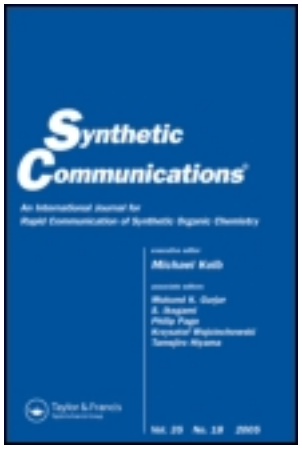

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Novel Zinc Ion-Catalyzed Synthesis of Unsymmetric Multisubstituted Pyridines

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NOVEL ZINC ION–CATALYZED SYNTHESIS OF UNSYMMETRIC MULTISUBSTITUTED PYRIDINES

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A facile and convenient synthesis of unsymmetric multisubstituted pyridines from β-ketoesters and ketene N,S-acetals or ketene N,N-acetals has been achieved in good yields catalyzed by $Zn(NO_3)_2 \cdot 6H_2O$ in the presence of triethylbenzylammonium (TEBA) chloride in ethanol. This reaction was carried out under economical, one-pot reaction conditions (using easily obtained starting materials, and inexpensive catalyst and solvent) and offers considerable improvements over traditional methodology.

INTRODUCTION

The development of new ways to make pyridines is of considerable interest. One reason for this interest is the fact that many natural products, such as vitamin B, nicotinamide, and nicotinic acid, which play important roles in metabolism and possess a wide spectrum of biological activities, contain a pyridine ring.[1,2] The main synthetic methods used for the preparation of pyridines with symmetrical substitution patterns include the Hantzsch reaction,[3,4] but the synthesis of multisubstituted pyridines with unsymmetric substitution patterns is often difficult and involves multistep sequences, so there is still a great need to develop new approaches to pyridines of this type.

It has been reported[5] that metal ions may promote the formation of a carbon–carbon bond between nitriles and the intercarbonyl methylene group in β-dicarbonyl compounds. Veronese et al.[6] first reported the synthesis of 4-aminopyridines via the reactions of β-enaminonitriles with β-ketoesters in the presence of stoichiometric amounts of tin(IV) chloride, and Zhao and coworkers[7] used similar chemistry for the synthesis of nicotinic acid derivatives. However, the scope of the reaction has not been properly investigated, and the literature does not describe optimized reaction conditions.

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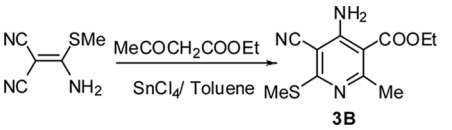
As a result of our interest in the synthesis of biologically active compounds, recently we have successfully applied this tin(IV) chloride–promoted reaction to the synthesis of multisubstituted pyridines **3B** (Eq. 1). However, we found that some issues associated with this method needed to be addressed. First, this method requires anhydrous conditions because tin(IV) chloride is readily hydrolyzed in water. Furthermore, the poor solubility of the reactants and the $SnCl_4$ catalyst in toluene, used as the solvent for the reaction, often leads to a poor yield and prolonged reaction time. And finally, the complex workup procedure involves the dilution of the reaction mixture with a saturated aqueous solution of sodium carbonate and extraction of the reactant mixture with ethyl acetate before the title compound can be isolated and purified by flash chromatography on silica gel.



3B (1)

To overcome these limitations, a new and facile approach for the synthesis of multisubstituted pyridine derivatives using the reaction of ketene *N,S*-acetals or ketene *N,N*-acetals with β-ketoesters in the presence of zinc(II) nitrate as a catalyst has been developed and is reported here.

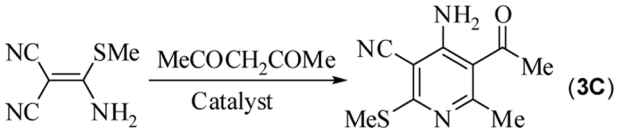
RESULTS AND DISCUSSION

In this study, various catalysts, different solvents, reaction times, and the molar ratios of reactants were tested to optimize the reaction conditions. The survey of reaction conditions and results are summarized in Table 1. The initial study was performed on the reaction of 2-(amino-methylthio-methylene)-malononitrile with acetylacetone in the presence of $SnCl_4$ (2 equiv.) in refluxing toluene, which gave a yield of 38% of **3C** (entry 1). Corresponding reactions carried out in polar solvents such as ethanol and dimethylformamide (DMF) led to none of the required product (entries 2 and 3). Using these experiments as starting points, the effect of altering other components of the reaction was studied.

Catalysts and solvents have a dramatic influence on the efficiency of the reaction, as summarized in Table 1. A variety of catalysts, such as $FeCl_3 \cdot 6H_2O$ (entry 4), $ZnCl_2$(entries 5–10), $Zn(OAc)_2 \cdot 2H_2O$ (entry 14), and $Zn(NO_3)_2$(entries 15–22), catalyze the reactions more efficiently than $SnCl_4$ (entries 1–3). A survey of solvents showed that ethanol was more efficient than toluene, benzene, acetonitrile, or DMF (entries 5–10, Table 1). When ethanol was used as the solvent, the sequence of the yields with different catalysts is $Zn(NO_3)_2$(entry 15) $\geq Zn(NO_3)_2 \cdot 6H_2O$ (entry 23) $\geq Zn(OAc)_2 \cdot 2H_2O$ (entry 14) $\geq ZnCl_2$(entry 9) $\geq ZnSO_4 \cdot 7H_2O$ (entry 11). Although $Zn(NO_3)_2$ provided better catalytic efficiency than $Zn(NO_3)_2 \cdot 6H_2O$ (entry 17 vs. entry 23, entry 22 vs. entry 25), the latter was chosen for further experiments because it is more easily obtained and handled.

We found that the molar ratio of the reactants has a modest effect on the efficiency of the reaction. Thus a ratio of *N,S*-acetal–β-ketoester–catalyst of 1:1:2

Table 1. Optimization of the reaction conditions



Entry	Catalyst	N,S-Acetal–ketoester–catalyst	Conditions	Time (h)	Yield (%)[a]
1	$SnCl_4$	1:1:2	Toluene/reflux	8	38
2	$SnCl_4$	1:1:2	Ethanol/reflux	8	Failed
3	$SnCl_4$	1:1:2	DMF/110	8	Failed
4	$FeCl_3 \cdot 6H_2O$	1:1:1	Toluene/reflux	8	58
5	$ZnCl_2$	1:1:1	Toluene/reflux	12	48
6	$ZnCl_2$	1:1:1	Benzene/reflux	12	45
7	$ZnCl_2$	1:1:1	CH_3CN/reflux	12	49
8	$ZnCl_2$	1:1:1	Ethanol/reflux	12	54
9	$ZnCl_2$	1:1:2	Ethanol/reflux	12	60
10	$ZnCl_2$	1:1:2	DMF/110	12	53
11	$ZnSO_4 \cdot 7H_2O$	1:1:2	Ethanol/reflux	12	31
12	$CuCI_2$	1:1:2	Ethanol/reflux	12	Failed
13	$Mg(ClO_4)_2$	1:1:2	Ethanol/reflux	12	Failed
14	$Zn(OAc)2 \cdot 2H_2O$	1:1:2	Ethanol/reflux	12	70
15	$Zn(NO_3)_2$	1:1:2	Ethanol/reflux	8	72
16	$Zn(NO_3)_2$	1:1:2	Ethanol/reflux	10	81
17	$Zn(NO_3)_2$	1:1:2	Ethanol/reflux	12	83
18	$Zn(NO_3)_2$	1:1:2	Ethanol/reflux	14	80
19	$Zn(NO_3)_2$	1:1:1	Ethanol/reflux	12	79
20	$Zn(NO_3)_2$	1:1:0.5	Ethanol/reflux	12	75
21	$Zn(NO_3)_2$	1:1:0.25	Ethanol/reflux	12	63
22	$Zn(NO_3)_2$	1:2:2	Ethanol/reflux	12	87
23	$Zn(NO_3)_2 \cdot 6H_2O$	1:1:2	Ethanol/reflux	12	73
24	$Zn(NO_3)_2 \cdot 6H_2O$	1:1:2	Ethanol/reflux	20	54
25	$Zn(NO_3)_2 \cdot 6H_2O$	1:2:2	Ethanol/reflux	12	80
26	$Zn(NO_3)_2 \cdot 6H_2O$	1:2:2	Ethanol/reflux	6	78
27	$Zn(NO_3)_2 \cdot 6H_2O$ +TBAB	1:2:2	Ethanol/reflux	6	86
28	$Zn(NO_3)_2 \cdot 6H_2O$ +TEBA	1:2:2	Ethanol/reflux	6	93

[a]Yield of pure isolated product.

gave a slightly better yield than a ratio of 1:1:1 (compare entries 17 and 19, respectively), and yields dropped when a lower proportion of the catalyst was used (entries 20 and 21). The greater concentration of β-ketoesters (2 equivalents) reduced the reaction time and slightly increased the yield (entry 18 vs. entry 22, entry 23 vs. entry 25).

The reaction time has not a remarkable effect on the efficiency of the reaction when using $Zn(NO_3)_2$ as catalyst. When the reaction time changed from 8 to 14 h (entries 15–18) and other variables were kept constant, the results revealed that 12 h was probably the most effective time for the cyclization reaction (entry 17, Table 1). However, when using $Zn(NO_3)_2 \cdot 6H_2O$ as catalyst, we found that a further increase in the reaction time led to lower yield (entry 23 vs. entry 24), and there was

almost no change on the reaction yields when the reaction time was reduced to 6 h within the conditions established (entry 25 vs. entry 26).

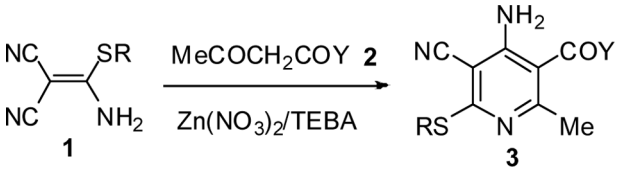
Reasoning that a phase-transfer catalyst may assist the solubility of the reactants, a catalytic amount of TBAB (tetrabutylammonium bromide) (entry 27) or TEBA (triethylbenzylammonium chloride) (entry 28) was added to some reactions. When the molar ratio of reactants was 1:2:2, using $Zn(NO_3)_2 \cdot 6H_2O$ and TEBA as the catalyst, at refluxing temperature for 6 h, a maximum amount of the title compound was obtained in pure ethanol (entry 28).

To investigate the scope of this reaction and establish its tolerance for different substrates under the optimized conditions, a range of different β-ketoesters **2** and ketene *N,S*-acetals **1** were heated at reflux in ethanol in the presence of stoichiometric amounts of zinc(II) nitrate and a catalytic amount of TEBA. In all the cases investigated (Table 2), the expected pyridine **3** was isolated in good to excellent yield (85–95%), and no regioisomeric products were detected. However, when the β-ketoester was replaced by ethyl cyanoacetate, no corresponding pyridine was obtained under these reaction conditions.

To illustrate the practicality of our protocol, different β-ketoesters **2** were allowed to react with a variety of ketene *N,N*-acetals **4** under the optimal reaction conditions. The expected novel multisubstituted pyridines **5** were isolated following simple workup and purification by recrystallization (Table 3). It is worth noting that the yields of the pyridines **5** were great when the amino group in the precursor carried a bulky benzyl substituent.

Although the detailed mechanism of this reaction is not clear at this stage, it is likely that the reaction proceeds through the Michael addition of β-ketoesters to the ketene *N,S*-acetal followed by subsequent ring closure. The zinc ion stabilized the enol carbanion for facilitating the reaction. Further investigations of the scope

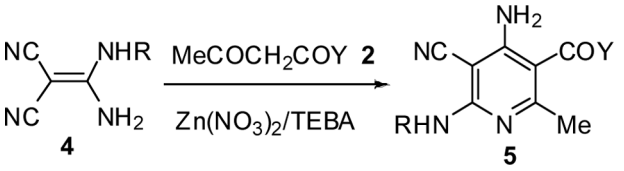
Table 2. Yields of compounds **3**



Entry	R	Y	Compounds	Yield (%)[a]
1	Me	MeO	**3A**	90
2	Me	EtO	**3B**	95
3	Me	Me	**3C**	93
4	Et	MeO	**3D**	86
5	Et	EtO	**3E**	91
6	Et	Me	**3F**	89
7	$PhCH_2$	MeO	**3G**	87
8	$PhCH_2$	EtO	**3H**	89
9	$PhCH_2$	Me	**31**	85

[a]Yield of pure isolated product.

Table 3. Yields of compounds **5**



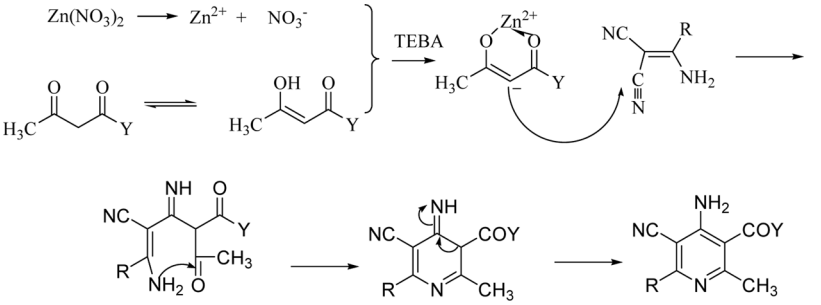
Entry	R	Y	Compounds	Yield (%)[a]
1	$(CH_2)_2CH_3$	EtO	**5A**	41
2	$(CH_2)_3CH_3$	EtO	**5B**	45
3	$PhCH_2$	EtO	**5C**	81
4	$PhCH_2$	MeO	**5D**	83
5	2-ClPhCH_2	Me	**5E**	75
6	4-MeOPhCH_2	EtO	**5F**	90

[a]Yield of pure isolated product.

and mechanism of the reaction are under way. A tentative mechanism for the formation of the multisubstituted pyridine derivative is shown in Scheme 1.

All the compounds obtained were fully characterized by spectroscopic analysis [infrared (IR), ^{1}H NMR ^{13}C NMR, and electron-impact mass spectrometry (EI-MS)] and elemental analysis. In the case of **3I**, the structure was additionally confirmed by single-crystal x-ray diffraction (Fig. 1). (Crystal structure of compound **3I** has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. CCDC 653953.)

In summary, we have developed a new and straightforward procedure for the preparation of multisubstituted pyridines with unsymmetrically positioned substituents. This procedure should be applicable to the synthesis of a variety of potentially bioactive pyridines, starting with readily available precursors such as ketene *N,S*- or *N,N*-acetals and β-ketoesters, $Zn(NO_3)_2 \cdot 6H_2O$, and TEBA as catalyst. The application of this strategy toward the synthesis of other multisubstituted pyridines is currently being explored.



Scheme 1. Possible mechanism of the synthesis of pyridines.

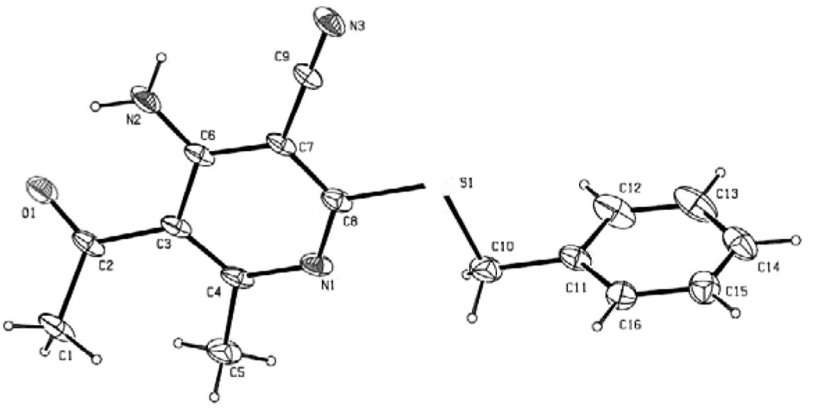


Figure 1. Perspective view of the x-ray crystal structure of **3I**.

EXPERIMENTAL

General

Melting points were measured on an electrothermal melting-point apparatus and are uncorrected. Mass spectra were measured on a Finnigan Trace MS 2000 spectrometer. IR spectra were recorded on a PE-983 IR spectrometer as KBr pellets with absorption in centimeters^{-1}. ^{1}H NMR spectra were recorded on a Varian Mercury 400 spectrometer using $CDCl_3$ as the solvent. Chemical shifts are given in parts per million (ppm) (δ) relative to tetramethylsilane (TMS) (δ 0.00 ppm). ^{13}C NMR spectra were recorded on a Varian Mercury 600 spectrometer using $CDCl_3$ as the solvent. Chemical shifts are given in ppm (δ) relative to $CDCl_3$ (δ 77.00 ppm). Elemental analyses were performed on a Vario EL III elemental analysis instrument. All of the solvents and materials were reagent grade and purified as required.

Synthesis of 4-Amino-5-cyano-2-methyl-6-alkylsulfanyl-nicotinic Acid Derivatives 3A–I

A mixture of 2-(amino-alkylthio-methylene)-malononitrile **2** (10 mmol) and $Zn(NO_2)_2 \cdot 6H_2O$ (20 mmol) and a catalytic amount of TEBA (0.2 mmol) were added to a stirred solution of β-ketoesters **1** (20 mmol) or acetylacetone **1** (20 mmol) in anhydrous ethanol (30 ml). The mixture was heated under reflux under nitrogen for 6 h and then cooled. The precipitate was recrystallized from ethanol–water to give 4-amino-5-cyano-2-methyl-6-alkylsulfanyl-nicotinic acid derivatives **3A–I** in good yields.

Selected Data

4-Amino-5-cyano-2-methyl-6-methylsulfanyl-nicotinic acid methyl ester 3A. White crystal; yield 90%; mp 141.2–143.2°C; ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm): 2.61 (s, 3H, SCH_3), 2.68 (s, 3H, py-$\underline{CH_3}$), 3.92 (s, 3H, OCH_3), 6.70 (s, 2H, NH_2); ^{13}C NMR (150 MHz $CDCl_3$) δ (ppm): 12.8, 27.6, 52.0, 89.1, 104.5, 114.5,

156.4, 163.7, 165.1, 168.2; MS (EI) m/z: 238 ($M^+ + 1$, 15), 237 (M^+, 100), 236 ($M^+ - 1$, 32), 205 (21), 177 (28); IR (KBr) υ (cm^{-1}): 3418, 3315, 3197, 3002, 2214 (CN), 1690 (C=O), 1610, 1550, 1238, 1096. Anal. calcd. for $C_{10}H_{11}N_3O_2S$: C, 50.62; H, 4.67; N, 17.71; S, 13.51. Found: C, 50.90; H, 4.92; N, 17.78; S, 13.88.

4-Amino-5-cyano-2-methyl-6-methylsulfanyl-nicotinic acid ethyl ester 3B. White crystal; yield 95%; mp 136.0–138.0°C; ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm): 1.41 (t, $J = 7.2$ Hz, 3H, $\underline{OCH_2}CH_3$), 2.62 (s, 3H, SCH_3), 2.70 (s, 3H, py-$\underline{CH_3}$), 4.39 (q, $J = 7.2$ Hz, 2H, $\underline{OCH_2}$), 6.68 (s, 2H, NH_2); ^{13}C NMR (150 MHz $CDCl_3$) δ (ppm): 12.8, 14.1, 27.6, 61.4, 89.1, 104.7, 114.5, 156.4, 163.6, 164.9, 167.8; MS (EI) m/z: 252 ($M^+ + 1$, 23), 251 (M^+, 100), 250 ($M^+ - 1$, 41), 223 (47), 205 (31), 177(30); IR (KBr) υ (cm^{-1}): 3406, 3309, 3200, 2983, 2219 (CN), 1682 (C=O), 1618, 1546, 1241, 1097. Anal. calcd. for $C_{11}H_{13}N_3O_2S$: C, 52.57; H, 5.21; N, 16.72; S, 12.76. Found: C, 52.75; H, 4.80; N, 16.89; S, 12.72.

5-Acetyl-4-amino-6-methyl-2-methylsulfanyl-nicotinonitrile 3C. White crystal; yield 93%; mp 164.8–165.1°C; ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm): 2.58 (s, 3H, $COCH_3$), 2.62 (s, 3H, SCH_3), 2.68 (s, 3H, py-$\underline{CH_3}$), 6.62 (s, 2H, NH_2); ^{13}C NMR (150 MHz $CDCl_3$) δ (ppm): 12.8, 27.2, 33.0, 89.3, 114.5, 114.6, 155.0, 161.0, 164.7, 202.3; MS (EI) m/z: 221 (M^+, 100), 206 (44), 204 (43), 177 (36), 160 (40); IR (KBr) υ (cm^{-1}): 3416, 3334, 3233, 3006, 2210 (CN), 1668 (C=O), 1619, 1542, 1235. Anal. calcd. for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99; S, 14.49. Found: C, 54.47; H, 4.70; N, 19.28; S, 14.22.

4-Amino-5-cyano-6-ethylsulfanyl-2-methyl-nicotinic acid methyl ester 3D. White crystal; yield 86%; mp 137.2–139.2°C; ^{1}H NMR(400 MHz $CDCl_3$) δ (ppm): 1.37 (t, $J = 7.2$ Hz, 3H, $SCH_2\underline{CH_3}$), 2.68 (s, 3H, Py-$\underline{CH_3}$), 3.25 (q, $J = 7.2$ Hz, 2H, $S\underline{CH_2}CH_3$), 3.92 (s, 3H, OCH_3), 6.72(s, 2H, NH_2); ^{13}C NMR (150 MHz $CDCl_3$) δ (ppm): 14.6, 24.4, 27.6, 51.9, 89.2, 104.4, 114.5, 156.5, 163.7, 164.9, 168.2; MS (EI) *m/z*: 251 (M^+, 66), 236 (26), 218 (81), 204 (15), 191 (100), 186 (41), 159 (47), 130 (29); IR (KBr) υ (cm^{-1}): 3406, 3310, 3276, 2951, 2871, 2213 (CN), 1689 (C=O), 1612, 1546, 1240, 1093. Anal. calcd. for $C_{11}H_{13}N_3O_2S$: C, 52.57; H, 5.21; N, 16.72; S, 12.76. Found: C, 52.90; H, 4.97; N, 16.60; S, 12.36.

4-Amino-5-cyano-6-ethylsulfanyl-2-methyl-nicotinic acid ethyl ester 3E. White crystal; yield 91%; mp 145.0–146.9°C; ^{1}H NMR(400 MHz $CDCl_3$) δ (ppm): 1.37 (t, $J = 7.2$ Hz, 3H, CH_3), 1.41 (t, $J = 7.2$ Hz, 3H, CH_3), 2.68 (s, 3H, Py-$\underline{CH_3}$), 3.25 (q, $J = 7.6$ Hz, 2H, $S\underline{CH_2}CH_3$), 4.38 (q, $J = 7.2$ Hz, 2H, $O\underline{CH_2}CH_3$), 6.69 (s, 2H, NH_2); ^{13}C NMR (150 MHz $CDCl_3$) δ (ppm): 14.6, 24.4, 27.6, 51.9, 61.3, 89.2, 104.4, 114.5, 156.5, 163.7, 164.9, 168.2; MS (EI) *m/z*: 265 (M^+, 36), 250 (7), 232 (30), 204 (62), 191 (99), 186 (57), 159 (100), 131 (50); IR (KBr) υ (cm^{-1}): 3411, 3305, 3268, 2978, 2874, 2213 (CN), 1680 (C=O), 1609, 1544, 1240, 1092. Anal. calcd. for $C_{12}H_{15}N_3O_2S$: C, 54.32; H, 5.70; N, 15.84; S, 12.08. Found: C, 54.53; H, 5.41; N, 16.04; S, 12.35.

5-Acetyl-4-amino-2-ethylsulfanyl-6-methyl-nicotinonitrile 3F. Yellow crystal; yield 89%; mp 133.2–135.2°C; ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm): 1.38 (t, $J = 7.2$ Hz, 3H, $SCH_2\underline{CH_3}$), 2.59 (s, 3H, $COCH_3$), 2.70 (s, 3H, py-$\underline{CH_3}$), 3.28 (q, $J = 5.6$ Hz, 2H, $S\underline{CH_2}CH_3$), 6.68 (s, 2H, NH_2); ^{13}C NMR (150 MHz $CDCl_3$) δ

(ppm): 14.6, 24.4, 27.2, 32.9, 89.4, 114.4, 114.5, 155.1, 161.0, 164.5, 202.3; MS (EI) m/z: 236 ($M^+ + 1$, 37), 235 (M^+, 100), 234 ($M^+ - 1$, 52), 220 (54), 202 (53), 192 (16), 160 (18); IR (KBr) υ (cm^{-1}): 3398, 3300, 3191, 2971, 2214 (CN), 1658 (C=O), 1606, 1532, 1228. Anal. calcd. for $C_{11}H_{13}N_3OS$: C, 56.15; H, 5.57; N, 17.86; S, 13.63. Found: C, 56.24; H, 5.88; N, 18.05; S, 13.60.

4-Amino-6-benzylsulfanyl-5-cyano-2-methyl-nicotinic acid methyl ester 3G. Yellow crystal; yield 87%; mp 139.4–141.7°C; ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm): 2.71 (s, 3H, Py-$\underline{CH_3}$), 3.92 (s, 3H, OCH_3), 4.51 (s, 2H, Ph$\underline{CH_2}$), 6.69 (s, 2H, NH_2), 7.24–7.41(m, 5H, Ph-H); ^{13}C NMR (150 MHz $CDCl_3$) δ (ppm): 27.6, 33.9, 52.1, 89.1, 104.8, 114.4, 127.3, 128.4, 129.1, 137.4, 156.6, 163.7, 164.2, 168.2; MS (EI) m/z: 314 ($M^+ + 1$, 17), 313 (M^+, 100), 312 ($M^+ - 1$, 27), 280 (18), 255 (4); IR (KBr) υ (cm^{-1}): 3426, 3307, 3004, 2211 (CN), 1677 (C=O), 1603, 1547, 1250. Anal. calcd. for $C_{16}H_{15}N_3O_2S$: C, 61.32; H, 4.82; N, 13.41; S, 10.23. Found: C, 61.41; H, 4.39; N, 13.33; S, 10.53.

4-Amino-6-benzylsulfanyl-5-cyano-2-methyl-nicotinic acid ethyl ester 3H. Yellow crystal; yield 89%; mp 109.7–112.0°C; ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm): 1.41 (t, $J = 7.2$ Hz, 3H, $OCH_2\underline{CH_3}$), 2.72 (s, 3H, Py-$\underline{CH_3}$), 4.38 (q, $J = 7.2$ Hz, 2H, $O\underline{CH_2}CH_3$), 4.51 (s, 2H, Ph$\underline{CH_2}$), 6.70 (s, 2 H, NH_2), 7.24–7.41(m, 5 H, Ph-H); ^{13}C NMR (150 MHz $CDCl_3$) δ (ppm): 14.1, 27.5, 33.9, 61.2, 88.9, 104.9, 114.3, 127.2, 128.4, 129.1, 137.4, 156.6, 163.5, 163.9, 167.7; MS (EI) m/z: 328 ($M^+ + 1$, 18), 327 (M^+, 100), 326 ($M^+ - 1$, 74), 299 (11), 255 (28), 212 (38); IR (KBr) υ (cm^{-1}): 3419, 3312, 2986, 2211 (CN), 1673 (C=O), 1606, 1546, 1237. Anal. calcd. for $C_{17}H_{17}N_3O_2S$: C, 62.36; H, 5.23; N, 12.83; S, 9.79. Found: C, 62.14; H, 4.97; N, 12.76; S, 9.63.

5-Acetyl-4-amino-2-benzylsulfanyl-6-methyl-nicotinonitrile 3I. Yellow crystal; yield 85%; mp 154.2–155.2°C; ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm): 2.58 (s, 3H, $COCH_3$), 2.70 (s, 3H, py-$\underline{CH_3}$), 4.50 (s, 2H, S$\underline{CH_2}$Ph), 6.62 (s, 2H, NH_2), 7.23–7.41 (m, 5H, Ph); ^{13}C NMR (150 MHz $CDCl_3$) δ (ppm): 27.1, 32.9, 33.9, 89.1, 114.3, 114.8, 127.2, 128.4, 129.1, 137.3, 155.1, 160.9, 163.7, 202.3; MS (EI) m/z: 298 ($M^+ + 1$, 22), 297 (M^+, 100), 296 ($M^+ - 1$, 48), 265 (18), 220 (11); IR (KBr) υ (cm^{-1}): 3447, 3341, 2975, 2207 (CN), 1663 (C=O), 1615, 1534, 1233. Anal. calcd. for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13; S, 10.78. Found: C, 64.97; H, 5.39; N, 14.21; S, 10.90.

Synthesis of 4-Amino-5-cyano-2-methyl-6-alkylamino-Nicotinic Acid Derivatives 5A–F

A mixture of N-substituted diaminomethylene-malononitrile **4** (10 mmol) and $Zn(NO_2)_2 \cdot 6H_2O$ (20 mmol) and a catalytic amount of TEBA (0.2 mmol) were added to a stirred solution of β-ketoesters **2** (20 mmol) or acetylacetone **2** (20 mmol) in anhydrous ethanol (30 ml). The mixture was heated under reflux for 6 h and then cooled. The precipitate was recrystallized from ethanol–water to give 4-amino-5-cyano-2-methyl-6-alkylamino-nicotinic acid derivatives **5A–F** in good yield.

Selected Data

4-Amino-6-propylamino-5-cyano-2-methyl-nicotinic acid ethyl ester 5A. White solid; yield 41%; Mp 141.0–142.0°C; ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm): 0.97(t, $J = 7.2$ Hz, 3H, $NHCH_2\underline{CH_3}$), 1.38 (t, $J = 7.2$ Hz, 3H, $OCH_2\underline{CH_3}$), 1.63 (m, 2H, $CH_2\underline{CH_2}CH_3$), 2.60 (s, 3H, Py-CH_3), 3.50 (q, $J = 6.8$ Hz, 2H, $NH\underline{CH_2}CH_2$), 4.33 (q, $J = 7.2$ Hz, 2H, $O\underline{CH_2}CH_3$), 5.12 (s, 1H, NH), 6.68 (s, 2H, NH_2); ^{T3}C NMR (150 MHz $CDCl_3$) δ (ppm): 11.3, 14.3, 22.9, 28.3, 42.8, 60.6, 72.5, 99.5, 116.3, 158.4, 158.5, 166.3, 168.2. Anal. calcd. for $C_{13}H_{18}N_4O_2$: C, 59.53; H, 6.92; N, 21.36. Found: C, 59.46; H, 6.74; N, 21.50.

4-Amino-6-butylamino-5-cyano-2-methyl-nicotinic acid ethyl ester 5B. White solid; yield 50%; Mp 129.8–131.2°C; ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm): 0.96 (t, $J = 7.2$ Hz, 3H, $CH_2\underline{CH_3}$), 1.36–1.43 (m, 5H, $OCH_2\underline{CH_3}$ $+CH_2\underline{CH_2}CH_3$), 1.58 (t, $J = 4.0$ Hz, 2H, $\underline{CH_2}CH_2CH_3$), 2.60 (s, 3H, Py-CH_3), 3.54 (q, $J = 6.4$ Hz, 2H, $NH\underline{CH_2}CH_2$), 4.32 (q, $J = 7.2$ Hz, 2H, $O\underline{CH_2}CH_3$), 5.14 (s, 1H, NH), 6.68 (s, 2H, NH_2); ^{13}C NMR (150 MHz $CDCl_3$) δ (ppm): 13.8, 14.3, 19.9, 28.3, 31.8, 40.8, 60.6, 72.5, 99.5, 116.3, 158.3, 158.4, 166.3, 168.2; MS (EI) m/z: 276 (M^+, 39), 261 (5), 247 (48), 234 (84), 219 (36), 205 (43), 187 (56), 174 (100), 162 (26); IR (KBr) υ (cm^{-1}): 3421, 3353, 2958, 2198 (CN), 1669 (C=O), 1612, 1505, 1563, 1273, 1094. Anal. calcd. for $C_{14}H_{20}N_4O_2$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.85; H, 6.99; N, 20.14.

4-Amino-6-benzylamino-5-cyano-2-methyl-nicotinic acid ethyl ester 5C. White solid; yield 61%; Mp 156.5–158.0°C; ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm): 1.39 (t, $J = 7.2$ Hz, 3H, $OCH_2\underline{CH_3}$), 2.62 (s, 3H, Py-CH_3), 4.34 (q, $J = 7.2$ Hz, 2H, $O\underline{CH_2}CH_3$), 4.75 (d, $J = 5.6$ Hz, 2H, $NH\underline{CH_2}$), 5.42 (s, 1H, NH), 6.74 (s, 2H, NH_2), 7.24–7.37 (m, 5H, Ph-H); ^{13}C NMR (150 MHz $CDCl_3$) δ (ppm): 14.2, 28.2, 44.8, 60.7, 72.8, 100.0, 116.1, 127.5, 127.8, 128.6, 138.6, 158.0, 158.5, 166.3, 168.1; MS (EI) m/z: 310 (M^+, 100), 281 (8), 263 (8), 236 (5), 205 (11), 159 (9), 106 (78), 91 (31); IR (KBr) υ (cm^{-1}): 3433, 3361, 2980, 2200 (CN), 1673 (C=O), 1602, 1504, 1564, 1241, 1025. Anal. calcd. for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.85; N, 18.05. Found: C, 65.75; H, 5.61; N, 17.82.

4-Amino-6-benzylamino-5-cyano-2-methyl-nicotinic acid methyl ester 5D. White solid; yield 73%; Mp 138.8–140.8°C; ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm): 2.62 (s, 3H, Py-CH_3), 3.88 (s, 3H, OCH_3), 4.75 (d, $J = 5.6$ Hz, 2H, $NH\underline{CH_2}$), 5.44 (s, 1H, NH), 6.74 (s, 2H, NH_2), 7.28–7.37 (m, 5H, Ph-H); ^{13}C NMR (150 MHz $CDCl_3$) δ (ppm): 28.2, 44.8, 51.5, 72.8, 99.8, 116.0, 127.5, 127.8, 128.6, 138.5, 158.1, 158.4, 166.4, 168.5; MS (EI) m/z: 296 (M^+, 100), 263 (11), 236 (6), 218 (8), 191 (16), 159 (10), 106 (66), 91 (27); IR (KBr) υ (cm^{-1}): 3423, 3345, 2949, 2202 (CN), 1673 (C=O), 1602, 1503, 1562, 1284, 1091. Anal. calcd. for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 65.28; H, 5.39; N, 18.74.

5-Acetyl-4-amino-2-(2-chlorobenzyl)amino-6-methyl-nicotinonitrile 5E. Yellow solid; yield 45%; Mp 191.2–192.5°C; ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm): 2.54 (s, 3H, $CO\underline{CH_3}$), 2.60 (s, 3H, Py-CH_3), 4.84 (d, $J = 5.6$ Hz, 2H, $NH\underline{CH_2}$), 5.63 (s, 1H, $N\underline{H}$), 6.88 (s, 2H, NH_2), 7.23–7.43(m, 4H, Ph-H); ^{13}C NMR (150 MHz $CDCl_3$) δ (ppm): 28.1, 33.3, 42.7, 79.1, 110.5, 115.8, 126.9, 128.9, 129.6,

130.0, 133.7, 135.9, 157.7, 157.8, 164.5, 201.1; MS (EI) m/z: 316 ($M^+ + 2$, 10), 315 ($M^+ + 1$, 15), 314 (M^+, 42), 299 (6), 279 (92), 203 (5), 175 (14), 160 (11), 140 (100), 125 (72); IR (KBr) υ (cm^{-1}): 3406, 3338, 2916, 2203 (CN), 1722 (C=O), 1583, 1503, 1554, 1280, 1038. Anal. calcd. for $C_{16}H_{15}ClN_4O$: C, 61.05; H, 4.80; N, 17.80. Found: C, 61.46; H, 4.54; N, 17.81.

4-Amino-5-cyano-6-(4-methoxybenzyl)amino-2-methyl-nicotinic acid ethyl ester 5F. White solid 0.82 g; yield 80%; Mp 133.7–135.8°C; ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm): 1.39 (t, $J = 7.2$ Hz, 3H, $OCH_2\underline{CH_3}$), 2.62 (s, 3H, Py-CH_3), 3.81 (s, 3H, OCH_3), 4.33 (q, $J = 7.2$ Hz, 2H, $O\underline{CH_2}CH_3$), 4.67 (d, $J = 2.8$ Hz, 2H, $NH\underline{CH_2}$), 5.36 (s, 1H, NH), 6.68 (s, 2H, NH_2), 6.86–7.27 (m, 4H, Ph-H); ^{13}C NMR (150 MHz $CDCl_3$) δ (ppm): 14.2, 28.2, 44.4, 55.2, 60.7, 72.7, 99.9, 113.9, 116.1, 129.2, 130.6, 157.9, 158.5, 158.9, 166.3, 168.1; MS (EI) m/z: 340 (M^+, 100), 325 (10), 293 (5), 205 (7), 136 (59), 121 (89), 77 (11); IR (KBr) υ (cm^{-1}): 3485, 3360, 2938, 2202 (CN), 1670 (C=O), 1594, 1510, 1561, 1246, 1024. Anal. calcd. for $C_{18}H_{20}N_4O_3$: C, 63.52; H, 5.92; N, 16.46. Found: C, 63.46; H, 5.64; N, 16.45.

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