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New MCR for the Rapid Construction of Polysubstituted Pyridines in Aqua Media Using $(Bu_3Sn)_2MoO_4$ as Green and Sustainable Catalyst

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A new combinatorial, rapid and single-pot multi-component sequence is developed for the synthesis of polysubstituted pyridines by using organotin-oxomolybdate coordination polymer as green catalyst in aqua media. New MCR utilizes benzaldehyde, ethynylbenzene / ethyl but-2-ynoate, amine / alcohol and malononitrile as components to produce diversified pyridines with excellent yields (94%–97%) using 10 mol% of $(Bu_3Sn)_2MoO_4$ catalyst in water at ambient temperature. All the isolated products are characterized by ^1H NMR, ^{13}C NMR, IR and Mass data. The catalyst was recovered and reused as many as six times without loss of activity. New protocol is scale amicable and compatible with broad range of substrates.

1. Introduction

Discovering new organic reactions using greener perspectives is prominent in chemical research and unanimously gained universal acceptance.[1] Typically, Green chemistry covers all the reactions that are nonhazardous to humans, enviromental friendly while preventing / minimizing pollution. Among various greener approches, using water as reaction media instead of organic solvent has received great significance owing to the intriguing research carried out by many scientists.[2]

Water is omni present and numerous biochemical processes occur in aqueous medium. It is used in numerous organic reactions such as pericyclic, reactions of carbanion and carbocation equivalent, reactions of radicals and carbenes, transition metal catalysis, condensation, oxidations, reductions, carbohydrates, etc.[3] Water-tolerant catalysts empower researchers to explore intriguing reactions in aqueous medium and invent new methadologies.

Coordination polymers (CPs) are a class of water-tolerant catalysts that are formed by transition metal ions and an organic multi-dentate ligand. CPs posseses unique properties such as crystalline and large porous structure, high specific surface area, easy recoverability, high thermal stabilities, diverse and tunable chemical components that enable them to emerge as efficient catalysts.[4] In the available CPs, Molybdenum and Tungsten based CPs are the attractive materials and these oxometalate compounds contain acid and redox properties.[5] The versatality of $(Bu_3Sn)_2MoO_4$ as catalyst is explored in different organic transformations like olefin epoxidation,[6] sulfoxidation,[7] *N*-oxidation of primary aromatic amines,[8] synthesis of dimethyl carbonate[9] and unsymmetrical organic carbonate,[10] synthesis of heterocyclic compounds like quinazolinones and dihydroquinazolinones[11] and 3-arylmethyl indoles.[12]

Multi-component (MCRs) follow green chemistry principles and are valuable in affording desired molecules with high functional group tolerance without isolation of intermediates. Current era scientists are more inclined towards the combinatorial synthesis of diversified (complex) hybrid compounds with high regio and stereo selectivity.[13]

Unarguably, pyridine core scaffold is a forum in pharmaceutical industry due to their diverse medicinal and biological activities.[14] As per FDA approved drugs list, pyridine motif along with piperazine ranks second among the nitrogen heterocycles.[15] Pyridines exhibit broad therapeutic and pharmacological properties like anti-inflammatory,[16] antiproliferative,[17] anticancer,[18] antimicrobial activity, and antiviral, etc[19] (Figure 1). Polysubstituted pyridines possess significant biological activities[20] and found to be an integral part of natural products and synthetic drugs.

In the previous decades, several elegant protocols[21] have been published in the literature for synthesizing multisubstituted pyridines and MCRs occupy major portion. MCRs employ various catalysts such as Wang-OSO_3H (under ultrasound),[22] $SnCl_2{\cdot}2H_2O$,[23] $Fe_3O_4@SiO_2@UBL$,[24] IRA-400 (OH),[25] ionic liquids,[26] etc., for the construction of polysubstituted pyridines. Though helpful, reported methods suffer from limitations such as high temperature, long reaction time, tedious work up, moderate yields, and use of nonreusable catalysts, etc. Thus, development of an efficient and single-pot multi-component

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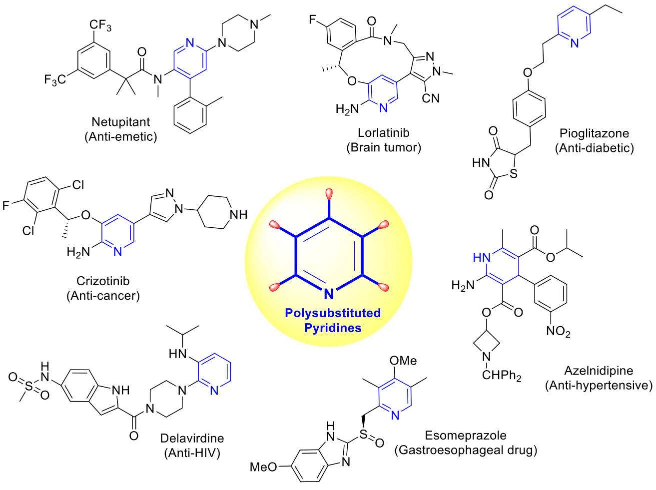


Figure 1. Bioactive pyridine scaffolds.

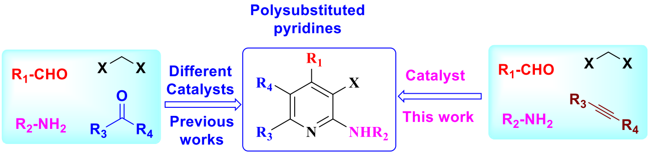
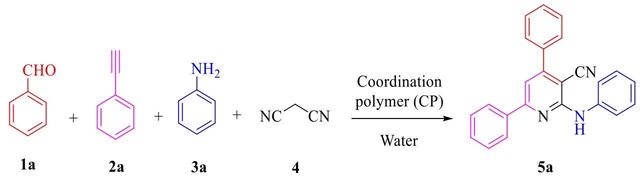


Figure 2. Synthesis of polysubstituted pyridines.



Scheme 1. Synthesis of polysubstituted pyridines.

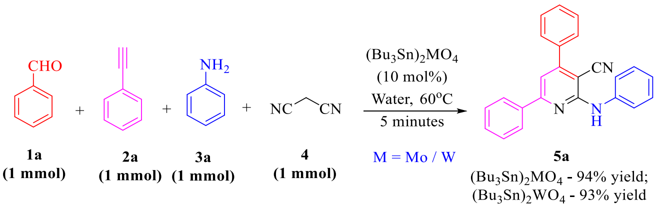
protocol under mild conditions using recyclable and greener catalyst is a major call in modern synthetic chemistry.[27]

Clasically, MCRs for building pyridine framework involves different aldehydes, aromatic amine, active methylene moiety and ketones in presence of catalyst. We envisaged that terminal alkyne drivatives are viable alternate to replace ketone derivatives for the synthesis of polysubstituted pyridines (Figure 2).

The green chemistry principles, importance of MCRs, efficient catalysis of CPs, curiosity to replace ketone derivative with terminal alkynes, ubiquitous nature of pyridines and demand for greener methadology have spurred an interest in us to design a novel startegy for the synthesis of polysustituted pyridines from benzaldehyde (**1a**), ethynylbenzene (**2a**), Aniline (**3a**), and malononitrile (**4**) using $(Bu_3Sn)_2MoO_4$ (CP) as resuable catalyst in water at ambient temperature (Scheme 1).

2. Results and Discussion

We embark our journey with the synthesis of two CPs, $(Bu_3Sn)_2MoO_4$ and $(Bu_3Sn)_2WO_4$. Both the catalysts were initially screend for the synthesis of polysubstituted pyridine (**5a**) starting from benzaldehyde (**1a**), ethynylbenzene (**2a**), Aniline (**3a**), and malononitrile (**4**) in water at 20–30 °C (Scheme 2) using 10 mol% of catalyst. To our delight, the reactions proceed for completion in 5 minutes affording 4,6-diphenyl-2-(phenylamino)nicotinonitrile (**5a**) in excellent yields. No significant variation observed with both catalysts with regard to reaction time and yield. Nevertheless, MoO_4 based compounds often exhibit better surface reactivity than WO_4 based compounds due to their electronic configuration and coordination environment, hence, we have decided to continue further development work with molybdenum-coordination polymer, $(Bu_3Sn)_2MoO_4$. It is noteworthy to mention that this reaction was not feasible without using $(Bu_3Sn)_2MoO_4$).



Scheme 2. Synthesis of polysubstituted pyridine, **5a**.

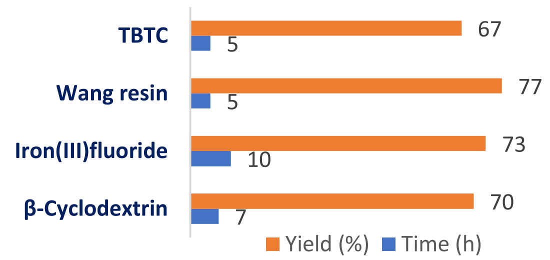


Figure 3. Screening of different catalysts^a for synthesis of **5a**. ^{a} **Reaction conditions**: Benzaldehyde (**1a**) (1.0 mmol), ethynyl benzene (**2a**) (1.0 mmol), Aniline (**3a**) (1.0 mmol) and malononitrile (**4**) (1.0 mmol), respective Catalyst (10 mol%) in Water (5 mL), 20–30 °C, reaction time (see table). Yields correspond to isolated products.

We next examined other catalysts such as β-Cyclodextrin, Iron(III)fluoride, Wang-OSO_3H resin, and Tributyltin chloride (TBTC) for the synthesis of **5a** under the reaction conditions followed for model reaction. Longer reaction times and low yields were observed, hence, none of the screened catalysts were as effective as two CPs (Figure 3).

To understand the kinetics, standard reaction was also studied in organic solvents such as acetonitrile, 1,4-dioxane, tertahydrofuran, Xylene, DMSO and DMF. Interestingly, synthesis of compound **5a** in these solvents took longer reaction time and yields are slightly low in comparison to water media (Figure 4). Reaction in ethanol for 75 minutes yielded 85% product using 10 mol% of $(Bu_3Sn)_2MoO_4$.

$(Bu_3Sn)_2MoO_4$ loading was studied for the synthesis of **5a** at 20–30 °C for 5 min using standard stoichiomerty of raw materials. 5 mol% of catalyst resulted 78% of **5a** and use of higher loading (10 mol% to 40 mol%) of catalyst afforded 93%–94% of product indicating there is no significant impact of catalyst above 10 mol% (Figure 5).

Green chemistry principles emphasize on recycling, recovery and reuse of the ctalyst as it reduces waste and minimizes

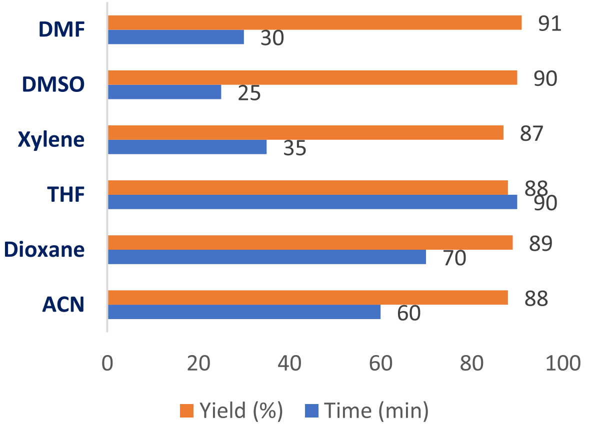


Figure 4. Screening of various solvents using (Bu3Sn)2MoO4.[a] [a] **Reaction conditions**: Benzaldehyde (**1a**) (1.0 mmol), ethynyl benzene (**2a**) (1.0 mmol), Aniline (**3a**) (1.0 mmol) and malononitrile (**4**) (1.0 mmol), $(Bu_3Sn)_2MoO_4$ (10 mol%) at 20–30 °C in solvent (5 mL), reaction time (see table). Yields correspond to isolated products.

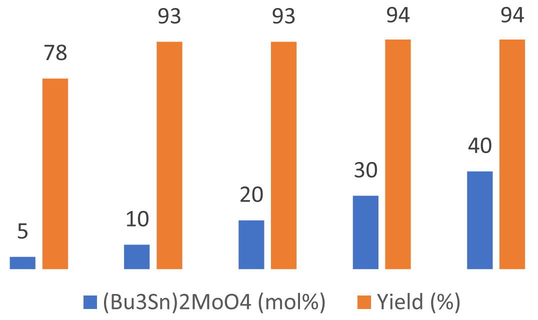


Figure 5. Screening of different mol % of $(Bu_3Sn)_2MoO_4$[a] [a]**Reaction conditions**: Benzaldehyde (**1a**) (1.0 mmol), ethynyl benzene (**2a**) (1.0 mmol), Aniline (**3a**) (1.0 mmol) and malononitrile (**4**) (1.0 mmol), $Bu_3Sn)_2MoO_4$ (refer Figure 5 for mol%) in Water (5 mL), 20–30 °C, 5 minutes. Yields correspond to isolated products.

energy. A sustainable and recyclable catalyst are highly desirable for industrial applications. To evaluate the long life and activity of $(Bu_3Sn)_2MoO_4$, we have recovered the catalyst by simple filtration, washed with excess 10% methanol-ethyl acetate mixture, dried at 40–50 °C for about 2 h, and used in next cycle. Recovery excercise was continued up to six cycles while obtaining consistent yields (92%–94%) which clearly demonstrates that the catalyst is robust and activity is intact. PXRD spectrum of fresh catalyst and six times used catalyst were recorded and both spectra perfectly overlay with each other having same 2θ values which further validates $(Bu_3Sn)_2MoO_4$ sustainability (Figure 6). Similarly, IR spectrum of fresh catalyst and used catalyst was generated and data found to be comparable (Figure 6).

Generality and substrate scope of the present methodology was explored through the reaction involving different aldehydes [benzaldehyde (**1a**), 4-methoxy benzaldehyde (**1b**), thiophene-2-carbaldehyde (**1c**) and isovaleraldehyde (**1d**)], aryl alkynes [ethynyl benzene (**2a**) and 1-ethynyl-4-methoxybenzene (**2b**)], anilines [aniline (**3a**), o-toluidine (**3b**), 2,3-dimethylaniline (**3c**) and 4-fluoroaniline (**3d**)] and malononitrile (**4**) as shown in Scheme 3. All the reactions proceeded smoothly within 5 minutes in water using 10 mol% of $(Bu_3Sn)_2MoO_4$ to afford desired products **5b** to **5h** in excellent yields (94%–97%). Different aldehydes namely benzaldehyde, 4-methoxy benzaldehyde, thiophene-2-carb aldehyde and isovaleraldehyde participated in the reaction efficiently providing respective polysubstituted pyridines (**5b–5d**, **5e,** and **5g** and **5h**) in high yields. Two alkyne variants, ethynylbenzene and 1-ethynyl-4-methoxybenzene also provided desired products in good yields. Similarly, various substituted anilines such as 2-methyl aniline, 2,3-dimethyl aniline and 4-fluoro aniline involved in new MCR with ease to give corrresponding pyridines in ≥ 94% yields.

Next, we extended our substrate scope reaction with ethyl but-2-ynoate (replacing ethynylbenzene) as shown in Scheme 4 under the standard reaction conditions. It is note worthy to mention that all the reactions progresses well with ethyl but-2-ynoate and different aryl aldehydes [benzaldehyde (**1a**), 4-methoxy benzaldehyde (**1b**), 4-cyano benzaldehyde (**1c**) and 4-nitro benzaldehyde (**1d**)], anilines [aniline (**3a**) and o-toluidine (**3b**)], and malanonitrile (**4**) to produce corresponding ethyl 5-cyano-2-methyl-4-phenyl-6-(phenylamino) nicotinate (**7a–7e**) respectively in high yields (94%–97%). We were delighted to see that aryl aldehydes having both electron-donating and electron-withdrawing groups are compatible in this MCR to produce multisubstistuted pyridines.

After synthesizing the pyridine derivatives (**5a–h** and **7a–7e**), we extrapolated the applicability of current protocol using different alcohols while replacing aniline (Scheme 5) under standard conditions to obtain tetrasubstituted pyridines. In this stream, various 6-(4-aryl)-2-alkoxy-4-phenylnicotinonitriles (**9a–9e**) are synthesized proving compability of benzaldehyde (**1a**), alkynes ethynyl benzene (**2a**), and 1-chloro-4-ethynylbenzene (**2b**) and 1-bromo-4-ethynylbenzene (**2c**)], alcohols [methanol (**8a**) and ethanol (**8b**)] and malanonitrile (**4**). It is noteworthy to mention that $(Bu_3Sn)_2MoO_4$ catalyzed construction of highly substituted pyridines is not dependent on the substitution of all components involved in these four component reactions which allows the broad substrate scope of new methodology.

To showcase the scale ability of present methadology, we have demonstrated synthesis of **5a** on 10 gram-scale under standard conditions and achieved 97% yield (Scheme 6). Reaction completed in 5–10 min at 20–30 °C and yields are comparable in milligram and gram scales which proves efficiency of catalyst and scale independency of new synthetic process.

Mechanism of the current single-pot four-component reaction is depicted in Scheme 7.[28] Initially, $(Bu_3Sn)_2MO_4$ activates the aldehyde (1) to form intermediate A which upon condensation with malanonitrile (4) results intermediate B. Michael type reaction between intermediate C (derived from 2) and intermediate B gives intermediate D. Nucleophilic attack by amine (3) on intermediate D followed by tamdem proton transfer and double bond migration leads to Intermediate F which undergoes an intramolecular cyclization (by elimination of water) to give intermediate G. Finally, oxidative aromatization of intermediate G affords desired product **5**. Overall, four new bonds were formed in a single pot operation to afford the polysubstituted pyridines **5**.

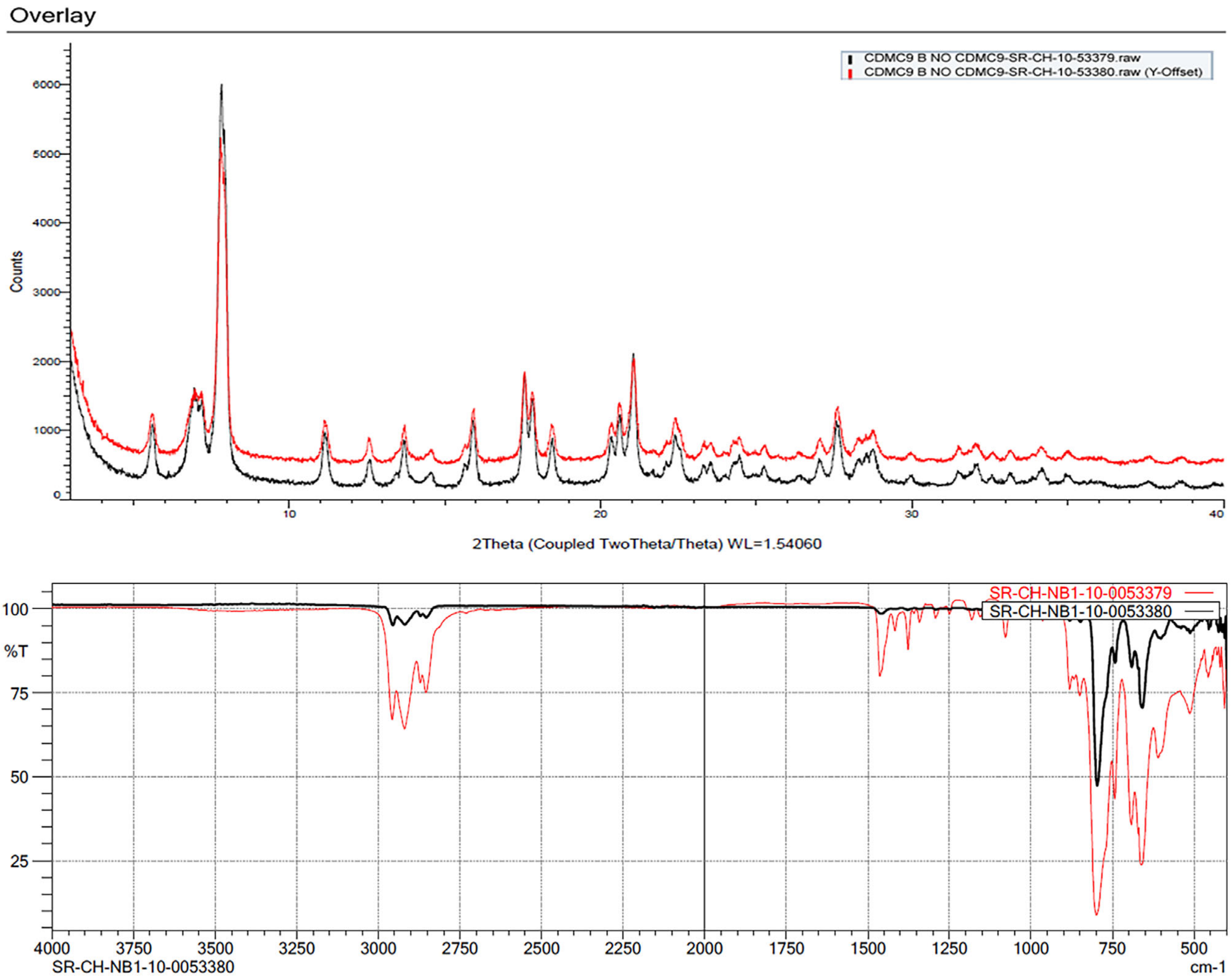
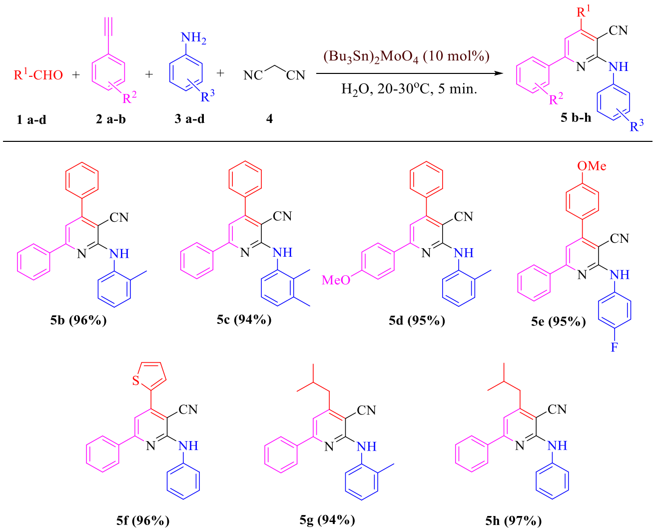
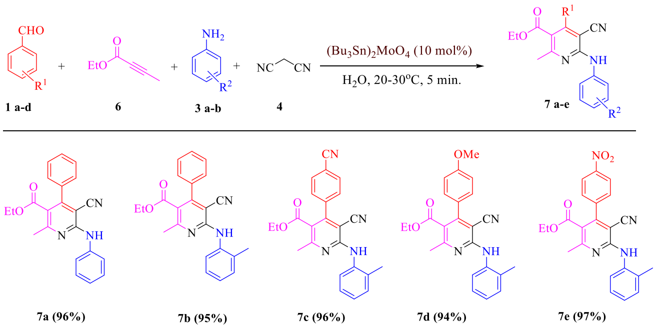


Figure 6. Overlay of PXRD & IR spectrum of fresh and six times used catalyst.



Scheme 3. Synthesis of 4,6-aryl/alkyl-2-(arylamino)nicotinonitriles (**5b–5h**).

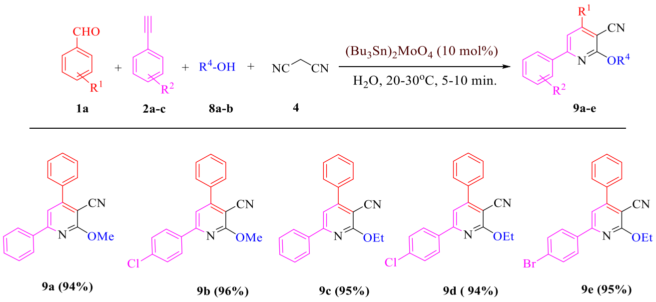


Scheme 4. Syntheiss of 5-cyano-2-methyl-4-aryl-6-(arylamino) nicotinates (**7a-7e**).

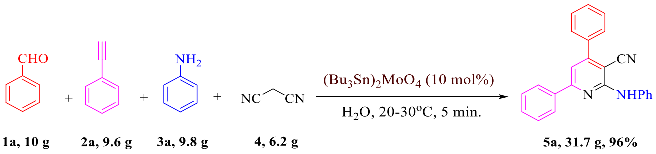
3. Conclusion

Overall, we have developed efficient and rapid process for the construction of various polysustituted pyridine templets in a one-pot multicomponent reaction using catalytic amount of $(Bu_3Sn)_2MoO_4$ in water.

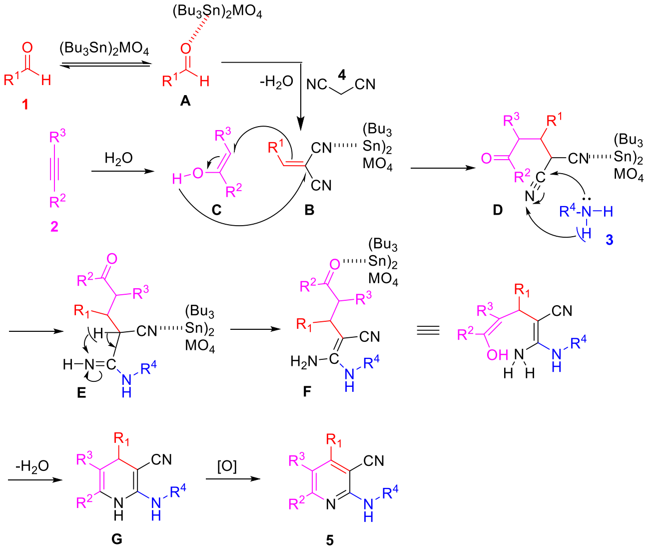
The remarkable features of current study are (i) green methodology (ii) sustainable and robust catalyst which can be



Scheme 5. Synthesis of 6-(4-aryl)-2-alkoxy-4-phenylnicotinonitriles.



Scheme 6. Gram scale reaction of polysubstituted pyridine.



Scheme 7. Plausible mechanism for substituted pyridine **5**.

recovered and reused (iii) only 10 mol% catalyst loading (iv) reaction in green solvent, i.e., water (v) minimum reaction time and high yields (vi) Aldehydes, anilines and alkynes can be varied widely, leading to pyridines having different potential points of diversity in > 90% yields (vii) scale independent.

Finally, these new seqences allows for the combinatorial synthesis of drug-like scaffold libraries suitable for lead discovery and optimization.

4. Experimental Section

4.1. General Information

All reagents were used as received and solvents from commercial sources without further purification or prepared as described in the literature. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}), visualizing with an ultraviolet light or ninhydrin charring. Product (Rf = ~0.5) chromatographic purification was carried out on silica gel (60–120 mesh). ^{1}H NMR and ^{13}C NMR spectra were determined in DMSO-d_6 and $CDCl_3$ solution by using 400 or 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethyl silane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. Melting points were determined using melting point B-540 apparatus. Mass spectra were recorded on an HP-5989A quadrupole mass spectrometer and uncorrected HRMS was determined using waters LCT premier XETOF ARE-047 apparatus Supporting Information.

4.2. General Procedure for the Synthesis of Polysubstituted Pyridines (5, 7, and 9)

A mixture of Amine/alcohol (1.0 equiv.), benzaldehyde (**1**) (1.0 equiv), malononitrile (**4**) (1.0 equiv.), ethynylbenzene / ethyl but-2-ynoate (1.0 equiv.), and $(Bu_3Sn)_2MoO_4$ (10 mol%) in water (5 mL) was stirred at room temperature for 1 h. After completion of the reaction, the reaction mixture was diluted with mixture of methanol-ethyl acetate (2:8) and filtered the catalyst. The filtered catalyst was repeatedly washed with ethyl acetate (3 x 5 mL). The layers were separated and the combined organic layers were washed with brine (1 x 10 mL) followed by water (1 x 10 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated, the residue was recrystallized in ethanol and dried to afford desired polysubstituted pyridines.

4.3. 4,6-Diphenyl-2-(phenylamino)nicotinonitrile (5a)

Pale yellow solid, mp: 213–215 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (dd, $J_{1,2}$ = 2.4 Hz, $J_{1,3}$ = 8.0 Hz, 2H), 7.77 (d, J = 7.2 Hz, 2H), 7.67–7.65 (m, 2H), 7.57–7.47 (m, 6H), 7.43 (t, J = 7.6 Hz, 2H), 7.33 (s, 1H), 7.27–7.26 (m, 1H), 7.16 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 158.9, 156.5, 155.4, 138.9, 137.8, 136.9, 130.3, 129.9, 128.9 (2C), 128.9 (2C), 128.8 (2C), 128.1 (2C), 127.4 (2C), 123.5, 120.5 (2C), 117.0, 111.4, 90.0; IR (KBr, cm^{-1}): 3335, 2215, 1602, 1582, 1497; HRMS (ESI) ([M] +1) calcd for $C_{24}H_{18}N_3$: 348.1501, found: 348.1514.

4.4. Ethyl 5-Cyano-2-Methyl-4-Phenyl-6-(phenylamino)nicotinate (7a)

White solid, mp: 205–206 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.4 Hz, 2H), 7.48 – 7.46 (m, 3H), 7.40 – 7.36 (m, 4H), 7.26 – 7.22 (m, 1 H), 7.16 – 7.13 (m, 1H), 3.99 (q, J = 7.0 Hz, 2H), 2.59 (s, 3H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 160.3, 155.3, 153.9, 138.3, 135.9, 129.4, 128.9 (2C), 128.6 (2C), 127.9 (2C), 124.0, 120.7 (2C), 120.5, 115.8, 90.8, 61.3, 23.8, 13.4; IR (KBr, cm-1): 3344, 2222, 1707, 1552, 1498, 1442, 1365, 1271, 1070, 748, 707; HRMS (ESI) ([M]+1) calcd for $C_{22}H_{20}N_3O_2$: 358.1556, found: 358.1554.

4.5. 2-Methoxy-4,6-Diphenylnicotinonitrile (9a)

Off-white color solid, mp:105–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.121– 8.097 (m, 2H), 7.674 – 7.650 (m, 2H), 7.544 – 7.526 (m, 5H), 7.513–7.505 (m, 1H), 7.496 (s, 1H), 4.215 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.187, 158.153, 156.802, 137.455, 136.458, 130.632, 130.133, 129.118 (2C), 129.031 (2C), 128.504 (2C), 127.460 (2C), 115.740, 113.680, 54.756; IR (KBr, cm^{-1}): 3061, 2225, 1585, 1578, 1455, 1309, 1081, 886, 642, 529; HRMS (ESI) ([M] +1) calcd for $C_{19}H_{15}N_2O$: 287.1184, found: 287.1189.

Supporting Information

The experimental section and additional information (^{1}H NMR, ^{13}C NMR and mass spectra) are given in the Supporting Information.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Keywords: Coordination Polymers · MCR · Polysubstituted pyridines · Recyclable catalyst

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