous report[14d] with α,β-unsaturated imine. The presence of two electron-rich nitrogen atoms in diazadiene (Scheme 1 and Scheme 2) increases the electron density and hence the reactivity of diene component towards Diels–Alder reactions. Consequently the more electron-deficient side of dienophile (namely the C=C bond, but not the C=N bond) is the more reactive. The resultant reorganization in HOMO (of diene) and LUMO (of denenophile) energy levels may be responsible for the stereoselective addition to the C=C bond but not to theC=N bond of the ketenimine (Scheme 1). Moreover, this [4+2] cycloaddition is highly stereoselective towards pyrido[1,2-*a*]pyrimidin-4-imine (diazadiene centre of *N*-arylidene-pyridin-2-amine) over the other possible product 1,8-naphthyridine (azadiene centre) (Scheme 2). The structure of pyrido[1,2-*a*]pyrimidine was unambiguously established by NMR and single-crystal X-ray analyses (Figure 1).[17]




**Scheme 2.** Stereoselective [4+2] cycloaddition towards pyrido[1,2-*a*]pyrimidin-4-imines.

Herein, we report our results on this unprecedented multicomponent reaction cascade involving sulfonyl azide, alkyne and *N*-arylidenepyridin-2-amine for the synthesis of medicinally relevant pyrido[1,2-*a*]pyrimidin-4-imines *via* an one-pot 1,3-dipolar [3+2] cycloaddition/ring-opening rearrangement/Diels–Alder [4+2] cycloaddition/aromatization sequence. The attractive features of this protocol are the ready aromatization without any oxidizing agents, the reversal of chemoselectivity, the excellent stereoselectivity and a new method for the synthesis of an important pharmacophore, pyrido[1,2-*a*]pyrimidine-4-imine with a diverse range of biological activities and applications at room temperature.




**Scheme 1.** Reversal of chemoselectivity with diazadiene.

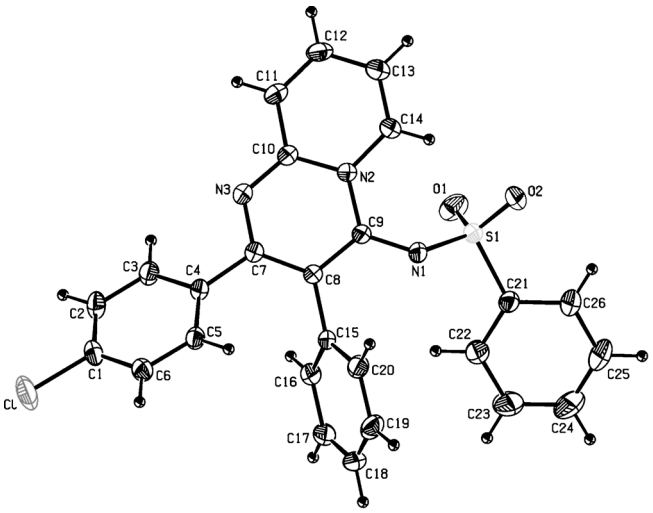
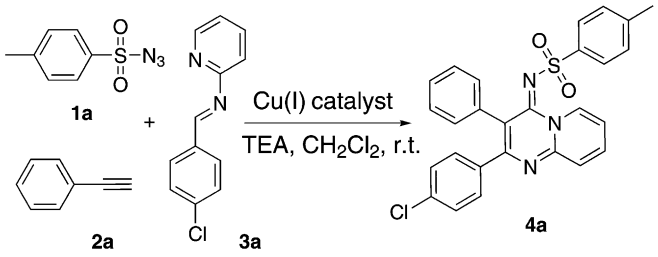



**Figure 1.** X-ray crystal structure of **4d**.

**Table 1.** Optimization of reaction conditions.[a]




| Entry | Catalyst | Base | Solvent | Yield [%][b] |
|---|---|---|---|---|
| 1 | CuI | TEA | DCM | 21[c] |
| 2 | CuI | TEA | DCM | 74 |
| 3 | CuBr | TEA | DCM | 69 |
| 4 | CuCl | TEA | DCM | 66 |
| **5** | **Cu(I)-Y** | **TEA** | **DCM** | **82** |
| 6 | Cu(I)-Y | DIPEA | DCM | 68 |
| 7 | Cu(I)-Y | $K_2CO_3$ | DCM | 71 |
| 8 | Cu(I)-Y | $K_3PO_4$ | DCM | 75 |
| 9 | Cu(I)-Y | TEA | MeCN | 54 |
| 10 | Cu(I)-Y | TEA | toluene | 51 |
| 11 | Cu(I)-Y | TEA | DMF | 77 |
| 12 | Cu(I)-Y | TEA | THF | 65 |

[a] *Reaction conditions:* tosyl azide (1 mmol), phenylacetylene (1 mmol), *N*-(4-chlorobenzylidene)pyridin-2-amine (1 mmol), TEA (2 mmol), catalyst (20 mg, 0.13 mmol)[18], solvent (2 mL), room temperature, 12 h.

[b] Isolated yield.

[c] Under an $N_2$ atmosphere

Preliminary studies were carried out with tosyl azide **1a**, phenylacetylene **2a** and (*E*)-*N*-(4-chlorobenzylidene)pyridin-2-amine **3a** (prepared by the condensation of 2-aminopyridine with 4-chlorobenzaldehyde), in the presence of CuI and triethylamine (TEA) under an $N_2$ atmosphere in dichloromethane (DCM). The pyrido[1,2-*a*]pyrimidin-4-imine **4a** was obtained in only 21% yield (Table 1, entry 1). On the other hand, in the presence of air a dramatic improvement in the yield (74%; Table 1, entry 2) was noticed. Other copper sources like CuCl and CuBr were also effective in catalyzing this reaction with marginal decreases in yields (Table 1, entries 3 and 4). With increasing environmental legislation, more ecofriendly methodologies for organic reactions employing solid and easy recyclable catalysts are desired. Consequently, a great deal of effort has been made in the development of organic reactions catalyzed by solid-supported catalysts.[19] As part of our ongoing interest in the use of cation exchanged zeolites and clays in organic synthesis,[15,16,20] Cu(I)-exchanged zeolites [Cu(I)-Y][21] was used as a reusable catalyst in the present study and this cascade reaction proceeds quite efficiently with higher yields (82%; Table 1, entry 5). TEA generally gave better yields. Besides DCM, other solvents such as MeCN, THF and toluene were also used and no significant improvement in yield was observed (Table 1, entries 9–12). Thus, the optimal reaction conditions for this copper-catalyzed cascade process are use of Cu(I)-Y as a catalyst and TEA as base in DCM in air for 12 h (Table 1, entry 5).

The scope of this one-pot, three-component cascade reaction was further extended to various substituted analogues. As depicted in Table 2, the reaction proceeded efficiently with different combinations of azides, alkynes and imines. In many cases, the pyrido-[1,2-*a*]pyrimidin-4-imines were isolated in good yields by column chromatography on silica gel. Both electron-rich and electron-deficient sulfonyl azides provided higher yields (Table 2, entries 1–4). Similarly, employment of different alkynes, bearing aryl or alkyl groups (Table 2, entries 1, 5–7), produced pyridines in good to excellent yields. To further widen the applicability of the procedure, we also tested a variety of imines. The imines derived from aryl aldehydes with electron-withdrawing as well as electron-donating groups are generally well tolerated in the cascade reactions (entries 8–13). Control experiments towards an one-pot sequential synthesis of pyrido[1,2-*a*]pyrimidin-4-imine from 2-aminopyridine, 4-chlorobenzaldehyde, tosyl azide, and phenylacetylene however resulted in poor yields.

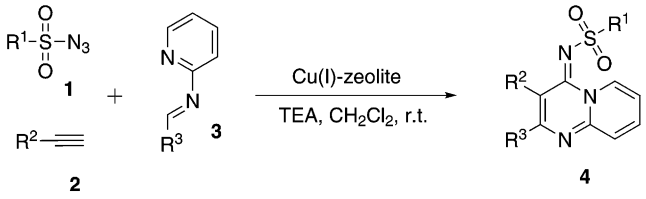
The observed preference of 1,3-diazadiene over azadiene as the diene compartment in stereoselective [4+2] cycloaddition in synthesis of pyrido[1,2-*a*]pyrimidines prompted us to verify this significant result with a terminal azadiene **3h** (Scheme 3). Interestingly, here also the cycloaddition is highly stereoselective towards the 1,3-diazadiene skeleton and the corresponding pyrido[1,2-*a*]pyrimidine was obtained in good yield (see the Supporting Information).

The recyclability of Cu(I)-Y was also investigated. After completion of the reaction, the catalyst was separated by simple filtration and washed with ethyl acetate (2 mL × 2). After air-drying, it was reused directly without any further purification. Almost consistent activity, with only a marginal decrease in yield, was observed upto 4 consecutive cycles (Table 3). The UV-Vis DRS of the reused Cu(I)-Y zeolite shows that Cu(I) is largely intact, within the zeolite framework without any significant oxidation.

A plausible mechanistic pathway for the present reaction cascade is depicted in Scheme 4. Sulfonyl azide **1** reacts readily with the terminal alkyne **2** in the presence of Cu(I)-Y and $Et_3N$ to give the ketenimine intermediate **B** *via* ring-opening rearrangement of the initially formed *N*-sulfonyl copper triazole species **A**, which then underwent a formal [4+2] cycloaddition with imine **3** to offer the dihydro intermediate **C**. Subsequent aromatization by air oxidation generated the pyrido[1,2-*a*]pyrimidin-4-imines (**4**). Efforts to isolate this dihydro intermediate were unsuccessful, which is attributed to the vulnerability of **C** towards oxidation

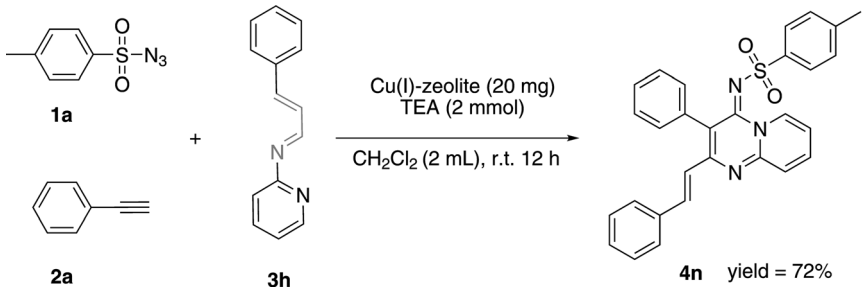
  

**Table 2.** Copper(I)-Y zeolite-catalyzed cascade synthesis of pyrido[1,2-*a*]pyrimidine-4-imines.[a]




| Entry | $R^1$ | $R^2$ | $R^3$ | Yield [%][b] |
|---|---|---|---|---|
| 1 | 4-$MeC_6H_4$ (**1a**) | Ph (**2a**) | 4-$ClC_6H_4$ (**3a**) | **4a**, 82 |
| 2 | 3-$CF_3C_6H_4$ (**1b**) | **2a** | **3a** | **4b**, 73 |
| 3 | 2-naphthyl (**1c**) | **2a** | **3a** | **4c**, 66 |
| 4 | Ph (**1d**) | **2a** | **3a** | **4d**, 85 |
| 5 | **1a** | 4-$MeC_6H_4$ (**2b**) | **3a** | **4e**, 70 |
| 6 | **1a** | 4-*n*-pentyl$C_6H_4$ (**2c**) | **3a** | **4f**, 58 |
| 7 | **1a** | cyclopropyl (**2d**) | **3a** | **4g**, 63 |
| 8 | **1a** | **2a** | 3-$ClC_6H_4$ (**3b**) | **4h**, 82 |
| 9 | **1a** | **2a** | 4-*i*Pr$C_6H_4$ (**3c**) | **4i**, 77 |
| 10 | **1a** | **2a** | Ph (**3d**) | **4j**, 78 |
| 11 | **1a** | **2a** | 4-$MeC_6H_4$ (**3e**) | **4k**, 71 |
| 12 | **1a** | **2a** | 4-$MeOC_6H_4$ (**3f**) | **4l**, 64 |
| 13 | **1a** | **2a** | 3-$MeOC_6H_4$ (**3g**) | **4m**, 76 |

[a] *Reaction conditions:* sulfonyl azide (1 mmol), alkyne (1 mmol), *N*-arylidenepyridin-2-amine (1 mmol), TEA (2 mmol), catalyst (20 mg, 0.13 mmol), solvent (2 mL), room temperature, 12 h.
[b] Isolated yield.




**Scheme 3.**

to yield the more stable aromatized product **4**. This [4+2]cycloaddition is chemoselective at the C=C double bond of the ketenimine intermediate **A.** It is also found to be highly stereoselective (with only the diazadiene component reacting) to yield pyrido[1,2-*a*]pyrimidin-4-imine. Absence of the alternative product 1,8-naphthyridine (Scheme 2), *via* an azadiene skeleton, is attributed to (i) the increased electron density, and (ii) the faster nucleophilic attack initiated *via* nitrogen atom in the case of the diazadiene unit.

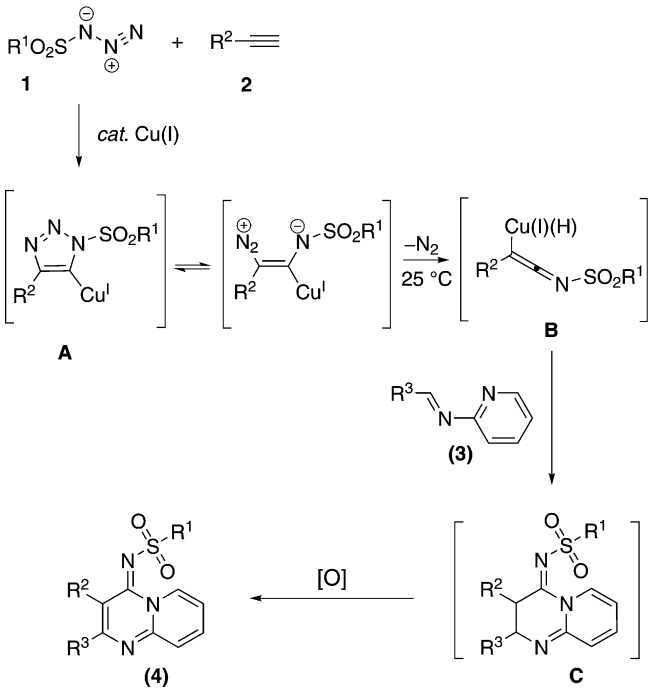
**Table 3.** Reusability of Cu(I)-Y zeolite in the cascade synthesis of pyrido[1,2-*a*]pyrimidin-4-imines.[a]

| Reuse | 1st | 2nd | 3rd | 4th |
|---|---|---|---|---|
| Yield[b] | 82 | 79 | 75 | 70 |

[a] *Reaction conditions:* tosyl azide (5 mmol), phenylacetylene (5 mmol), *N*-(4-chlorobenzylidene)pyridin-2-amine (5 mmol), TEA (10 mmol), catalyst (100 mg, 0.65 mmol), solvent (8 mL), room temperature, 12 h.
[b] Isolated yield.

In conclusion, a novel copper(I)-catalyzed three-component reaction of sulfonyl azide, alkyne and imine to generate the fused heterocycles having the pyrido[1,2-*a*]pyrimidine pharmacophore has been successfully developed. This reaction proceeds *via* a cascade azide/alkyne cycloaddition–ring opening rearrangement–ketenimine/*N*-arylidinepyridin-2-amine cycloaddition–aromatization sequence. This methodology demonstrates for the first time, an efficient one-pot synthesis of *N*-substituted pyrido[1,2-*a*]pyrimidines and offers advantages in terms of simplicity of the procedure, ready variation in building blocks, and mild reaction conditions. The much simpler experimental protocol and product isolation procedure,




**Scheme 4.** Plausible mechanistic pathway.

combined with ease of recovery and reuse of catalyst are other notable advantages of this method. Further investigations on the mechanism, the substrate scope, and the application of this methodology to natural product synthesis are in progress.

## Experimental Section

### General Procedure for the Cu(I)-Zeolite-Catalyzed One-Pot Synthesis of Pyrido[1,2-*a*]pyrimidin-4-imines

A solution of alkyne (1 mmol) in one mL of DCM was added slowly to a mixture of Cu(I)-zeolite (20 mg), sulfonyl azide (1 mmol), *N*-arylidenepyridin-2-amine (1 mmol) and $Et_3N$ (2 mmol) taken in 1 mL of DCM under an air atmosphere. After stirring at room temperature for 12 h, the mixture was diluted with ethyl acetate (5 mL). After removing the catalyst by filtration, followed by solvent evaporation under reduced pressure, the resulting crude product was finally purified by column chromatography on silica gel (60–120 mesh) with petroleum ether and ethyl acetate as eluting solvent to give the desired product. The recovered catalyst was thoroughly washed with ethyl acetate and used for the next run

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