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An efficient substituent dependent synthesis of congested pyridines and pyrimidines☆

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Abstract—An efficient and versatile synthesis of various congested pyridines **3a–h**, **6a**,**b**, **8a–n**, **10a–g**, and **16a**,**b**, and (pyrimidin-4-yl)-acetonitriles **13a–g** has been delineated by base catalyzed ring transformation of suitably functionalized 2*H*-pyran-2-ones **1a–h**, **5**, **7**, and **15** by formamidine acetate **2a**, acetamidine hydrochloride **2b**, *S*-methylisothiourea **9a**, pyrazol-1-yl-carboxamidine **9b**, and arylamidine hydrochloride **12** separately in the presence of powdered KOH in dry DMF.

1. Introduction

The importance of the pyridine ring in the chemistry of biological system has been greatly realized because of their presence as substructure in many natural products of therapeutic importance, involved in oxidation–reduction process. The potent biological activity of various vitamins and drugs[1–4] is primarily contributed to by the presence of pyridine ring in their molecular make-up. In addition to various therapeutic applications, the importance of pyridines in the preparative organic chemistry cannot be ignored. 4-Dimethylaminopyridine (DMAP), a highly demanding reagent, is used as catalyst in acylation reaction and also in activation of carboxylic acids without racemization of α-chiral center.[5] The ability of pyridine derivatives to complex various metal ion has made them highly sensitive analytical reagents, sensor systems, luminescent agents and building block for supramolecular chemistry.[6] Alkene pendent pyridine polymers are industrially useful as acid scavengers[3] and materials for chemical separations.

Pyrimidine rings are an integral part of DNA bases and various natural products.[7] They serve as building blocks for numerous pharmaceuticals and occupy a unique place in heterocyclic and medicinal chemistry. This class of compounds also have coordinating ability similar to pyridyl ligands in supramolecular metallo-gridlike architecture[8] and in novel inorganic–organic hybrid molecular wires.[9] In addition, they are pharmacologically active and display anticonvulsant,[10] anti-inflammatory,[11] antibacterial,[12] and antimycotic[13] activities.

The wide-ranging applications of various pyridine and pyrimidine derivatives in the pharmaceutical and agricultural fields[14] have significantly augmented the development of novel methodology devoid from the shortfalls of the past procedures in terms of generality, multistep sequences, and complex work-up in the construction of this ring system.

Numerous methods are reported for the construction of pyridines by varying substitution pattern around the ring. A very common approach for the synthesis of pyridines[15] is the condensation of 1,5-diketone with ammonia followed by nitric acid oxidation. 2-Acetylfuran has also been used as a 1,5-dicarbonyl equivalent for the preparation of congested pyridines and dipyridyls.[16] Katritzky et al. have reported[17] an elegant approach for the preparation of nicotinonitriles from the reaction of dienamine and ketone in the presence of Vilsmeier type 1-substituted-1,2,3-benzotriazole reagent. 2-Amino-4-arylpyridine-3,5-dinitriles have been prepared[18] by base catalyzed reaction of malononitrile with an aldehyde. The reaction of 1,3-dicarbonyl compounds and 3-aminoenones or nitriles is one of the most versatile approaches for the construction of unsymmetrically substituted pyridines.[1] 2*H*-Pyran-2-ones have been used as a diene equivalent for the preparation[19] of congested ethyl nicotinates on reaction with aryl nitriles under Diels–Alder conditions. Base catalyzed ring transformation of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-ones by cyanamide yields 2-aminonicotinonitriles.[20] The synthesis of trisubstituted pyridines has been reported[21,22] from the reaction of deoxybenzoin, vinamidium species, and ammonia in good yields and act as Cox-2 inhibitors.

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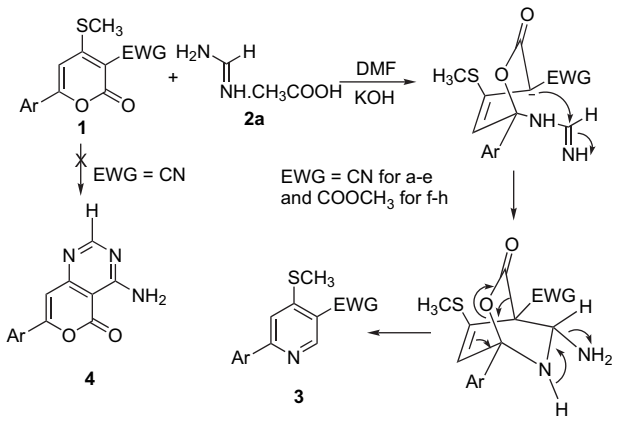
The synthesis of dihydro- or tetrahydropyridines has been achieved by interactions of 2-azadiene with a suitable dienophile. 1,2,4-Triazines,[23,24] a 2-azadiene equivalent on reaction with suitable alkyne provided highly substituted pyridines in excellent yields. Piperidine substituted nicotinic acid derivatives have also been obtained[25] from the reaction of enamine with alkynone. Thiopyridines such as 2-amino-3,5-dicyano-6-sulfanylpyridines and corresponding 1,4-dihydropyridines have been prepared[26] from the reaction of an aldehyde, malononitrile, and a thiol. Cyclotrimerization of a nitrile and two alkynes in the presence of cobalt(I) catalyst[27] is an alternative approach for the construction of highly functionalized pyridines. A regioselective synthesis of 6-amino-5-benzoyl-1-substituted-2-(1*H*)-pyridones has also been reported recently from the reaction of a cyclic ketene aminal with propiolic acid ester.[28,29]

The pyrimidine ring, being electron deficient, resists electrophilic substitution and facilitates nucleophilic addition and substitution reactions.[30] A common approach for the construction of pyrimidine rings is through condensation of 1,3-dicarbonyl compounds with amidines.[31] However, 2,4,6-triaryl pyrimidines are constructed stepwise.[31] The use of formamide or an orthoester in combination with ammonia[32] as a potential surrogate NCN reagent has been reported in the synthesis of pyrimidines. Tris(formylamino)-methanes,[33] 2-amino-2-formylmalonaldehyde,[34] and 3-methyl-5-nitro-3*H*-pyrimidin-4-one[35] have also been used as 1,3-dicarbonyl equivalents in pyrimidine synthesis. A simple cyclocondensation of amidine salts with chalcones also yields pyrimidines.[36]

Herein, we report a convenient and efficient regioselective synthesis of highly functionalized aryl tethered nicotinonitriles, methyl nicotinates, methyl 2-oxo-1,2-dihydronicotinates, and (pyrimidin-4-yl)acetonitriles in moderate to high yields through ring transformation of suitably functionalized 2*H*-pyran-2-ones by different amidines. The methodology is general and flexible to introduce functional groups at appropriate positions by maneuvering the reactants used in the ring transformation reactions.

2. Result and discussion

Our strategy to synthesize 6-aryl-4-methylsulfanyl-pyridine-3-carbonitriles **3a–e** was based on the nitrogen nucleophile induced ring transformation of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles[37] **1a–e** by formamidine acetate **2a** as shown in Scheme 1. The effect of milder electron-withdrawing –$COOCH_3$ substituent at C-3 of the pyran ring was also studied, using methyl 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carboxylates **1f–h** as synthon for the ring transformation reactions by formamidine acetate **2a** in DMF/KOH at room temperature, which yielded methyl 6-aryl-4-methylsulfanylnicotinates **3f–h** regioselectively in moderate yields. The poor electron-withdrawing property of $COOCH_3$ compared to CN could be the reason for moderate yield (Table 1). In this reaction, nucleophile preferentially attacks at C-6 but not at C-4 due to high electrophilic nature of the former ruled out the possibility for the formation of **4** (Scheme 1).



Scheme 1.

Table 1

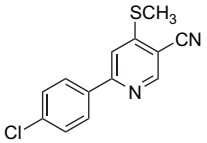
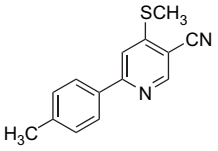
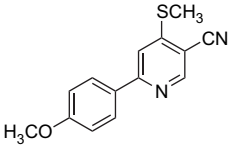
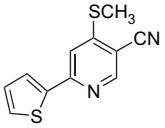
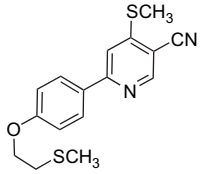
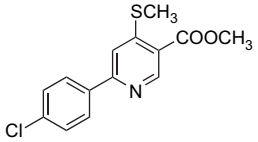
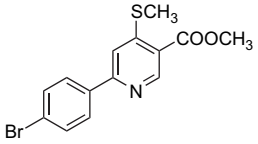
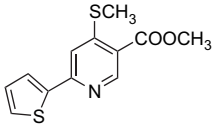
1,3	Product	Duration (h)	Yield (%)
a		1	89
b		1.5	90
c		1	87
d		1	87
e		1	85
f		5	65
g		6	59
h		5	61

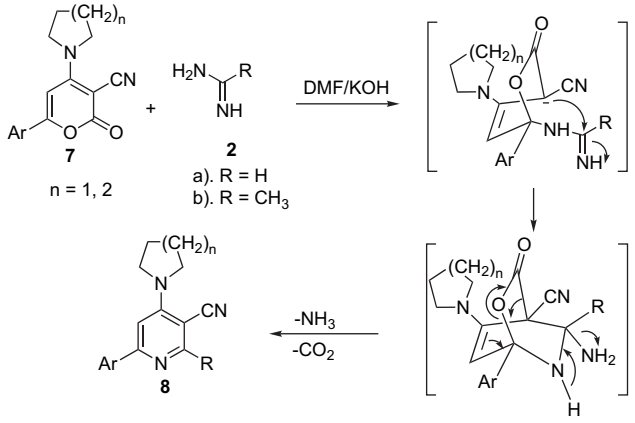
Table 2

6	R	Duration (h)	Yields (%)
A	H	5	75
B	OCH_3	6	82

This study was further generalized by carrying out a ring transformation of 5,6-diaryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles[38] **5** by formamidine acetate **2a**, which exclusively afforded 5,6-diaryl-4-methylsulfanylnicotinonitriles **6** in good yields (Table 2). The presence of an aryl substituent at position 5 of the pyran ring did not affect the course of reaction (Scheme 2).

The C-4 position of the 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles is electrophilic in nature due to the presence of an electron-withdrawing CN substituent and extended conjugation that facilitates the amination[39] with secondary amines in boiling ethanol. Thus, a reaction of **1** with pyrrolidine and piperidine in boiling ethanol afforded 6-aryl-4-secondary amino-2*H*-pyran-2-one-3-carbonitriles[39,40] **7**, which were used further as precursors for the ring transformation studies. Thus, stirring a mixture of **7** and formamidine acetate **2a** in DMF using powdered KOH as a base afforded 6-aryl-4-secondary aminonicotinonitriles **8a–g** in excellent yields while with acetamidine hydrochloride **2b**, the reaction was quite sluggish and produced 6-aryl-4-secondary amino-2-methylnicotinonitriles **8h–n** in poor yields because of the positive inductive effect of the methyl substituent of acetamidine, which hinders the progress of reaction (Scheme 3). In attempts to improve the yields of **8h–n**, different bases such as $NaOCH_3$, KO^tBu, and NaH were tried in different solvents but this exercise was futile. In another set of experiments, reaction of **7** and **2b** in dry pyridine at reflux was carried out for 5–8 h using triethylamine as a base. Though this experiment provided **8h–n**, no significant improvement in their yield was recorded. The ring transformation of **1a–h** and **7** by **2** followed the same course of reaction. The initial step in these reactions is the attack of nitrogen nucleophile at C-6 of the 2*H*-pyran-2-one with ring closure followed by elimination of carbon dioxide and ammonia to form 6-aryl-4-methylsulfanylnicotinonitriles **3a–e** and 6-aryl-4-secondary aminonicotinonitriles **8a–n**. It was conspicuous that a reaction of **1a–e** and **2a** regioselectively provided **3a–e** without any formation of mechanistically obvious product **4** through nucleophilic attack at C-4 in **1** followed by cyclization involving CN function. Attempts to force the reaction to obtain 3-amino-7-aryl-4-oxopyrano[3,4-*d*]pyrimidine **4** by using different bases, solvents, and also varying temperature did not succeed (Table 3).

To assess the effect of substituents attached to amidine carbon on the course of reactions, *S*-methylisothiourea **9a**

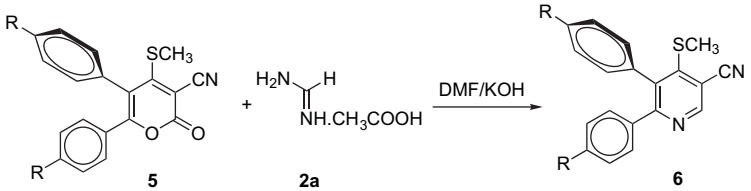


Scheme 3.

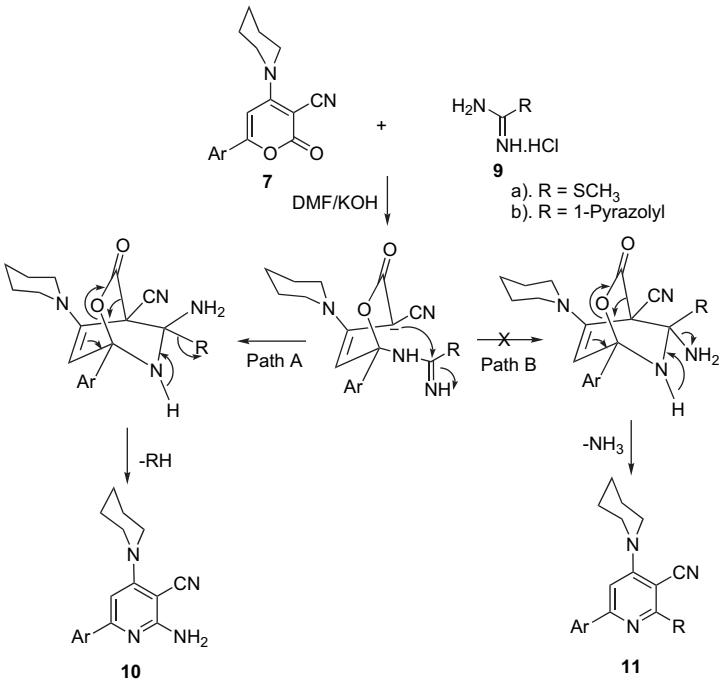
Table 3. Reaction conditions with yields for product **8** using KOH as a base

8	Ar	*n*	R	Yields (%)	*t* (min.)
a	C_6H_5	2	H	98	50
b	4-Cl–C_6H_4	2	H	96	60
c	4-CH_3–C_6H_4	2	H	97	50
d	4-CH_3O–C_6H_4	2	H	98	60
e	2-Thienyl	1	H	96	70
f	3,4-OCH_2O–C_6H_4	2	H	97	70
g	2-Naphthyl	2	H	94	80
h	C_6H_5	2	CH_3	25	60
i	4-Cl–C_6H_4	2	CH_3	15	50
j	4-Br–C_6H_4	2	CH_3	18	60
k	4-Cl–C_6H_4	1	CH_3	28	60
l	4-CH_3O–C_6H_4	2	CH_3	24	50
m	2-Thienyl	2	CH_3	32	60
n	2-Naphthyl	2	CH_3	22	70

and pyrazole-1-carboxamidine hydrochloride **9b** were used as amidine equivalents. The reaction of **7** with *S*-methylisothiourea sulfate **9a** and pyrazole-1-carboxamidine **9b** in DMF using powdered KOH as a base separately under analogous reaction conditions gave 6-aryl-2,4-diaminonicotinonitriles[20] **10** through path A without formation of theoretically obvious product **11** by following path B as shown in Scheme 4. In this reaction also the nitrogen nucleophile attacks at C-6 of the 2*H*-pyran-2-ones-3-carbonitriles **7** with ring closure followed by elimination of carbon dioxide and methyl mercaptan or 1*H*-pyrazole to yield **10**. The possibility for the formation of product **11** with the elimination of ammonia in lieu of methyl mercaptan or pyrazole was never observed and always only one product **10** was isolated regioselectively possibly due to the presence of better leaving group, which is easily eliminated under applied experimental conditions. This reaction demonstrated that the good leaving substituents attached to amidine carbon directs the regioselectivity. Use of *S*-methylisothiourea **9a** as



Scheme 2.



Scheme 4.

nucleophile for the ring transformation produced superior yields of **10** than pyrazol-1-yl-carboxamidine **9b** (Table 4).

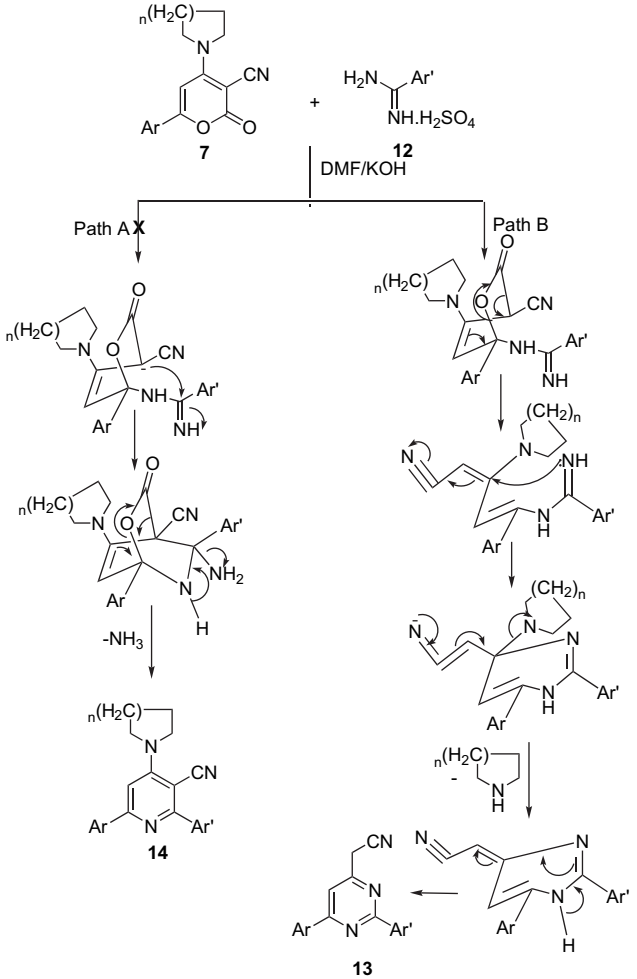
The reaction of arylamidinium salts **12** with 6-aryl-4-secondary amino-2*H*-pyran-2-one-3-carbonitriles **7** at room temperature in the presence of powdered KOH in dry DMF provided (2,6-diaryl-pyrimidin-4-yl)acetonitriles[41] **13** in high yields. Thus, arylamidine **12** used as nitrogen nucleophile, attacks at C-6 position followed by ring closure involving C-4 carbon of the pyran ring and nitrogen atom of arylamidine with loss of carbon dioxide and secondary amine to yield (2,6-diarylpyrimidin-4-yl)acetonitriles **13**. The possibility for the formation of product **14** also exists but under applied experimental conditions product **13** has been regioselectively isolated due to facile elimination of secondary amine compared to ammonia. The plausible mechanism of the reaction is depicted in Scheme 5 (Table 5).

The reactions of **15**[38] with formamidine under analogous reaction conditions did not yield pyridine derivatives, but gave methyl 5,6-diaryl-4-methylsulfanyl-2-oxo-1,2-dihydronicotinates **16** in good yields by following the different course of reaction due to the presence of C-5 aryl substituent. In

Table 4. Reaction conditions and isolated yields of **10**

10	Ar	Yields[a] (%)	*t* (min)	Yields[b] (%)	*t* (min)
a	C_6H_5	72	60	75	75
b	4-Cl–C_6H_4	74	70	71	80
c	4-Br–C_6H_4	74	60	76	80
d	4-CH_3–C_6H_4	72	65	76	90
e	3,4-Cl_2–C_6H_3	71	60	65	80
f	2-Thienyl	69	60	73	70
g	3,4-OCH_2O–C_6H_4	76	70	72	75

[a] Reaction carried out using pyrazol-1-carboxamidine.
[b] Reaction using *S*-methylisothiourea as nucleophiles.



Scheme 5.

Table 5. Duration of reaction and yields of different pyrimidines

13	Ar	Ar′	Yields (%)
a	C_6H_5	C_6H_5	85
b	4-Cl–C_6H_4	C_6H_5	79
c	4-Br–C_6H_4	C_6H_5	84
d	2-Thienyl	C_6H_5	83
e	4-F–C_6H_4	C_5H_4N	75
f	4-CH_3O–C_6H_4	C_5H_4N	83
g	4-CH_2O_2–C_6H_4	C_5H_4N	85

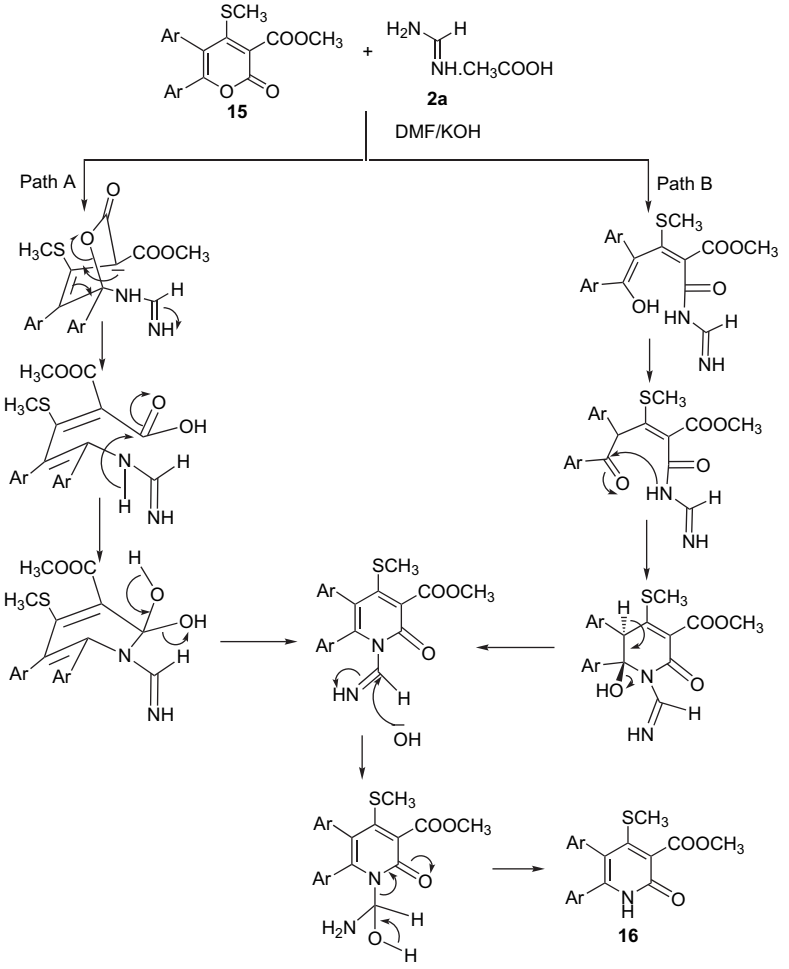
this case also the reaction is initiated by attack of nucleophile at C-6 with ring opening followed by ring closure involving carboxylic and amino group of amidine with loss of water and formamide to yield methyl 5,6-diaryl-4-methylsulfanyl-2-oxo-1,2-dihydronicotinates **16a**,**b** following path A. The other possible mechanism for the formation of **16** could be through the attack of formamidine at C-2 rather at C-6 with ring opening followed by cyclization with loss of water. The cyclized intermediate thus formed loses formamide to form **16** under experimental reaction conditions as shown in Scheme 6. It is interesting to note that in the presence of 5-aryl substituent, cyclization involved acid and amino groups of intermediate formed, while in absence, usual cyclization led to the formation of **3f**–**h**. In Scheme 2, it was observed that the presence of cyano substituent at C-3 followed the usual way of reaction to produce desired compound **6** while in the presence of $COOCH_3$, the reaction followed different course due to difference in their electronegativity to produce **16** in good yield. These observations indicated that the presence of additional aryl group at C-5 and electronic effects of $COOCH_3$ at C-3 decide the course of reaction (Table 6).

Table 6

16	Ar	Duration (h)	Yields (%)
a	C_6H_5	12	61
b	4-CH_3O–C_6H_4	10	89

3. Conclusions

In summary, reactions of suitably functionalized 2*H*-pyran-2-ones with different amidines result in the formation of highly substituted pyridines, pyrimidines, and pyridones. The methodology provides an easy access to the synthesis of 2-picolines, methyl 3-nicotinates, nicotinonitriles, and aminonicotinonitriles, and (pyrimidin-4-yl)acetonitriles in excellent yields. Our approach for the construction of congested pyridines and pyrimidines ring system is novel and opens a new avenue for the generation of molecular diversity, employing economical reagents without use of any catalyst. The work-up of the reaction is very simple.



Scheme 6.

4. Experimental

4.1. General

All reactions were conducted in flame-dried glasswares. Pre-coated Merck TLC plates were used for monitoring the reaction. Column chromatographic separation was performed on neutral alumina and silica gel (60–120 mesh). IR spectra were recorded on a Shimadzu 8201 PC FTIR spectrophotometer. ^{1}H NMR spectra were recorded on Bruker DRX 200 as well as on Bruker DRX 300 spectrometer in deuterated solvents with TMS as internal reference. Mass spectra were recorded on JEOL SX-102 (FAB) spectrometer. HRMS were recorded on JEOL JMS-600H (HRMS) spectrometer. Melting points were determined on Büchi-530 capillary melting point apparatus and are uncorrected.

4.2. General procedure for the synthesis of 6-aryl-4-methylsulfanylnicotinonitriles (3a–f and 6a–b)

These were obtained by stirring a mixture of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitrile **1** (1 mmol) and formamidine acetate (1.5 mmol) in the presence of KOH (2 mmol) in dry DMF (8 mL). Completion of reaction was monitored by TLC. After completion, the reaction mixture was poured onto crushed ice (60 g) with vigorous stirring. The precipitate obtained was filtered, washed with water, dried, and purified through neutral alumina column chromatography using 40% hexane in chloroform as eluant.

4.2.1. 6-(4-Chlorophenyl)-4-methylsulfanylnicotinonitrile (3a). Cream colored powder; yield: 202 mg (89%); R_f ($CHCl_3$) 0.5; mp 180–182 °C; IR (KBr): 2818, 2366, 2341, 2215, 1584, 1515, 1463, 1430, 1383, 1346, 1268, 1091, 1008, 973, 829, 770, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.66 (s, 3H, SCH_3), 7.46–7.49 (m, 3H, ArH), 7.95 (d, J=8.0 Hz, 2H, ArH), 8.69 (s, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): 14.46, 106.35, 114.65, 115.64, 129.12, 129.65, 136.41, 137.29, 152.97, 155.91, 158.88; MS *m*/*z* 261 (M^++1); HRMS (EI, 70 eV): calcd for $C_{13}H_9ClN_2S$ 260.01750 (M^+), found for *m*/*z* 260.01745.

4.2.2. 4-Methylsulfanyl-6-(*p*-tolyl)nicotinonitrile (3b). Cream colored solid; yield: 216 mg (90%); R_f ($CHCl_3$) 0.5; mp 190–192 °C; IR (KBr): 2947, 2854, 2361, 2155, 1584, 1514, 1440, 1397, 1308, 1229, 1136, 1072, 1005, 850, 823, 780 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3), 2.65 (s, 3H, SCH_3), 7.31 (d, J=8.1 Hz, 2H, ArH), 7.48 (s, 1H, ArH), 7.89 (d, J=8.1 Hz, 2H, ArH), 8.69 (s, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): 14.43, 21.82, 105.78, 114.54, 115.90, 127.74, 130.18, 135.23, 141.42, 152.98, 155.34, 160.16; MS *m*/*z* 241 (M^++1); HRMS (EI, 70 eV): calcd for $C_{14}H_{12}N_2S$ 240.07212 (M^+), found for *m*/*z* 240.07212.

4.2.3. 6-(4-Methoxyphenyl)-4-methylsulfanylnicotinonitrile (3c). White powder; yield: 223 mg (87%); R_f ($CHCl_3$) 0.56; mp 178–180 °C; IR (KBr): 2927, 2376, 2341, 2213, 1576, 1510, 1454, 1430, 1383, 1336, 1261, 1091, 1018, 971 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.68 (s, 3H, SCH_3), 3.89 (s, 3H, OCH_3), 7.00 (d, J=8.6 Hz, 2H, ArH), 7.43 (s, 1H, ArH), 7.96 (d, J=8.6 Hz, 2H, ArH), 8.65 (s, 1H, ArH); MS *m*/*z* 257 (M^++1); HRMS (EI, 70 eV): calcd for $C_{14}H_{12}N_2OS$ 256.06703 (M^+), found for *m*/*z* 256.06734.

4.2.4. 4-Methylsulfanyl-6-(thiophen-2-yl)nicotinonitrile (3d). White amorphous solid; yield: 202 mg (87%); R_f ($CHCl_3$) 0.52; mp 200–202 °C; IR (KBr): 2367, 2215, 1572, 1514, 1462, 1430, 1340, 1267, 1175, 1089, 1007, 973, 828, 739, 704 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.62 (s, 3H, SCH_3), 7.13–7.16 (m, 1H, ArH), 7.38 (s, 1H, ArH), 7.52 (d, J=5.9 Hz, 1H, ArH), 7.68 (d, J=3.7 Hz, 1H, ArH), 8.57 (s, 1H, ArH); MS *m*/*z* 233 (M^++1); HRMS (EI, 70 eV): calcd for $C_{11}H_8N_2S_2$ 232.01289 (M^+), found for *m*/*z* 232.01267.

4.2.5. 4-Methylsulfanyl-6-[4-(2-methylsulfanylethoxy)-phenyl]nicotinonitrile (3e). White powder; yield: 270 mg (85%); R_f ($CHCl_3$) 0.6; mp 184–186 °C; IR (KBr): 2921, 2833, 2363, 2215, 1602, 1520, 1464, 1430, 1352, 1309, 1285, 1247, 1174, 1078, 1015, 832, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.21 (s, 3H, SCH_3), 2.62 (s, 3H, SCH_3), 2.88 (t, J=6.8 Hz, 2H, SCH_2), 4.20 (t, J=6.8 Hz, 2H, OCH_2), 6.98 (d, J=8.4 Hz, 2H, ArH), 7.41 (s, 1H, ArH), 7.94 (d, J=8.4 Hz, 2H, ArH), 8.63 (s, 1H, ArH); MS *m*/*z* 317 (M^++1); HRMS (EI, 70 eV): calcd for $C_{16}H_{16}N_2OS_2$ 316.07040 (M^+), found for *m*/*z* 316.07040.

4.2.6. Methyl 6-(4-chlorophenyl)-4-methylsulfanylnicotinate (3f). White amorphous solid; yield: 191 mg (65%); R_f ($CHCl_3$) 0.53; mp 158–160 °C; IR (KBr): 2996, 2922, 2849, 2364, 1706, 1584, 1510, 1464, 1437, 1344, 1293, 1228, 1183, 1131, 1089, 1068, 1009, 963, 830, 784, 720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.53 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 7.45 (d, J=8.4 Hz, 2H, ArH), 7.48 (s, 1H, ArH), 7.95 (d, J=8.4 Hz, 2H, ArH), 9.09 (s, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): 15.24, 52.64, 115.00, 121.08, 129.08, 129.48, 136.62, 137.27, 152.19, 155.76, 158.57, 166.16; MS *m*/*z* 294 (M^++1); HRMS (EI, 70 eV): calcd for $C_{14}H_{12}ClNO_2S$ 293.02773 (M^+), found for *m*/*z* 293.02719.

4.2.7. Methyl 6-(4-bromophenyl)-4-methylsulfanylnicotinate (3g). White powder; yield: 199 mg (59%); R_f (10% hexane in $CHCl_3$) 0.5; mp 134–136 °C; IR (KBr): 2854, 2364, 2371, 2197, 1611, 1557, 1499, 1359, 1289, 1252, 1211 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 3H, SCH_3), 3.96 (s, 3H, OCH_3), 7.50 (s, 1H, ArH), 7.61 (d, J=8.4 Hz, 2H, ArH), 7.90 (d, J=8.4 Hz, 2H, ArH), 9.11 (s, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): 15.26, 52.67, 115.01, 121.13, 125.03, 126.61, 128.09, 129.36, 132.47, 137.74, 152.23, 155.82, 158.67, 166.19; MS *m*/*z* 339 (M^++2); HRMS (EI, 70 eV): calcd for $C_{14}H_{12}BrNO_2S$ 336.97720 (M^+), found for *m*/*z* 336.97711.

4.2.8. Methyl 4-methylsulfanyl-6-(thiophen-2-yl)nicotinate (3h). White powder; yield: 162 mg (61%); R_f ($CHCl_3$) 0.55; mp 142–144 °C; IR (KBr): 3177, 2918, 2848, 2364, 1703, 1648, 1581, 1512, 1467, 1436, 1399, 1344, 1303, 1229, 1133, 1070, 1003, 963, 814, 784, 729, 706 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.52 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.12–7.16 (m, 1H, ArH), 7.45 (s, 1H, ArH), 7.48–7.50 (m, 1H, ArH), 7.67–7.69 (m, 1H, ArH), 9.01 (s, 1H, ArH); MS *m*/*z* 266 (M^++1); HRMS (EI,

70 eV): calcd for $C_{12}H_{11}NO_2S_2$ 265.02312 (M^+), found for *m/z* 265.02331.

4.2.9. 4-Methylsulfanyl-5,6-diphenylnicotinonitrile (6a). White powder; yield: 227 mg (75%); R_f ($CHCl_3$) 0.42; mp 148–150 °C; IR (KBr): 2823, 2726, 2374, 2341, 2221, 1595, 1480, 1553, 1063, 1023, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.52 (s, 3H, SCH_3), 7.11–7.15 (m, 2H, ArH), 7.19–7.24 (m, 5H, ArH), 7.33–7.35 (m, 3H, ArH), 8.87 (s, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): 18.84, 110.40, 117.01, 128.19, 128.73, 128.84, 128.99, 130.16, 130.87, 136.39, 137.83, 139.18, 153.09, 160.59; MS *m/z* 303 (M^++1); HRMS (EI, 70 eV): calcd for $C_{19}H_{14}N_2S$ 302.08777 (M^+), found for *m/z* 302.08748.

4.2.10. 5,6-Bis-(4-methoxyphenyl)-4-methylsulfanylnicotinonitrile (6b). White powder; yield: 297 mg (82%); R_f ($CHCl_3$) 0.40; mp 142–144 °C; IR (KBr): 2928, 2364, 2340, 2221, 1588, 1526, 1425, 1384, 1351, 1283, 1242, 1061, 929, 832, 798, 767 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.49 (s, 3H, SCH_3), 3.78 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.74 (d, *J*=8.9 Hz, 2H, ArH), 6.89 (d, *J*= 8.8 Hz, 2H, ArH), 7.04 (d, *J*=8.8 Hz, 2H, ArH), 7.22 (d, *J*= 8.9 Hz, 2H, ArH), 8.80 (s, 1H, ArH); MS *m/z* 363 (M^++1); HRMS (EI, 70 eV): calcd for $C_{21}H_{18}N_2O_2S$ 362.10890 (M^+), found for *m/z* 362.10890.

4.3. General procedure for the synthesis of 6-aryl-4-*sec*-amino-2-*H*/methylnicotinonitriles (8a–n)

A mixture of 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitrile **7** (1 mmol) and acetamidine hydrochloride (1.5 mmol) was stirred in the presence of KOH (2 mmol) in the dry DMF (8 mL). After completion, the reaction mixture was poured onto crushed ice (60 g) with vigorous stirring. The precipitate obtained was filtered, washed with water, dried, and purified through column chromatography using 30% hexane in chloroform as eluant.

In order to improve the yield of 6-aryl-4-*sec*-amino-2-methyl nicotinonitriles (**8h–n**), this reaction was also carried out by refluxing a mixture of 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitrile (1 mmol) and acetamidine hydrochloride (1.5 mmol) in pyridine (10 mL) for 5–8 h. After completion, the excess of pyridine was removed under reduced pressure and the residue poured onto crushed ice (50 g). The precipitate obtained was filtered, washed with water, dried, and purified through neutral alumina column chromatography using 30% hexane in chloroform as eluant.

4.3.1. 6′-Phenyl-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (8a). White powder; yield: 259 mg (98%); R_f (10% hexane in $CHCl_3$) 0.40; mp 102–104 °C; IR (KBr): 2936, 2836, 2363, 2210, 1588, 1524, 1443, 1416, 1381, 1284, 1231, 1159, 1123, 1072, 1024, 984, 873, 782, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.72–1.79 (m, 6H, CH_2), 3.57 (t, *J*=5.1 Hz, 4H, CH_2NCH_2), 7.10 (s, 1H, ArH), 7.43–7.50 (m, 3H, ArH), 7.91–7.94 (m, 2H, ArH), 8.61 (s, 1H, ArH); MS *m/z* 264 (M^++1); HRMS (EI, 70 eV): calcd for $C_{17}H_{17}N_3$ 263.14225 (M^+), found for *m/z* 263.14210.

4.3.2. 6′-(4-Chlorophenyl)-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (8b). White powder; yield: 285 mg (96%); R_f (10% hexane in $CHCl_3$) 0.40; mp 123–125 °C; IR (KBr): 2935, 2848, 2365, 2211, 1588, 1562, 1526, 1442, 1384, 1314, 1282, 1230, 1162, 1089, 1082, 984, 833, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.74–1.83 (m, 6H, CH_2), 3.57 (t, *J*=4.5 Hz, 4H, CH_2NCH_2), 7.07 (s, 1H, ArH), 7.44 (d, *J*=7.9 Hz, 2H, ArH), 7.88 (d, *J*=7.9 Hz, 2H, ArH), 8.59 (s, 1H, ArH); MS *m/z* 298 (M^++1); HRMS (EI, 70 eV): calcd for $C_{17}H_{16}ClN_3$ 297.10327 (M^+), found for *m/z* 297.10276.

4.3.3. 6′-*p*-Tolyl-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (8c). White solid; yield: 267 mg (97%); R_f (10% hexane in $CHCl_3$) 0.40; mp 144–146 °C; IR (KBr): 2936, 2853, 2363, 2206, 1593, 1528, 1446, 1353, 1235, 1166, 1111, 1045, 1020, 950, 871, 825, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.72–1.79 (m, 6H, CH_2), 2.43 (s, 3H, CH_3), 3.56 (t, *J*=5.1 Hz, 4H, CH_2NCH_2), 7.10 (s, 1H, ArH), 7.29 (d, *J*=8.2 Hz, 2H, ArH), 7.85 (d, *J*= 8.2 Hz, 2H, ArH), 8.61 (s, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): 21.74, 24.42, 26.11, 51.05, 96.53, 107.56, 118.83, 127.50, 129.93, 136.19, 140.56, 156.04, 159.31, 161.13; MS *m/z* 278 (M^++1); HRMS (EI, 70 eV): calcd for $C_{18}H_{19}N_3$ 277.15790 (M^+), found for *m/z* 277.15767.

4.3.4. 6′-(4-Methoxyphenyl)-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (8d). White powder; yield: 287 mg (98%); R_f (10% hexane in $CHCl_3$) 0.40; mp 138–140 °C; IR (KBr): 2984, 2931, 2839, 2362, 2206, 1585, 1527, 1451, 1285, 1253, 1231, 1183, 1115, 1027, 951, 831, 745, 717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.69–1.79 (m, 6H, CH_2), 3.55 (t, *J*=5.1 Hz, 4H, CH_2NCH_2), 3.88 (s, 3H, OCH_3), 7.00 (d, *J*=8.7 Hz, 2H, ArH), 7.06 (s, 1H, ArH), 7.93 (d, *J*=8.7 Hz, 2H, ArH), 8.59 (s, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): 24.42, 26.11, 51.06, 55.80, 96.24, 106.96, 114.57, 118.89, 129.03, 131.43, 155.99, 159.34, 160.70, 161.64; MS *m/z* 294 (M^++1); HRMS (EI, 70 eV): calcd for $C_{18}H_{19}N_3O$ 293.15282 (M^+), found for *m/z* 293.15294.

4.3.5. 4-(Pyrrolidin-1-yl)-6-(thiophen-2-yl)nicotinonitrile (8e). White powder; yield: 245 mg (96%); R_f (10% hexane in $CHCl_3$) 0.44; mp 173–175 °C; IR (KBr): 3093, 2971, 2868, 2366, 2207, 1593, 1531, 1459, 1419, 1353, 1307, 1255, 1137, 1137, 1055, 1023, 959, 871, 817, 727 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.01–2.05 (m, 4H, CH_2), 3.68–3.72 (m, 4H, CH_2NCH_2), 6.78 (s, 1H, ArH), 7.11 (dd, *J*=3.8 and 3.8 Hz, 1H, ArH), 7.43 (dd, *J*=0.8 and 0.8 Hz, 1H, ArH), 7.58 (dd, *J*=0.8 and 0.8 Hz, 1H, ArH), 8.57 (s, 1H, ArH); MS *m/z* 256 (M^++1); HRMS (EI, 70 eV): calcd for $C_{14}H_{13}N_3S$ 255.08302 (M^+), found for *m/z* 255.08310.

4.3.6. 6′-(Benzo[1,3]dioxol-5-yl)-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (8f). White powder; yield: 298 mg (97%); R_f (10% hexane in $CHCl_3$) 0.38; mp 165–167 °C; IR (KBr): 3061, 2928, 2844, 2363, 2217, 1585, 1530, 1480, 1445, 1381, 1350, 1239, 1159, 1105, 1034, 957, 931, 851, 825, 762, 724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.72–1.80 (m, 6H, CH_2), 3.55 (t, *J*=5.1 Hz, 4H, CH_2NCH_2), 6.05 (s, 2H, OCH_2O), 6.91 (d, *J*=8.1 Hz, 1H, ArH), 7.02 (s, 1H, ArH), 7.47–7.50 (m, 2H, ArH), 8.57 (s, 1H, ArH); MS *m/z* 308 (M^++1); HRMS (EI, 70 eV): calcd for $C_{18}H_{17}N_3O_2$ 307.13208 (M^+), found for *m/z* 307.13196.

4.3.7. 6′-Naphthalen-2-yl-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (8g). White powder; yield: 294 mg (94%); R_f ($CHCl_3$) 0.40; mp 136–138 °C; IR (KBr): 2939, 2848, 2362, 2208, 1587, 1528, 1438, 1284, 1233, 1159, 1121, 1035, 964, 899, 862, 823, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.75–1.82 (m, 6H, CH_2), 3.62 (t, J=5.1 Hz, 4H, CH_2NCH_2), 7.28 (s, 1H, ArH), 7.53–7.56 (m, 2H, ArH), 7.88–7.98 (m, 3H, ArH), 8.04–8.07 (m, 1H, ArH), 8.47 (s, 1H, ArH), 8.68 (s, 1H, ArH); MS m/z 314 (M^++1); HRMS (EI, 70 eV): calcd for $C_{21}H_{19}N_3$ 313.15790 (M^+), found for m/z 313.15727.

4.3.8. 2′-Methyl-6′-phenyl-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (8h). White powder, yield: 69 mg (25%); R_f ($CHCl_3$) 0.40; mp 115–117 °C; IR (KBr): 2937, 2858, 2358, 2207, 1586, 1447, 1359, 1236, 1084, 899, 774 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.73–1.78 (m, 6H, CH_2), 2.75 (s, 3H, CH_3), 3.45–3.50 (m, 4H, CH_2NCH_2), 6.99 (s, 1H, ArH), 7.44–7.49 (m, 3H, ArH), 7.91–7.96 (m, 2H, ArH); MS m/z 278 (M^++1); HRMS (EI, 70 eV): calcd for $C_{18}H_{19}N_3$ 277.15790 (M^+), found for m/z 277.15784.

4.3.9. 6′-(4-Chlorophenyl)-2′-methyl-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (8i). White powder; yield: 47 mg (15%); R_f (5% hexane in $CHCl_3$) 0.40; mp 116–118 °C; IR (KBr): 2927, 2366, 2205, 1850, 1628, 1592, 1532, 1458, 1403, 1352, 1231, 1093, 1013, 821, 770 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.71–1.78 (m, 6H, CH_2), 2.73 (s, 3H, CH_3), 3.45–3.50 (m, 4H, CH_2NCH_2), 6.95 (s, 1H, ArH), 7.43 (d, J=8.6 Hz, 2H, ArH), 7.89 (d, J=8.6 Hz, 2H, ArH); MS m/z 312 (M^++1); HRMS (EI, 70 eV): calcd for $C_{18}H_{18}Cl\ N_3$ 311.11892 (M^+), found for m/z 311.11909.

4.3.10. 6′-(4-Bromophenyl)-2′-methyl-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (8j). White solid; yield: 64 mg (18%); R_f (5% hexane in $CHCl_3$) 0.40; mp 138–140 °C; IR (KBr): 2941, 2362, 2251, 2204, 1580, 1444, 1400, 1350, 1272, 1238, 1123, 1089, 1029, 990, 896, 854, 821, 767 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.73–1.78 (m, 6H, CH_2), 2.73 (s, 3H, CH_3), 3.45–3.50 (m, 4H, CH_2NCH_2), 6.95 (s, 1H, ArH), 7.58 (d, J=8.6 Hz, 2H, ArH), 7.82 (d, J=8.6 Hz, 2H, ArH); MS m/z 355 (M^+), 357 (M^++2); HRMS (EI, 70 eV): calcd for $C_{18}H_{18}BrN_3$ 355.06841 (M^+), found for m/z 355.06818.

4.3.11. 6-(4-Chlorophenyl)-2-methyl-4-(pyrrolidin-1-yl)-nicotinonitrile (8k). White powder; yield: 83 mg (28%); mp 140–142 °C; IR (KBr): 2937, 2873, 2728, 2365, 2205, 1590, 1533, 1455, 1402, 1352, 1232, 1093, 1012, 904, 822, 786 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.01–2.08 (m, 4H, CH_2), 2.70 (s, 3H, CH_3), 3.73 (t, J=6.6 Hz, 4H, CH_2NCH_2), 6.65 (s, 1H, ArH), 7.41 (d, J=8.6 Hz, 2H, ArH), 7.87 (d, J=8.6 Hz, 2H, ArH); MS m/z 298 (M^++1); HRMS (EI, 70 eV): calcd for $C_{17}H_{16}ClN_3$ 297.10327 (M^+), found for m/z 297.10405.

4.3.12. 6′-(4-Methoxyphenyl)-2′-methyl-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (8l). White amorphous solid; yield: 74 mg (24%); mp 136–138 °C; IR (KBr): 2918, 2828, 2362, 2206, 1581, 1533, 1441, 1408, 1381, 1352, 1296, 1255, 1234, 1169, 1110, 1028, 979, 904, 866, 830, 761 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.70–1.77 (m, 6H, CH_2), 2.72 (s, 3H, CH_3), 3.42–3.48 (m, 4H, CH_2NCH_2), 3.86 (s, 3H, OCH_3), 6.93–6.99 (m, 3H, ArH), 7.89–7.94 (m, 2H, ArH); MS m/z 308 (M^++1); HRMS (EI, 70 eV): calcd for $C_{19}H_{21}N_3O$ 307.16846 (M^+), found for m/z 307.16846.

4.3.13. 2′-Methyl-6′-(thiophen-2-yl)-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (8m). White powder; yield: 91 mg (32%); R_f ($CHCl_3$) 0.42; mp 118–120 °C; IR (KBr): 3088, 2928, 2854, 2366, 2206, 1576, 1530, 1444, 1376, 1266, 1230, 1162, 1085, 984, 834, 743, 711 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.72–1.77 (m, 6H, CH_2), 2.68 (s, 3H, CH_3), 3.42–3.47 (m, 4H, CH_2NCH_2), 6.92 (s, 1H, ArH), 7.08–7.13 (m, 1H, ArH), 7.42–7.46 (m, 1H, ArH), 7.59–7.62 (m, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): 24.43, 24.69, 26.18, 51.65, 96.85, 104.17, 118.45, 126.28, 128.52, 129.36, 144.58, 154.57, 161.39, 164.45; MS m/z 284 (M^++1); HRMS (EI, 70 eV): calcd for $C_{16}H_{17}N_3S$ 283.11432 (M^+), found for m/z 283.11432.

4.3.14. 2′-Methyl-6′-naphthalen-2-yl-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (8n). White amorphous solid; yield: 72 mg (22%); R_f ($CHCl_3$) 0.40; mp 162–164 °C; IR (KBr): 2940, 2824, 2364, 2204, 1585, 1442, 1380, 1351, 1271, 1241, 1158, 1121, 1090, 1028, 987, 897, 852, 817 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.73–1.83 (m, 6H, CH_2), 2.78 (s, 3H, CH_3), 3.47–3.53 (m, 4H, CH_2NCH_2), 7.11 (s, 1H, ArH), 7.97–7.52 (m, 2H, ArH), 7.81–7.94 (m, 3H, ArH), 8.01–8.06 (m, 1H, ArH), 8.43 (s, 1H, ArH); MS m/z 328 (M^++1); HRMS (EI, 70 eV): calcd for $C_{22}H_{21}N_3$ 327.17355 (M^+), found for m/z 327.17349.

4.4. General procedure for the synthesis of 6-aryl-4-methylsulfanyl-2-aminonicotinonitriles (10a–g)

These were obtained by stirring a mixture of 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitriles **7** (1 mmol) and *S*-methylisothiourea **9a** or pyrazol-1-yl-carboxamidine **9b** (1.5 mmol) in the presence of KOH (2 mmol) in dry DMF (6 mL). After completion, the reaction mixture was poured onto crushed ice (50 g) with vigorous stirring. The precipitate obtained was filtered, washed with water, dried, and purified through neutral alumina column chromatography using 4% ethyl acetate in hexane as eluant.

4.4.1. 2′-Amino-6′-phenyl-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (10a). White powder; yield: 201 mg (72%); R_f (6% ethyl acetate in hexane) 0.40; mp 121–123 °C; IR (KBr): 3432, 3390, 2937, 2850, 2369, 2341, 2191, 1631, 1583, 1530, 1422, 1352, 1282, 1239, 1218, 1158, 1119, 1048, 1019, 998, 929, 850, 818, 765, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.61–1.74 (m, 6H, CH_2), 3.49 (t, J=5.1, 4H, CH_2NCH_2), 5.15 (br s, 2H, NH_2), 6.54 (s, 1H, ArH), 7.40–7.46 (m, 3H, ArH), 7.84–7.90 (m, 2H, ArH); MS m/z 279 (M^++1); HRMS (EI, 70 eV): calcd for $C_{17}H_{18}N_4$ 278.15315 (M^+), found for m/z 278.15361.

4.4.2. 2′-Amino-6′-(4-chlorophenyl)-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (10b). White amorphous solid; yield: 231 mg (74%); R_f (6% ethyl acetate in

hexane) 0.43; mp 190–192 °C; IR (KBr): 3405, 3389, 2924, 2854, 2364, 2341, 2192, 1591, 1527, 1496, 1428, 1385, 1352, 1282, 1242, 1216, 1157, 1088, 1014, 928, 846, 807, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.66–1.78 (m, 6H, CH_2), 3.49 (t, J=4.9 Hz, 4H, CH_2NCH_2), 5.16 (br s, 2H, NH_2), 6.50 (s, 1H, ArH), 7.39 (d, J=8.9 Hz, 2H, ArH), 7.82 (d, J=8.9 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 22.89, 24.56, 49.71, 97.99, 116.91, 127.14, 127.48, 134.40, 136.15, 157.26, 160.26, 160.42; MS m/z 313 (M^++1); HRMS (EI, 70 eV): calcd for $C_{17}H_{17}ClN_4$ 312.11417 (M^+), found for m/z 312.11411.

4.4.3. 2′-Amino-6′-(4-bromophenyl)-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (10c). White powder; yield: 264 mg (74%); R_f (7% ethyl acetate in hexane) 0.45; mp 198–200 °C; IR (KBr): 2889, 2394, 2333, 2218, 1599, 1470, 1534, 1063, 1023, 861 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.67–1.75 (m, 6H, CH_2), 3.49 (t, J=4.8 Hz, 4H, CH_2NCH_2), 5.14 (br s, 2H, NH_2), 6.50 (s, 1H, ArH), 7.55 (d, J=8.3 Hz, 2H, ArH), 7.75 (d, J=8.3 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 22.88, 24.56, 49.69, 76.68, 97.94, 116.86, 122.77, 127.40, 130.43, 136.62, 157.29, 160.25, 160.43; MS m/z 358 (M^++2); HRMS (EI, 70 eV): calcd for $C_{17}H_{17}Br\ N_4$ 356.06365 (M^+), found for m/z 356.06345.

4.4.4. 2′-Amino-6′-(*p*-tolyl)-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (10d). White amorphous solid; yield: 211 mg (72%); R_f (8% ethyl acetate in hexane) 0.45; mp 170–172 °C; IR (KBr): 3434, 3398, 2937, 2369, 2191, 1637, 1530, 1428, 1352, 1272, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.67–1.77 (m, 6H, CH_2), 2.38 (s, 3H, CH_3), 3.48 (t, J=5.0 Hz, 4H, CH_2NCH_2), 5.28 (br s, 2H, NH_2), 6.51 (s, 1H, ArH), 7.23 (d, J=8.0 Hz, 2H, ArH), 7.77 (d, J=8.0 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 20.04, 22.91, 24.57, 49.74, 76.66, 97.90, 116.96, 126.63, 128.89, 134.67, 138.60, 158.33, 160.27, 160.34; MS m/z 293 (M^++1); HRMS (EI, 70 eV): calcd for $C_{18}H_{20}N_4$ 292.16879 (M^+), found for m/z 292.16824.

4.4.5. 2′-Amino-6′-(3,4-dichlorophenyl)-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (10e). White powder; yield: 246 mg (71%); R_f (6% ethyl acetate in hexane) 0.40; mp 168–170 °C; IR (KBr): 3409, 3399, 2924, 2347, 2197, 1591, 1496, 1428, 1289, 1242 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.68–1.75 (m, 6H, CH_2), 3.51 (t, J= 4.9 Hz, 4H, CH_2NCH_2), 5.14 (br s, 2H, NH_2), 6.48 (s, 1H, ArH), 7.48 (d, J=8.4 Hz, 1H, ArH), 7.72 (dd, J=2.1 and 2.1 Hz, 1H, ArH), 7.99 (d, J=2.0 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 22.85, 24.56, 49.68, 76.70, 96.93, 116.72, 124.89, 127.76, 129.18, 131.58, 132.38, 137.63, 155.81, 160.16, 160.40; MS m/z 347 (M^++1); HRMS (EI, 70 eV): calcd for $C_{17}H_{16}Cl_2N_4$ 346.07520 (M^+), found for m/z 346.07504.

4.4.6. 2′-Amino-6′-thiophen-2-yl-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (10f). White powder; yield: 197 mg (69%); R_f (8% ethyl acetate in hexane) 0.40; mp 120–122 °C; IR (KBr): cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.67–1.77 (m, 6H, CH_2), 3.46 (t, J=5.0 Hz, 4H, CH_2NCH_2), 5.16 (br s, 2H, NH_2), 6.50 (s, 1H, ArH), 7.08 (dd, J=3.8 and 3.8 Hz, 1H, ArH), 7.39 (dd, J=1.1 and 1.1 Hz, 1H, ArH), 7.55 (dd, J=0.8 and 0.8 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 22.89, 24.54, 49.70, 76.64, 97.27, 116.94, 124.50, 126.66, 127.19, 143.01, 152.97, 160.21, 160.31; MS m/z 285 (M^++1); HRMS (EI, 70 eV): calcd for $C_{15}H_{16}N_4S$ 284.10957 (M^+), found for m/z 284.10957.

4.4.7. 2′-Amino-6′-benzo[1,3]dioxol-5-yl-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-3′-carbonitrile (10g). White powder; yield: 245 mg (76%); R_f (6% ethyl acetate in hexane) 0.35; mp 170–172 °C; IR (KBr): 3383, 2933, 2853, 2364, 2341, 2195, 1587, 1501, 1424, 1387, 1352, 1247, 1157, 1102, 1038, 1005, 932, 857, 807, 766, 724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.66–1.74 (m, 6H, CH_2), 3.47 (t, J=4.9 Hz, 4H, CH_2NCH_2), 5.09 (br s, 2H, NH_2), 6.00 (s, 2H, CH_2), 6.46 (s, 1H, ArH), 6.86 (d, J=7.9 Hz, 1H, ArH), 7.40–7.43 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 22.92, 24.56, 49.75, 97.63, 100.11, 106.26, 117.04, 120.15, 132.11, 146.79, 147.69, 158.02, 160.35; MS m/z 323 (M^++1); HRMS (EI, 70 eV): calcd for $C_{18}H_{18}N_4O_2$ 322.14297 (M^+), found for m/z 322.14300.

4.5. General procedure for the synthesis of [2,6-diarylpyrimidin-4-yl]acetonitriles (13a–h)

A mixture of 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitriles **1** (1 mmol) and arylamidine hydrochloride (1.5 mmol) in presence of KOH (2 mmol) in dry DMF (8 mL) was stirred for 2–3 h. Completion of reaction was monitored by the TLC. Thereafter, reaction mixture was poured onto crushed ice (60 g) with vigorous stirring. The precipitate obtained was filtered, washed with water, dried, and purified through neutral alumina column chromatography using 40% chloroform in hexane as eluant.

4.5.1. (2,6-Diphenylpyrimidin-4-yl)acetonitrile (13a). White powder; yield: 198 mg (73%); R_f (0.5% ethyl acetate in chloroform) 0.50; mp 110–112 °C; IR (KBr): 2925, 2828, 2367, 2341, 2254, 1591, 1460, 1356, 1169, 1069, 1025, 927, 832, 746, 712 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.97 (s, 2H, CH_2), 7.41–7.54 (m, 6H, ArH), 7.74 (s, 1H, ArH), 8.21–8.26 (m, 2H, ArH), 8.52–8.57 (m, 2H, ArH); MS m/z 272 (M^++1); HRMS (EI, 70 eV): calcd for $C_{18}H_{13}N_3$ 271.11095 (M^+), found for m/z 271.11101.

4.5.2. [6-(4-Chloro-phenyl)-2-phenylpyrimidin-4-yl]-acetonitrile (13b). White powder; yield: 240 mg (79%); R_f (0.5% ethyl acetate in chloroform) 0.50; mp 118–120 °C; IR (KBr): 3010, 2819, 2368, 2341, 2258, 1592, 1381, 1351, 1092, 1014, 855, 752 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.98 (s, 2H, CH_2), 7.46–7.52 (m, 5H, ArH), 7.71 (s, 1H, ArH), 8.19 (d, J=8.5 Hz, 2H, ArH), 8.50–8.55 (m, 2H, ArH); MS m/z 306 (M^++1); HRMS (EI, 70 eV): calcd for $C_{18}H_{12}ClN_3$ 305.07197 (M^+), found for m/z 305.07189.

4.5.3. [6-(4-Bromo-phenyl)-2-phenylpyrimidin-4-yl]-acetonitrile (13c). White powder; yield: 283 mg (81%); R_f (0.5% ethyl acetate in chloroform) 0.54; mp 124–126 °C; IR (KBr): 2926, 2819, 2371, 2340, 2257, 1592, 1487, 1383, 1175, 1072, 1009, 929, 827, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.97 (s, 2H, CH_2), 7.46–7.51 (m, 3H, ArH), 7.66 (d, J=8.6 Hz, 2H, ArH), 7.70 (s, 1H, ArH), 8.11 (d, J=8.6 Hz, 2H, ArH), 8.49–8.54 (m, 2H ArH); MS m/z 349 (M^+), 351 (M^++2); HRMS (EI, 70 eV): calcd for $C_{18}H_{12}BrN_3$ 349.02145 (M^+), found for m/z 349.02160.

4.5.4. (2-Phenyl-6-thiophen-2-ylpyrimidin-4-yl)acetonitrile (13d). White powder; yield: 230 mg (83%); R_f (0.5% ethyl acetate in chloroform) 0.45; mp 120–122 °C; IR (KBr): 2938, 2896, 2369, 2258, 1582, 1429, 1361, 1236, 1204, 1168, 1121, 1068, 1026, 925, 840, 789, 751, 712 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.92 (s, 2H, CH_2), 7.14–7.18 (m, 1H, ArH), 7.45–7.55 (m, 5H, ArH), 7.85–7.87 (m, 1H, ArH), 8.46–8.51 (m, 2H ArH); MS *m/z* 278 (M^++1); HRMS (EI, 70 eV): calcd for $C_{16}H_{11}N_3S$ 277.06737 (M^+), found for *m/z* 277.06750.

4.5.5. [6-(4-Fluoro-phenyl)-2-pyridin-4-ylpyrimidin-4-yl]acetonitrile (13e). White powder; yield: 218 mg (75%); R_f (0.5% ethyl acetate in chloroform) 0.55; mp 160–162 °C; IR (KBr): 2816, 2366, 2340, 2258, 1547, 1512, 1381, 1353, 1223, 1159, 1097, 1061, 993, 928, 839, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.05 (s, 2H, CH_2), 7.24–7.29 (m, 2H, ArH), 7.81 (s, 1H, ArH), 8.25–8.29 (m, 2H, ArH), 8.40 (d, J=6.0 Hz, 2H, ArH), 8.82 (d, J=4.5, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 25.45, 112.11, 114.29, 114.91, 115.19, 120.85, 128.38, 130.72, 142.87, 149.33, 159.12, 161.74, 162.27, 163.49; MS *m/z* 291 (M^++1); HRMS (EI, 70 eV): calcd for $C_{17}H_{11}FN_4$ 290.09677 (M^+), found for *m/z* 290.09659.

4.5.6. [6-(4-Methoxy-phenyl)-2-pyridin-4-ylpyrimidin-4-yl]acetonitrile (13f). White powder; yield: 242 mg (80%); R_f (0.5% ethyl acetate in chloroform) 0.50; mp 176–178 °C; IR (KBr): 3021, 2967, 2367, 2206, 1585, 1534, 1462, 1402, 1374, 1298, 1257, 1217, 1179, 1031, 929, 838, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.90 (s, 3H, OCH_3), 4.00 (s, 2H, CH_2), 7.05 (d, J=8.6 Hz, 2H, ArH), 7.73 (s, 1H, ArH), 8.21 (d, J=8.6 Hz, 2H, ArH), 8.38 (d, J=6.5 Hz, 2H, ArH), 8.79 (d, J=5.4 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 25.22, 54.21, 111.42, 113.30, 114.50, 120.86, 126.85, 127.84, 134.14, 149.17, 158.61, 161.51, 164.02; MS *m/z* 303 (M^++1); HRMS (EI, 70 eV): calcd for $C_{18}H_{14}N_4O$ 302.11676 (M^+), found for *m/z* 302.11615.

4.5.7. (6-Benzo[1,3]dioxol-5-yl-2-pyridin-4-ylpyrimidin-4-yl)acetonitrile (13g). White powder; yield: 262 mg (84%); R_f (0.5% ethyl acetate in chloroform) 0.45; mp 202–204 °C; IR (KBr): 3059, 2919, 2368, 2340, 2250, 1587, 1507, 1450, 1384, 1303, 1248, 1153, 1107, 1036, 994, 910, 846, 820, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.00 (s, 2H, CH_2), 6.08 (s, 2H, CH_2), 6.95 (d, J= 9.0 Hz, 1H, ArH), 7.69 (s, 1H, ArH), 7.75–7.77 (m, 2H, ArH), 8.36 (d, J=6.6 Hz, 2H, ArH), 8.79 (d, J=4.9 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 25.45, 100.63, 106.11, 107.49, 111.64, 114.46, 120.84, 121.22, 128.77, 142.96, 147.47, 149.22, 149.69, 158.76, 161.49, 163.82; MS *m/z* 317 (M^++1); HRMS (EI, 70 eV): calcd for $C_{18}H_{12}N_4O_2$ 316.09603 (M^+), found for *m/z* 316.09643.

4.5.8. Methyl 4-methylsulfanyl-2-oxo-5,6-diphenyl-1,2-dihydropyridine-3-carboxylate (16a). White powder; yield: 215 mg (61%) R_f (0.2% methanol in chloroform) 0.40; mp >250 °C; IR (KBr): 3430, 2940, 2823, 2367, 2341, 1722, 1630, 1598, 1495, 1440, 1351, 1351, 1239, 1194, 1121, 1058, 977, 850, 760 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.08 (s, 3H, SCH_3), 3.87 (s, 3H, OCH_3), 7.11–7.37 (m, 10H, ArH), 10.87 (br s, 1H, NH); MS *m/z* 352 (M^++1); HRMS (EI, 70 eV): calcd for $C_{20}H_{17}NO_3S$ 351.09292 (M^+), found for *m/z* 351.09313.

4.5.9. Methyl 5,6-bis-(4-methoxyphenyl)-4-methylsulfanyl-2-oxo-1,2-dihydropyridine-3-carboxylate (16b). White amorphous solid; yield: 366 mg (89%); R_f (0.2% methanol in chloroform) 0.40; mp >250 °C; IR (KBr): 3425, 2830, 2363, 1717, 1663, 1511, 1466, 1355, 1248, 1193, 1127, 1061, 1026, 900, 840, 722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.11 (s, 3H, SCH_3), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.75 (d, J=8.8 Hz, 2H, ArH), 6.80 (d, J=9.1 Hz, 2H, ArH), 7.04 (d, J=8.8 Hz, 2H, ArH), 7.07 (d, J=9.1 Hz, 2H, ArH), 10.90 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.78, 51.19, 53.84, 54.91, 112.31, 112.44, 124.53, 125.88, 129.38, 131.67, 142.86, 157.77, 158.49, 158.86, 165.25; MS *m/z* 412 (M^++1); HRMS (EI, 70 eV): calcd for $C_{22}H_{21}NO_5S$ 411.11404 (M^+), found for *m/z* 411.11437.

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