$SnCl_2 \cdot 2H_2O$ as a precatalyst in MCR: Synthesis of pyridine derivatives *via* a 4-component reaction in water

Dinne Naresh Kumar Reddy, Kothapalli Bannoth Chandrasekhar, Yaddanapudi Sesha Siva Ganesh, Burra Sathish Kumar, Raju Adepu, Manojit Pal

PII: S0040-4039(15)00989-2
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.06.008
Reference: TETL 46400

To appear in: *Tetrahedron Letters*

Received Date: 14 April 2015
Revised Date: 29 May 2015
Accepted Date: 3 June 2015

Please cite this article as: Reddy, D.N.K., Chandrasekhar, K.B., Ganesh, Y.S.S., Kumar, B.S., Adepu, R., Pal, M., $SnCl_2 \cdot 2H_2O$ as a precatalyst in MCR: Synthesis of pyridine derivatives *via* a 4-component reaction in water, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.06.008

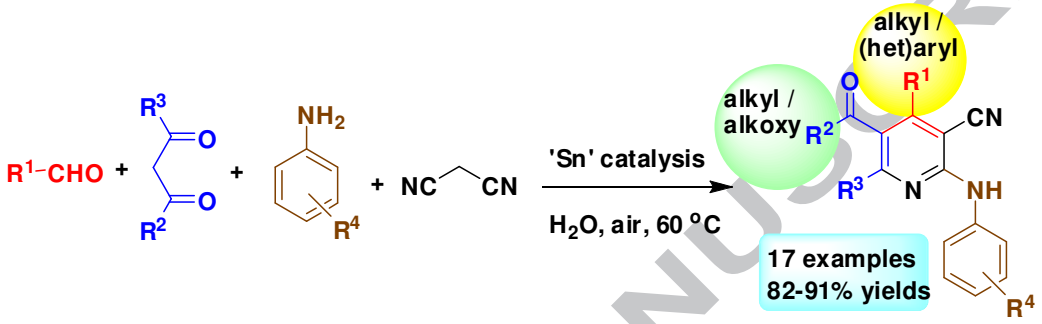
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

$SnCl_2 \cdot 2H_2O$ as a precatalyst in MCR: synthesis of pyridine derivatives via a 4-component reaction in water

Leave this area blank for abstract info.

Dinne Naresh Kumar Reddy, Kothapalli Bannoth Chandrasekhar, Yaddanapudi Sesha Siva Ganesh, Burra Sathish Kumar, Raju Adepu and Manojit Pal*



Tetrahedron Letters
journal homepage: www.elsevier.com

$SnCl_2 \cdot 2H_2O$ as a precatalyst in MCR: synthesis of pyridine derivatives *via* a 4-component reaction in water

Dinne Naresh Kumar Reddy,[a,b] Kothapalli Bannoth Chandrasekhar, [b] Yaddanapudi Sesha Siva Ganesh,[a] Burra Sathish Kumar,[a] Raju Adepu [c] and Manojit Pal[c,*]

[a] *Custom Pharmaceutical Services, Dr. Reddys Laboratories Limited, Bollaram road, Miyapur, Hyderabad 500 049, India.*
[b] *College of Engineering, Jawaharlal Nehru Technological University, Anantapur 533 003, Andhra Pradesh, India.*
[c] *Dr Reddy's Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad 500 046, India*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Pyridine
MCR
water
$SnCl_2$

ABSTRACT

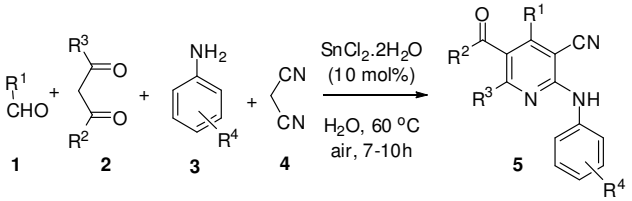
For the first time $SnCl_2 \cdot 2H_2O$ has been identified as a convenient precatalyst for the synthesis of pyridine derivatives *via* an MCR in water. The 4-component reaction of alkyl / (hetero)aryl aldehydes, β-keto esters (or 1,3-diketones), anilines and malononitrile afforded a range of new polysubstituted pyridines including 4-alkyl/heteroaryl derivatives in 78-91% yields. The use of less expensive catalyst in aqueous media and good yield of products with wider substrate scope are the key features of this methodology.

Development of cost effective and environmentally friendly MCRs (multicomponent reactions) is of tremendous importance in both organic and medicinal chemistry as these protocols provide easy and quick access to the diversity based combinatorial library of small molecules useful for new drug discovery effort. One of the important features of MCRs is that they offer highly convergent and rapid routes to densely functionalized molecules. Additionally, these methods do not require the isolation and purification of intermediates thereby reducing the time, cost and more importantly waste production.[1] It is therefore not a surprising fact that MCRs have attracted considerable attention of researchers especially working in the area of organic / medicinal / pharmaceutical chemistry. Indeed, MCRs have been used largely to generate library of small organic molecules having diverse substituents.[2] These libraries of potentially bioactive molecules were found to be attractive for high-throughput pharmacological screen leading to the identification of a pre-hit or lead molecule in a particular therapeutic area. While various transition metal catalysts including gold, silver[3] and iron salts[4] have been employed in a range of MCRs earlier, the use of tin catalysts in MCRs are rather uncommon. However, in view of their easy availability and low cost tin based salts seemed to have potential and are worth exploring as catalysts in MCRs. While $SnCl_2 \cdot 2H_2O$ has been explored as an effective and eco-friendly catalyst for a number of organic transformations,[5a,b] only few examples of using $SnCl_2 \cdot 2H_2O$ as a mild Lewis acid catalyst in MCRs (e.g. Biginelli reaction,[5c] 3-component synthesis of homoallylic amines[5d] and 4(3*H*)-quinazolinones[5e]) have been reported and none as a precursor of Sn(IV) species in a MCR. Moreover, as a Lewis acid, $SnCl_4$ has been used in several chemical transformations (e.g. the reduction of glycopyranosyl azides,[5f] the ring-opening of 4,5-dihydropyrroles,[5g] conversion of glucose into 5-hydroxymethylfurfural[5h] and synthesis of tetracyclic terpenoids[5i]) highlighting its potential as an effective catalyst. However, $SnCl_4$ being a colorless liquid at room temperature (that fumes on contact with air) is inconvenient to handle as a catalyst. The aqueous solution of $SnCl_2$ in the presence of air on the other hand is known to produce $SnCl_4$ *in situ*. This prompted us to explore $SnCl_2 \cdot 2H_2O$ as a convenient precatalyst for the synthesis of pyridine derivatives *via* an MCR.

The pyridine nucleus has been found to be an integral part of many natural products[6] (e.g. coenzyme vitamin B_6 family and numerous alkaloids) and biologically active compounds.[7] Several elegant and effective methods have been reported for the synthesis of pyridine derivatives[8] including MCRs.[9] For example, in 2012 we reported the synthesis of pyridine derivatives *via* a montmorillonite K-10 catalyzed 4-component reaction of β-ketoester, arylaldehyde, malononitrile and an alcohol.[10] More recently, a $FeCl_3$-catalyzed similar 4-component reaction (using arylamine in place of alcohol as a nucleophile) has been reported for the synthesis of pyridine derivatives in 38-86% yield *via* a

* Corresponding author: Tel.: +91 40 6657; fax: +91 40 6657 1581
E-mail address: manojitpal@rediffmail.com (M. Pal)

nucleophilic addition / intermolecular cyclization.[11] We anticipated that this type of 4-component reaction can be performed under more environmentally friendly conditions with better yield and wider substrate scope by using a tin salt as a catalyst and water as a solvent. Being a stable solid, easily handled and less corrosive, $SnCl_2 \cdot 2H_2O$ appeared to be an attractive precursor for Sn(IV) based Lewis acid catalyst in aqueous media. Due to our longstanding interest in the synthesis of pyridine derivatives[10,12] we now report the Sn(IV)-catalyzed 4-component reaction of alkyl/(hetero)aryl aldehydes (**1**), β-keto esters (or 1,3-diketones) (**2**), anilines (**3**) and malononitrile (**4**) leading to a range of pyridine derivatives (Scheme 1).

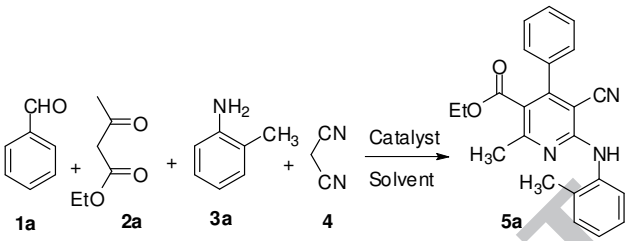


Scheme 1. Sn-catalyzed synthesis of pyridines *via* a 4-component reaction.

The reaction of benzaldehyde (**1a**), ethyl acetoacetate (**2a**), *o*-toluidine (**3a**) and malononitrile (**4**) was examined in the presence of air under various conditions as shown in Table 1. Initially, a recyclable phosphomolybdic acid (PMA)-SiO_2 (10 mol%) was used as a catalyst and water as a solvent which afforded the desired compound **5a** though in low yield (entry 1, Table 1). This prompted us to examine this 4-component reaction in water in the presence of other catalysts to achieve better product yield. However, the use of catalysts like amberlite, indion resin and silicon dioxide did not improve the product yield (entries 2-4, Table 1). We then examined the use of $SnCl_2 \cdot 2H_2O$ that to our satisfaction afforded **5a** with improved yield (entry 5, Table 1). Several other inorganic / organic catalysts e.g. $BiCl_3$, clay (montmorillonite K-10), $CeCl_3.7H_2O$ (entries 6, 8 and 9, Table 1), and L-proline, citric acid, PTSA (entries 7, 10-11, Table 1) also afforded **5a** but with decreased yield. While all these reactions were performed in water the use of other solvents like MeOH, *i*-PrOH, MeCN and PEG-400 was examined and found to be less effective (entry 5 vs entries 12-15, Table 1). Except entry 12, 16 and 17 the MCR was performed at 80 ºC for 10h in all the cases. However, we observed that the product yield was not affected when the reaction was performed at 60 ºC for 8h (entry 16, Table 1). A further decrease in reaction time and temperature decreased the yield of **5a**. Generally, 10 mol% catalyst was used in all our study as decrease in catalyst quantity decreased the product yield significantly. Notably, the reaction did not proceed in the absence of a catalyst indicating the key role played by the catalyst in the present MCR (entry 17, Table 1). Overall, the use of 10 mol% $SnCl_2.2H_2O$ in water at 60 °C for 8 h in the presence of air was found to be optimum for the present MCR.

Having optimized the reaction conditions for the synthesis of a polysubstituted pyridine derivative in water we then examined the scope of the MCR and results are presented in Table 2. Thus a wide range of pyridine derivatives were prepared[13] by using this $SnCl_2$-mediated MCR. The benzaldehyde (entry 1-4, Table 2) and its derivatives containing groups like OMe, Br and F participated well in this reaction (entries 5-9, Table 2). Aryl aldehydes containing electron withdrawing groups like CN and NO_2 also participated in this MCR affording the desired pyridine derivatives (entries 10-11, Table 2). Other aldehydes e.g. heteroaryl (entries 12-15, Table 2) and aliphatic aldehydes (entries 16-19, Table 2) also afforded the corresponding products (entry 12-19, Table 2). The use of three types of carbonyl group containing reactants e.g. ethyl acetoacetate (**2a**), methyl 3-oxovalerate (**2b**) and acetyl acetone (**2c**) was examined. All these

Table 1: Effect of reaction conditions on the MCR of **1a**, **2a**, **3a** and **4**.[a]



Entry	Catalyst	Solvent	Temp (°C)/ Time (h)	Yield (%)[b]
1	PMA-SiO_2	H_2O	80/10	40
2	Amberlite	H_2O	80/10	30
3	Indion resin	H_2O	80/10	32
4	SiO_2	H_2O	80/10	15
5	$SnCl_2.2H_2O$	H_2O	80/10	82
6	$BiCl_3$	H_2O	80/11	65
7	L-proline	H_2O	80/10	40
8	Clay	H_2O	80/10	17
9	$CeCl_3.7H_2O$	H_2O	80/10	50
10	Citric acid	H_2O	80/10	35
11	PTSA	H_2O	80/10	30
12	$SnCl_2.2H_2O$	CH_3OH	65/10	60
13	$SnCl_2.2H_2O$	iPrOH	80/10	50
14	$SnCl_2.2H_2O$	CH_3CN	80/14	15
15	$SnCl_2.2H_2O$	PEG-400	90/10	65
16	$SnCl_2.2H_2O$	H_2O	60/8	82
17	No catalyst	H_2O	60/8	15[c]

[a] Reactions were carried out using **1a** (1 mmol), **2a** (1 mmol), **3a** (1 mmol), 4 (1 mmol) and 10 mol% catalyst in solvent (4 mL) under open air.

[b] Isolated yield.

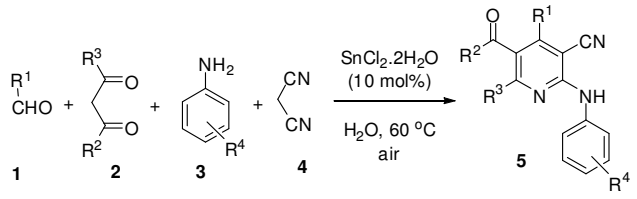
[c] Reaction was performed without catalyst.

reactants participated well in this MCR. Similarly, arylamines (in addition to aniline) containing substituents like CH_3, F and Br (**3a-d**) also participated well in the reaction. Thus, all the polysubstituted pyridine derivatives were isolated in good yields (82-91%). Since alkyl / heteroaryl aldehydes (in addition to aryl aldehydes) and 1,3-diketones (in addition to β-keto esters) were used in the present MCR hence the methodology offers wider substrate scope compared to that reported earlier.[11]

Except compound **3d** all other synthesized compounds are new and are characterized by spectral (NMR, IR, MS and HRMS) data. The presence of –CN and carbonyl group (ketone or ester) was confirmed by the IR absorptions near 2210 and 1710 or 1690 cm^{-1}, respectively. Additionally, a signal near 167 or 203 ppm in the ^{13}CNMR spectra indicated the presence of ester or keto group.

Our earlier synthesis of pyridine derivative via an MCR involved the use of microwave irradiation.[10] We examined if the same pyridine derivative can be prepared by using the present MCR without using any microwave irradiation. Accordingly, the MCR of **1a**, **2a, 4** and EtOH was performed under the present condition and the desired product **6** was obtained in 80% yield (Scheme 2).

Table 2: Synthesis of poly substituted pyridines in aqueous media[a]

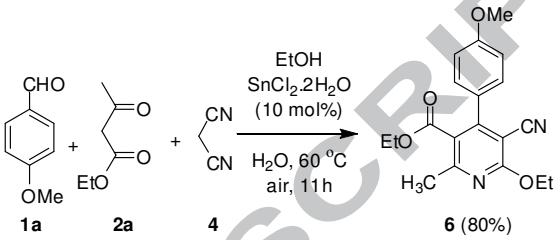


1 2 3 4 5

Entry	Aldehyde R^1 (**1**)	Ketone R^2, R^3 (**2**)	Aniline R^4 (**3**)	Time (h)	Product R^1, R^2, R^3, R^4 (**5**)	Yield (%)[b]
1	Ph, **1a**	OEt, CH_3 **2a**	2-CH_3, **3a**	8	Ph, OEt, CH_3, 2-CH_3, **5a**	82
2	**1a**	OMe, Et **2b**	**3a**	8	Ph, OMe, Et, 2-CH_3, **5b**	85
3	**1a**	CH_3, CH_3 **2c**	**3a**	9	Ph, CH_3, CH_3, 2-CH_3, **5c**	89
4	**1a**	**2a**	H, **3b**	8	Ph, OEt, CH_3, H, **5d**	84
5	4-MeO-Ph, **1b**	**2a**	**3a**	8	4-OMe-Ph, OEt, CH_3, 2-CH_3, **5e**	86
6	**1b**	**2a**	2,3-di CH_3, **3c**	10	4-OMe-Ph, OEt, CH_3, 2,3-di CH_3, **5f**	88
7	4-Br-Ph, **1c**	**2c**	**3a**	8	4-Br-Ph, CH_3, CH_3, 2-CH_3, **5g**	86
8	2-F-Ph, **1d**	**2c**	4-F, **3d**	8	2-F-Ph, CH_3, CH_3, 4-F, **5h**	90
9	**1d**	**2c**	4-Br, **3e**	9	2-F-Ph, CH_3, CH_3, 4-Br, **5i**	87
10	4-CN-Ph, **1e**	**2a**	**3a**	7	4-CN-Ph, OEt, CH_3, 2-CH_3, **5j**	90
11	4-NO_2-Ph, **1f**	**2a**	**3a**	7	4-NO_2-Ph, OEt, CH_3, 2-CH_3, **5k**	89
12	2-Thienyl, **1g**	**2a**	**3b**	9	2-Thienyl, OEt, CH_3, H, **5l**	86
13	**1g**	**2c**	**3b**	8	2-Thienyl, CH_3, CH_3, H, **5m**	91
14	2-Furyl, **1h**	**2c**	**3b**	10	2-Furyl, CH_3, CH_3, H, **5n**	85
15	**1h**	**2c**	**3d**	9	2-Furyl, CH_3, CH_3, 4-F, **5o**	88
16	^{i}Bu, **1i**	**2c**	**3a**	9	^{i}Bu, CH_3, CH_3, 2-CH_3, **5p**	85
17	**1i**	**2c**	**3b**	8	^{i}Bu,CH_3, CH_3, H, **5q**	90
18	n-Pr, **1j**	**2c**	**3a**	8	n-Pr, CH_3, CH_3, 2-CH_3 **5r**	81
19	i-Pr, **1k**	**2c**	**3a**	8	i-Pr, CH_3, CH_3, 2-CH_3 **5s**	78

[a] Reactions were carried out using **1a** (1 mmol), **2a** (1 mmol), **3a** (1 mmol), **4** (1 mmol) and 10 mol% catalyst in H_2O (4 mL) at 60 °C under open air.

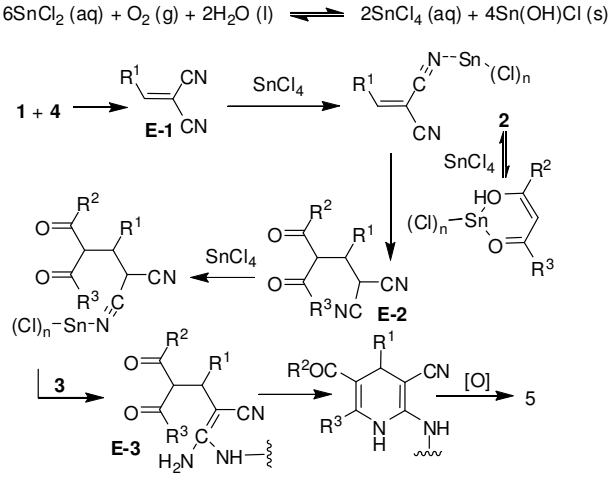
[b] Isolated yield.



1a 2a 4 **6** (80%)

Scheme 2: Synthesis of 2-ethoxy substituted pyridine.

A probable reaction mechanism of the present one-pot 4-component reaction is shown in Scheme 3. The aqueous solution of $SnCl_2$ is known to produce $SnCl_4$ *in situ* in the presence of air.[14] Moreover, comparison of the DSC (Differential Scanning Calorimetry) thermal analysis and IR spectra obtained for the commercially available $SnCl_2.2H_2O$ used in the MCR and the solid obtained from the reaction mixture after completion of the reaction (by treating the mixture with EtOAc followed by filtration) clearly indicated a change in the nature of Sn(II) salt employed (see Fig.S-1 and S-2 in the supplementary data file). Thus, Sn(IV) species appeared to be the actual catalysts in the present reaction.[15] Consequently, coordination of the nitrogen lone pair of intermediate **E-1** (formed *via* the Knoevenagel condensation between **1** and **4**) with the Sn(IV) species could facilitate the Michael type of reaction with the enol form of **2** affording the intermediate **E-2**. A further coordination of nitrogen lone pair of **E-2** with the $SnCl_4$ could facilitate a nucleophilic attack by the arylamine **3** followed by isomerization of the resulting species to give the intermediate **E-3**. An intramolecular cycloaddition of **E-3** (*via* the loss of a water molecule) followed by oxidative aromatization afforded the desired product **5**. Overall, four new bonds were formed in a single pot operation to afford the polysubstituted pyridines **5** under environmentally friendly conditions.



Scheme 3. The probable reaction mechanism

In conclusion, $SnCl_2 \cdot 2H_2O$ has been found to be an effective precatalyst for the synthesis of pyridine derivatives *via* an MCR in pure water. The methodology involved 4-component reaction of alkyl / (hetero)aryl aldehydes, β-keto esters (or 1,3-diketones), anilines and malononitrile in the presence of air. The reaction seemed to proceed *via* in situ generation of Sn(IV) species that actually catalyzed the MCR in water. This operationally simple methodology afforded a range of polysubstituted pyridines including 4-alkyl/heteroaryl derivatives in good (78-91%) yields. Many of these pyridines are amenable for further functionalization to generate diversity based library of molecules of potential pharmacological interest. The use of less expensive catalyst in aqueous media and good yield of products with wider substrate scope are the key features of this methodology. The methodology therefore may find applications both in organic and medicinal chemistry.

Acknowledgements

D. N. K. Reddy thanks Dr. Krishanji Thadipatri, Dr. H Ramamohan, Dr. Vilas Dhanukar and the management of CPS, DRL, Hyderabad, India for support and encouragements.

Supplementary data

Supplementary data associated with this article can be found, in the on line version, at xxxxxxxxx

References and notes

1. (a) Maiti, S.; Biswas, S.; Jana, U. *J. Org. Chem.* **2010**, *75*, 1674; (b) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439; (c) Gu, Y. L. *Green Chem.* **2012**, *14*, 2091; (d) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *112*, 3168; (e) Gers, C. F.; Nordmann, J.; Kumru, C.; Frank,W.; Muller, T. J. J. *J. Org. Chem.* **2014**, *79*, 3296.
2. (a) Maiti, B.; Chanda, K.; Selvaraju, M.; Tseng, C. -C.; Sun, C. -M. *ACS Comb. Sci.* **2013**, *15*, 291; (b) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463; (c) Isambert, N.; Duque, M. M. S.; Plaquevent, J. C.; Genisson, Y.; Rodriguez, J.; Constantieux, T. *Chem. Soc. Rev.* **2011**, *40*, 1347; (d) Bhattacharya, A. K.; Rana, K. C.; Raut, D. S.; Mhaindarkar, V. P.; Khan, M. I. *Org. Biomol. Chem.* **2011**, *9*, 5407.
3. (a) For a review, see: Abbiati, G. and Rossi, E. *Beilstein J. Org. Chem.* **2014,** *10,* 481.
4. (a) Hatakeyama,T.; Imayoshi, R.;Yoshimoto,Y.; Ghorai, S. K.; Jin, M.; Takaya, H.; Norisuye, K.; Sohrin,Y.; Nakamura, M. *J. Am. Chem. Soc.* **2012**, *134*, 20262; (b) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *J. Am. Chem. Soc.* **2013**, *135*, 118; (c) Li, W.-J.; Zheng, X.-J.; Li, Z.-P. *Adv. Synth. Catal.* **2013**, *355*, 181; (d) Sengoden, M.; Punniyamurthy, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 572; (e) Sengupta, T.; Gayen, K. S.; Pandit, P.; Maiti, D. K. *Chem. Eur. J.* **2012**, *18*, 1905; (f) Zhu,S.-F.; Xiao, Y.-L.; Guo, Z.-J.; Jiang, H.-F. *Org. Lett.* **2013**, *15*, 898; (g) Becerra-Figueroa, L.; Ojeda-Porras, A.; Gamba-Sanchez, D. *J. Org. Chem.* **2014**, *79*, 4544.
5. (a) Taylor, R. J. K.; Reid, M. *Tetrahedron Lett.* **2004**, *45*, 4181; (b) Taylor, R. J. K.; Schmidt, P. J.; Moyon, C. M.; Cox, R. J.; Cayley, A. N. *Tetrahedron Lett.* **2007**, *48*, 6556; (c) Russowsky, D.; Lopes, F. A.; da Silva, V. S. S.; Canto, K. F. S.; D'Oca, M. G. M.; Godoi, M. N. *J. Braz. Chem. Soc.* **2004**, *15*, 165; (d) Akiyama**,** T.; Onuma, Y. *J. Chem. Soc., Perkin Trans. 1,* **2002**, 1157; (e) Wang, M.; Song, Z.; Zhang, T. *J. Heterocyclic Chem.* **2010**, *47*, 468. (f) Sahoo, L.; Singhamahapatra, A.; Paul, K. J. V.; Loganathan, D. *Tetrahedron Lett.* **2013**, *54*, 5361. (g) Zhang, Z. G.; Wang, D.; Wang, B.; Liu, Q. F.; Liu, T. X.; Zhang, W.; Yuan, B. B.; Zhao, Z. J.; Han, D. D.; Zhang, G. S. *Tetrahedron* **2013**, *69*, 9063. (h) Hu, S.Q.; Zhang, Z. F.; Song, J. L.; Zhou, Y. X.; Han, B.X. *Green Chem.* **2009**, *11*, 1746. (i) Zhao, Y. J.; Loh, T. P. *Chem. Commun.* **2008**, 1434.
6. For reviews, see: (a) Plunkett, A. O. *Nat. Prod. Rep.* **1994**, *11*, 581; (b) Daly, J. W.; Pinder, A. R. *Nat. Proc. Rep.* **1992**, *9*, 491; (c) Spande, T. F. In The Alkaloids; Brossi, A., Ed.; Academic Press: New York, 1987; Vol.31.
7. For selected example, see: (a) Sutherland, A.; Gallagher, T.; Sharples, C. G. V.; Wonnacott, S. *J. Org. Chem.* **2003**, *68*, 2475; (b) Cosford, N. D. P.; Tehrani, L.; Roppe, J.; Schweiger, E.; Smith, N. D.; Anderson, J.; Bristow, L.; Brodkin, J.; Jiang, X.; McDonald, I.; Rao, S.; Washburn, M.; Varney, M. A. *J. Med. Chem.* **2003**, *46*, 204; (c) Enyedy, I. J.; Sakamury, S.; Zaman, W. A.; Johnson, K. M.; Wang, S. *Biorg. Med. Chem. Lett.* **2003**, *13*, 513; (d) Faul, M. M.; Ratz, A. M.; Sullivan, K. A.; Trankle, W. G.; Winnerroski, L. L. *J. Org. Chem.* **2001**, *66*, 5772.
8. (a) Chenand, M. Z.; Micalizio, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 1352, and references therein; (b) Henry, G. D. *Tetrahedron*, **2004**, *60*, 6043; (c) Murugan, R.; Scriven, E. F. *J. Heterocycl. Chem.* **2000**, *37*, 451.
9. (a) Siddiqui, Z. N.; Ahmed, N.; Farooq, F.; Khan, K. *Tetrahedron Lett.* **2013**, *54*, 3599; (b) Evdokimov, N. M.; Magedov, I. V.; Kireev, A. S.; Kornienko, A. *Org. Lett.* **2006,** *8,* 899; (c) Evdokimov, N. M.; Kireev, A. S.; Yakovenko, A. A.; Antipin, M. Y.; Magedov, I. V.; Kornienko, A. *J. Org. Chem.* **2007**, 72, 3443; (d) Ranu, B. C.; Jana, R.; Sowmiah, S. *J. Org. Chem.* **2007**, *72*, 3152; (e) Sridhar, M.; Ramanaiah, B. C.; Narsaiha, C.; Mahesh, B.; Kumarswamy, M.; Mallu, K. K. R.; Ankathi, V. M.; Rao, P. S. *Tetrahedron Lett.* **2009,** *50*, 3897; (f) Thirmurugan, P.; Perumal, P. T. *Tetrahedron* **2009**, *65*, 7620; (g) Xin, X.; Wang, Y.; Kumar, S.; Liu, X.; Lin, Y.; Dong, D. *Org. Biomol. Chem.* **2010,** *8*, 3078; (h) Shaabani, A.; Seyyedhamzeh, M.; Maleki, A.; Behnam, M.; Rezazadeh, F. *Tetrahedron Lett* **2009**, *50*, 2911.
10. Reddy, T. R.; Reddy, G. R.; Reddy, L. S.; Jammula, S.; Lingappa, Y.; Kapavarapu, R.; Meda, C. L. T.; Parsa, K. V. L.; Pal, M. *Eur. J. Med. Chem.* **2012**, *48*, 265.
11. He, X.; Shang, Y.; Yu, Z.; Fang, M.; Zhou, Y.; Han, G.; Wu, F. *J. Org. Chem.* **2014**, *79*, 8882.
12. (a) Pal, M.; Batchu, V. R.; Dager, I.; Swamy, N. K.; Padakanti, S. *J. Org. Chem.* **2005**, *70*, 2376; (b) Gade, N. R.; Devendram, V.; Pal, M.; Iqbal, J. *Chem. Commun.* **2013**, *49*, 7926.
13. **Typical procedure for the synthesis of 5a:** To a mixture of benzaldehyde (**1a**, 1 mmol), ethyl aceto acetate (**2a**, 1 mmol), *o*-toluedine (**3a**, 1 mmol), and malononitrile (**4**, 1 mmol) in water (4 mL) was added $SnCl_2.2H_2O$ (10 mol%) at room temp. The mixture was then stirred at 60 °C for 8h in the presence of air. After completion of the reaction (indicated by TLC) the mixture was diluted with EtOAc (4 mL), and filtered. The residue was washed with EtOAc (3 x 2 mL). The filtrates were combined. The separated organic layer was collected, washed with cold water (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under low vacuum. The residue was purified by column chromatography over silica gel using EtOAc-hexane to give the desired productas an off white solid; mp: 178.2-180.6 °C; R_f = 0.62, mobile phase: 20% Ethyl acetate: Hexane; IR (KBr): 3344, 2214, 1717, 1559, 1479, 1446, 1366, 1275, 1137, 1077, 770, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.0 Hz, 1H), 7.48-7.45 (m, 3H), 7.40-7.37 (m, 2H), 7.28-7.27 (m, 1H), 7.26-7.25 (m, 1H), 7.14-7.11 (m, 1H), 7.07 (s, 1H), 3.98 (q, *J* = 7.2 Hz, 2H), 2.53 (s, 3H), 2.34 (s, 3H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 160.4, 155.8, 153.8, 136.4, 135.9, 130.6, 130.2, 129.4, 128.5 (2C), 127.8 (2C), 126.5, 125.0, 123.0, 120.2, 115.9, 90.5, 61.2, 23.8, 18.07, 13.4; HRMS (ESI) ([M] $^+$1) calcd for $C_{23}H_{22}N_3O_2$: 372.1712, found: 372.1704. Spectral data of **5b**: off white solid; mp: 193.6-195.6 °C; R_f = 0.65, mobile phase: 20% Ethyl acetate: Hexane; IR (KBr): 3407, 2215, 1719, 1680, 1557, 1520, 1479, 1430, 1215, 1046, 771, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.49-7.46 (m, 3H), 7.39-7.37 (m, 2H), 7.26-7.21 (m, 2H), 7.20-7.17 (m, 1H), 7.13-7.05 (m, 1H), 3.48 (s, 3H), 2.82 (q, *J* = 7.6 Hz, 2H), 2.54 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 161.5, 156.1, 153.6, 136.5, 135.7, 130.5, 129.5, 128.6 (2C), 127.8 (2C), 127.2, 127.1, 126.4, 124.7, 122.9, 116.0, 90.4, 52.0, 25.0, 18.0, 12.7; HRMS (ESI) ([M] $^+$1) calcd for $C_{23}H_{22}N_3O_2$: 372.1712, found 372.1730.
14. Nechamkin, H. The Chemistry of the Elements. New York: McGraw-Hill, 1968.
15. For further confirmation we have performed the reaction of **1a** (1 mmol), **2a** (1 mmol), **3a** (1 mmol) and **4** (1 mmol) in the presence of $SnCl_4$ (10 mol%) in water (4 mL) at 60° C for 8h when the desired product **5a** was isolated in 84% yield. It is therefore evident that $SnCl_4$ generated *in situ* from $SnCl_2$ is the actual catalytic species in the present MCR.