EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

# Accepted Article

**Title:** Silver Catalyzed Synthesis of Substituted Pyridine Derivatives from N-Propargylic α-Enamino Esters

**Authors:** Sakthivel Shanmugam, Ashish Sharma, and Rengarajan Balamurugan



**To be cited as:** *Eur. J. Org. Chem.* 10.1002/ejoc.201700559

**Link to VoR:** http://dx.doi.org/10.1002/ejoc.201700559

**Supported by**
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201700559

WILEY-VCH

COMMUNICATION

# Silver Catalyzed Synthesis of Substituted Pyridine Derivatives from *N*-Propargylic *α*-Enamino Esters

Shanmugam Sakthivel,[a] Ashish Sharma,[a] and Rengarajan Balamurugan*[a]

Dedication ((optional))

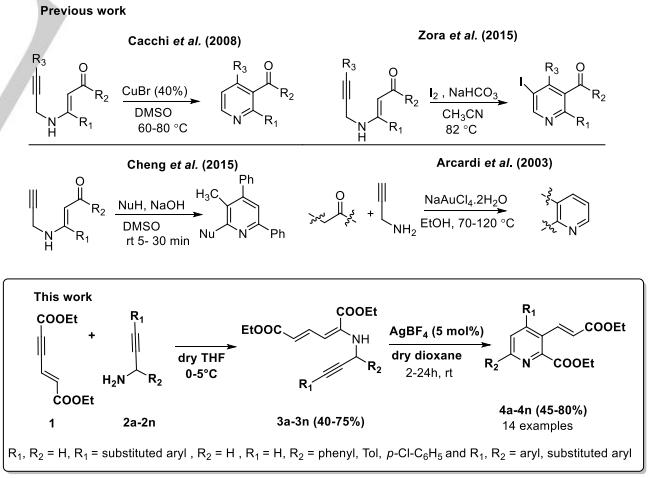
**Abstract:** A wide range of substituted pyridine derivatives were synthesized in moderate to good yields from a *N*-propargylic α-enamino ester. The synthetic strategy involves regioselective addition of propargyl amine to the α-carbon of the alkynyl ester to produce *N*-propargylic α-enamino ester which acts as the key intermediate for the synthesis of the pyridine derivatives.

.

## Introduction

Pyridine is one of the most privileged structural motif present in several biologically important natural products.[1] In fact, a number of marketed drugs and pharmaceutically important compounds contain pyridine subunit and the number is growing steadily.[2] The diverse bioactivitities of the pyridine derivatives persistently attract the researchers to develop alternate protocols for their synthesis. In addition to the conventional Hantzsch, Chichibabin, Bohlmann-Rahtz and Bonnemann methods for the synthesis of pyridine derivatives,[3] different approaches have been developed for the synthesis of pyridine derivatives in recent years.[4] Still, owing to the growing medicinal importance of pyridine heterocycles, alternate methods to access highly functionalized derivatives under mild reaction conditions are always in demand.

*N*-Propargylic *β*-enaminones are important and versatile intermediates in organic synthesis and have been used for the synthesis of many important *N*-heterocyclic compounds.[5] Pyridine derivatives can also be synthesized from *N*-propargylic *β*-enaminones using transition metal catalysts. In this context, a pioneering work was reported by Cacchi *et al*. for the synthesis of pyridine derivatives from *N*-propargylic *β*-enaminones through $Cu^{I}$ catalyzed intramolecular cyclization.[6] Later, Wan *et al*. reported the synthesis of substituted pyridine derivatives using *N*-sulfonyl, *N*-propargylic *β*-enaminones by one pot reaction comprising of aza-Claisen rearrangement, electrocyclization and elimination cascade.[7] Iodine and base-mediated synthesis of pyridine derivatives was reported by Zora *et al*. in 2015.[8] This reaction involves iodine-mediated electocyclization in acetonitrile under reflux conditions. In 2015, an interesting method was reported by Cheng *et al*. for the synthesis of substituted pyridines. In this method external nucleophiles were used with *N*-propargylic *β*-enaminone under basic conditions.[9] Arcadi and co-workers developed a gold catalyzed approach for the synthesis of pyridine derivatives involving initial amination, annulation followed by aromatization.[10] In this reaction, propargylamine reacts with ketone/aldehyde bearing *α*-hydrogens under gold and copper catalysis. Few other reports for the synthesis of pyridine derivatives from carbonyl compounds and propargyl amines are also known.[11] As seen above, most of the known methods employ *N*-propargylic *β*-enaminones either as starting material or intermediate. However, studies addressing the reactivity and synthetic utility of corresponding α-enaminone/α-enamino ester counterparts are very limited.[12] In 2005, Ramachandran *et al.* reported the quantitative conversion of alkyl propiolate into (*E*)-dialkyl hex-2-en-4-ynedioate using catalytic DABCO.[13] (*E*)-Dialkyl hex-2-en-4-ynedioate undergo *α*-addition regioselectively upon reaction with amine nucloeophiles.[14] Shih-Ching and co-workers reported many interesting synthetic methodologies using $PPh_3$ nucleophile for *α*-addition with (*E*)-diethyl hex-2-en-4-ynedioate.[15] Here in, we report the preparation of *N*-propargylic *α*-enaminones from the reaction of (*E*)-diethyl hex-2-en-4-ynedioate with propargyl amines and their cyclization using silver catalyst as an alternate protocol for the synthesis of highly functionalized pyridine derivatives.




## Results and Discussion

In continuation of our research to utilize the easily accessible (*E*)-diethyl hex-2-en-4-ynedioate **1** as building block for the synthesis of interesting organic compounds,[16] we started our studies towards the preparation of the key intermediate *N*-propargylic *α*-enamino esters. The advantage of this substrate is that it has two esters and an alkene functionalities which can be synthetically manipulated to introduce complexity and more importantly it can easily be accessed. Initially, we treated the enyne diester **1** with

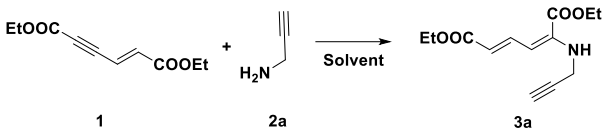
[a] S.Sakthivel, A. Sharma, Prof. Dr. R Balamurugan
School of Chemistry, University of Hyderabad,
Gachibowli, Hyderabad 500046, India
Fax: +91-40-2301-2460
E-mail: bala@uohyd.ac.in

10.1002/ejoc.201700559


# COMMUNICATION

commercially available propargyl amine in dichloromethane at room temperature for 24 h and isolated the compound **3** in 28% of yield. The configuration of the diene was found to be *E*, *E* as reported in the simple amine addition.[14a] The reaction condition was optimized to improve the yield of the product and only selected results are presented in table 1.[17] After extensive optimization, it was found that *N*-propargylic *α*-enamino ester **3** was obtained in 56% yield when the reaction was carried out using 2 equivalents of propargyl amine with respect to enyne diester **1** in THF at 0-5 °C.

**Table 1** Optimization of reaction condition for the preparation *N*-propargylic α-enamino esters **3**




**1** **2a** **3a**

| S.No | Solvent | Time (h) | Temperature (°C) | Enyne/ amine ratio | Yield %[a] |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 21 | rt | 1:1 | 28 |
| 2 | Ethanol | 26 | rt-reflux | 1:1 | 35 (7)[b] |
| 3 | Toluene | 24 | rt-reflux | 1:1 | 33 (9)[b] |
| 4 | THF | 20 | 0-5 | 1:2 | 56 |
| 5 | THF | 12 | 0-10 | 1:2 | 50 |

[a] isolated yield. [b] % of recovered enyne diester.

Having optimized condition in our hand, different substituted propargyl amines were reacted with (*E*)-diethyl hex-2-en-4-ynedioate **1** and corresponding *N*-propargylic *α*-enamino esters **3a-3o** were prepared in moderate to good yields. Reaction of phenyl propargyl amine **2b** with (*E*)-diethyl hex-2-en-4-ynedioate (**1**) resulted in better yield of the product **3b** 75% than that with simple propargyl amine **2a**. Phenyl propargyl amines having electron donating group in the meta position and electron withdrawing substituents resulted in moderate yields of the products **3c**, **3f** and **3h**. Similar trend was observed in the synthesis of **3l**, **3m** and **3n** as well. *α*-Phenyl substituted propargyl amines resulted in the formation of corresponding *N*-propargylic *α*-enamino esters **3i-3k** as an inseparable mixture of *E*, *E* diene with small amounts of *E*, *Z* diene. The substituted propargyl amines **2b-2n** were prepared following literature protocols and the details are presented in the supporting information.

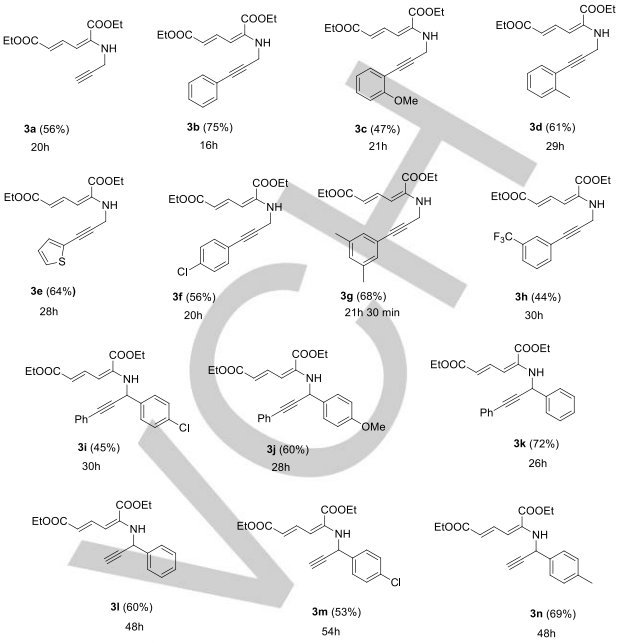



**Figure 1**. Synthesis of *N*-propargylic α-enamino ester derivatives**.**

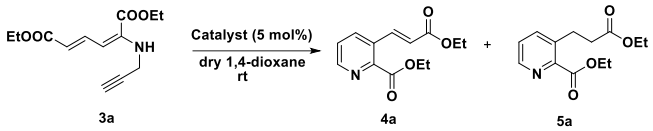
We then started our investigation to understand the reactivity of *N*-propargylic *α*-enamino ester **3a** for the synthesis of substituted pyridines using different transition metal catalysts. The results of screening experiments are summarized in table 2. Initially, we observed the formation of pyridine derivative **4a** in 48% along with the corresponding *α*, *β*-saturated analogue **5a** in 34% of yield, using $PPh_3AuCl/AgSbF_6$ catalytic system. $Au^I$ catalyst alone was inactive for the transformation whereas oxophilic $Au^{III}$ catalyst could transform *N*-propargylic *α*-enamino ester **3a** into pyridine derivative **4a** in lower yields (Table 2, entries 3-5). Copper catalysts were also tested for the same conversion. Among them, copper triflate resulted in 67% of the expected product along with 1% of *α*, *β*-saturated analogue **5** (Table 2, entry 6) and other copper catalysts resulted in lower yields of the product and poor conversion (Table 2, entries 7-10). Interestingly, silver salts were found to catalyze the reaction more efficiently (Table 2, entries 12-15). Among them $AgBF_4$ resulted the formation of the pyridine derivative in 80% yield along with 4% of *α*, *β*-saturated analogue (Table 2, entry 14).[18] In addition, other metal based Lewis acids, such as $Sn(OTf)_2$ and $FeCl_3$ were found to be ineffective to promote the transformation (Table 2, entries 11 and 16).

$AgBF_4$ was chosen for further optimization to find out appropriate solvent. Among the different solvents used for screening, dioxane was found to be superior solvent which resulted in 77% yield of the product **4a** along with 3% of *α*, *β*-saturated analogue **5a** in 2 h (Table 3, entry 5). Although dichloromethane was equally efficient in terms of yield, more amount of **5a** was obtained (Table 3, entry 7).

10.1002/ejoc.201700559


# COMMUNICATION

**Table 2.** Catalyst Screening



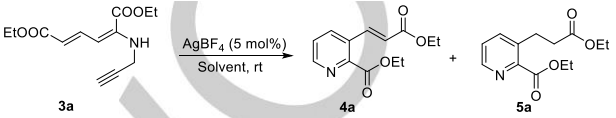

| S.No. | Catalyst (5 mol %) | Time (h) | Yield % (4:5)[a] |
|---|---|---|---|
| 1 | $PPh_3AuCl$ | 24 | No reaction |
| 2 | $PPh_3AuCl/AgSbF_6$ | 7 | 82 (58:42) |
| 3 | $NaAuCl_4$ | 30 | 11 (87:13) |
| 4 | $AuCl_3$ | 24 | 38.0 |
| 5 | $AuCl_3/AgSbF_6$ | 4 | 38 (93:7) |
| 6 | $Cu(OTf)_2$ | 2 | 67 (99:1) |
| 7 | CuI | 24 | 11 (78:12) (30)[b] |
| 8 | $CuBr_2$ | 24 | 35 (95:5) (9)[b] |
| 9 | $CuCl_2$ | 24 | 8 (97:3) (22)[b] |
| 10 | $Cu(OAc)_2$ | 24 | 3 (93:7) |
| 11 | $Sn(OTf)_2$ | 24 | No reaction |
| 12 | AgOTf | 10 | 79 (93:7) |
| **13** | $AgSbF_6$ | 2 | 78 (93:7) |
| **14** | **$AgBF_4$** | **2** | **80 (96:4)** |
| 15 | $AgNTf_2$ | 5 | 77 (84:16) |
| 16 | $FeCl_3$ | 24 | No reaction |

[a] % of *α*, *β*-saturated analogue. [b] % of recovered starting material.

Then one pot domino sequence was attempted. Reacting compound **1** with 2 equivalents of **2a** in the presence of $AgBF_4$ did not result in the corresponding pyridine derivative. This reaction resulted in Michael product in 10-15% yield. In another reaction catalyst was added after the formation of Michael adduct. But the propargylamine present in the reaction deactivated the catalyst and no pyridine product was obtained. Therefore a reaction was set up using equimolar amounts of **1** and **2a**. However, in this reaction Michael adduct formation was very sluggish and addition of $AgBF_4$ after 24 h resulted in only 3% of the pyridine product. Therefore reacting Michael adduct with $AgBF_4$ is the appropriate way to obtain the pyridine product.

After identifying the optimum condition for the cyclization of *N*-propargylic *α*-enamino ester derivative **3a** compounds **3b-3o** which were prepared by trivial protocols were attempted. Substrates having both electron donating and withdrawing groups in the aryl ring were subjected to cyclization using $AgBF_4$ catalyst in dry dioxane to obtain substituted pyridine derivatives in moderate to good yields. α-Enaminono ester with simple phenyl substituent **3b** resulted in lower yield of **4b** (50%) compared to the compound **3a**, (80% of **4a**). Formation of thiophene substituted pyridine **4e** and di aryl substituted pyridines **4i**-**4k** required longer reaction times ranging from 11 to 29 hours. Longer reaction times required for the formation of compounds **4i**-**4k** might be attributed to the steric crowding present in the corresponding N-propargylic α-enamino esters **3i**-**3k**. Even 2,3,6-trisubstituted pyridines (**4m**-**4o**) could be obtained by starting from corresponding benzyl propargyl amines added substrates (**3m**-**3o**).

**Table 3.** Solvent screening with $AgBF_4$




| S.No. | Solvent | Yield % (4:5)[a] | Time (h) |
|---|---|---|---|
| 1 | $CH_3CN$ | 71 (92:8) | 26 |
| 2 | Ethanol | 61 (77:23) | 26 |
| 3 | Toluene | 56 (77:23) | 24 |
| 4 | $CH_3NO_2$ | 45 (76:24) | 24 |
| 5 | **1,4-Dioxane** | **80 (96:4)** | **2.0** |
| 6 | DCE | 74 (80:20) | 15 |
| **7** | $CH_2Cl_2$ | 79 (65:35) | 24 |

[a] % of *α*, *β*-saturated analogue.

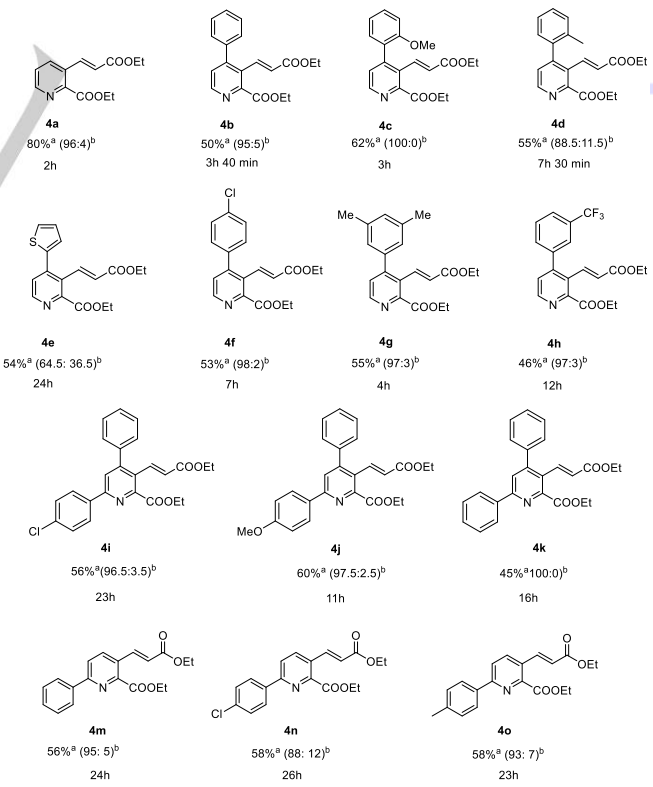



**Figure 2.** Synthesized pyridine derivatives

10.1002/ejoc.201700559


# COMMUNICATION

A plausible mechanism for the formation of pyridine derivatives is outlined in figure 3**.** Initially, the silver salt coordinates with the alkyne of **I** and facilitates an intramolecular nucleophilic attack of the enamine to the activated alkyne **II** by a 6-endo-dig cyclization to result in the intermediate **III**. Protodemetalation in intermediate **III** regenerates the catalyst for further catalytic cycle and the obtained intermediate **IV** upon aromatization leads to the formation pyridine derivative **V**.[6] Formation of small amounts of *α*, *β*-saturated analogue **VI** might be due to the reduction of double bond by the hydride transfer from intermediate **IV** during the course of its aromatization process similar to hydrogenation reaction using Hantzsch ester.[19]

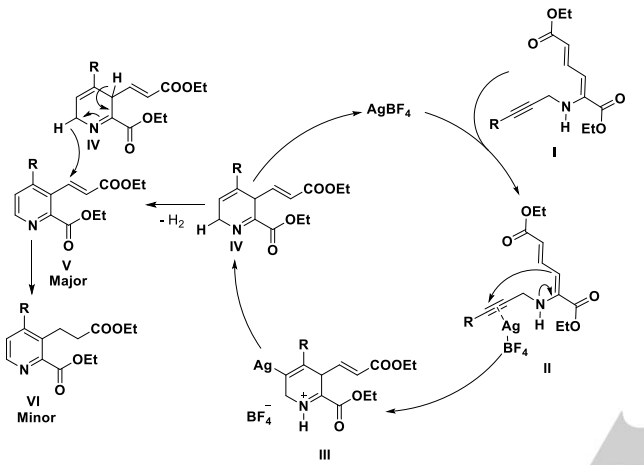



**Figure 3**. Plausible mechanism for the formation of the pyridine derivatives.

## Conclusions

In summary, we have developed a facile method for the synthesis of highly substituted pyridine derivatives from an easily accessible six carbon building block. Silver catalyst alone could effect the cyclization of *N*-propargylic *α*-enamino ester to pyridine compounds at room temperature. In addition to conventional *β*-enamino esters for the synthesis of pyridine derivatives, we have shown that *α*-enamino esters can also be used as valuable synthetic intermediates for the synthesis of substituted pyridine derivatives. Presence of additional functional groups such as α,β-unsaturated ester and ester could, in principle, be exploited for further synthetic manipulations.

## Experimental Section

**General procedure for the preparation of *N*-propargylic *α*-enamino ester derivatives (3a-3n):** To a stirred solution of propargyl amine **2** (2 equiv.) in THF (1 mL), a solution of enyne diester **1** (1 equiv.) in THF (4 mL/mmol of **1**) was added at 0°C. After completion of the reaction, as monitored by TLC, the solvent was evaporated and the obtained crude product was purified by column chromatography using EtOAc/hexanes as eluent to get the desired compounds **3**.

**General procedure for the synthesis of pyridine derivatives (4a-4n):** To a stirred solution of **3a** (1 equiv.) in dry dioxane (4 mL/mmol) in a round bottom flask, $AgBF_4$ (0.05 equiv.) was added at room temperature. After completion of the reaction, as monitored by TLC, solvent was evaporated and the crude product was purified using column chromatography to get the desired compounds **4**.

## Acknowledgements

The authors thank UPE-2, Unversity of Hyderabad, for financial support. S.S thanks the Council of Scientific and Industrial Research (CSIR), India for a fellowship.

**Keywords:** *α*-addition • enamine • silver catalysis • propargyl amine • pyridine

[1] a) A. M. M. N. Gonçalves, A. B. Lima, M. C. S. Barbosa, L. F. Camargos , J. T. Oliveira, C. S. Barbosa, J. A. F. P. Villar, A. C. Costa, I. V. G. Silva, L. M. Silva, F. P. Varotti , F. V. Santos, G. H. R. Viana, *Mar. Drugs* **2014**, *12*, 4361; b) V. A. F. F. M. Santos, L. O. Regasini, C. R. Nogueira, G. D. Passerini, I. Martinez, V. S. Bolzani, M. A. S. Graminha, R. M. B. Cicarelli, M. Furlan, *J. Nat. Prod.* **2012**, *75*, 991; b) T.-J. Hsieh, F.-R. Chang, Y.-C. Chia, C.-Y. Chen, H.-F. Chiu, Y.-C. Wu, *J. Nat. Prod.* **2001**, *64*, 616; c) J. Kobayashi, T. Murayama, Y. Ohizumi, Tetrahedron *Lett.* **1989**, 30, 4833.

[2] A. E. Goetz, Garg, N. K. *Nature* **2013**, *5*, 54.

[3] a) A. Hantzsch, *Annalen der Chemie* **1882**, *215,* 1; b) R. L. Frank, R. P. Seven. *J. Am. Chem. Soc.* **1949**, *71,* 2629; c) F. Bohlmann, D. Rahtz, *Chem. Ber.* **1957**, *90*, 2265.

[4] a) G. Wang, J. Cao, L. Gao, W. Chen, W. Huang, X. Cheng, S. Li, *J. Am. Chem. Soc.* **2017**, *139*, 3904; b) X.-J. Liu, S**.-**Li**.** You**,** *Angew. Chem. Int. Ed.* **2017**, *56*, 4002; c) M.-N. Zhao, L. Yu, N.-F. Mo, Z.-H. Ren, Y.-Y. Wang, Z.-H. Guan, *Org. Chem. Front.* **2017**, DOI: 10.1039/C6QO00809G; d) J. Sheng, Y. Wang, X. Su, R. He, C. Chen, *Angew. Chem.* **2017**, *129*, 4902; e) Z. Chen, Z. Dai, Z. Zhu, X. Yang, *Tetrahedron Lett.* **2017**, *58*, 1258; f) Y. Jiang, C.-M. Park, T.-P. Loh, *Org. Lett*. **2014**, *16*, 3432; g) J. M. Neely, T. Rovis, *J. Am. Chem. Soc.* **2013**, *135*, 66; h) Y. Wei, N. Yoshikai, *J. Am. Chem. Soc.* **2013**, *135*, 3756; i) Y. Jiang, C.-M. Park, T.-P. Loh, *Org. Lett*. **2014**, *16*, 3432; j) Y. Jiang, C.-M. Park, T.-P. Loh, *Org. Lett*. **2014**, *16*, 3432; k) M. D. Hill, *Chem. Eur. J.* **2010**, 16, 12052; l) J. R. Manning, H. M. L. Davies, *J. Am. Chem. Soc.* **2008**, *130*, 8602; m) K. Parthasarathy, M. Jeganmohan, C.-H. Cheng, *Org. Lett.* **2008,** *10*, 325; n) H. Bonnemann, *Angew. Chem, Int. Ed.* **1985**, *24*, 248. o) D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 3645.

[5] a) S. Arshadi, E. Vessally, L. Edjlali, E. G.-Kalhor, R. H.-Khanmiri, *RSC Adv.* **2017**, *7*, 13198; b) E. Vessally, A. Hosseinian, L. Edjlali, A. Bekhradnia, M. D. Esrafili, *RSC Adv.* **2016**, *6*, 71662.

[6] S. Cacchi, G. Fabrizi, E. Filisti, *Org. Lett.* **2008**, *10*, 2629.

[7] X. Xin, D. Wang, X. Li, B. Wan, *Tetrahedron* **2013**, 69, 10245.

[8] S. Karabiyikoglu, Y. Kelgokmen, M. Zora, *Tetrahedron* **2015**, *71*, 4324.

[9] G. Cheng, Y. Weng, X. Yang, X. Cui, *Org. Lett.* **2015**, *17*, 3790.

[10] G. Abbiati, A. Arcadi, G. Bianchi, S. D .Giuseppe, F. Marinelli, E. Rossi, *J. Org. Chem*. **2003**, *68*, 6959.

[11] a) H. Wei, Y. Li, K. Xiao, B. Cheng, H. Wang, L. Hu, H. Zhai, *Org. Lett.* **2015**, *17*, 5974; b) J.-Z. Yan, J. Li. G.-W. Rao, *Steroids* **2007**, *72*, 736.

[12] a) N. Fei, H. Yin, S. Wang, H. Wang, Z.-J. Yao, *Org. Lett.* **2011***, 13,* 4208; b) C. Jiang, M. Xu, S. Wang, H. Wang, Z.-J. Yao, *J. Org. Chem.* **2010**, *75*, 4323; c) N. Fei, Q. Hou, S. Wang, H. Wang, Z.-J. Yao, *Org. Biomol. Chem.* **2010**, *8*, 4096; d) K. C. Majumdar, B. Chattopadhyay, *Synthesis* **2008**, *6,* 921.

[13] P. V. Ramachandran, M. T. Rudd, M. V. R. Reddy. *Tetrahedron Lett.* **2005**, *46*, 2547.

[14] a) A. S. Chavan, J.-C. Deng, S.-C. Chuang, *Molecules* **2013**, *18,* 2611; b) L.-H. Zhou, X.-Q. Yu b, L. Pu, *Tetrahedron Lett*. **2010**, 51, 425.

[15] a) A.-J. Wu, P.-Y. Tseng, W.-H. Hsu, S.-C. Chuang, *Org. Lett.* **2016**, *18*, 224; b) S.-C. Chuang, S.-P. Sung, J.-C. Deng, M.-F. Chioua, D.-S. Hsub, *Org. Biomol. Chem.* **2016**, *14*, 2306; c) J.-C. Deng, W.-Y. Chen, C. Zhu, S.-C. Chuang, *Adv. Synth. Catal.* **2015**, *357*, 1453; d) S.-C. Chuang, J.-C. Deng. F.–W. Chan, S.-Y. Chen, W.-J. Huang, L.-H. Lai, V. Rajeshkumar, *Eur. J. Org. Chem.* **2012**, 2606; e) J.-C, Deng, S.-C. Chuang, *Org. Lett.* **2011**, *13*, 2248.

[16] T. Chandrahas, T. Ganesh Kumar, R. Balamurugan, *Eur. J. Org. Chem.* **2016**, 5855.

[17] For complete information on optimization refer supporting information.

[18] For a related silver catalyzed synthesis of dihydropyridines from N-propargylic β-enaminones, see: M. A. P. Martins, M. Rossatto, C. P. Frizzo, E. Scapin, L. Buriol, N. Zanatta, H. G. Bonacorso, *Tetrahedron Lett.* **2013**, *54*, 847.

[19} C. Zheng, S.-L. You, *Chem. Soc. Rev*. **2012**, *41*, 2498.

10.1002/ejoc.201700559

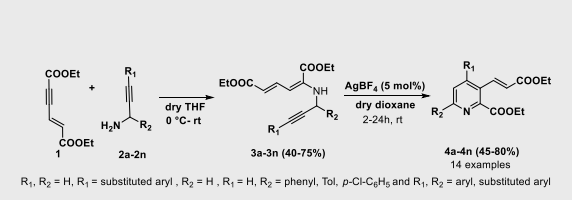
WILEY-VCH



**Entry for the Table of Contents** (Please choose one layout)

Layout 2:

# COMMUNICATION




Efficient synthesis of substituted pyridines via cyclization of easily accessible *N*-propargylic *α*-enamino esters

**Key Topic*** Pyridines synthesis

*Shanmugam Sakthivel, Ashish Sharma and Rengarajan Balamurugan**

***Page No. – Page No.***

**Silver Catalyzed Synthesis of Substituted Pyridine Derivatives from *N*-Propargylic *α*-Enamino Esters**