Received: 9 May 2019 | Revised: 11 October 2019 | Accepted: 14 October 2019

DOI: 10.1002/jhet.3806

COMMUNICATION

WILEY

SO_4^{-2}/SnO_2–catalyzed cyclocondensation for the synthesis of fully functionalized pyridines

Ramesh Goud Koduri[1] | **Ramakanth Pagadala**[2] | **Sathyanarayana Boodida**[3] | **Ravi Varala**[1]

[1] Department of Chemistry, RGUKT Basar (IIIT Basar), Nirmal, India

[2] Chemistry Division, H&S Department, CVR College of Engineering, Ibrahimpatnam, Hyderabad, India

[3] Department of Chemistry, JNTUH College of Engineering, Jagityal, India

Correspondence
Sathyanarayana Boodida, Department of Chemistry, JNTUH College of Engineering, Jagityal, India.
Email: bsnarayana77@gmail.com

Ravi Varala, Department of Chemistry, RGUKT Basar (IIIT Basar), Nirmal, India.
Email: ravivarala@gmail.com

Abstract

An efficient and promising synthetic approach to assemble skeletons of multifunctionalized pyridine derivatives in presence of recyclable heterogeneous sulfated tin oxide (STO) catalyst has been evolved. The STO catalyst was used as a promoter for the cyclocondensation process in ethanol at 70°C. Overall performance of this catalyst was attributed to the cooperative contribution of its Lewis and Brønsted-Lowry acidic sites. Nanosized STO catalyst was synthesized by using sol-gel process and characterized by Fourier transform infrared (FTIR) spectroscopy, X-ray diffraction (XRD), ^{1}H-NMR, and scanning electron microscopy (SEM). This catalyst tolerates most of the substrates, and protocol shows precious capabilities consist of high yields, operational simplicity, less reaction time, and eco-friendly conditions. The newly synthesized heterogeneous catalyst was easily separated and reused. All the reactions are carried out for subsequent cycles without significant loss of catalytic activity and with good proficiency.

1 | INTRODUCTION

The pyridine ring is a structurally important motif in several synthetic compounds because of its metabolic activities in pharmaceutical interest.[1] Pyridine ring has noticeable applications in preparation of chiral ligands[2] and preparation of new materials with electrochemical and photochemical properties.[3] Natural products like vitamin B, nicotinamide, and nicotinic acid with pyridine skeleton plays an important role in biological and metabolic activities.[4,5] 2-Amino-3-cyanopyridine derivatives have eminent significance for allowing access to many demonstrated bioactive agents[6] such as novel IKK-b inhibitors,[7] A2A adenosine receptor antagonists,[8] and potent inhibitor of HIV-1 integrase.[9]

Multiple component and one pot reactions have established extensive attention for the synthesis of heterocyclic compounds.[10] The most common and conventional methods reported for the construction of pyridine ring involved several steps,[11] long time consumption, high temperature or microwave support,[12] low yield, and with toxic solvents.[13] In recent years, several rules and legislations are made on environmental emission, considering that efficient catalytical methods are much desirable. The replacement of homogeneous Lewis acids by heterogeneous solid super-acids has predictable advantages like easy separation from the reaction mixture, noncorrosiveness, low cost, easy maintenance, tolerating continuous operation, regeneration, and recycling with the same efficiency.[14,15] Sulfated metal oxides were used as solid super-acid catalysts since they had Lewis and Brønsted acid sites, and they were also nontoxic, atmospherically stable, and thermally stable in nature.[16–19]

Sulfated tin oxide (STO) is used as a heterogeneous catalyst for the last few years because of its large surface area.[20,21] It is also found as an efficient catalyst in aldol condensation, Mukaiyama reactions, benzoylation, and trans-esterification of keto esters.[22] Various gas phase reactions including hydration, dehydration, alkylation, isomerization, esterification, and polymerization,

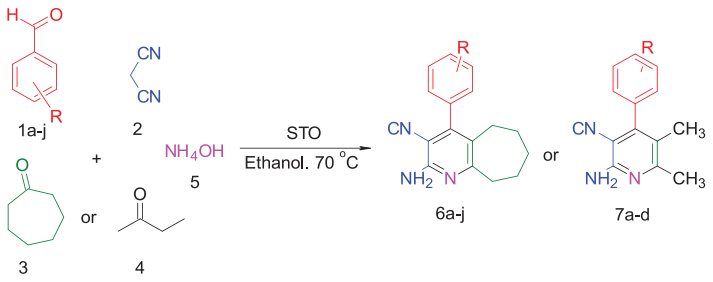
biodiesel production, β-acetamido ketones, aryl dibenzo[*a*,*j*]xanthenes, 2,4,5-triaryl-1*H*-imidazole, and 2,4-diphenyl-4,6,7,8-tetrahydro chromen-5-one are also being catalyzed.[23–31] STO has not been explored as a catalyst for the synthesis of multifunctionalized pyridine derivatives.

The synthesis of fully substituted pyridines is an important in synthetic organic chemistry because these compounds find significant attention as powerful inhibitors of HIV-1.[32] The development of a greatly proficient process for the preparation of fully substituted pyridines is of great attention. Earlier, many researchers have shown synthetic routes for the preparation of fully substituted pyridines and reported that most of the strategies suffer from many important limitations.[33] In such a scenario, the development of economically friendly methodology to deliver fully substituted pyridine derivatives will provide a green conventional approach.

Hence, we have chosen to develop multisubstituted pyridines using STO because of its wide catalytic applications. STO can be easily regenerated and repeatedly used for another fresh reaction with the same catalytical efficiency.

2 | RESULTS AND DISCUSSION

To identify the feasibility of this route, we commenced our work with the development of a less expensive and green process for the synthesis of 2-amino-3-cyanopyridine derivatives with simply accessible starting materials by using STO catalyst (Scheme 1). We initially started a model reaction of benzaldehyde, malononitrile, cycloheptanone, and ammonium hydroxide with different catalysts and solvents (Table 1). Keeping in view of environmental concern, water was used as the solvent in reaction without and with catalyst, but it was confirmed that the reaction did not progress in water (Table 1, entries 2 and 3). In order to establish the real effectiveness of the solvent and catalyst for the synthesis of fully substituted pyridines, a test reaction was performed with and without catalyst using ethanol at high temperature. It was found that only 25% of product was obtained in ethanol without catalyst at 80°C even after 8 hours (Table 1, entry 4). To increase the yield of the target compounds, the same test reaction was performed with pTSA (Table 1, entry 5), SnO_2 (Table 1, entry 6), and STO (Table 1, entry 7). Significantly, when the reaction was conducted in the presence of STO (10 mg), 92%



SCHEME 1 Four-component reaction for the synthesis of 2-amino-3-cyanopyridines (**6a**-**g** and **7a**-**d**). [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Screening of cyclocondensation reaction

Entry	Product No.	Catalyst	Amount	Solvent	Temperature, °C	Time, h	Yield,a %
1	**6a**	-	-	Water	Rt	8.0	b
2	**6a**	-	-	Water	80	6.0	b
3	**6a**	STO	20.0 mg	Water	80	6.0	b
4	**6a**	-	-	EtOH	80	8.0	25
5	**6a**	PTSA	20.0 mg	EtOH	70	6.0	c
6	**6a**	SnO_2	20.0 mg	EtOH	70	5.0	40
7	**6a**	STO	10.0 mg	EtOH	70	2.0	92
8	**6a**	STO	10.0 mg	EtOH	Rt	8.0	30
9	**6a**	STO	20.0 mg	EtOH	70	1.5	98
10	**6a**	STO	30.0 mg	EtOH	70	1.5	98

[a]Isolated yields.

[b]Product was not found.

[c]Trace.

of yield was produced. Gratifyingly, the yield of the desired target compound was further improved up to 98% by conducting the reaction with STO catalyst amount of 20 mg (Table 1, entry 9).

STO was used as catalyst and ethanol was chosen as the solvent for this one-pot cyclocondensation transformation. After optimizing the conditions, all the reactions were carried out under identical conditions and were examined by the reaction of several substituted arylaldehyde using STO in ethanol at 80°C; the results are shown in Table 2. The STO could be regenerated and activated by calcinations at 400°C to 500°C temperature for 1 hour and reused for the next five cycles without significant loss of activity (Table 3). A straightforward and simple catalytic cyclocondensation mechanism for the pyridine formation is depicted in Scheme 2. STO catalyst acts as both Lewis and Brownsted acids. In the presence of STO, Knoevenagel condensation between the malononitrile and aryl aldehydes generated arylidenemalononitrile intermediate, which undergo Michael addition with ketone and form Michael adduct. This Michael adduct further condensed with ammonium hydroxide and was followed by intramolecular cyclization, yielding pyridines. The resulting fully substituted title compounds were characterized by Fourier transform infrared (FTIR) spectroscopy, ^{1}H NMR, ^{13}C NMR, and mass spectrometry. All the synthesized compounds were further identified by ^{15}N NMR (GHSQC) to confirm the presence of the $-NH_2$ group in their structure (Supporting Information).

The IR spectra of the STO catalyst shows that the presence of sulfated group appeared at 1381, 1190, 1150, and 1075 cm^{-1}, and the acidic nature of the catalyst was studied by proton NMR spectra (Supporting Information).

TABLE 2 Multicomponent reaction for the synthesis of multisubstituted pyridines (**6a-g** and**7a-d**)

Entry	Product No.	R	Time, h	Yield,a %
1	**6a**	H	2.0	95.0
2	**6b**	4-OCH_3	2.5	91.0
3	**6c**	4-Br	2.0	92.0
4	**6d**	2-Cl	1.5	93.0
5	**6e**	2-Br	2.0	88.0
6	**6f**	2-OCH_3	3.0	85.0
7	**6g**	4-N $(CH_3)_2$	2.0	90.0
8	**7a**	H	3.0	88.0
9	**7b**	4-OCH_3	3.5	80.0
10	**7c**	4-Br	3.0	84.0
11	**7d**	2-Cl	3.0	82.0

[a]Isolated yields.

TABLE 3 Recyclability of STO catalyst tested for compound (**6a**)

Entry	Catalyst	Time, h	Yield,a %
1	Fresh	2.0	98.0
2	Second run	2.0	98.0
3	Third run	2.0	97.0
4	Fourth run	2.0	97.0
5	Fifth run	2.0	96.0

[a]Isolated yields.

2.1 | Powder XRD

In order to understand the structural properties of STO sample, X-ray diffraction (XRD) analyses of STO sample were carried out in the 20° to 80° range using CuKα radiation. XRD shows a pattern of STO sample that was found to display well-distinguished XRD peaks at 26.6°, 33.8°, 37.9°, 51.7°, 54.8°, etc, and they are the diffractions of (1 1 0), (1 0 1), (2 0 0), and (2 1 1) planes corresponding to characteristic tetragonal phase of SnO_2, which match well with the reported JCPDS file no. 41-1445 of SnO_2, confirming its tetragonal nature. This clearly indicates that the presence of sulfate (SO_4^{-2}) and the calcination temperature also stabilizes the tetragonal phase structure of SnO_2, and such stabilization of SnO_2 and other oxides in presence of SO_4^{-2} has been reported in the literature.[34,35] The addition of SO_4^{-2} causes a decrease in crystalline size and prevents their glomeration during annealing. This can be confirmed by the gradual decrease in intensity of bands in graph.

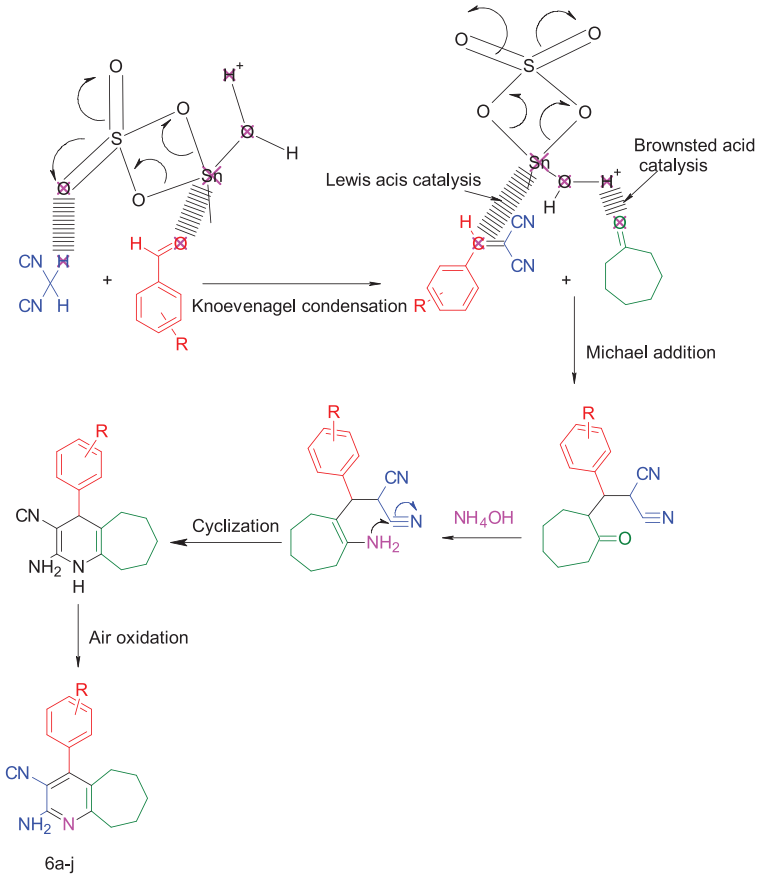
2.2 | Scanning electron micrograph

Figure 1 depicts the scanning electron micrograph (SEM) of STO nanopowder annealed at 600°C that reveals the presence of irregularly shaped particles. Larger particles observed in the figure are aggregates of small particles ranging in the sizes of 100 to 190 nm. Interestingly, the STO catalyst morphologies as indicated with uniform size, reflecting the homogeneity in shapes and high crystallinity.

3 | EXPERIMENTAL

3.1 | Procedure for the preparation of STO catalyst

A total of 22.56 g of stannous chloride was weighed, dissolved in 200 mL of distilled water, and a clear solution



SCHEME 2 Plausible reaction mechanisms for the formation of (**6a**-**g**) [Color figure can be viewed at wileyonlinelibrary.com]

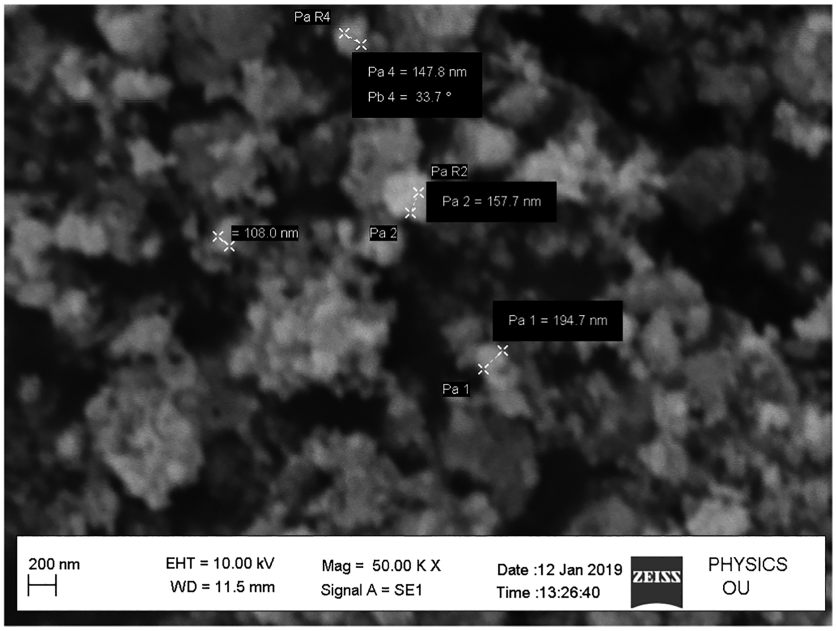


FIGURE 1 Scanning electron micrograph (SEM) images of the STO catalyst

was prepared. To the clear solution, 25 mL of aqueous ammonium hydroxide was added drop by drop with continues stirring magnetically until the pH of the solution reaches to 8. The obtained yellow precipitate was filtered and washed well with deionized water. The precipitate was dried at 120°C for 12 hours in hot air oven to get 17.8 g of stannous hydroxide. Five grams of stannous hydroxide was mixed with 25 mL of 2N H_2SO_4 and evaporated to dryness on water bath carefully and then crushed into powder form. The powder was calcinated

at 600°C for 3 hours in a desiccator to get STO and stored in the closed bottle until it was used.

3.2 | Preparation of fully functionalized pyridine derivatives

Benzaldehyde (1 mmol), ethanol (3 mL), malononitrile (1 mmol), cyclohexanone or methyl ethyl ketone (2 mmol), and ammonium hydroxide (4 mL) were added to a round-bottom flask in the same sequence, refluxed with a condenser and magnetically stirred. The reaction mixture was heated at 70°C for the appropriate time mentioned in the Table 2. The progress of the reaction was monitored by TLC (ethylacetate/n-hexane = 4:6). After completion of the reaction, the mixture was cooled and extracted in ethyl acetate, filtered, and washed with water, and STO was collected. The filtrate was dried over anhydrous sodium sulfate, and the solvent was completely removed. The obtained precipitate was recrystallized in ethanol to get more pure aimed compound (**6a**). The recycled STO was activated and reused for the next cycle. Compound **6a**; Light yellow solid: mp 226°C to 227°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.46-1.51 (2H, m), 1.70-1.83 (4H, m), 2.45 (2H, t, J = 5.4 Hz), 2.93 (2H, t, J = 5.5 Hz), 5.10 (2H, s, NH_2), 7.22-7.50 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.17, 28.04, 28.96, 31.97, 39.66, 89.32, 116.93, 126.43, 128.37, 128.59, 128.67, 136.85, 153.12, 157.23, 167.95; IR (KBr, cm^{-1}): 3315 (NH_2), 2211 (CN); Mass spectra, m/z = 286 (M + Na, 100%); Anal. calc ($C_{17}H_{17}N_3$): C 77.54, H 6.51, N 15.96 %. Found: C 77.62, H 6.49, N 15.98%.

4 | CONCLUSION

In summary, we have successfully synthesized multifunctionalized pyridines from the simple reagents like benzaldehyde, malononitrile, ketones, and ammonium hydroxide in the presence of catalyst STO. The extra benefits of this protocol are huge scope, mild conditions, easy operation, low price catalyst, good yield, smooth regeneration of catalyst, and potential for reuse with the same efficiency. This approach also provides simple, green conditions and direct method for the synthesis of target compound. In addition, exploration of the sustainable applicability of the STO to the equated and other reactions with divergent techniques like ultrasonic and electronic methods is presently underway.

ACKNOWLEDGMENTS

The authors are thankful to the management of CVR College of engineering, JNTUH College of Engineering, Jagityal, and RGUKT Basar (IIIT Basar), Nirmal, India, for support and encouragement during this research work.

ORCID

Ramakanth Pagadala https://orcid.org/0000-0002-9248-1846

REFERENCES AND NOTES

[1] J. A. Joule, K. Mills, *Heterocyclic Chemistry*, 5th ed., Wiley-Blackwell, Oxford, UK **2010**.

[2] (a) F. Durola, J. P. Sauvage, O. S. Wenger, *Chem. Commun.* **2006**, 171. (b) B. A. Sweetman, H. Muller-Bunz, P. Guiry, *J. Tetrahedron Lett.* **2005**, *46*, 4643. (c) V. N. Kozhevnikov, D. N. Kozhevnikov, T. V. Nikitina, V. L. Rusinov, O. N. Chupakhin, M. Zabel, B. Koenig, *J. Org. Chem.* **2003**, *68*, 2882.

[3] (a) B. Tang, F. Yu, P. Li, L. Tong, X. Duan, T. Xie, X. Wang, *J. Am. Chem. Soc.* **2009**, *131*, 3016. (b) F. Havas, N. Leygue, M. Danel, B. Mestre, C. Galaup, C. Picard, *Tetrahedron* **2009**, *65*, 7673. (c) B. P. Yan, C. C. C. Cheung, S. C. F. Kui, H. F. Xiang, V. A. L. Roy, S.-J. Xu, C.-M. Che, *Adv. Mater.* **2007**, *19*, 3599. (d) C. Kaes, A. Katz, M. W. Hosseini, *Chem. Rev.* **2000**, *100*, 3553.

[4] D. Yildiz, *Toxicon.* **2004**, *43*, 619.

[5] (a) N. S. Cutshall, K. A. Kucera, R. Ursion, J. Latham, N. C. Ihle, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1517. (b) R. Ling, M. Yoshida, P. S. Mariano, *J. Org. Chem.* **1996**, *61*, 4439.

[6] (a) B. C. H. May, J. A. Zorn, J. Witkop, J. Sherrill, A. C. Wallace, G. Legname, S. B. Prusiner, F. E. Cohen, *J. Med. Chem.* **2007**, *50*, 65. (b) K. Guo, R. Mutter, W. Heal, T. K. R. Reddy, H. Cope, S. Pratt, M. J. Thompson, B. Chen, *Eur. J. Med. Chem.* **2008**, *43*, 93. (c) M. T. Cocco, C. Congiu, V. Lilliu, V. Onnis, *Bioorg. Med. Chem.* **2007**, *15*, 1859.

[7] T. Murata, M. Shimada, S. Sakakibara, T. Yoshino, H. Kadono, T. Masuda, M. Shimazaki, T. Shintani, K. Fuchikami, K. Sakai, H. Inbe, K. Takeshita, T. Niki, M. Umeda, K. B. Bacon, K. B. Ziegelbauer, T. B. Lowinger, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 913.

[8] M. Mantri, O. De Graaf, J. Van Veldhoven, A. Göblyös, J. K. Von Frijtag Drabbe Künzel, T. Mulder-Krieger, R. Link, H. De Vries, M. W. Beukers, J. Brussee, A. P. Ijzerman, *J. Med. Chem.* **2008**, *51*, 4449.

[9] J. Deng, T. Sanchez, L. Q. Al-Mawsawi, R. Dayam, R. A. Yunes, A. Garofalo, M. B. Bolger, N. Neamati, *Bioorg. Med. Chem.* **2007**, *15*, 4985.

[10] (a) K. Shravan Kumar, P. Ramakanth, M. Suresh, V. Chandra Sekhar, B. Sreekantha, *J. RSC Advances* **2015**, *5*, 105446. (b) P. Ramakanth, K. Devendar Reddy, R. Surjyakanta, M. Suresh, M. Brenda, B. J. Sreekantha, *RSC Advances* **2015**, *5*, 5627. (c) M. Suresh, R. Surjyakanta, P. Ramakanth, K. Shravan Kumar, M. Suryanarayana, B. J. Sreekantha, *Cat. Comm.* **2015**, *61*, 26. (d) M. Suresh, P. Ramakanth, R. Surjyakantha, K. Shravan Kumar, B. Sreekantha, *J. Res. Chem. Interm.* **2015**, *41*, 8269. (e) P. Ramakanth, M. Suresh, B. J. Sreekantha, *J. Het. Chem.* **2015**, *52*, 1226. (f) P. Ramakanth, M. Suresh, R. Surjyakanta, B.

Sreekantha, *J. RSC Advances* **2014**, *4*, 6602. (g) P. Ramakanth, M. Suresh, D. B. C. D. Venkata, B. Sreekantha, *J. Cat. Comm.* **2014**, *45*, 148. (h) P. Ramakanth, M. Suresh, B. Sreekantha, *J. Ultrason. Sonochem.* **2014**, *21*, 472. (i) S. Adaikalam, R. Somi Santharam, V. P. Rakkappan, R. Raju, *J. Org. Chem.* **2018**, *83*, 14084.

[11] A. S. Girgis, A. Kalmouch, H. M. Hosni, *Amino Acids* **2004**, *26*, 139.

[12] (a) F. Shi, S. J. Tu, F. Fang, T. Li, *J. Arkivoc* **2005**, 137. (b) T. G. Aaron, S. C. Elizabeth, C. D. Dexter, W. L. Craig, *J. Org. Chem.* **2019**, *84*, 5855. (c) L. Yi, W. Guodong, H. Guifeng, W. Jie-Ping, *Tetrahedron Lett.* **2019**, *17*, 219.

[13] S. Kambe, K. Saito, *Synthesis* **1980**, 366.

[14] (a) X. Bokhimi, A. Morales, E. Ortiz, T. Lopez, R. Gomez, J. Navarrete, *J. Sol-Gel Sci. Tech.* **2004**, *29*, 31. (b) P. Ramakanth, M. Suresh, M. Vashen, E. V. Z. Werner, B. J. Sreekantha, *Tetrahedron Lett.* **2014**, *55*, 4006. (c) K. Ramaiah, K. Shravankumar, K. Laxma Reddy, *Synthetic Comm.* **2018**, *48*, 1777. (d) A. Mojgan, P. Sjjad Abbasi, D. Maryam, Y. E. A. Afshin, *Appl. Organometal Chem.* **2017**, *32*, e4103.

[15] Lonyi, F; Valyon, J.; Engelhardt, J.; and Mizukami, F.; *J. Catalysis*, **1996**, *160*, 279.

[16] J. Deutsch, H. A. Prescott, D. Müller, E. Kemnitz, H. Lieske, *J. Catalysis* **2005**, *231*, 269.

[17] M. V. Luzgin, K. Thomas, J. Gestel, J. P. Gilson, A. G. Stepanov, *J. Catalysis* **2004**, *223*, 290.

[18] H. Ma, J. Xiao, B. Wang, *J. Hazardous Mater.* **2009**, *166*, 860.

[19] D. Zhai, Y. Nie, Y. Yue, H. He, W. Hua, Z. Gao, *Cat. Comm.* **2011**, *12*, 593.

[20] C. P. Nicholas, T. Marks, *J. Nano Letters* **2004**, *4*, 1557.

[21] H. Matsuhashi, H. Miyazaki, Y. Kawamura, H. Nakamura, K. Arata, *Chem. Materials* **2001**, *13*, 3038.

[22] M. K. Lam, K. T. Lee, A. R. Mohamed, *App. Cat. B: Env. 93*, 134.

[23] S. R. Sarda, V. A. Puri, A. B. Rode, T. N. Dalawe, W. N. Jadhav, R. P. Pawar, *Arkivoc* **2007**, 246.

[24] M. A. Naik, B. G. Mishra, A. Dubey, G. D. Hota, *Bull. Cat. Society of India* **2009**, *8*, 35.

[25] M. Sowmiya, A. Sharma, A. Parsodkar, B. G. Mishra, A. Dubey, *App. Catalysis A* **2007**, *333*, 272.

[26] S. P. Chavan, P. K. Zubaidha, S. W. Dantale, A. Kesava-Raja, A. V. Ramaswamy, T. Ravindranathan, *Tetrahedron* **1996**, *37*, 233.

[27] Q. Lu, W. M. Xiong, W. Z. Li, Q. X. Guo, X. F. Zhu, *Bioresource Technology* **2009**, *100*, 4871.

[28] Y. Du, S. S. Liu, Y. Zhang, C. Yin, Y. Di, F. S. Xiao, *Catalysis Letters* **2006**, *108*, 155.

[29] S. Furuta, H. Matsuhashi, K. Arata, *App. Catalysis A* **2004**, *269*, 187.

[30] J. I. Moreno, R. James, R. Gómez, M. E. Niño-Gómez, *Catalysis Today* **2011**, *172*, 34.

[31] S. A. Dake, M. B. Khedkar, G. S. Irmale, S. J. Ukalgaon-Kar, V. V. Thorat, S. A. Shintre, R. P. Pawar, *Synthetic Communications* **2012**, *42*, 1509.

[32] (a) T. Murata, M. Shimada, S. Sakakibara, T. Yoshino, H. Kadono, T. Masuda, M. Shimazaki, T. Shintani, K. Fuchikami, K. Sakai, H. Inbe, K. Takeshita, T. Niki, M. Umeda, K. B. Bacon, K. B. Ziegelbauer, T. B. Lowinger, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 913. (b) J. Deng, T. Sanchez, L. Q. Al-Mawsawi, R. Dayam, R. A. Yunes, A. Garofalo, M. B. Bolger, N. Neamati, *Bioorg. Med. Chem.* **2007**, *15*, 4985.

[33] (a) A. Christophe, G. Jean-Marie, R. Jean, C. Thierry, *Chem. Rev.* **2014**, *114*, 10829.

[34] M. Hino, K. Arata, *Chem. Commun.* **1979**, 1148.

[35] M. Hino, K. Arata, *J. Am. Chem. Soc.* **1979**, *101*, 6439.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Koduri RG, Pagadala R, Boodida S, Varala R. SO_4^{-2}/SnO_2–catalyzed cyclocondensation for the synthesis of fully functionalized pyridines. *J Heterocyclic Chem*. 2019;1–6. https://doi.org/10.1002/jhet.3806