Article

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Chemodivergent One-pot Multi-Component Synthesis of Pyrroles and Tetrahydropyridines under Solvent free, Catalyst free and Grinding method

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Abstract

A highly efficient, chemoselective synthesis of a library of polysubstituted pyrroles and tetrahydropyridines has been achieved through the one-pot, multi-component reactions of ethyl (*E*)-3-(aryl/alkyl amino) acrylates, 2,2-dihydroxy-1-arylethan-1-ones and malononitrile under solvent and catalyst free grinding conditions. The selective formation of pyrrole or tetrahydropyridines relied on the substitution in the *N*-aryl of ethyl (*E*)-3-(4-arylamino) acrylates. These reactions presumably occurred via a domino Knoevenagel condensation, Michael addition followed by intramolecular cyclization sequence of reactions in a single transformation.

Key words
Grinding, chemoselective, multi-component, tetrahydropyridines, solvent-free, catalyst-free

Introduction

Multicomponent reactions (MCRs) are versatile protocols employed for the synthesis of a variety of complex heterocycles and natural products.[1-3] These reactions involve the formation of multiple bonds in a single transformation in a one-pot process without the isolation of intermediates.[4-8] Consequently, MCRs have been significantly used for the synthesis of wide range of heterocyclic compounds. [9]

Nitrogen containing heterocycles are wide spread in nature[10] and play a significant role in chemical biology. Among these, pyrroles and pyridines are associated with unique biological activities.[11-13] For instance, arecoline, a naturally occurring tetrahydropyridine derivative exhibits stimulating effect as muscarinic acetylcholine receptor (Figure 1).[14] In addition several synthetic tetrahydropyridines have been shown to display important biological activities. On the other hand 2,3,5-trisubstituted pyrroles have also been studied to exhibit significant biological activities.[15,16] The tetrahydropyridines and pyrroles may be synthesised *via* a number of classical methods which also include the treatment of allylic alcohols with potassium bis(trimethylsilyl)amide,[17-21] intermolecular amido carbonylation of carbomates[22] and intramolecular condensations of aldehydes with enamides. Several methods such as transition metal catalysed cycloadditions, coupling of enamides with alkynes[23] and oxidative cyclization of *N*-allyamines are available for the syntheses of polysubstituted pyrroles.[24-27] However most of these methods have drawbacks such as the use of expensive reagents or catalysts, lower yields and poor selectivity. In the present work, we have developed an efficient domino protocol for the synthesis of polysubstituted pyrroles **4** and tetrahydropyridines **5** from the one-pot three-component domino reactions of 2,2-dihydroxy-1-arylethan-1-ones **1**, malononitrile **2** and ethyl (*E*)-3-(4-arylamino) acrylates **3** under catalyst and solvent free conditions under grinding method (Scheme 1).

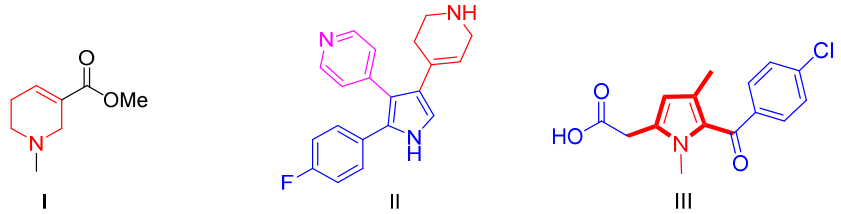

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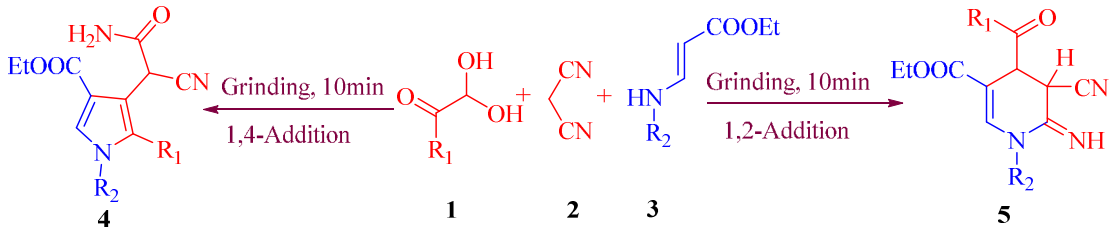
Figure 1 Selected drugs comprising tetrahydropyridine and pyrrole core

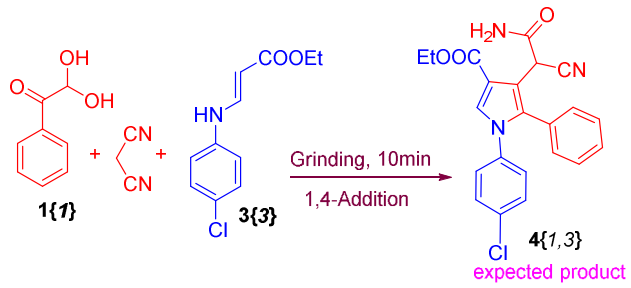


Scheme 1 Synthesis of pyrroles **4** and tetrahydropyridines **5**

Results and discussion

Initially, to optimize the reaction conditions a representative reaction of 2,2-dihydroxy-1-phenylethan-1-one **1{*1*}**, malononitrile **2{*1*}** and ethyl (*E*)-3-((4-bromophenyl) amino) acrylate **3{*3*}** that presumably affords the pyrrole **4{*1,3*}** was performed under various conditions (Table 1).

Table 1 Optimization of the reaction conditions



Entry	Solvent	Temperature (°C)	Time	Yield of 4{1,1,3} (%)[b]
1	EtOH	Reflux	30 min	80
2	EtOH	RT	2 h	50
3	MeOH	Reflux	2 h	65
4	MeOH	RT	30 min	62
5	MeOH	RT	2 h	50
6	MeCN	Reflux	4 h	60
7	THF	Reflux	6 h	35
8	$CHCl_3$	RT	6 h	50
9	CH_2Cl_2	RT	6 h	32
10	H_2O	Reflux	6 h	40
11	-[a]	Grinding	10 min	85
12	-[a]	Grinding	20 min	83
13	-[a]	Grinding	30 min	80

[a]*Solvent free condition* [b]*Isolated yield*

To begin with, the above reactants were refluxed in ethanol and monitored by TLC intermittently. After 30 min of continuous reflux the reaction attained completion as evident from the TLC analysis. Then the reaction mixture was treated with cold ethanol (3 mL) and the resultant precipitate was filtered and dried to obtain **4{*1,3*}** in 80% yield (Table 1, entry 1) as shown by the ESI mass and NMR studies (Figure-2) disclosed the formation of pyrrole **4{*1,3*}**.

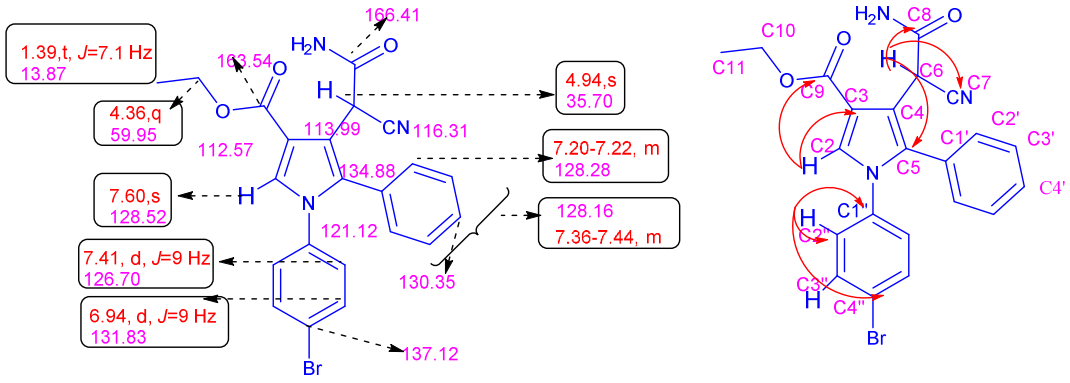


Figure 2 ^{1}H and ^{13}C chemical shifts and HMB correlations of **4{*1,3*}**

In contrast the above reaction took 2 h for 50 % completion at room temperature (Table 1, entry-2). Further exploration on the reaction conditions with a view to increase the yield of **4{*1,3*}** was done by employing solvents such as MeOH, MeCN, THF, $CHCl_3$, CH_2Cl_2 and water under RT as well as reflux. From Table 1 it is evident that refluxing the reactants in ethanol was the optimum condition (Entry 1). However, inspired by solvent-free reactions, we investigated the reaction under the solvent-free grinding method. To our surprise the reaction afforded ***4{1,3}*** in 85% yield after 10 min (Table 1, entry 11). We found that the solvent-free grinding method gave superior yields in less time when compared to other conditions (Table 1).

Having optimized the reaction conditions, we then explored its applicability for library production employing various aryl 2,2-dihydroxy-1-arylethan-1-ones **1{*1-5*}** and ethyl (*E*)-3-(arylamino)acrylates **3{*1-11*}** (Figure 3 and Scheme 2). The reaction occurred well in all these cases affording good yields of the product (Table 2). Moreover, with the available variations we noted an interesting trend in the reaction with respect to the substitutions in the *N*-phenyl ring of enamine **3**. In general, the *N*-phenyl, *N*-heterocycle and the presence of electron withdrawing substituent in the *N*-phenyl ring in **3** afforded the expected pyrroles **4**

(Table 2, Entries 1–7), whereas the enamines **3** with electron donating substituents led to the unprecedented formation of tetrahydropyridines **5** under similar reaction conditions (Table 2, Entries 8–19). The formation of **5** was ascertained from the NMR spectroscopy. As a representative case, in the ^{1}H NMR of **5{*3,7*}** the characteristic H-4 and H-3 protons appeared as doublets at 5.21 and 4.39 ppm (J =7.2, 6.9 Hz), respectively. This revealed the selective formation of tetrahydropyridines **5** and precluded the formation of pyrrole **4** (Figure 4). The structure of all the pyrroles **4** and the tetrahydropyridines **5** was elucidated with the help of NMR spectroscopy.

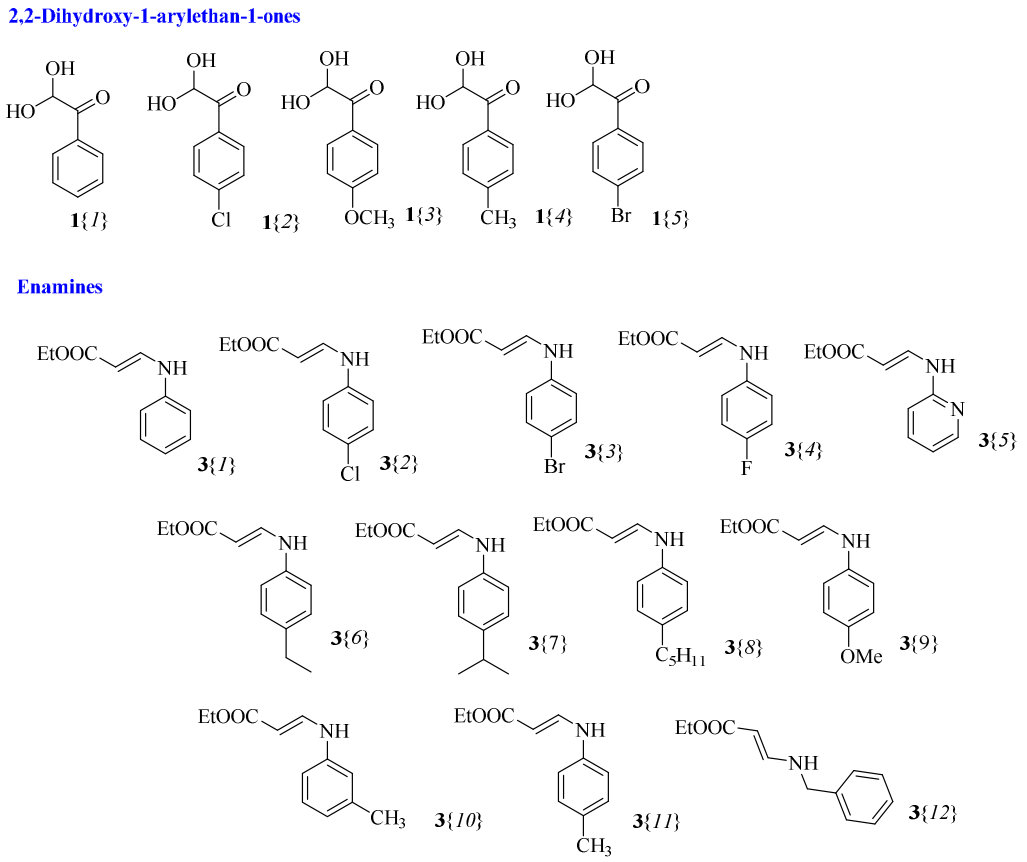
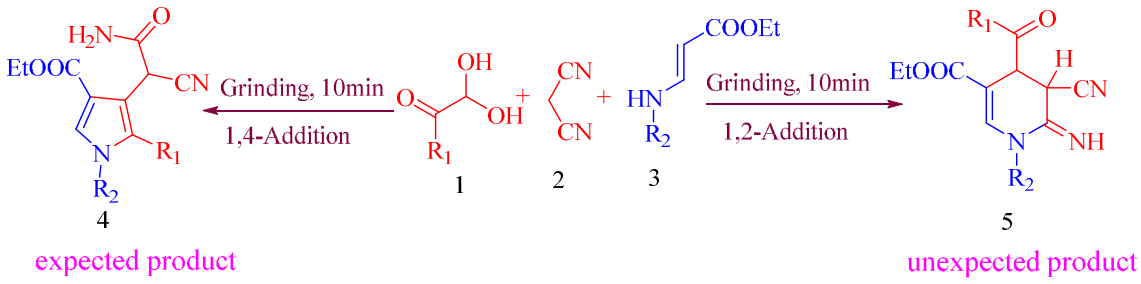


Figure 3 Diversity of reactants



Scheme 2 Synthesis of pyrroles **4** and tetrahydropyridines **5**

Table-2 Yield of pyrrole **4** and tetrahydropyridine **5**

Entry	Comp	R_1	R_2	Yield (%)[a]
1	**4*{1,1}***	C_6H_5	C_6H_5	82
2	**4*{1,2}***	C_6H_5	4-ClC_6H_4	80
3	**4*{1,3}***	C_6H_5	4-BrC_6H_4	84
4	**4*{1,4}***	C_6H_5	4-FC_6H_4	78
5	**4*{1,5}***	C_6H_5	2-Pyridyl	70
6	**4*{3,1}***	4-$OMeC_6H_5$	C_6H_5	83
7	**4*{4,1}***	4-MeC_6H_4	C_6H_5	82
8	**5*{1,6}***	C_6H_5	4-$C_2H_5C_6H_4$	82
9	**5*{1,7}***	C_6H_5	4-$^{i}PrC_6H_4$	84
10	**5*{1,8}***	C_6H_5	4-$C_5H_{11}C_6H_4$	79
11	**5*{1,9}***	C_6H_5	4-$OMeC_6H_4$	70
12	**5*{1,10}***	C_6H_5	3-MeC_6H_4	75
13	**5*{2,9}***	4-ClC_6H_4	4-$OMeC_6H_4$	70
14	**5*{2,11}***	4-ClC_6H_4	4-MeC_6H_4	76
15	**5*{3,6}***	4-$OMeC_6H_4$	4-$C_2H_5C_6H_4$	83
16	**5*{3,7}***	4-$OMeC_6H_4$	4-$^{i}PrC_6H_4$	85
17	**5*{3,8}***	4-$OMeC_6H_4$	4-$C_5H_{11}C_6H_4$	80
18	**5*{4,6}***	4-MeC_6H_4	4-$C_2H_5C_6H_4$	75
19	**5*{5,11}***	4-BrC_6H_4	4-MeC_6H_4	72
20	**4*{1,12}***	C_6H_5	-CH_2-C_6H_5	79
21	**4*{2,12}***	4-ClC_6H_4	-CH_2-C_6H_5	75
22	**4*{3,12}***	4-$OMeC_6H_5$	-CH_2-C_6H_5	80

[a]*Isolated yields after filtration*

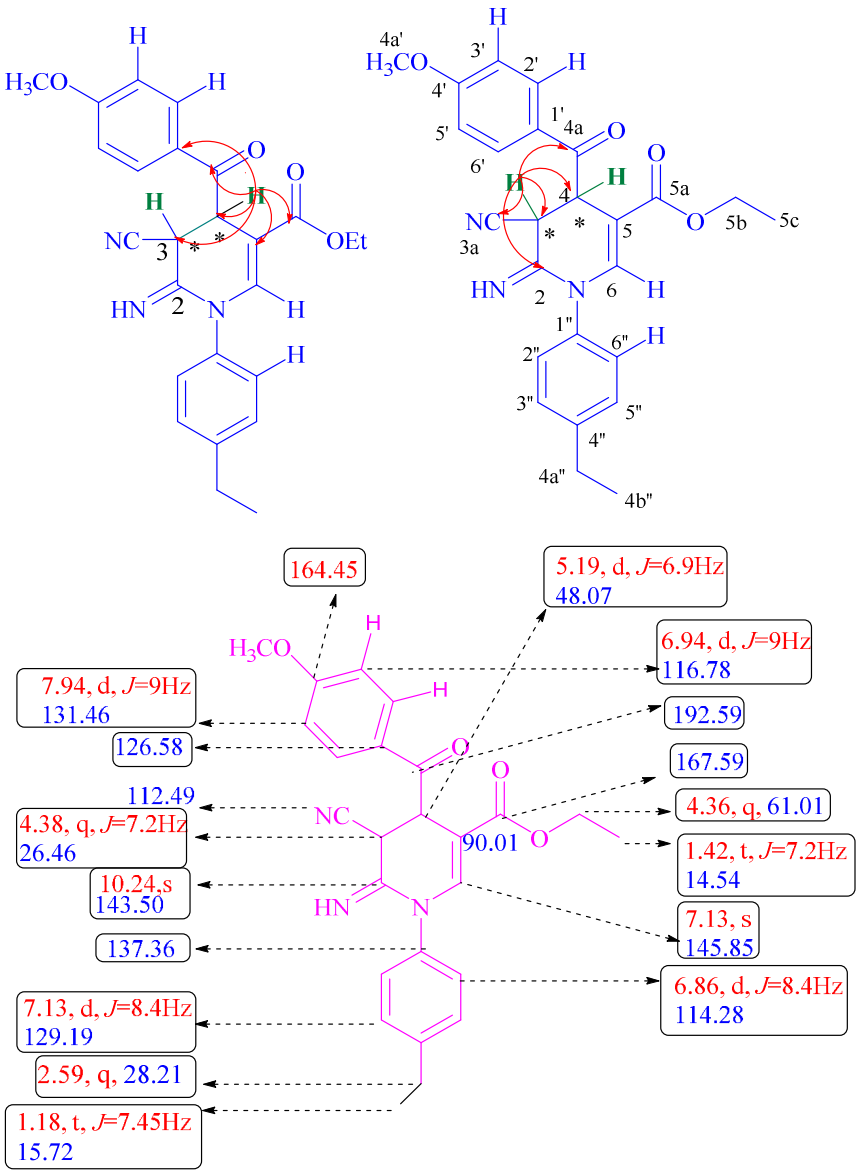
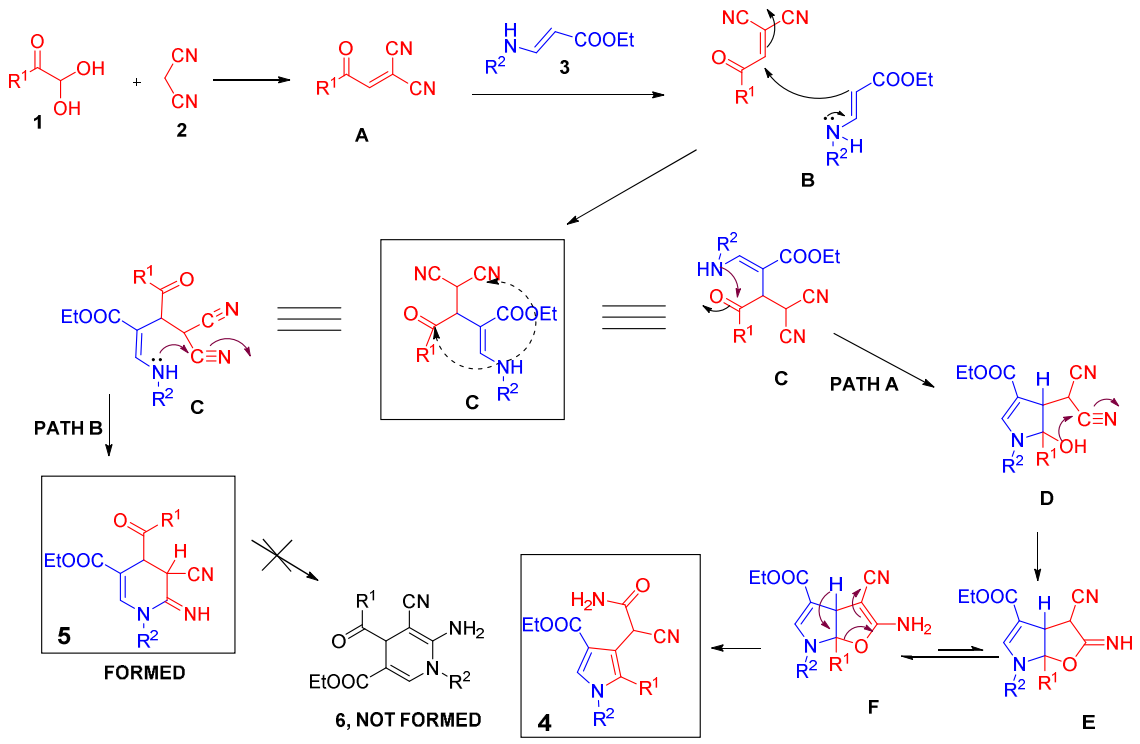


Figure 4 HMB correlations and ^{1}H and ^{13}C NMR chemical shifts of **5{*3,6*}**

A plausible mechanism for the formation of **5** is depicted in Scheme 3. Initially, the Knoevenagel condensation of 2,2-dihydroxy-1-arylethan-1-one **1** and malononitrile **2** furnishes 2-(2-oxo-2-arylethylidene)malononitrile **A**. Further, the Michael addition of **A** with enamine **3** affords intermediate **C**. The subsequent intramolecular *N*-cyclization of **C** may presumably involve the secondary amine group and the carbonyl or the nitrile functions *via* path A or B, respectively as shown in Scheme 3. Interestingly, in the cases of *N*-phenyl, *N*-heterocycle and the presence of electron withdrawing substituent in the *N*-phenyl ring in **C**,

cyclization involving the secondary amine group and the carbonyl is favoured and proceeds through path A leading to the formation of intermediate **D**, which then undergoes cyclization to afford **E**. The bicyclic intermediate **E** further undergoes ring opening via intermediate **F** to afford the polysubstituted pyrroles **4**.[27] On the other hand, the presence of electron donating substituents in the *N*-phenyl ring of the intermediate **C** favours the cyclization involving the secondary amine group and the nitrile function to afford the tetrahydropyridine **5** via path B. These tetrahydropyridine **5** were reluctant towards tautomerization to afford the dihydropyridine isomer **6**. Furthermore, it is to be noted that albeit the formation of two contiguous stereocentres, the reaction afforded a single diastereomer of the product **5**. The above two factors were evident from the NMR studies.



Scheme 3 Plausible mechanism for formation of tetrahydropyridines and pyrroles

With the above interesting results in hand we then studied the outcome of the above domino reaction in the presence of ethyl (*E*)-3-(benzylamino)acrylate **3{*12*}** with a view to investigate the selectivity involved in the reaction. However, the reaction afforded the expected pyrrole **4** as a sole product under similar conditions (Scheme 2 and Table 2, Entries 20–22). The structure of these pyrroles was elucidated with NMR spectroscopy and in one

representative case *viz*. **4{*1,12*}**, the structure was further confirmed from the single crystal X-ray studies (Figure 5).

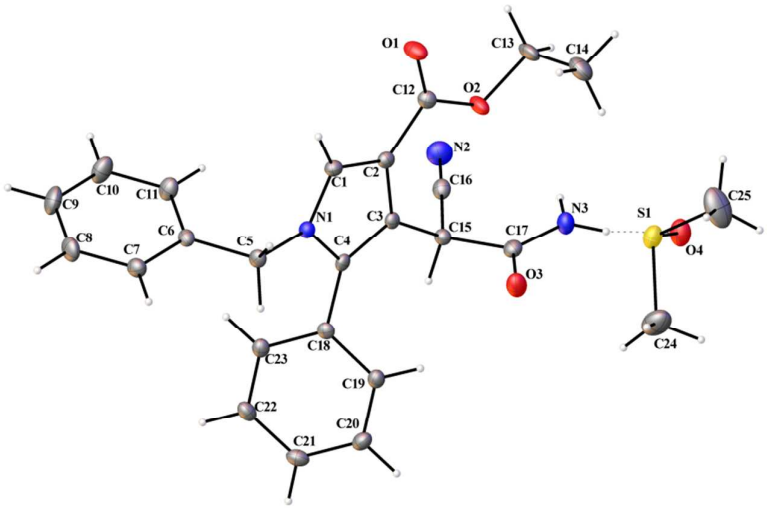
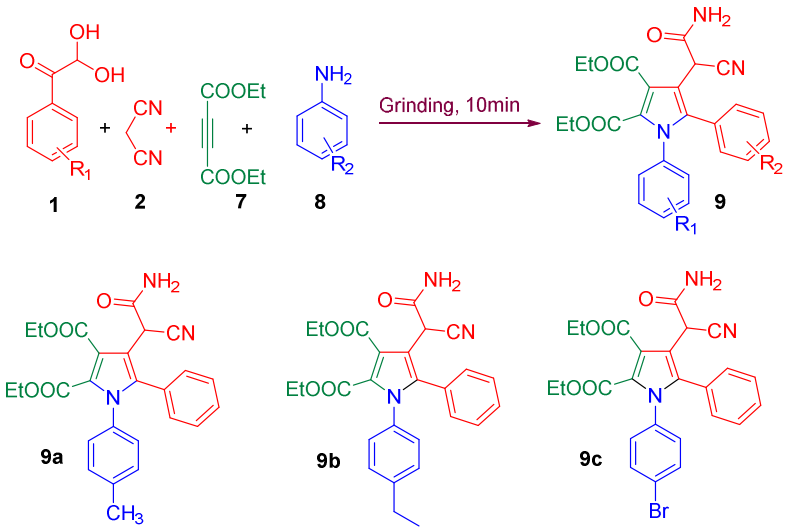


Figure 5 ORTEP diagram of **4{*1,12*}** (CCDC No.1428613)

It is to be noted that the four-component reactions of 2,2-dihydroxy-1-phenylethan-1-one **1**, malononitrile **2**, diethyl acetylene carboxylate **7** and aromatic amines **8** have been reported by the Feng *et al*. [27] This reaction in ethanol under reflux for 30 min led to the formation of pyrroles **9** up to 80% yields. We investigated this reaction under our optimized conditions with a view to study the selectivity involved, *viz*., whether the reaction affords pyrrole or tetrahydropyridine. Accordingly a mixture of 2,2-dihydroxy-1-phenylethan-1-one **1**, malononitrile **2**, diethyl acetylene carboxylate **7**, aromatic amines **8** was ground well for 10 min (Scheme 4). The reaction afforded pyrroles **9a-c** as the sole products in up to 85% yield Substrate scope of these reaction conditions were explored with aromatic amines comprising electron withdrawing or electron releasing substituents. However, in all these cases the reaction afforded pyrrole **9** as the sole product.



Scheme 4 Synthesis of fully substituted pyrroles **9a-c**

Conclusions

In conclusion, we have developed a facile method for synthesis of a library of polysubstituted pyrroles and tetrahydropyridines chemoselectively in excellent yields *via* a one-pot, multi-component domino reactions of ethyl (*E*)-3-(4-arylamino) acrylates, 2,2-dihydroxy-1-arylethan-1-ones and malononitrile under solvent and catalyst-free conditions under grinding. The chemoselectivity depended on the substitution in the *N*-phenyl ring of ethyl (*E*)-3-(4-arylamino) acrylates.

Experimental Procedures

General procedure for synthesis of 4 and 5

A mixture of 2,2-dihydroxy-1-arylethan-1-one **1** (1 mmol), malononitrile **2** (1 mmol) and ethyl (*E*)-3-(4-arylamino)acrylate **3** (1 mmol) was taken in a mortar and ground continuously for 10 min. The reaction was monitored by TLC until completion. The syrupy formed was washed with cold ethanol and filtered through the filtration flask to afford the pure product.

Ethyl 4-(2-amino-1-cyano-2-oxoethyl)-1-(4-bromophenyl)-5-phenyl-1H-pyrrole-3-carboxylate **4*{1,3}***

White solid, yield: 84% (394mg), mp: 190–193 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.38 – 7.31 (m, 3H), 7.24 – 7.18 (m, 2H), 6.95 (d, *J* = 8.2 Hz, 2H), 5.61 (s, 2H), 4.94 (s, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.21, 163.54, 137.13, 134.89, 131.84, 130.35, 128.52, 128.28, 128.12, 126.71, 121.12, 116.32, 113.99, 112.57, 59.95, 35.70, 13.87 ppm; LC-MS. calcd. *m/z* 451.05 found 452.25 $(M+H)^+$. Anal. Calcd. For $C_{22}H_{18}BrN_3O_3$ calcd. C, 58.42; H, 4.01; N, 9.29, found C, 58.43; H, 4.03; N, 9.28%.

Ethyl 5-cyano-1-(4-ethylphenyl)-6-imino-4-(4-methoxybenzoyl)-1,4,5,6-tetrahydropyridine-3-carboxylate **5{*3,6*}**

White solid, yield: 83% (373mg), mp: 125–126 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.27 (s, 1H), 7.95 (d, *J* = 9 Hz, 2H), 7.21 (s, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 9 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.21 (d, *J* = 6.3 Hz, 1H), 4.41 (d, *J* = 7.2 Hz,1H), 4.36 (q, *J* = 7.4 Hz, 2H), 2.63 (q, 2H), 1.42 (t, *J* = 7.2 Hz 3H), 1.18 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.59, 167.59, 164.45, 145.34, 140.50, 137.35, 131.46, 129.18, 129.04, 126.57, 116.77, 112.68, 112.49, 90.65, 61.01, 55.67, 48.78, 28.21, 26.42, 15.71, 14.54 ppm; LC-MS. calcd. *m/z* 431.18, found 432.22 $(M+H)^+$. Anal. Calcd. For. $C_{25}H_{25}N_3O_4$ calcd. C, 69.59; H, 5.84; N, 9.74, found C, 69.57; H, 5.82; N, 9.75%.

Diethyl 4-(2-amino-1-cyano-2-oxoethyl)-5-phenyl-1-(p-tolyl)-1H-pyrrole-2,3-dicarboxylate **9a**

White solid, yield: 86% (232mg) mp:189–190 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 8.3, 2.7 Hz, 4H), 7.18 – 7.14 (m, 2H), 7.04 (d, *J* = 7.4 Hz, 4H), 6.77 (s, 1H), 5.67 (s, 2H), 4.89 (s, 1H), 4.37 (dd, *J* = 14.2, 7.1 Hz, 2H), 4.15 (dd, *J* = 14.3, 7.1 Hz, 2H), 2.30 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 166.79, 163.83, 161.53, 138.98, 137.30, 134.08, 131.07, 130.70, 129.46, 129.20, 128.59, 128.15, 127.57, 116.32, 114.24, 111.71, 61.95, 61.30, 36.25, 21.18, 14.12, 13.80 ppm; LC-MS. calcd. *m/z* 459.18 found, 458.07 $(M-H)^-$. Anal. Calcd. For $C_{26}H_{25}N_3O_5$ calcd. C, 67.96; H, 5.48; N, 9.14, found C, 68.47; H, 5.21; N, 10.42%.

ASSOCIATED CONTENT

Supporting Information

Experimental details and Spectroscopic characterization of 4a-j, 5a-l and 9a-c and X-ray crystallographic information for compound **4{*1,12*}** are available in supporting information.

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NOTES

The authors declare no competing financial interest

REFERENCE

1. (a) Das,P.; Njardarson J. T.; Synthesis of 1,2,3,6-Tetrahydropyridines via Aminophosphate Enabled Anionic Cascade and Acid Catalyzed Cyclization Approaches. *Org. Lett.* **2015**, 17, 4030; (b) Toure B. B; Hall, D. G. Natural product synthesis using multicomponent reaction strategies. *Chem. Rev*. **2009**, 109, 4439; (c) Balme, G.; Bossharth, E.; Monteiro, N. Pd-Assisted Multicomponent Synthesis of Heterocycles. *Eur. J. Org. Chem.* **2003**, 21, 4101; (d) Hulme C.; Gore, V. Multi-component reactions: emerging chemistry in drug discovery from xylocain to crixivan. *Curr.Med. Chem.* **2003**, 10, 51; (e) Orru R. V. A.; de Greef, M. Recent Advances in Solution-Phase Multicomponent Methodology for the Synthesis of Heterocyclic Compounds. *Synthesis.* **2003**, 10, 1471; (f) Zhu, J. Recent Developments in the Isonitrile-Based Multicomponent Synthesis of Heterocycles. *Eur. J. Org. Chem.* **2003**,

7, 1133; (g) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. Maximizing Synthetic Efficiency: Multi-Component Transformations Lead the Way. *Chem.–Eur. J.* **2000**, 6, 3321.

2. (a) Mass, G. *Science of Synthesis,* Thieme, New York, **2001**; (b) Ferriera, V. *Org. Prep. Proced. Int.* **2001**, 33, 411; (c) Handbook of Heterocyclic Chemistry, Pergamon, San Diego, 2nd edn, **2000**. Part of recently reported examples of transition-metal catalyzed mediated synthesis of pyrroles.
3. (a) Chen, Z.; Lu, B.; Ding, Z.; Gao, K.; Yoshikai, N. α-Palladation of imines as entry to dehydrogenative Heck reaction: aerobic oxidative cyclization of N-allylimines to pyrroles. *Org. Lett*. **2013**, 15, 1966; (b) Yang, W.; Huang, L.; Liu, H.; Wang, W.; Li, H. Efficient synthesis of highly substituted pyrroles through a $Pd(OCOCF_3)_2$-catalyzed cascade reaction of 2-alkenal-1,3-dicarbonyl compounds with primary amines. *Chem. Commun.* **2013**, 49, 4667.
4. (a) Ran, L.; Ren, Z.H.; Wang, Y.Y.; Guan, Z.H. Copper-catalyzed homocoupling of ketoxime carboxylates for synthesis of symmetrical pyrroles *Green Chem.* **2014**, 16, 112; (b) Gao, M.; He, C.; Chen, H.; Bai, R.; Cheng, B. Lei, A. Synthesis of pyrroles by click reaction: silver-catalyzed cycloaddition of terminal alkynes with isocyanides. *Angew. Chem. Int. Ed.* **2013**, 52, 6958; (c) Tang, X.; Huang, L.; Qi, C.; Wu, W.; Jiang, H. An efficient synthesis of polysubstituted pyrroles via copper-catalyzed coupling of oxime acetates with dialkyl acetylenedicarboxylates under aerobic conditions *Chem. Commun*. **2013**, 49, 9597.
5. (a) Zhang, M.; Neumann, H.; Beller, M. Selective ruthenium-catalyzed three-component synthesis of pyrroles. *Angew. Chem. Int. Ed.* **2013**, 52, 597; (b) Schranck, J.; Tlili, A. Beller, M. More sustainable formation of C-N and C-C bonds for the synthesis of N-heterocycles. *Angew. Chem. Int. Ed.* **2013**, 52, 7642; (c) Abdulkader, A.; Xue, Q.; Lin, A.; Zhang, M.; Cheng, Y.; Zhu, C. Gold-catalyzed cascade C–C and C–N bond formation: synthesis of polysubstituted indolequinones and pyrroles. *Tetrahedron Lett.* **2013**, 54, 5898.
6. (a) Wang, X.; Xu, X.P.; Wang, S.Y.; Zhou, W.; Ji, S. Highly efficient chemoselective synthesis of polysubstituted pyrroles via isocyanide-based multicomponent domino reaction. *J. Org. Lett.* **2013**, 15, 4246; (b) Dunford, D. G.; Knight, D. W.; Wheeler, R. C. An efficient copper-catalysed pyrrole synthesis. *ARKIVOC,* **2012**, 7, 253; (c) Zhao, M.; Wang, F.; Li, X. Cross-Dehydrogenative Coupling between Enamino Esters and Ketones: Synthesis of Tetrasubstituted Pyrroles. *Org. Lett.* **2012**, 14, 1412

7. (a) Li, Q.; Fan, A.; Lu, Z.; Cui, Y.; Lin, W.; Jia, Y. One-Pot AgOAc-Mediated Synthesis of Polysubstituted Pyrroles from Primary Amines and Aldehydes: Application to the Total Synthesis of Purpurone. *Org. Lett.* **2010**, 12, 4066 (b) Chen, J. X.; Liu, M. C.; Yang, X. L.; Ding, J. C.; Wu, H.Y. synthesis Indium(III)-catalyzed synthesis of N-substituted pyrroles under solvent-free conditions. *Braz. J. Chem. Soc.* **2008**, 19, 877 (c) Martın, R.; Larsen, C. H.; Cuenca, A.; Buchwald, S. L. Cu-catalyzed Tandem C–N Bond Formation for the Synthesis of Pyrroles and Heteroaryl pyrroles. *Org. Lett*. **2007**, 9, 3379.
8. Dannhardt, G.; Bauer, A.; Nowe, U. Non-steroidal anti-inflammatory agents. Part 23. Synthesis and pharmacological activity of enaminones which inhibit both bovine cyclooxygenase and 5-lipoxygenase. *J. Prakt.Chem.* **1998**, 340, 256.
9. (a) Reidlinger, C.; Dworczak, R.; Junk, H. Cyanoacetophenone as a Synthon for1,4,5-Substituted Pyrazole. *Monatsh. Chem.* **1998**, 129, 1207; (b) Al-Omran, A. Z. A.; Elassar, A.; El-Khair, A. Synthesis of condensed heteroaromatics: novel synthesis of aminoquinolizinone derivatives as anti-HIV agents. *Tetrahedron,* **2001**, 57, 10163; (c) Wiberg, K. B.; Snoonian, J. R. Ring Expansion and Contraction of a Two-Carbon Bridged Spiropentane. *J. Org. Chem.* **1998**, 63, 1390; (d) Katritzky, A. R.; Fang, Y.; Donkor, A.; Xu, J. Imine Acylation via Benzotriazole Derivatives: The Preparation of Enaminones. *Synthesis*, **2000**, 47, 2029.
10. (a) Giralt, M.; Diez, E. A. Eds. Elsevier. New York. **1991**, Vol. 43; (b) Kubota, H.; Fujii, M.; Ikeda, K.; Takeuchi, M.; Shibanuma, T.; Isomura, Y. Spiro-substituted piperidines as neurokinin receptor antagonists. I. Design and synthesis of (+/-)-N-[2-(3,4-dichlorophenyl)-4-(spiro [isobenzofuran-1(3H),4'piperidin]-1'-yl)butyl]-N-methylbenzamide, YM-35375, as a new lead compound for novel neurokinin receptor antagonists. *Chem. Pharm. Bull.* **1998**, 46, 351; (c) Jain, R.; Chen, D.; White, R. J.; Patel, D. V.; Yuan, Z. bacterial peptide deformylase inhibitors a new class of antibacterial agents. *Curr Med. Chem*. **2005**, 12, 1607.
11. Balme, G. Pyrrole Syntheses by Multicomponent Coupling Reactions. *Angew. Chem. Int. Ed*. **2004**, 43, 6238.
12. (a)Foster, J. E.; Nicholson, J. M.; Butcher, R.; Stables, J. P.; Edafiogho, I.O.; Goodwin, A. M.; Henson, M. C.; Smith, C. A.; Scott, K. R. Synthesis, characterization and anticonvulsant activity of enaminones. Synthesis of substituted vinylic benzamides as potential anticonvulsants. *Bioorg. Med. Chem.* **1999**, 7, 2415; (b) Edafiogho, I. O.;

Moore, J. A.; Alexander, M. S.; Scott, K. R. Nuclear magnetic resonance studies of anticonvulsant enaminones. *J. Pharm. Sci.* **1994**, 83, 1155.

13. (a) Michael, J. P.; Koning, C. B.; Hosken G. D.; Stanbury, T. V. Reformatsky reactions with N-arylpyrrolidine-2-thiones: synthesis of tricyclic analogues of quinolone antibacterial agents *Tetrahedron*, **2001**, 57, 9635; (b)Valduga, C. J.; Braibante H. S.; Braibante, E. F. J. *J. Heterocycl. Chem.* **1998**, 35, 189; (c) Ferraz, H. M. C.; Oliveira, E. O.; Payret-Arrua, M. E.; Brandt, C. A. *J. Org.Chem.***1995**, 60, 7357.
14. Yang, Y.R.; Chang, K.C.; Chen, C.L.; Chiu, T.H. Arecoline excites rat locus coeruleus neurons by activating the M2-muscarinic receptor. *Chin. J. Physiol.* **2000**, 43, 23.
15. Nakao, A.; Ohkawa, N.; Nagasaki, T.; Kagari, T.; Doi, H.; Shimozato, T.; Ushiyama, S.; Aoki, K. Tetrahydropyridine derivatives with inhibitory activity on the production of proinflammatory cytokines: part 1. *Bioorg. Med. Chem. Lett.* **2009**, 19, 4607.
16. (a) Vulter, A.; Buettner, R.; Kowolik, C.; Liang, W.; Smith, D.; Boschelli, F. and Jove, R. SKI-606 (bosutinib), a novel Src kinase inhibitor, suppresses migration and invasion of human breast cancer cells. *Mol. Cancer Ther.* **2008**, 7, 1185; (b) Smith, P. C.; Mc Donagh, A. F. and Benet, L. Z. Irreversible binding of zomepirac to plasma protein in vitro and in vivo. *J. Clin. Invest.* **1986**, 77, 934; (c) Castro, A. J. Antimalarial activity of prodigiosin. *Nature*, **1967**, 213, 903.
17. (a) Ichikawa, E.; Suzuki, M.; Yabu, K.; Albert, M.; Kanai, M.; Shibasaki, M. New entries in Lewis acid-Lewis base bifunctional asymmetric catalyst: catalytic enantioselective Reissert reaction of pyridine derivatives. *J. Am. Chem. Soc.* **2004**, 126, 11808; (b) Sun, Z.; Yu, S.; Ding, Z.; Ma, D. Enantioselective addition of activated terminal alkynes to 1-acylpyridinium salts catalyzed by Cu-Bis(oxazoline) complexes. *J. Am. Chem. Soc*. **2007**, 129, 9300; (c) Wu, J.; Tang, W.; Pettman, A.; Xiao, *J. Adv. Synth. Catal.* **2013**, 355, 35; (d) Singh, S. K.; Sharma, V. K. Efficient and Chemoselective Reduction of Pyridines to Tetrahydropyridines and Piperidines *via* Rhodium-Catalyzed Transfer Hydrogenation. *Curr. Org. Chem.* **2014**, 18, 1159.
18. (a) Bolig, A. D.; Brookhart, M. Activation of sp^3 C-H Bonds with Cobalt(I): Catalytic Synthesis of Enamines *J. Am. Chem. Soc.* **2007**, 129, 14544; (b) Takasu, N.; Oisaki, K.; Kanai, M. Iron-Catalyzed Oxidative C(3)-H Functionalization of Amines. *Org. Lett.* **2013**, 15, 1918;

19. (a) Wen, L. R.; Shi, Y. J.; Liu, G. Y.; Li, M. Modulating the Reactivity of Functionalized N,S-Ketene Acetal in MCR: Selective Synthesis of Tetrahydropyridines and Thiochromeno[2,3-b]pyridines via DABCO-Catalyzed Tandem Annulation. *J. Org. Chem*. **2012**, 77, 4252; (b) S. Chen, Mercado, B. Q.; Bergman, R. G.; Ellman, J.A. Regio- and Diastereoselective Synthesis of Highly Substituted, Oxygenated Piperidines from Tetrahydropyridines. *J. Org. Chem.* **2015**, 80, 6660.(c) Liu, L.; Sarkisian, R.; Deng, Y.; Wang, H.; Sc(OTf)3-Catalyzed Three-Component Cyclization of Arylamines, β,γ- Unsaturated α-Ketoesters, and 1,3-Dicarbonyl Compounds for the Synthesis of Highly Substituted 1,4-Dihydropyridines and Tetrahydropyridines. *J. Org. Chem.* **2013**, 78, 5751.

20. (a) Simal, C.; Bates, R. H.; Ureña, M.; Gimenez, I.; Koutsou, C.; Infantes, L.; Pradilla, R. F.; Viso, A. Synthesis of Enantiopure 3-Hydroxypiperidines from Sulfinyl Dienyl Amines by Diastereoselective Intramolecular Cyclization and [2,3]- Sigmatropic Rearrangement. *J. Org. Chem.* **2015**, 80, 7674; (b) Schmitt,́ S.; Brown, R. C. D.; Perrio, C. Diastereoselective Syntheses of (3R, 4R)- and (3R,4S)-4-Aryl-3- methyl-4-piperidinemethanol and Fluoro Analogues. *J. Org. Chem.* **2013**, 78, 1222; (c) Clark, R. C.; Pfeiffer, S. S.; Boger, D. L. Diastereoselective Diels−Alder Reactions of N-Sulfonyl-1-aza-1,3-butadienes with Optically Active Enol Ethers: An Asymmetric Variant of the 1-Azadiene Diels−Alder Reaction. *J. Am. Chem. Soc.* **2006**, 128, 2587. (d) Han, B.; Li, J. L.; Ma, C.; Zhang, S. J.; Chen, Y.-C. Organocatalytic asymmetric inverse-electron-demand aza-Diels-Alder reaction of N-sulfonyl-1-aza-1,3-butadienes and aldehydes. *Angew. Chem. Int. Ed.* **2008**, 47, 9971. (e) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. New tandem catalysis: preparation of cyclic enol ethers through a ruthenium-catalysed ring-closing metathesis-olefin isomerization sequence. *J. Am. Chem. Soc.* **2002**, 124, 13390.

21. Greenhill, J. V. Enaminones. *Chem. Soc. Rev*. **1977**, 6, 277.

22. (a) Ren, H.; Wulff, W. D. Total Synthesis of Sedum Alkaloids via Catalyst Controlled aza-Cope Rearrangement and Hydroformylation with Formaldehyde. *Org. Lett.* **2013**, 5, 242; (14) (b) Suryavanshi, P. A.; Sridharan, V.; Maiti, S.; Menendez, J. C. Fully diastereoselective synthesis of polysubstituted, functionalized piperidines and decahydroquinolines based on multicomponent reactions catalyzed by cerium(IV) ammonium nitrate. *Chem.-Eur. J.* **2014**, 20, 8791. (c) Suryavanshi, P. A.; Sridharan, V.; Menendez, J. C. A β-enaminone-initiated multicomponent domino reaction for the synthesis of indoloquinolizines and benzoquinolizines from acyclic precursors. *Chem.-*

Eur. J. **2013**, 19, 13207; (d) Shi, F.; Tan, W.; Zhu, R.-Y.; Xing, G.-J.; Tu, S. Catalytic Asymmetric Five-Component Tandem Reaction: Diastereo- and Enantioselective Synthesis of Densely Functionalized Tetrahydropyridines with Biological Importance. *J. Adv. Synth. Catal.* **2013**, 355, 1605. (e) Gawande, M. B.; Bonifacio, V. D. B.; Varma, R. S.; Nogueira, I. D.; Bundaleski, N.; Ghumman, C. A. A.; Teodoro, O. M. N. D.; Branco, P. S. Magnetically recyclable magnetite–ceria (Nanocat-Fe-Ce) nanocatalyst – applications in multicomponent reactions under benign conditions. *Green Chem*. **2013**, 15, 1226; (f) Khidre, R. E.; Abdel-Wahab, B. F. Application of Benzoylaceteonitrile in the Synthesis of Pyridines Derivatives. *Curr. Org. Chem*. **2013**, 17, 430.

23. (a) Li, B.; Wang, N.; Liang, Y.; Xu, S.; Wang, B. Ruthenium-catalyzed pyrrole synthesis via oxidative annulation of enamides and alkynes. *Org. Lett*. **2013**, 15, 136; (b) Wang, L. and Ackermann, L. Versatile pyrrole synthesis through ruthenium (II)-catalyzed alkene C-H bond functionalization on enamines. *Org. Lett.* **2013**, 15, 176; (c) Rakshit , S.; Patureau, F. W.; Glorius, F. Pyrrole synthesis via allylic sp3 C-H activation of enamines followed by intermolecular coupling with unactivated alkynes. *J. Am. Chem. Soc.* **2010**, 132, 9585; (d) Yan, R. L; Luo, J.; Wang, C. X.; Ma, C. W.; Huang, G. S.; Liang, Y. M. Cu (I)-catalyzed synthesis of polysubstituted pyrroles from dialkyl ethylenedicarboxylates and beta-enamino ketones or esters in the presence of O_2. *J. Org. Chem*. **2010**, 75, 5395.
24. (a) Meng, L.; Wu, K.; Liu, C.; Lei, A. Palladium-catalysed aerobic oxidative Heck-type alkenylation of Csp3-H for pyrrole synthesis. *Chem. Commun*. **2013**, 49, 5853; (b) Shi, Z.; Suri, M.; Glorius, F.; Aerobic synthesis of pyrroles and dihydropyrroles from imines: palladium (II)-catalyzed intramolecular C-H dehydrogenative cyclization. *Angew. Chem. Int. Ed.* **2013**, 52, 4892; (c) Chen, Z.; Lu, B.; Ding, Z.; Gao, K.; Yoshikai, N. α-Palladation of imines as entry to dehydrogenative Heck reaction: aerobic oxidative cyclization of N-allylimines to pyrroles. *Org. Lett.* **2013**, 15, 1966.
25. Muthusaravanan, S.; Perumal, S.; Almansour, A. I. Facile catalyst-free pseudo five-component domino reactions in the expedient synthesis of 5-aroyl-1,3-diarylhexahydropyrimidines. *Tetrahedron Lett.* **2012**, 53, 1144.
26. (a) Patil, V. S.; Nandre, K. P.; Ghosh, S.; Rao, V. J.; Chopade, B. A.; Bhosale, S. V.; Bhosale, S. V. Synthesis and glycosidase inhibitory activity of novel (2-phenyl-4H-benzopyrimedo[2,1-b]-thiazol-4-yliden)acetonitrile derivatives. *Bioorg. Med. Chem. Lett.* **2012**, 22, 7011 (b) Cai, L. 1.; Chin, F. T; Pike, V. W.; Toyama, H.; Liow, J. S.; Zoghbi, S. S.; Modell, K.; Briard, E.; Shetty, H. U.; Sinclair, K.; Donohue, S.; Tipre, D.;

Kung, M. P; Dagostin, C.; Widdowson, D. A.; Green, M.; Gao, W.; Herman, M.M.; Ichise, M.; Innis, R. B. Synthesis and evaluation of two 18F-labeled 6-iodo-2-(4'-N,N-dimethylamino)phenylimidazo[1,2-a]pyridine derivatives as prospective radioligands for beta-amyloid in Alzheimer's disease. *J. Med. Chem.* **2004**, 47, 2208; (c) Cai, L. 1.; Chin, F. T.; Pike, V. W.; Toyama, H.; Liow, J. S.; Zoghbi, S. S.; Modell, K.; Briard, E.; Shetty, H. U.; Sinclair, K.; Donohue, S.; Tipre, D.; Kung, M. P.; Dagostin, C.; Widdowson, D. A.; Green, M.; Gao, W.; Herman, M. M.; Ichise, M.; Innis, R. B.; Synthesis and evaluation of two 18F-labeled 6-iodo-2-(4'-N,N-dimethylamino) phenylimidazo[1,2-a]pyridine derivatives as prospective radioligands for beta-amyloid in Alzheimer's disease. *J. Med. Chem.* **2005**, 48, 292; (d) Yang, Q. Q.; Xiao, C.; Lu, L. Q.; An, J.; Tan, F.; Li, B. J.; Xiao, W. J. Synthesis of indoles through highly efficient cascade reactions of sulfur ylides and N-(ortho-chloromethyl)aryl amides. *Angew. Chem. Int. Ed.* **2012**, 51, 9137; *Angew. Chem. Int. Ed.* **2012**, 124, 9271.

27. Feng, X.; Wang, Q.; Lin, W.; Dou, G. L.; Huang, Z. B. and Shi, D. Q. Highly efficient synthesis of polysubstituted pyrroles via four-component domino reaction. *Org. Lett*. **2013**. 15, 2542.

Graphical abstract