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Synthesis of alkynyl/alkenyl-substituted pyridine derivatives *via* heterocyclization and Pd-mediated Sonogashira/Heck coupling process in one-pot: A new MCR strategy

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Abstract: A new class of 2-amino-4-(3/2-(alkynyl)/3-(alkenyl)phenyl)-6-phenylnicotinonitriles (**6**, **7** & **9**) has been synthesized with good to excellent isolated yields by the multi-component reaction (MCR) of bromobenzaldehyde (**1**), malononitrile (**2**), acetophenone (**3**), NH_4OAc (**4**) and a series of terminal alkynes(**5**)/alkenes(**8**) in presence of pyrrolidine and Pd-catalyst in a mixture of H_2O-DME (1:4 ratio) under reflux conditions in a single step. The Heck-type coupling with terminal olefins takes place stereoselectively with exclusive formation of *E*-isomers. This new MCR strategy opens new avenues in the development of i) diversity-oriented new cyano pyridine based compound library and ii) new chemical entities other than the present reported molecules.

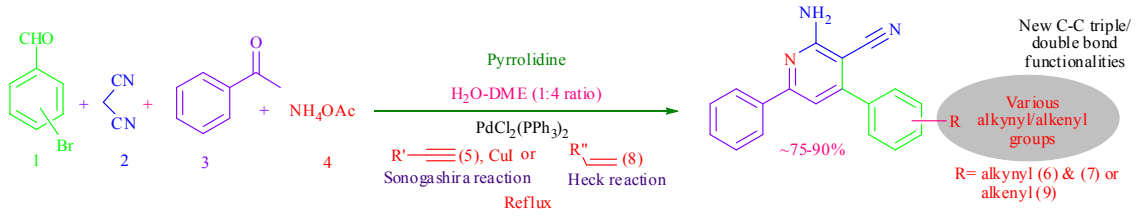
Key words: Multi-component reaction (MCR), Pyridines, heterocyclization, C-C coupling, Sonogashira reaction, Heck reaction

1. Introduction

The pyridine ring system is an 'Important structural motif' in a large number of natural products and also in clinically useful molecules. Among this plethora of compounds, cyanopyridine derivatives have attracted great attention due to their wide range of biological activities such as antimicrobial,[1,2] antipyretic,[3] anti-hyperglycemic properties,[4] Ca^{2+}-channel blockers,[5] vasodilator,[6] antitumor,[7,8] anti-diabetic agents.[9] In addition, they have been evaluated as IKK-β inhibitors,[10] Protein Kinase B (PKB/Akt) inhibitors,[11] protein kinase Cθ (PKCθ) inhibitors,[12] melanin-concentrating hormone receptor 1 (MCH-R1) antagonists,[13] A_{2A} adenosine receptor antagonists,[14] carbonic anhydrase inhibitors,[15] dipeptidyl peptidase-IV (DPP-IV) inhibitors with anti-hyperglycemic activity,[16] analgesic agents,[17] monoamine oxidases (MAO), cholinesterase inhibitors for the treatment of Alzheimer's disease,[18] metabotropic glutamate receptor5 (mGluR5) negative allosteric modulators,[19] C-Jun NH_2 terminal kinase (JNKs) inhibitors,[20] prion disease therapeutics[21] and RET tyrosine kinase inhibitors[22] and also useful in the development of non-linear optical (NLO) materials[23] and nondoped organic light-emitting devices (OLEDs) too.[24] As a result, cyanopyridine derivatives are regarded as "significant structural motif" and a huge number of strategies are developed for their synthesis.[25, 26] In addition, the development of multi-component reactions (MCRs) strategies have attracted great attention from organic chemists[27-34] to prepare these useful pyridine frameworks. Multi-component reactions (MCRs) are powerful strategies for the quick synthesis of diverse and complex organic

molecules of potential interest particularly in the area of material science and drug discovery.[35-39] MCRs have attracted much attention owing to their excellent synthetic efficiency, intrinsic atom economy, high selectivity, procedural simplicity and environmental friendliness.[40-43] Therefore, the development of new multi-component reaction (MCR) strategies for the preparation of diversity-oriented complex molecules have recently gained considerable interest from the organic chemists.[45-49] In particular, structural elaboration on heterocyclic compounds with terminal alkynyl/alkenyl functionalities using Sonogashira and Heck coupling reactions is quite interesting.[50-56] However, attempts are not made to investigate the structural elaboration of cyano pyridine derivatives using Pd-mediated Sonogashira and Heck coupling reactions *via* a one-pot multicomponent reaction (MCR).

Herein, we report a new MCR strategy for the synthesis of 2-amino-4-(3/2-(alkynyl)/3-(alkenyl)phenyl)-6-phenylnicotinenitriles (**6**, **7** & **9**) with 80-90% isolated yields *via* heterocyclization from bromobenzaldehyde (**1**), malononitrile (**2**), acetophenone (**3**) and NH_4OAc (**4**) in the presence of pyrrolidine followed by Pd-mediated Sonogashira and Heck coupling reactions using a variety of terminal alkynes(**5**)/alkenes (**8**) in a mixture of H_2O-DME (1:4 ratio) under reflux-conditions as shown in scheme 1. The present communication addresses several challenging issues *e.g.* (i) MCR based synthesis of alkynyl/alkenyl substituted-heterocyclic molecules *via* heterocyclization followed by C-C coupling in one-pot, (ii) the optimal base, catalyst system and reaction conditions and (iii) synthesis in view to develop alkynyl/alkenyl substituted heterocyclic compounds based synthetic precursors suitable for further functional group transformations in the development of diversity oriented new compound library.



Scheme 1 Synthesis of 2-amino-4-(3/2-(alkynyl)/3-(alkenyl)phenyl)-6-phenylnicotinenitriles via multi-component reaction.

2. Experimental

Melting points of various products obtained are determined (uncorrected). ^1H and ^{13}C NMR spectra are recorded on a Varian 400 MHz. Chemical shifts are reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The data are reported as follows: chemical shift (ppm) and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br s = broad singlet), coupling

constant(s) in Hz, integration assignment. High-resolution mass spectra (HRMS) and compound purity data are acquired on a Waters LCT premier XE TOF HRMS single quadrupole system equipped with electro spray ionization (ESI) source. Thin-layer chromatography is performed on 0.25 mm Merck silica gel plates and visualized with UV light. Column chromatography is performed on silica gel (200-300 mesh). Chemicals and solvents are purchased from Sigma Aldrich and Merck. Isolated compounds are characterized by physical and spectroscopic data.

Typical experimental procedure for the preparation of 2-amino-4-(3-(3-hydroxyprop-1-ynyl)phenyl)-6-phenylnicotinonitrile (6a):

A mixture of 3-bromobenzaldehyde (**1**) [10.0 mmol], malononitrile (**2**) [11.0 mmol], acetophenone (**3**) [11.0 mmol] and NH_4OAc (**4**) [20.0 mmol] in presence of pyrrolidine (5.0 mmol) in a mixture of H_2O-DME (1:4 ratio) (10 vol) is stirred at reflux for 1.0 hr. The first phase progress of the reaction is monitored by TLC. After the completion of the reaction, the reaction mixture is cooled to RT and then, prop-2-yn-1-ol **5a** [15.0 mmol], $PdCl_2(PPh_3)_2$ [0.002 mmol] and CuI [0.005 mmol] are added. Again the entire reaction mixture is kept under reflux condition for 3.0 hrs in open air. Final stage progress is monitored by TLC. After the completion of the reaction, the whole reaction mixture is cooled to RT and the solvent is removed under reduced pressure. The obtained crude product is purified by column chromatography using silica gel and 1:9 ratio of EtOAc - Petroleum ether (PE) to obtain pure compound **6a**. The isolated yield of product **6a** is 91%. The same procedure is followed for the preparation of 2-amino-4-(3-(alkynyl)phenyl)-6-phenylnicotinonitrile derivatives (**6b-k**) listed in **Table-2.** All the synthesised compounds (**6a-k**) gave satisfactory spectroscopic data in accordance with their proposed structures.

Typical experimental procedure for the preparation of 2-amino-4-(2-(3-hydroxyprop-1-ynyl)phenyl)-6-phenylnicotinonitrile (7a):

A mixture of 2-bromobenzaldehyde (**1a**) [10.0 mmol], malononitrile (**2**) [11.0 mmol], acetophenone (**3**) [11.0 mmol] and NH_4OAc (**4**) [20.0 mmol] in the presence of pyrrolidine (5.0 mmol) in a mixture of H_2O-DME (1:4 ratio) (10 vol) is stirred at reflux for 1.0 hr. The first phase progress of the reaction is monitored by TLC. After the completion of the reaction, the reaction mixture is cooled to RT and then, prop-2-yn-1-ol **5a** [17.0 mmol], $PdCl_2(PPh_3)_2$ [0.002 mmol] and CuI [0.005 mmol] are added. Again the entire reaction mixture is kept under reflux condition for 3.5 hrs in open air. Final stage progress is monitored by TLC. After the completion of the reaction, the whole reaction mixture is cooled to RT and the solvent is removed under reduced pressure. The obtained crude product is purified by column chromatography using silica gel and 1:9 ratio of EtOAc - Petroleum ether (PE) to obtain pure product **7a**. The isolated yield of product 7**a** is 80%. The same procedure is followed for the preparation of 2-amino-4-(2-(alkynyl)phenyl)-6-phenylnicotinonitrile derivatives (**7b-d**) listed in

Table-3. Synthesized compounds (**7a-d**) gave satisfactory spectroscopic data in accordance with their proposed structures.

Typical experimental procedure for the preparation of (*E*)-methyl 3-(3-(2-amino-3-cyano-6-phenylpyridin-4-yl)phenyl)acrylate (9a):

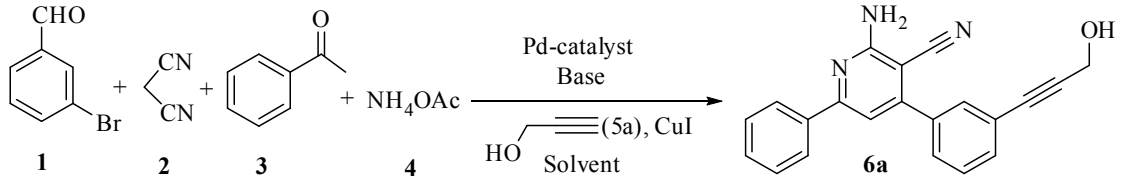
A mixture of 3-bromobenzaldehyde (**1**) [10.0 mmol], malononitrile (**2**) [11.0 mmol], acetophenone (**3**) [11.0 mmol] and NH_4OAc (**4**) [20.0 mmol] in presence of pyrrolidine (5.0 mmol) in a mixture of H_2O-DME (1:4 ratio) (10 vol) is stirred at reflux for 1.0 hr. The first phase progress of the reaction is monitored by TLC. After the completion of the reaction, the reaction mixture is cooled to RT and then, methyl acrylate (**8a**) [16.0 mmol] and $PdCl_2(PPh_3)_2$ [0.002 mmol] are added. Again, the entire reaction mixture is kept under reflux condition for 3.0 hrs in open air. Final stage progress is monitored by TLC. After the completion of the reaction, the whole reaction mixture is cooled to RT and the solvent is removed under reduced pressure. The obtained crude product is purified by column chromatography using silica gel and 1:9 ratio of EtOAc - Petroleum ether (PE) to obtain pure compound **(9a)**. The isolated yield of product **9a** is 88%. The same procedure is followed for the preparation of 2-amino-4-(3-(alkenyl)phenyl)-6-phenylnicotinonitrile derivatives (**9b-f**) listed in **Table-4.** Synthesized compounds (**9a-f**) gave satisfactory spectroscopic data in accordance with their proposed structures. Based on ^1H NMR data, all the prepared alkenes (**9a-f**) are confirmed as '*E*' isomers (J= 16.0 - 16.5 Hz).

3. Results and discussion

In the present study, our initial objective is to identify well-suited reaction conditions for the heterocyclization along with Pd-mediated C-C coupling process in a single step operation. Accordingly, we have studied the effect of bases, solvents, reaction temperature and Pd-catalysts as well as effect of concentration of base for the construction of pyridine frame work followed by Sonogashira/Heck coupling in one-pot. Therefore, in an initial experiment, 3-bromobenzaldehyde (**1**), malononitrile (**2**), acetophenone (**3**) and NH_4OAc (**4**) in presence of K_2CO_3 in H_2O is stirred at reflux for 10.0 hrs. After the completion of the reaction, the reaction mixture is cooled to RT and then, prop-2-yn-1-ol [**5a**], $PdCl_2(PPh_3)_2$ and CuI are added. After workup and purification, the desired product 2-amino-4-(3-(3-hydroxyprop-1-ynyl)phenyl)-6-phenylnicotinonitrile (**6a**) is isolated in 5.0% yield (entry 1, Table 1). The obtained yield of the product (**6a**) is not impressive; this may be due to insolubility of the reactants. To improve the solubility of the reactants and thereby the yield of the product (**6a**), H_2O is replaced by organic solvents such as THF, Dioxane, DME, mixture of H_2O-DME (1:4 ratio), DMF and DMSO. The obtained yields are 48%, 56%, 64%, 71% and 62%, respectively (entries 2-7, Table 1). Initial effect of solvent study revealed that mixture of H_2O-DME (1:4 ratio)

provided acceptable yield (71%) of the product **6a** (entry 5). To increase the yield of the product (**6a**) further, various bases such as Na_2CO_3 (entry 8), Et_3N (entry 9) and pyrrolidine (entry 10) are employed which resulted a yield of 56%, 78% and 91%, respectively in a mixture of H_2O-DME (1:4 ratio). The evaluation of suitable base revealed that pyrrolidine is more efficient in producing the maximum yield (91%) of product **6a** (entry 10) in a mixture of H_2O-DME (1:4 ratio). Subsequently, the effects of temperature, Pd-catalyst and concentration of base and terminal alkyne, prop-2-yn-1-ol (**5a)** are investigated on the course of MCR. Lower yields (25-72%) are obtained when the same reaction is conducted at less than 80°C in a mixture of H_2O-DME (1:4 ratio). In this case, it is observed that some portions of the reactants are still remaining and resulting lower yields of the desired product (**6a**). Then, the same reaction has been conducted at reflux temperature and the obtained yield of the product (**6a**) has dramatically increased to 91%. In order to study the effect of other Pd-catalysts on the course of the C-C coupling reaction, various Pd-catalysts such as $Pd(PPh_3)_4$, $Pd(dppf)Cl_2$ and 20% $Pd(OH)_2$ have been employed which afforded 72%, 68% and 75% yields, respectively (entries 11-14). The results show the superiority of the $PdCl_2(PPh_3)_2$ catalyst to obtain maximum yield (91%) of the product (**6a**) within 4.0 hrs. The effect of pyrrolidine base load is studied on the course of MCR reaction; for example 2.0, 5.0, 10.0, 15.0 and 20.0 mmol of pyrrolidine provided 72%, 91%, 78%, 71% and 65% yields of product (**6a**), respectively. From the results, it is concluded that 5.0 mmol of pyrrolidine offered best yield (91%) of product (**6a**). Variation of terminal alkyne concentration also effected the yields significantly; 10.0, 15.0, 20.0 and 25.0 mmol of prop-2-yn-1-ol **5a** resulted 68%, 91%, 84% and 78% yields and the optimum concentration of terminal alkyne concentration is 15.0 mmol for maximum yield.

Table 1. Optimization of reaction conditions for the MCR based synthesis of 2-amino-4-(3-(3-hydroxyprop-1-ynyl)phenyl)-6-phenylnicotinonitrile (**6a**) through heterocyclization followed by Sonogashira reaction[a]



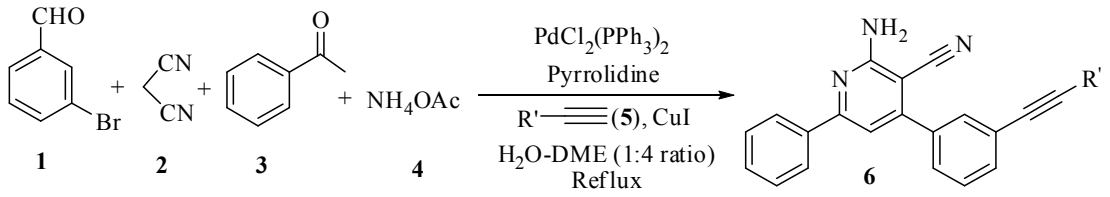
Entry	Catalyst	Solvent	Base	Time(hrs)/Temp(°C)	Yield[b] (%)
1	$PdCl_2(PPh_3)_2$	H_2O	K_2CO_3	24.0; reflux	5
2	$PdCl_2(PPh_3)_2$	THF	K_2CO_3	16.0; reflux	48
3	$PdCl_2(PPh_3)_2$	Dioxane	K_2CO_3	12.0; reflux	56
4	$PdCl_2(PPh_3)_2$	DME	K_2CO_3	9.0; reflux	64
5	$PdCl_2(PPh_3)_2$	H_2O-DME (1:4 ratio)	K_2CO_3	7.0; reflux	71

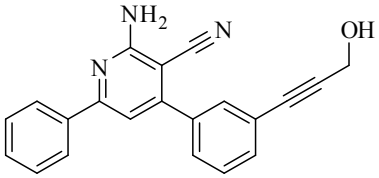
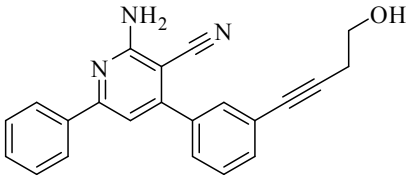
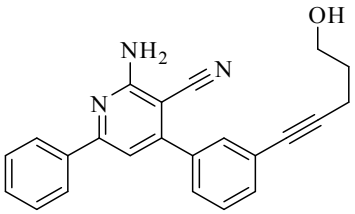
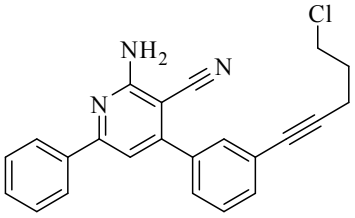
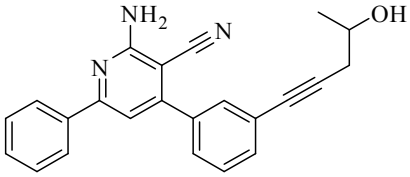
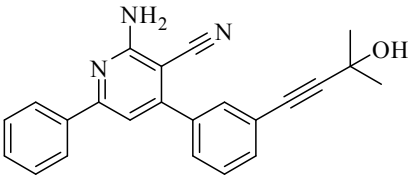
6	$PdCl_2(PPh_3)_2$	DMF	K_2CO_3	8.0; 90-100	62
7	$PdCl_2(PPh_3)_2$	DMSO	K_2CO_3	6.0; 90-100	65
8	$PdCl_2(PPh_3)_2$	H_2O-DME (1:4 ratio)	Na_2CO_3	9.0; reflux	56
9	$PdCl_2(PPh_3)_2$	H_2O-DME (1:4 ratio)	Et_3N	6.0; reflux	78
10	$PdCl_2(PPh_3)_2$	H_2O-DME (1:4 ratio)	Pyrrolidine	4.0; reflux	91
11	$Pd(PPh_3)_4$	H_2O-DME (1:4 ratio)	Pyrrolidine	10; reflux	68
12	$Pd(PPh_3)_4$	H_2O-DME (1:4 ratio)	Pyrrolidine	8.0; reflux	72
13	$Pd(dppf)Cl_2$	H_2O-DME (1:4 ratio)	Pyrrolidine	7.0; reflux	68
14	$20\%Pd(OH)_2$[c]	H_2O-DME (1:4 ratio)	-	6.0; reflux	75

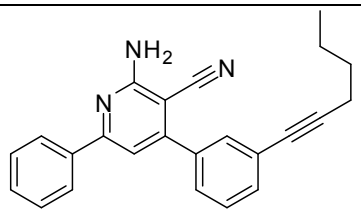
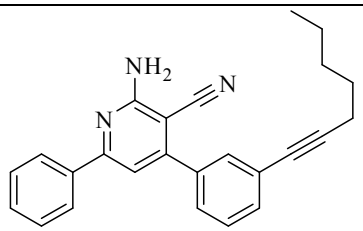
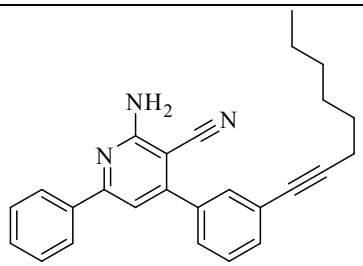
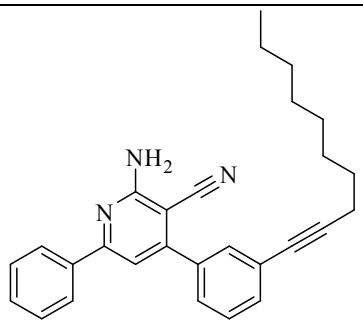
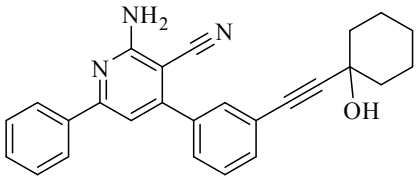
[a]**Reagents and conditions**: 3-bromobenzaldehyde **1** (10.0 mmol), malononitrile **2** (11.0 mmol), acetophenone **3** (11.0 mmol), NH_4OAc **4** (20.0 mmol), base (5.0 mmol); prop-2-yn-1-ol **5a** (15.0 mmol), $PdCl_2(PPh_3)_2$ (0.002 mmol)and CuI (0.005 mmol) in a solvent or mixture of solvents (10 vol) at specified temperature; [b] Isolated yield; [c] Act as catalyst cum base.

Having prepared 2-amino-4-(3-(3-hydroxyprop-1-ynyl)phenyl)-6-phenylnicotinonitrile (**6a**) through heterocyclization followed by Sonogashira reaction efficiently under optimized reaction conditions, it is further investigate the further substrate scope and generality of this process using various terminal alkynes i.e. **6a-k** and the obtained results are presented in Table 2. From this study, it is found that various functional groups of terminal alkyne substrates (**6a-k**) are well tolerated to the reaction conditions and provided good yields of the desired products (**6a-k**).

Table 2. MCR based synthesis of 2-amino-4-(3-(alkynyl)phenyl)-6-phenylnicotinonitriles (**6**) *via* heterocyclization followed by Sonogashira reaction[a]



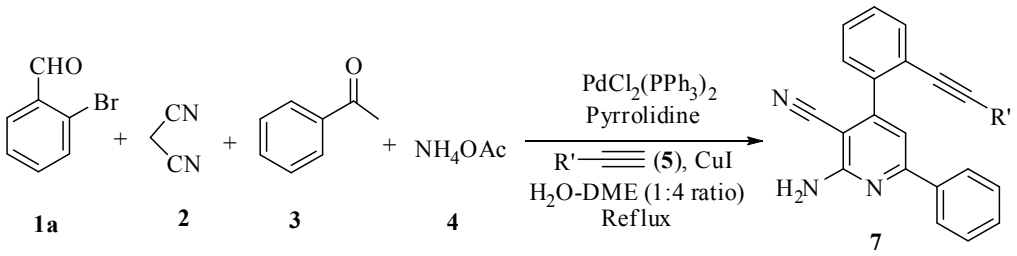
Entry	R' of terminal alkyne (5) substrate	Product (6)	Time (hrs)	Yield[b] (%)	R_f[c]
1	CH_2OH (**5a**)	 **6a**	4.0	91	0.4
2	CH_2CH_2OH (**5b**)	 **6b**	4.0	89	0.45
3	$CH_2CH_2CH_2OH$ (**5c**)	 **6c**	3.5	85	0.5
4	$CH_2CH_2CH_2Cl$ (**5d**)	 **6d**	3.5	87	0.7
5	$CH_2CH(OH)CH_3$(**5e**)	 **6e**	4.0	89	0.4
6	(OH) C $(CH_3)_2$ (**5f**)	 **6f**	5.0	85	0.4

7	$CH_2(CH_2)_2CH_3$ (**5g**)	 **6g**	4.5	88	0.75
8	$CH_2(CH_2)_3CH_3$ (**5h**)	 **6h**	4.5	86	0.8
9	$CH_2(CH_2)_4CH_3$ (**5i**)	 **6i**	4.5	88	0.85
10	$CH_2(CH_2)_6CH_3$ (**5j**)	 **6j**	4.5	87	0.85
11	1-Hydroxy-1-cyclohexyl (**5k**)	 **6k**	5.0	85	0.45

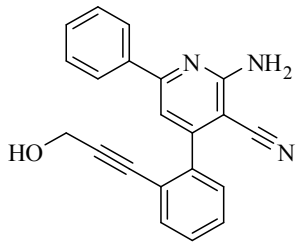
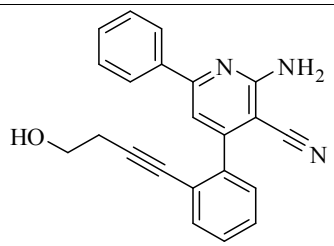
[a]**Reagents and conditions**: 3-bromobenzaldehyde **1** (10.0 mmol), malononitrile **2** (11.0 mmol), acetophenone **3** (11.0 mmol), NH_4OAc **4** (20.0 mmol), Pyrrolidine (5.0 mmol); terminal alkynes **5a-k** (15.0 mmol), $PdCl_2(PPh_3)_2$ (0.002 mmol)and CuI (0.005 mmol) in a mixture of H_2O-DME (1:4 ratio) (10 vol) at reflux; [b] Isolated yield.; [c] Retention factor: 40% EtOAc in PE.

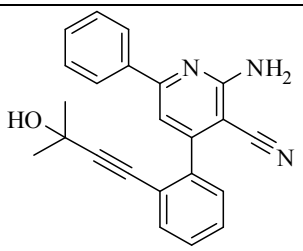
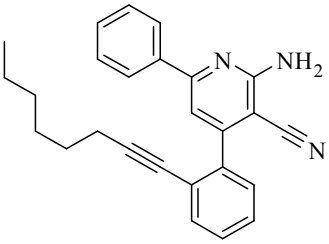
The results obtained reveal that 3-bromobezaldehyde (**1**) can act as an efficient key starting material in the formation of 2-amino-4-(3-(alkynyl)phenyl)-6-phenylnicotinonitriles (**6a-k**) *via* heterocyclization followed by Sonogashira reaction (Table 2); further it is found that the scope of the same reaction with 2-bromobenzandehyde (**1a**) as a key starting material resulted in the production of desired products(**7a-d**) presented in Table 3. The study reveal that lower yields of final products (**7a-d**) are obtained due to steric hindrance in the course of the C-C coupling process. It is found that lower yields of products (**7a-d**) are offered in all cases (entries 1-4, Table 3) irrespective of the nature of substituents present on terminal alkyne substrates (**5a**, **5b**, **5f** and **5i**) when 2-bromobenzandehyde (**1a**) is used instead of 3-bromobenzandehyde (**1**).

Table 3: MCR based synthesis of 2-amino-4-(2-(**alkynyl**)phenyl)-6-phenylnicotinonitriles (**7**) *via* heterocyclization followed by Sonogashira reaction[a]



1a **2** **3** **4** **7**

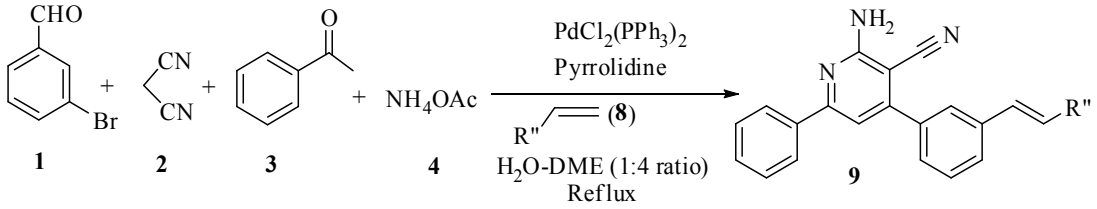
Entry	R' of terminal alkyne(5) substrate	Product (7)	Time (hrs)	Yield[b] (%)	R_f[c]
1	CH_2OH (**5a**)	 **7a**	4.5	81	0.35
2	CH_2CH_2OH (**5b**)	 **7b**	4.5	78	0.4

3	$(OH)C(CH_3)_2$ (**5f**)	 **7c**	5.5	76	0.4
4	$CH_2(CH_2)_4CH_3$ (**5i**)	 **7d**	5.0	79	0.85

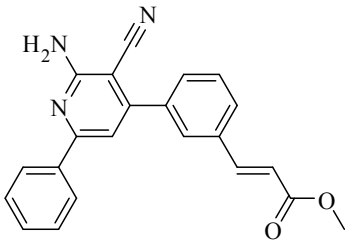
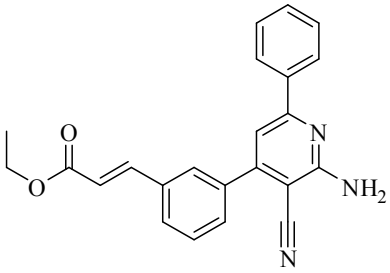
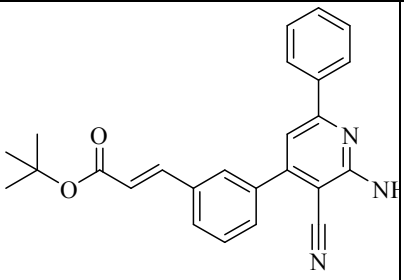
[a] **Reagents and conditions**: 2-bromobenzaldehyde **1a** (10.0 mmol), malononitrile **2** (11.0 mmol), acetophenone **3** (11.0 mmol), NH_4OAc **4** (20.0 mmol), Pyrrolidine (5.0 mmol); terminal alkynes **5a/b/f/i** (15.0 mmol), $PdCl_2(PPh_3)_2$ (0.002 mmol)and CuI (0.005 mmol) in a mixture of H_2O-DME (1:4 ratio) (10 vol) at reflux; [b] Isolated yield.; [c] Retention factor: 40% EtOAc in PE.

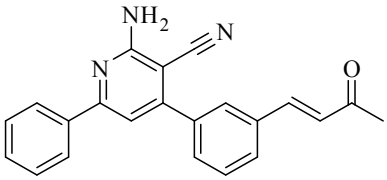
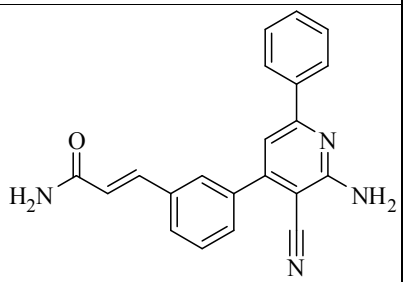
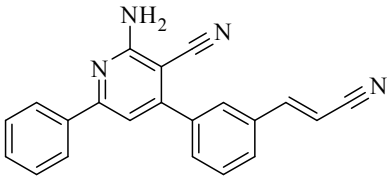
Further substrate scope is investigated to assess the generality of the proposed MCR under Heck reaction conditions as shown in Table 4. Towards this direction, a mixture of 3-bromobenzaldehyde (**1**) malononitrile (**2**), acetophenone (**3**), NH_4OAc (**4**) and methyl acrylate (**8a**) in presence of $PdCl_2(PPh_3)_2$ and pyrrolidine in a mixture of H_2O-DME (1:4 ratio) (10 vol) are stirred for 5.0 hrs at reflux temperature to obtain product **9a.** The yield (88%) of product **9a** is good (entry 1, Table 4). Further, a series of terminal alkenes i.e. **8b-f** are tested for the preparation of desired alkenyl-substituted pyridine derivatives (**9b-f**) and found that various sensitive functional groups of terminal alkenes (**8a-f**) are well tolerated to the reaction conditions and provided good yields of the desired products (**9b-f**) (entries 2-6, Table 4). Based on the obtained ^1H NMR data, all the prepared 2-amino-4-(3-(alkenyl)phenyl)-6-phenylnicotinonitrile derivatives (**9a-f**) are confirmed as '*E'* isomers (*J*= 16.0 - 16.5 Hz).

Table 4: MCR based synthesis of 2-amino-4-(3-(alkenyl)phenyl)-6-phenylnicotinonitriles (**9**) *via* heterocyclization followed by Heck reaction[a]



1 **2** **3** **4** **9**

Entry	R'' of terminal Alkene (8) substrate	Product (9)	Time (hrs)	Yield[b] (%)	R_f[c]
1	$COOCH_3$ (**8a**)	 **9a**	5.0	88	0.55
2	$COOCH_2CH_3$ (**8b**)	 **9b**	5.5	82	0.55
3	$COOC(CH_3)_3$ (**8c**)	 **9c**	5.0	83	0.6

4	$COCH_3$ (**8d**)	 **9d**	5.5	86	0.4
5	$CONH_2$ (**8e**)	 **9e**	5.5	87	0.1
6	CN (**8f**)	 **9f**	4.5	85	0.3

[a]**Reagents and conditions**: 3-bromobenzaldehyde **1** (10.0 mmol), malononitrile **2** (11.0 mmol), acetophenone **3** (11.0 mmol), NH_4OAc **4** (20.0 mmol), pyrrolidine (5.0 mmol) and terminal alkenes **8a-f** (16.0 mmol), $PdCl_2(PPh_3)_2$ (0.002 mmol) in a mixture of H_2O-DME (1:4 ratio) (10 vol) at reflux; [b] Isolated yield.; [c] Retention factor: 30% EtOAc in PE.

4. Conclusions

In summary, general syntheses of a new library of structurally diverse alkynyl/alkenyl-substituted pyridine derivatives (**6**, **7** & **9**) have been accomplished *via* heterocyclization and subsequent Pd-mediated structural elaboration under Sonogashira and Heck coupling reactions in single step. Interestingly, the Heck coupling with terminal alkenes takes place stereoselectively with exclusive formation of the *E*-isomers. This MCR strategy offers advantages like easy isolation of products, simple construction of diversity oriented library of highly substituted pyridine derivatives and wide applications in the synthesis of valuable heterocyclic synthetic precursors bearing carbon-carbon triple and double bond functionalities other than the present reported molecules. The prepared synthetic precursors

will be suitable for further functional group transformations in the development of new and novel heterocyclic molecules of potential pharmacological interest.

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References

1. A. Bogdanowicz, H. Foks, K. Gobis, A. Kędzia, E. Kwapisz, A. Olczak and M. L. Główka, *J. Heterocycl. Chem.*, 2013, **50**, 544-550.
2. P. Patel, S. Koregaokar, M. Shah and H. Parekh, *Farmaco,* 1996, **51**, 59-63.
3. F. Manna, F. Chimenti, A. Bolasco, A. Filippelli, A. Palla, W. Filippelli, E. Lampa and R. Mercantini, *Eur. J. Med. Chem.,* 1992, **27**, 627-632.
4. K. R. Kim, S. D. Rhee, H. Y. Kim, W. H. Jung, S. D. Yang, S. S. Kim, J. H. Ahn and H. G. Cheon, *Eur. J. Pharmacol.,* 2005, **518**, 63-70.
5. T. Godfraind, R. Miller and M. Wibo, *Pharmacol. Rev.,* 1986, **38**, 321-416.
6. J. J. Baldwin, *U S patent*, No.4000282, December, 28, 1976.
7. H. A. El-Sayed, A. H. Moustafa, E. Z. Haikal, R. A. El-Halawa and E. S. H. El Ashry, *Eur. J. Med. Chem.*, 2011, **46**, 2948-2954.
8. Z. Pinghu, Y. Xiaohui, Z. Luyong, Z. Yonghong and W. Zhimin, *China patent,* No. CN102875462A, 16th Jan 2013.
9. J. H. Ahn, H. M. Kim, S. H. Jung, S. K. Kang, K. R. Kim, S. D. Rhee, S. D. Yang, H. G. Cheon, S. S. Kim, *Bioorg. Med. Chem. Lett.,* 2004, **14**, 4461-4465.
10. T. Murata, M. Shimada, S. Sakakibara and T. Yoshino et al., *Bioorg. Med. Chem. Lett.,* 2004, **14**, 4019-4022.
11. M. T. Bilodeau, M. E. Duggan, J. C. Hartnett, C. W. Lindsley, Z. Wu and Z. Zhao, *U S patent,* No.7579355 B2, Aug. 25, 2009.
12. L. N. Tumey, N. Bhagirath, A. Brennan, N. Brooijmans, J. Lee, X. Yang, D. H. Boschelli, *Bioorg. Med. Chem.*, 2009, **17**, 7933-7948.

13. D. Meibom, A. Vakalopoulos, B. Albrecht-Kiipper, K. Zimmermann, P. Nell and F. SiiBmeier, *U S patent*, No. 8,426,602 B2, 23rd Apr.2013.
14. 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 and A. P. Ijzerman, *J. Med. Chem.,* 2008, **51**, 4449-4455.
15. S. Ayvaz, M. Çankaya, A. Atasever and A.Altuntas, *J. Enzyme. Inhib. Med. Chem.,* 2013, **28**, 305-310.
16. K. R. Kim, S. D. Rhee, H. Y. Kim, W. H. Jung, S. D. Yang, S. S. Kim, J. H. Ahn and H. G. Cheon, *Eur. J. Pharmacol.,* 2005, **518**, 63-70.
17. J. Ji , W. H. Bunnelle, D. J. Anderson, C. Faltynek, T. Dyhring, P. K. Ahring, L. E. Rueter, P. Curzon, M. J. Buckley, K. C. Marsh, A. Kempf-Grote and M. D. Meyer, *Biochem. Pharmacol.,* 2007, **74**, 1253-1262.
18. A. Samadi, M. Chioua, I. Bolea, C. de los Ríos, I. Iriepa, I. Moraleda, A. Bastida, G. Esteban, M. Unzeta, E. Gálvez and J. Marco-Contelles, *Eur. J. Med. Chem.*, 2011, **46**, 4665-4668.
19. T. M. Keck, M. F. Zou, P. Zhang, R. P. Rutledge and A. H. Newman, *ACS Med. Chem. Lett.*, 2012, **3**, 544–549.
20. H. Zhao, M. D. Serby, Z. Xin, B. G. Szczepankiewicz, M. Liu, C. Kosogof, B. Liu, L. T. J. Nelson, E. F. Johnson, S. Wang, T. Pederson, R. J. Gum, J. E. Clampit, D. L. Haasch, C. Abad-Zapatero, E. H. Fry, C. Rondinone, J. M. Trevillyan, H. L. Sham and G. Liu, *J. Med. Chem.*, 2006, **49**, 4455–4458.
21. T. R. K. Reddy, R. Mutter, W. Heal, K. Guo, V. J. Gillet, S. Pratt and B. Chen, *J. Med. Chem.*, 2006, **49**, 607–615.
22. W. Brandt, L. Mologni, L. Preu, T. Lemcke, C. Gambacorti-Passerini and C. Kunick, *Eur. J. Med. Chem.,* 2010, **45**, 2919-2927.
23. V. Raghukumar, D. Thirumalai, V. T. Ramakrishnan, V. Karunakaran and P. Ramamurthy, *Tetrahedron*, 2003, **59**, 3761-3768.
24. N. Li, S. L. Lai, P. Wang, F. Teng, Z. Liu, C. Lee and S. T. Lee, *Appl. Phys. Lett.*, 2009, **95**, 133301.
25. D. Spitzner, *Pyridines,* In *Science of Synthesis*, Vol. 15; Black, D., Ed.; Georg Thieme Verlag: Stuttgart, **2004**, 11.
26. Md. N. Khan, S. Pal, S. Karamthulla and L. H. Choudhury, *RSC Adv.*, 2014, **4**, 3732-3741

27. B. Jiang, X. Wang, F. Shi, S. –J. Tu and G. Li. *Org. Biomol. Chem.*, 2011, **9**, 4025-4028.
28. F. Liéby-Muller, C. Allais, T. Constantieux and J. Rodriguez, *Chem. Commun.,* 2008, 4207–4209.
29. L. Shen, S. Cao, J. Wu, J. Zhang, H. Li, N. Liu and X. Qian, *Green Chem*., 2009, **11**, 1414–1420.
30. C. Allais, T. Constantieux and J. Rodriguez, *Chem. Eusr. J.,* 2009, **15**, 12945–12948.
31. J. Liu, C. Wang, L. Wu, F. Liang and G. Huang, *Synthesis,* 2010, **24**, 4228–4234.
32. M. Syamala, *Org. Prep. Proced. Int.*, 2005, **37**, 103-171.
33. T. J. Donohoe, J. A. Basutto, ,J. F. Bower, J. Zhu and H. Bienaymé, Eds. *Multicomponent Reactions;* Wiley-VCH: Weinheim, Germany, 2005.
34. A. Rathi, *Org. Lett.,* 2011, **13**, 1036–1039 and references cited therein.
35. Z. Geng, Y. Ju, Q. Wang, W.Wang and Z. Li, *RSC Adv.*, 2013, **3**, 14798-14806.
36. M. S.Singh and S. Chowdhury, *RSC Adv.*, 2012, **2**, 4547-4592.
37. U. Sharma, S. Ahmed and R. C. Boruah, *Tetrahedron Lett.,* 2000, **41**, 3493-3495.
38. S. Brauch, S. S. van Berkel and B. Westermann, *Chem. Soc. Rev.,* 2013, **42**, 4948-4962.
39. K. Shekarrao, P. P. Kaishap, S. Gogoi and R.C. Boruah., *RSC Adv.*, 2014, DOI: 10.1039/C3RA46722H
40. For review see: A. Domling and I. Ugi, *Angew. Chem., Int. Ed.,* 2000, ***39***, 3168-3210.
41. For recent review, see: B. B. Toure and D. G. Hall, *Chem. Rev.,* 2009, ***109***, 4439-4486.
42. H. Bienayme, C. Hulme, G. Oddon and P. Schmitt, *Chem. Eur. J.,* 2000, **6,** 3321-3329.
43. B. M. Trost, *Science*, 1991, 254, 1471-1477.
44. L. F. Tietze, *Chem. Rev*., 1996, 96, 115-136.
45. E.Yamaguchi , F. Shibahara and T. Murai, *Chem. Eur. J.,* 2010, **16**, 12746-12753.
46. E. Yamaguchi, F. Shibahara, and T. Murai, *J. Org. Chem.*, 2011, **76**, 6146–6158.
47. D. M. D'Souza and T. J. J. Müller, *Nature Protocols,* 2008, **3**, 1660-1665.
48. F. Yu, X. D. Lian and S. M. Ma, *Org. Lett.,* 2007, **9**, 1703 –1706.
49. K. T. Yip, N. Y. Zhu and D. Yang, *Org. Lett.* 2009, **11**, 1911 –1914.
50. J. J. Li, G. W. Gribble, In '*Palladium in Heterocyclic Chemistry*', Pergamon, Oxford, 2000, pp. 183.
51. J. Namyslo and D. E. Kaufman, *Synlett.*, 1999, **6**, 804-806 and references cited therein.
52. N. Robert, C. Hoarau, S. Ce´lanire, P. Ribe´reau, A. Godard, G. Que´guiner and F. Marsais, *Tetrahedron*, 2005, **61**, 4569-4576.
53. P. Nussbaumer, I. Leitner, K. Mraz and A. Stuetz, *J. Med. Chem.*,1995, **38**, 1831–1836.

54. I. N. Houpis, D. Shilds, U. Nettekoven, A. Schnyder, E. Bappert, K. Weerts, M. Canters and W. Vermuelen, *Org. Process Res. De*V., 2009, **13**, 598–606.
55. H. Li, Z. Xia, S. Chen, K. Koya, M. Ono and L. Sun, *Org. Process Res. De*V., 2007, **11**, 246–250.
56. P. Sun, X. Qu, T. Li, Y. Zhu, H. Yang, Z. Xing and J. Mao, *Synlett.,* 2012, **23**, 150-154.