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ARTICLE TYPE

Silver(I)-*N*-heterocyclic carbene catalyzed multicomponent reactions: a facile synthesis of multisubstituted pyridines

Shravankumar Kankala,[a] Ramakanth Pagadala,[a] Suresh Maddila,[a] Chandra Sekhar Vasam*[b,c] and Sreekantha B. Jonnalagadda*[a]

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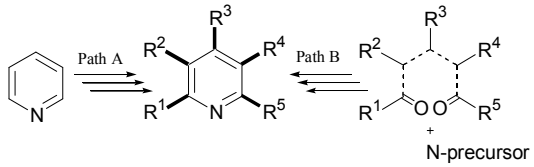
A four component one-pot reaction between aromatic aldehyde, malononitrile, ammonium acetate and ketone mediated by Ag(I) *N*-heterocyclic carbene to produce multisubstituted and fused pyridines in short reaction time (~10 min) in ethanol at room temperature is described.

Substituted pyridines are building blocks for many pharmaceuticals, agrochemicals, organic intermediates, supramolecules, nanoparticles, OLED, solar cells and polymers.[1] The two well-known synthetic pathways to afford substituted pyridines are either by modifying the pyridine core (Scheme 1, Path A)[2] or by condensing the appropriately substituted (mostly carbonyl and amine functionalities) precursors (Scheme 1, Path B).[3]



Scheme 1 Multicomponent approach to multifunctionalized pyridines.

While the substitution reactions of the pyridine core path-A frequently suffer from the low reactivity of the electron-deficient heteroaromatic system, the synthetic protocols reported for path-B in most cases are not eco-friendly. In this context, catalyzed (metal or organo) multicomponent reactions (MCR), a special class of tandem reactions, have emerged as highly atom and resource efficient to obtain substituted pyridines in one-pot.[3g,4]

Despite the myriad of organic transformations using transition metal based catalysts,[5] recently organocatalysis[6] has witnessed a spectacular rise in homogeneous catalysis. At this juncture it has been envisaged that the cooperative dual catalysis[7] i.e. combining transition metal catalysis and organocatalysis enables unprecedented organic transformations not currently possibly by use of each catalytic systems alone (acidic/basic). Nevertheless, one of the key challenges is catalysis compatibility i.e. the search of metal and organic catalysts pair that can work together cooperatively without quenching each other i.e. preventing the possible metal coordination to organocatalysts.[7] Various efforts have been made to overcome metal/organocatalysts, quenching task such as the (**i**) use of additional coordinating ligands to minimize the coordination of organocatalysts, (**ii**) sequential addition of catalysts and (**iii**) use of early transition metals.[7f-h]

However, recent research reveals that the right selection of metal/organo catalysts pair[8] facilitates the cooperative dual catalysis without the need for above mentioned precautions (**i**), (**ii**) & (**iii**). Specifically the compatibility and cooperativity between metal ion and organo *N*-heterocyclic carbenes (organo-NHC) was found to be highly effective to achieve unprecedented organic transformations particularly under 'weak' base conditions.[8] While the metal ion and *in situ* generated organo-NHC catalyst pair was found to co-exist with a significant level of concentrations under weak base conditions, metal-to-NHC ligand coordination was noticed under strong base conditions.

We are interested to investigate the possible cooperativity between Ag(I) and organo-NHC in catalyzing a multicomponent one-pot reaction of aromatic aldehyde, malononitrile, ammonium acetate and ketone for efficient synthesis of highly substituted pyridines. According to the previous reports, the metal and organo-NHC catalysts were brought into the reaction system from the two individual precursors.[8] However, the generation of organo-NHC from the corresponding imidazolium salt using an external base (strong/mild) may possibly hamper the aldehyde involving MCR. Mild base catalyzed aldol condensation reactions are also known.[9] We would like to employ the pre-synthesized Ag(I)-NHC complexes as source for both organo-NHCs and Ag(I) ions for the MCR due to the following reasons.

i) Ag(I)-NHC have been recognized as efficient organo-NHC delivery agents in solution,[10] despite of their prime role as NHC transfer agents to other metal ions.[11]

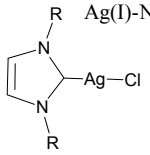
ii) The reported equilibrium between ionic and neutral forms of pre-synthesized Ag(I)-NHCs[10,11] in solution and the soft/labile nature of Ag(I)-NHC bond could facilitate the intermediary of both Lewis basic organo-NHC and Lewis acidic Ag(I) catalysts for cooperative catalysis. (i.e. it is not necessary to introduce Ag(I) and NHC catalyst precursors separately for cooperative catalysis since Ag(I)-NHC bond is labile in solution).

iii) Ag(I)-NHCs can be obtained simply by mixing Ag_2O with imidazolium salt without the need for additional base and solvent pre-treatment.[11]

The aptness of organo-NHC catalysis is mainly attributed to their reactivity umpolung.[12] While the NHC lone pair is highly

nucleophilic, the empty *p*-orbital is able to accept electron density and stabilizes the accumulation of negative charge in the vicinity i.e. reactivity umpolung.[12] As a consequence, the use of NHCs as Lewis/Brønsted base catalysts facilitate the formation various reactive modes (acyl anions, homoenolates, acylvinyl anions and enolate) to produce carbo- and heterocyclic compounds. Furthermore, NHCs and their precursors (imidazolium salts) are good example of conjugate acid-base pairs. Proton-shuttling strategy using NHCs as brønsted base in catalysis is also a well-known phenomenon. Based on this information, previously Wu and co-workers reported cooperativity between Ag(I) and organo-NHC catalysts during the umpolung reaction of hydrazides with α, β-unsaturated aldehydes.[13]

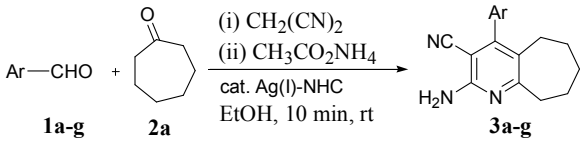
In furtherance of our research work in the fields of (**i**) MCRs[14] and (**ii**) NHCs[11,15] herein we report for the first time the use of Ag(I)-NHCs as pre-catalysts i.e. as source of Ag(I) ion and organo-NHC delivery agents (Fig. 1) to promote a click-type fast MCR protocol for the synthesis of multisubstituted and fused pyridines at room temperature (RT) in ethanol.



Ag(I)-NHC (**a**): R = mesityl
(**b**): R = *iso*-propyl
(**c**): R = cyclohexyl
(**d**): R = *tert*-butyl
(**e**): R = adamentyl
(**f**): R = 2,6-di^{i}propylphenyl

Fig. 1 Ag(I)-NHCs used in the present work.

Initially we choose to investigate a four component sequential one-pot reaction (MCR) between malononitrile, aromatic aldehyde (**1a**), ammonium acetate and ketone (**2a**) in ethanol and the scope of a variety of potential catalyst materials. The details of the reaction and the results are given in Scheme 2 and Table 1 respectively.



1a-g **2a** **3a-g**

Ar = 4-$OCH_3C_6H_4$ (**3a**), 4-BrC_6H_4 (**3b**), C_6H_5 (**3c**), 2-ClC_6H_4 (**3d**), 2-BrC_6H_4 (**3e**), 2-$OCH_3C_6H_4$ (**3f**), 4-$N(CH_3)_2C_6H_4$ (**3g**).

Scheme 2 Synthesis of multifunctional pyridines (**3a-g**).

There was no MCR sequence observed without any catalyst (Table 1, entry1). There was also no progress in the above MCR at RT conditions, when silver salts, AgOAc, AgOTf, $AgSbF_6$ or $AgNO_3$ were employed as catalysts (Table 2, entries 2-5). However, when Ag(I)-NHC ((**a**), Fig. 1) was employed a catalyst, the results were impressive producing the substituted pyridine (**3a**) selectively just in 10 minutes and in good yields (94%, Table 1, entry 6). On the other hand, previous reports describe that a similar MCR sequence (aldehydes, ketones, malononitrile, and ammonium acetate) of both catalyzed[16] and uncatalyzed processes[17] was accomplished only under refluxing or microwave conditions and longer reaction times. This information indicates the efficiency of Ag(I)-NHC pre-catalyst in mediating the MCR. The solid product of **3a** obtained in our work was further identified and quantified on the basis of its analytical, spectral and single crystal X-ray crystallographic data (ESI). The single crystals of **3a** were grown from ethyl acetate/*n*-hexane. The ORTEP drawing of **3a** is show in Fig. 2.

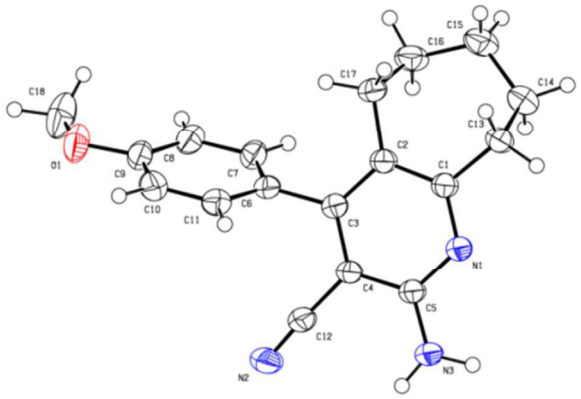
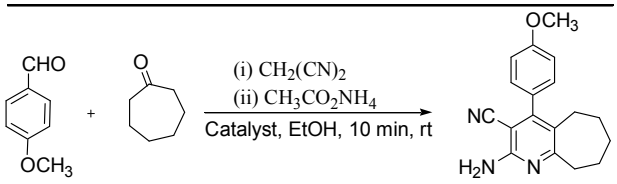


Fig. 2 The ORTEP diagram of **3a**.

Table 1 Optimization of reaction parameters for the synthesis of **3a**.



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

Entry	Catalyst	Yield (%)[a]
1	No Catalyst	--
2	AgOAc	--
3	AgOTf	--
4	$AgSbF_6$	--
5	$AgNO_3$	--
6	Ag(I)-NHC (**a**)	94
7	Ag(I)-NHC (**b**)	86
8	Ag(I)-NHC (**c**)	90
9	Ag(I)-NHC (**d**)	90
10	Ag(I)-NHC (**e**)	88
11	Ag(I)-NHC (**f**)	91
12	Organo-NHC	32
13	Organo-NHC + AgOAc	84
14	Organo-NHC + AgOTf	80

[a] GC Yields

Continuing the work, we have also investigated the above MCR using various other Ag(I)-NHC catalysts (**b-f**, Fig. 1) which have different N-substituents on NHC. The results summarised in Table 1 (Entries 7-11) show higher yields of product **3a** with Ag(I)-NHC (**a**) (Table 1, entry 6). Results of the effect of Ag(I)-NHC (**a**) concentration on the reaction yields of **3a** are also summarised (ESI). The catalyzed MCRs of present study in ethanol are found to be slightly exothermic in the beginning as observed in other works. It is also important to note that the above catalyzed reaction was observed to be sluggish and non-

selective in non-protic solvents, CH_2Cl_2, THF and CH_3CN and finally ended up with mixture of products. This information outlines that the choice of solvent is also one of the key factors in this catalyzed MCR.

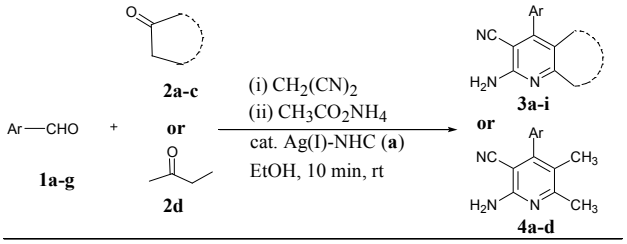
The data presented in Table 1 suggests the possible mediation of MCR by both Ag(I) and free organo-NHC, which were released from soft/labile Ag(I)-NHC in the MCR. To support this hypothesis, we have conducted an additional experiment of the title reaction using a pre-generated free organo-NHC 1,3-dimesitylimidazol-2-ylidene that obtained from the corresponding imidazolium salt. We have noticed that the Ag(I) free organo-NHC is also able to facilitate the formation of substituted pyridines under inert conditions, but the reaction was relatively slow and the yields of pyridine were poor (Table 1, entry 12). We have also conducted another experiment to confirm the role of silver(I) in the free organo-NHC (1,3-dimesitylimidazol-2-ylidene) mediated MCR. When the silver salts (AgOAc or AgOTf) were introduced to the organo-NHC (1,3-dimesitylimidazol-2-ylidene) mediated MCR during the reaction course, the MCR was accomplished fast and improved the yield (Table 1, entry 13 & 14) than the free organo-NHC alone mediated MCR. Besides, in order to expand the the scope of this MCR, we have also investigated the abilities of various acid-base catalyst combinations (i) Ag(I) salts with bases (DABCO, DBU, TEA, K_2CO_3, NaOAc) i.e. other than NHCs, (ii) other Lewis acids (Cu(II), Sc(III), Al(III), Ni(II)) with NHC, (iii) Lewis acids other than Ag(I) with bases other than NHCs. The results of MCR obtained with above catalyst combinations are summarized in ESI (Table S1). Only Knoevenagel condensed products instead of MCR products (pyridines) were observed when the MCR was conducted in the presence of (i) Ag(I) and bases other than NHC (ESI) and (ii) other Lewis acids and bases (not Ag(I) and NHC). On the other hand, the catalyst combination of NHC and Lewis acids other than Ag(I) has also facilitated the MCR but produced the pyridine **3a** in less yields (ESI). At this juncture, it is rational to propose that there could be a effective cooperative catalysis between Ag(I) and organo-NHC catalysts those were released from labile Ag(I)-NHC during the course of MCR in solution. On the other hand, un-dissociable metal-NHCs formation suppressed the dual catalysis and decreased the yields of MCR products (ESI) when Lewis acids other than Ag(I) were employed as partner to NHC.

Employing the same reaction conditions for the synthesis of **3a** (RT, Ag(I)-NHC (**a**) (2 mol%, 10 min, ethanol), we investigated the scope of the reaction with a variety of structurally different aldehydes (**1b-g**) in combination with cyclic (**2a-c**) and acyclic ketones (**2d**), malononitrile and ammonium acetate for the four component condensation reaction. The results are depicted in Table 2. The substrates of MCR bearing electron donating or electron-withdrawing groups on the aromatic ring proceeded smoothly and formed the corresponding multisubstituted pyridines in good yields under the chosen conditions.

Structures of the substituted pyridines **(3a-i & 4a-d,** Table 2**)** were established on the basis of elemental analysis and spectral data (^{1}H NMR, ^{13}C NMR and Mass). The details of the product characterization are presented in the experimental and ESI.

Literature reports reveal that pyridines with 2,3,4,5 and 6 substitutions still remain a challenge to synthesise.[3,4] An examination of the results and conditions depicted in Table 2 for the selective synthesis of multisubstituted pyridines (**3a-i** & **4a-d**) suggests our yields are comparable or even better than those for the closely related multisubstituted pyridines in earlier reports[3,4] by following metal or organo or base catalyzed MCRs, or the methodologies following the Scheme 1.

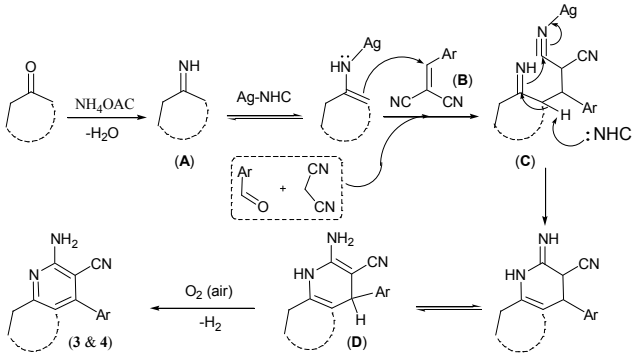
Table 2 Synthesis of multisubstituted pyridines by Ag(I)-NHC (**a**) (**3a-i & 4a-d**).[a]



Entry	Ar (**1a-g**)	Ketone	Product	yield (%)[b]
1	4-$OCH_3C_6H_4$ (**1a**)	(**2a**)	**3a**	94
2	4-BrC_6H_4 (**1b**)	**2a**	**3b**	90
3	C_6H_5 (**1c**)	**2a**	**3**c	92
4	2-ClC_6H_4 (**1d**)	**2a**	**3**d	89
5	2-BrC_6H_4 (**1e**)	**2a**	**3**e	83
6	2-$OCH_3C_6H_4$ (**1f**)	**2a**	**3**f	90
7	4-$N(CH_3)_2C_6H_4$ (**1g**)	**2a**	**3**g	90
8	**1c**	(**2b**)	**3h**	86
9	**1c**	(**2c**)	**3i**	91
10	**1c**	(**2d**)	**4a**	92
11	**1d**	**2d**	**4b**	88
12	**1e**	**2d**	**4c**	92
13	**1a**	**2d**	**4d**	92

[a] All products were characterized by NMR and mass spectral analysis.
[b] Isolated yields.

Based on previous reports[16,17] and current results in the MCR synthesis of multisubstituted pyridines, a plausible mechanism is proposed in Scheme 3 by emphasizing the cooperativity between Ag(I) and organo-NHC catalysts. The reaction may proceed *via* forming enamine (**A**) (condensed product of ketone and ammonium acetate), and then activated by Ag(I), which then reacts with alkylidenemalononitrile (**B**) (Knoevenagel condensed product of aldehyde with malononitrile) to give intermediate (**C**) (Michael adduct). The Michael adduct then undergoes cycloaddition and isomerisation to give 1,4-dihydropyridine (**D**). The subsequent oxidative aromatization of 1,4-dihydropyridine (**D**) under air atmosphere will produce the desired multisubstituted and fused pyridines (**3a-i & 4a-d**) as shown in Scheme 3. Tracking of the H of NH_2 with D_2O exchange study and the results of D_2O exchange are depicted in the ESI. Furthermore, ^{15}NNMR (GHSQC) data has also confirmed the formation of the amino pyridine product.



Scheme 3 Possible mechanism for the formation of multisubstituted pyridines *via* catalyzed by Ag(I)-NHC.

Conclusions

In conclusion, we have demonstrated that using pre-synthesized Ag(I)-NHCs as source of both Ag(I) and organo-NHC catalyst delivery agents, a room temperature and click-type fast MCR protocol can be put into practice for the synthesis of multisubstituted and fused pyridines from simple starting materials in eco-friendly ethanol. Further studies are warranted to address the nature of the active catalysts under these conditions. The soft and labile nature of Ag(I)-NHC bond and the reported equilibrium between neutral and ionic forms of Ag(I)-NHCs in solution[11a-c] indicate the possible intermediacy role of free NHC and as well as Ag(I) cation in MCR for the cooperative dual catalysis. Our results indicates that it is not necessary to introduce Ag(I) and NHC catalyst precursors separately into MCR and the use of pre-synthesized Ag(I)-NHCs is a good choice for cooperative dual catalysis.

Acknowledgments

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Experimental Section

General

All commercially available reagents were used without further purification. Reaction solvents were dried by standard methods before use. Purity of the compounds was checked by TLC using Merck 60F254 silica gel plates. Elemental analyses were obtained with an Elemental Analyser Perkin-Elmer 240C apparatus. ^{1}H and ^{13}C NMR spectra were recorded with a Mercuryplus 400 spectrometer (operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C); chemical shifts were referenced to TMS. The FT-IR spectroscopy of samples was carried out on a Perkin Elmer Precisely 100 FT-IR spectrometer in the 400-4000 cm^{-1} region. ESI-MS spectra were determined on a LCQ ion trap mass spectrometer (Thermo Fisher, San Jose, CA, USA), equipped with an ESI source. Elemental analyses were carried out using a Perkin-Elmer CHNS Elemental Analyzer model 2400. Melting points were recorded on a hot stage melting point apparatus Ernst Leitz Wetzlar, Germany and were uncorrected. The single-crystal X-ray diffraction data was collected on a Bruker SMART 1K CCD diffractometer.

General procedure for the synthesis of polysubstituted pyridines (3a-i & 4a-d). Aromatic aldehydes (**1a-g**) (1 mmol) and malononitrile (1 mmol) was dissolved in EtOH (10 ml) and added the ethanolic solution of cyclic ketone/ethyl methyl ketone (**2a-c** or **2d**) (1.5 mmol), Ag(I)-NHC (**a**) (2 mol%) and ammonium acetate (1.5 mmol) were stirred over a period of 2 minutes at room temperature and stirring was continued for 10 minutes. Complete consumption of starting material as judged by TLC and GC analysis. The reaction mass was filtered and obtained off-white solid crude product which was subjected to column chromatography (silica gel, 60-120 mesh, eluent; n-hexane/EtOAc gradient) to afford pure products (**3a-i & 4a-d**).

2-Amino-4-(4-methoxy-phenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridine-3-carbonitrile (3a). Off-white solid: mp 223-224 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.48-1.53 (m, 2H), 1.70-1.84 (m, 4H), 2.49 (t, 2H, *J* = 5.4 Hz), 2.91 (t, 2H, *J* = 5.4 Hz), 3.85 (s, 3H, OCH_3), 5.07 (s, 2H, NH_2), 6.98 (d, 2H, *J* = 8.6), 7.15 (d, 2H, *J* = 8.6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 26.20, 28.06, 28.91, 32.0, 39.69, 55.28, 89.59, 114.03, 117.21, 126.69, 128.97, 129.82, 152.94, 157.24, 159.82, 167.86 ppm. IR (KBr): 3318 (NH_2), 2213 (CN) cm^{-1}. MS (ESI), *m/z* = 294 $[M+H]^+$. EA calcd (%) for $C_{18}H_{19}N_3O$ (293.36): calcd. C 73.69, H 6.53, N 14.32; found. C 73.72, H 6.55, N 14.39.

2-Amino-4-(4-bromo-phenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridine-3-carbonitrile (3b). Off-white solid: mp 236-237 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 1.48-1.51 (m, 2H), 1.70-1.84 (m, 4H), 2.44 (t, 2H, *J* = 5.4 Hz), 2.92 (t, 2H, *J* = 5.4 Hz), 5.14 (s, 2H, NH_2), 7.10 (d, 2H, *J* = 8.3), 7.60 (d, 2H, *J* = 8.3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 26.14, 27.99, 28.97, 31.92, 39.67, 88.90, 116.76, 123.13, 126.26, 130.10, 131.93, 135.68, 151.73, 157.26, 168.25 ppm. IR (KBr): 3307 (NH_2), 2213 (CN) cm^{-1}. MS (ESI), *m/z* = 343 $[M+H]^+$. EA calcd (%) for $C_{17}H_{16}BrN_3$ (342.23): calcd. C 59.66, H 4.71, N 12.28; found. C 59.74, H 4.68, N 12.35.

2-Amino-4-phenyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridine-3-carbonitrile (3c). Off-white solid: mp 227-228 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 1.47-1.52 (m, 2H), 1.69-1.82 (m, 4H), 2.46 (t, 2H, *J* = 5.4 Hz), 2.92 (t, 2H, *J* = 5.5 Hz), 5.11 (s, 2H, NH_2), 7.21-7.49 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 26.18, 28.03, 28.97, 31.98, 39.67, 89.33, 116.94, 126.42, 128.38, 128.60, 128.68, 136.85, 153.11, 157.22, 167.96 ppm. IR (KBr): 3316 (NH_2), 2212 (CN) cm^{-1}. MS (ESI), *m/z* = 264 $[M+H]^+$. EA calcd (%) for $C_{17}H_{17}N_3$ (263.34): calcd. C 77.54, H 6.51, N 15.96; found. C 77.62, H 6.49, N 15.98.

2-Amino-4-(2-chloro-phenyl)-6,7,8,9-tetrahydro-5*H*-

cyclohepta[b]pyridine-3-carbonitrile (3d). Off-white solid: mp 273-274 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 1.39-2.96 (m, 10H), 5.18 (s, 2H, NH_2), 7.15-7.52 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 26.11, 27.57, 29.27, 32.01, 39.77, 89.24, 116.34, 126.78, 127.12, 129.87, 129.91, 130.20, 132.58, 135.81, 150.33, 157.21, 168.07 ppm. IR (KBr): 3313 (NH_2), 2214 (CN) cm^{-1}. MS (ESI), *m/z* = 298 $[M+H]^+$. EA calcd (%) for $C_{17}H_{16}ClN_3$ (297.78): calcd. C 68.57, H 5.42, N 14.11; found. C 68.65, H 5.46, N 14.09.

2-Amino-4-(2-bromo-phenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridine-3-carbonitrile (3e). Off-white solid: mp 261-262 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 1.38-3.0 (m, 10H), 5.14 (s, 2H, NH_2), 7.14-7.70 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 26.11, 27.54, 29.27, 32.01, 39.80, 89.17, 116.28, 122.30, 126.58, 127.71, 129.79, 130.29, 133.03, 137.91, 151.86, 157.13, 168.14 ppm. IR (KBr): 3312 (NH_2), 2214 (CN) cm^{-1}. MS (ESI), *m/z* = 343 $[M+H]^+$. EA calcd (%) for $C_{17}H_{16}BrN_3$ (342.23): calcd. C 59.66, H 4.71, N 12.28; found. C 59.69, H 4.76, N 12.32.

2-Amino-4-(2-methoxy-phenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridine-3-carbonitrile (3f). Off-white solid: mp 244-245 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 1.42-2.94 (m, 10H), 3.78 (s, 3H, OCH_3), 5.03 (m, 2H, NH_2), 6.99-7.43 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 26.18, 27.65, 29.40, 32.13, 39.76, 55.46, 90.08, 111.11, 117.03, 120.74, 125.59, 127.36, 130.0, 130.39, 150.33, 156.11, 157.16, 167.37 ppm. IR (KBr): 3296 (NH_2), 2210 (CN) cm^{-1}. MS (ESI), *m/z* = 294 $[M+H]^+$. EA calcd (%) for $C_{18}H_{19}N_3O$ (293.36): calcd. C 73.69, H 6.53, N 14.32; found. C 73.62, H 6.56, N 14.30.

2-Amino-4-(4-dimethylamino-phenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridine-3-carbonitrile (3g). Light yellow solid: mp 230-231 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 1.52-1.81 (m, 6H), 2.56 (t, 2H, *J* = 5.3 Hz), 2.91 (t, 2H, *J* = 5.4 Hz), 3.01 (s, 6H, $N(CH_3)_2$), 4.96 (s, 2H, NH_2), 6.76 (d, 2H, *J* = 8.6), 7.11 (d, 2H, *J* = 8.6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 26.25, 28.15, 28.90, 32.06, 39.73, 40.26, 88.90, 111.77, 123.13, 124.04, 126.79, 129.63, 135.68, 150.42, 153.68, 157.28, 167.58 ppm. IR (KBr): 3312 (NH_2), 2210 (CN) cm^{-1}. MS (ESI), *m/z* = 307 $[M+H]^+$. EA calcd (%) for $C_{19}H_{22}N_4$ (306.40): calcd. C 74.48, H 7.24, N 18.29; found. C 74.56, H 7.28, N 18.32.

2-Amino-4-phenyl-5,6,7,8,9,10-hexahydro-cycloocta[b]pyridine-3-carbonitrile (3h). Off-white solid: mp 234-235 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 1.27-1.38 (m, 6H), 1.68 (s, 2H), 2.38-2.80 (m, 4H), 6.58 (s, 2H, NH_2), 7.23-7.51 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 25.26, 25.76, 26.01, 30.01, 30.56, 34.87, 88.35, 116.59, 121.64, 127.91, 128.29, 128.40, 137.14, 153.75, 158.21, 165.19 ppm. IR (KBr): 3316 (NH_2), 2216 (CN) cm^{-1}. MS (ESI), *m/z* = 278 $[M+H]^+$. EA calcd (%) for $C_{18}H_{19}N_3$ (277.36): calcd. C 77.95, H 6.90, N 15.15; found. C 77.98, H 6.92, N 15.18.

2-Amino-4-phenyl-6,7-dihydro-5*H*-[1]pyrindine-3-carbonitrile (3i). Off-white solid: mp 220-221 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 1.90-1.98 (m, 2H), 2.60 (t, 2H, *J* = 7.3 Hz), 2.80 (t, 2H, *J* = 7.6 Hz), 6.66 (s, 2H, NH_2), 7.42-7.51 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 22.22, 28.78, 34.50, 85.52, 117.39, 123.02, 128.24, 128.49, 128.92, 135.92, 149.16, 160.99, 169.64 ppm. IR (KBr): 3301 (NH_2), 2205 (CN) cm^{-1}. MS (ESI), *m/z* = 236 $[M+H]^+$. EA calcd (%) for $C_{15}H_{13}N_3$ (235.28): calcd. C 76.57, H 5.57, N 17.86; found. C 76.59, H 5.58, N 17.89.

2-Amino-5,6-dimethyl-4-phenyl-nicotinonitrile (4a). Off-white solid: mp 240-241 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 1.95 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 5.05 (s, 2H, NH_2), 7.23-7.50 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 15.30, 23.72, 89.72, 116.80, 119.69, 128.33, 128.64, 128.77, 136.79, 153.86, 157.23, 161.57 ppm. IR (KBr): 3330 (NH_2), 2211 (CN) cm^{-1}. MS (ESI), *m/z* = 224 $[M+H]^+$. EA calcd (%) for $C_{14}H_{13}N_3$ (223.27): calcd. C 75.31, H 5.87, N 18.82; found. C 75.37, H 5.89, N 18.78.

2-Amino-4-(2-chloro-phenyl)-5,6-dimethyl-nicotinonitrile (4b). Off-white solid: mp 251-252 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 1.88 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 5.03 (s, 2H, NH_2), 7.17-7.53 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.89, 23.66, 116.20, 120.43, 127.0, 127.22, 129.81, 129.94, 130.16, 130.30, 132.45, 151.14, 157.13, 161.71 ppm. IR (KBr): 3329 (NH_2), 2211 (CN) cm^{-1}. MS (ESI), *m/z* = 258 $[M+H]^+$. EA calcd (%) for $C_{14}H_{12}ClN_3$ (257.72): calcd. C 65.25, H 4.69, N 16.30; found. C 65.29, H 4.74, N 16.36.

2-Amino-4-(4-bromo-phenyl)-5,6-dimethyl-nicotinonitrile (4c). Off-white solid: mp 265-266 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 1.94 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 5.02 (s, 2H, NH_2), 7.11 (d, 2H, *J* = 8.2 Hz), 7.63 (d, 2H, *J* = 8.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 15.3, 23.79, 89.94, 112.48, 119.53, 129.72, 130.07, 131.98, 132.12, 153. 68, 157.23, 161.92 ppm. IR (KBr): 3327 (NH_2), 2212 (CN) cm^{-1}. MS (ESI), *m/z* = 303 $[M+H]^+$. EA calcd (%) for $C_{14}H_{12}BrN_3$ (302.17): calcd. C 55.65, H 4.0, N 13.91; found. C 55.57, H 4.04, N 13.87.

2-Amino-4-(4-methoxy-phenyl)-5,6-dimethyl-nicotinonitrile (4d). Off-white solid: mp 276-277 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 1.97 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 5.0 (s, 2H, NH_2), 6.98 (d, 2H, *J* = 8.5 Hz), 7.17 (d, 2H, *J* = 8.5 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 15.36, 23.78, 55.29, 89.94, 114.05, 119.95, 128.90, 129.58, 129.81, 153.68, 157.25, 159.89, 161.46 ppm. IR (KBr): 3320 (NH_2), 2215 (CN) cm^{-1}. MS (ESI), *m/z* = 254 $[M+H]^+$. EA calcd (%) for $C_{15}H_{15}N_3O$ (253.30): calcd. C 71.13, H 5.97, N 16.59; found. C 71.18, H 5.99, N 16.64.

Notes and references

[a] *School of Chemistry & Physics, University of Kwazulu-Natal, Westville Campus, Chiltern Hills, Durban-4000, South Africa. Fax: +27 31 260 3091; Tel: +27 31 260 7325/3090; E-mail: jonnalagaddas@ukzn.ac.za*
[b] *Department of Chemistry, Satavahana University, Karimnagar, India.*
[c] *Department of Pharmaceutical Chemistry, Telangana University, Nizamabad, India. Fax: +91-878-2255933; Tel: +91-9000285433; E-mail: vasamcs@yahoo.co.in*

† Electronic Supplementary Information (ESI) available: Optimization of reaction parameters, Catalayst load table, and all the spectra of multisubstituted pyridine derivatives **3a-i & 4a-d** and crystallographic data of compound **3a**. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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Graphilcal Abstract

Silver(I)-*N*-heterocyclic carbene catalyzed multicomponent reactions: a facile synthesis of multisubstituted pyridines

Shravankumar Kankala,[a] Ramakanth Pagadala,[a] Suresh Maddila,[a] Chandra Sekhar Vasam,*[b] Sreekantha B. Jonnalagadda*[a]

A room temperature four component reaction between aromatic aldehydes (**1a-g**), malononitrile and ammonium acetate with ketones (**2a-d**) mediated by Ag(I) N-heterocyclic carbene pre-catalysts to produce multisubstituted and fused pyridines in short reaction time (~10 min) in eco-friendly ethanol was described.