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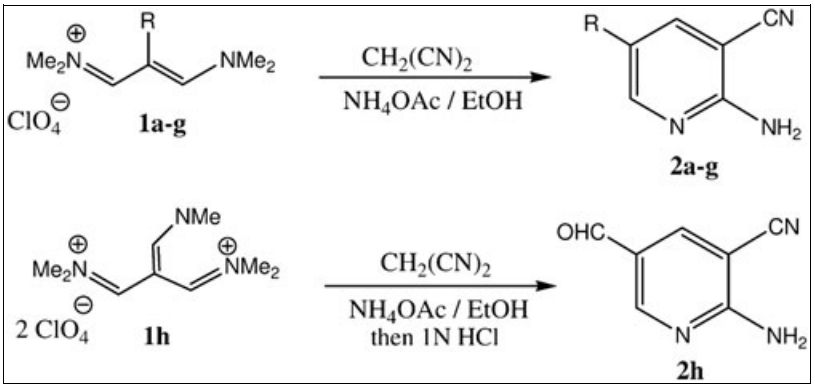

The symmetrical vinamidinium salts were allowed to react with malononitrile in refluxing ethanol in the presence of ammonium acetate for 12 h to afford the 2-amino-5-aryl or formylpyridine-3-carbonitriles.

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INTRODUCTION

In our quest to utilise vinamidinium salts as three-carbon synthons in the formation of heterocyclic compounds, we have reported the preparation of pyridine-2-ones [1, 2] and pyrimidines [3]. The pyridine ring is one of the most well-known systems among the naturally occurring heterocycles [4]. Classical methods for the formation of pyridines have been used extensively. Such methods include the Friedländer condensation of enaminoketones of β-ketoesters with 1,3-diketones [5], the Hantzsch pyridine synthesis from β-dicarbonyl compounds in the presence of an aldehyde and ammonia [6] and the related Knovenagel cyclisation of β-aminoacrylates with α,β-unsaturated carbonyl compounds [7]. The synthesis of trisubstitued pyridines has been reported [8, 9] from the reaction of deoxybenzoin, vinamidinium species and ammonia in good yields and act as Cox-2 inhibitors. 2-Aminopyridine are promising substituted pyridines which have been shown to be biologically active molecules [10]. Additionally, because of their chelating abilities, 2-aminopyridines are commonly used as ligands in inorganic and organometallic chemistry [11]. This class of compounds and their derivatives are valuable synthetic target compounds and their synthesis has been extensively reviewed [12–17].

RESULTS AND DISCUSION

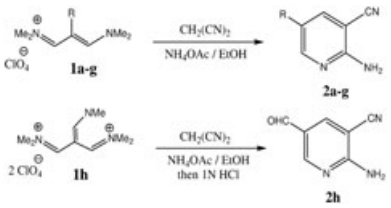
We report here a simple method for the synthesis of 2-amino-5-aryl or formylpyridine-3-carbonitriles in one-step procedure by condensation of symmetrical vinamidinium salts with malononitrile and ammonium acetate.

The vinamidinium salts (**1a**–**g**) used in this study were prepared by the standard Vilsmeir–Haack reaction of the appropriate aryl acetic [18]. During the course of our studies on the synthetic application of vinamidinium salts, we succeeded in a very simple access to 2-dimethylaminomethylene-1,3-bis(dimethylimonio)propane diperchlorate **1h** from malonic acid [19]. All of these salts, were isolated as the perchlorate and were used without further purification for the synthesis of 3,5-disubstituted 2-aminopyridines. As shown in Scheme 1, the symmetrical vinamidinium salts (**1a**–**h**) were allowed to react with malononitrile in refluxing ethanol in the presence of ammonium acetate for 12 h to afford the 2-amino-5-aryl or formylpyridine-3-carbonitriles (**2a**–**h**). For the most part the reactions were rather clean and proceed in excellent yields (Table 1).

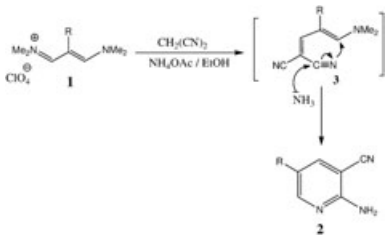
Additionally, as shown in Table 1, the phenylsulfonyl at the C_5-substituent (**2g**) affected the cyclocondensation reaction. This may be the result of the "push–pull" relationship between the strong electron-withdrawing sulfonyl group at C_2 position and enamine group, in the corresponding vinamidinium salts allowing the imino group to behave like an isolated moiety.

The proposed mechanism delineated in Scheme 2 involves addition of malononitrile to vinamidinium salts (**1**) and should lead to the formation of enamine (**3**). Alternatively, intramolecular cyclisation of this intermediate induced by ammonium acetate with elimination of

Scheme 1



Scheme 2. Proposed reaction mechanism.



dimethylamine would give the 5-substituted 2-aminopyridine-3-carbonitrile (**2**).

CONCLUSION

In summary, we have demonstrated that malononitrile react with vinamidinium salts in the presence of ammonium acetate to give in one-step the corresponding 2-amino-5-aryl or formylpyridine-3-carbonitriles in fair to excellent yields. Therefore, the aldehyde group becomes a convenient vehicle for functional group interconversion.

EXPERIMENTAL

Melting points were determined in a capillary tube and are uncorrected. The ^{1}H-NMR spectra were recorded on a Brucker AC 300 MHz spectrometer in $CDCl_3$ containing tetramethylsilane as an internal standard. Elemental analyses were determined by using Perkin-Elmer 240c elemental analyzer. Thin layer chromatography (TLC) was performed on precoated silica gel plates (0.25 mm, Merck). Column chromatography was performed on Merck silica gel having size 0.063–0.200 mm.

General procedure for the heteroannulation. A mixture of vinamidinium salt **1** (0.48 mmol), malononitrile (1 mmol), ammonium acetate (3.36 mmol), and anhydrous ethanol (8 mL) were combined in a reaction flask and allowed to reflux overnight at which time the reaction mixture was allowed to cool at room temperature and the solvent was removed by rotary evaporation. The resulting residue was partitioned between methylene chloride and water. The aqueous layer was extracted with fresh methylene chloride and the combined organic layers were dried over sodium sulphate. The drying agent was removed by filtration and the solvents were removed in vacuo to give the crude material. The crude product was purified by a column chromatography (10% EtOAc in hexane) to give product **2a**–**g**. However, for trisubstituted pyridine **2h**, after evaporation of the solvent, 6 mL of THF and 6 mL of 1 N HCl are added. The mixture is allowed to stir at room temperature for 2 h, then neutralized with satured aqueous $NaHCO_3$ and extracted with three portions of methylene chloride.

Table 1

Synthesis of 2-amino-5-aryl or formylpyridine-3-carbonitriles **2a–h**.

Compound[a]	R	R′	Yield (%)
2a	Ph	Ph	96
2b	4-CH_3OPh	4-CH_3OPh	97
2c	4-CH_3Ph	4-CH_3Ph	95
2d	4-BrPh	4-BrPh	91
2e	4-ClPh	4-ClPh	94
2f	Naphtyl	Naphtyl	92
2g	SO_2Ph	SO_2Ph	82
2h	$HC=\overset{\oplus}{N}(Me)_2$	CHO	78

[a]All products were characterized from their ^{1}H NMR, ^{13}C NMR, and mass spectroscopic data.

Representative spectral data of selected compounds.

2-Amino-5-phenylpyridine-3-carbonitrile (2a). Yield: 96%; yellow solid; mp = 132–134°C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.72 (s, 2H), 7.40–7.60 (m, 5H), 7.83–7.7.84 (d, 1H, *J* = 2.6 Hz), 8.41–8.42 (d, 1H, *J* = 2.6 Hz); Anal. calcd. for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52%. Found: C, 73.79; H, 4.60; N, 21.48%. Mass *m/z* (EI, 30 eV): *m/z* = 195 (M^+).

2-Amino-5-(4-methoxyphenyl)pyridine-3-carbonitrile (2b). Yield: 97%; yellow solid; mp = 137–139°C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.42 (s, 3H), 5.81 (s, 2H), 6.91–6.96 (m, 2H), 7.11–7.16 (m, 2H), 7.49–7.50 (m, 2H, *J* = 2.4 Hz), 7.94–7.95 (d, 1H, *J* = 2.4 Hz); ^{13}C-NMR ($CDCl_3$) δ = 55.8, 107.6, 113.9, 128.8, 132.6, 132.8, 135.8, 136.2, 137.1, 145.7, and 159.9. Anal. calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.65%. Found: C, 69.28; H, 4.89; N, 18.62%. Mass *m/z* (EI, 30 eV): *m/z* = 225 (M^+)

2-Amino-5-(1-naphtyl)pyridine-3-carbonitrile (2f). Yield: 92%; yellow solid; mp = 148–150°C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.51 (s, 2H), 7.40–7.87 (m, 5H), 7.83–7.84 (d, 1H, *J* = 2.4 Hz), 8.41–8.42 (d, 1H, *J* = 2.4 Hz); ^{13}C-NMR ($CDCl_3$) δ = 125.53, 126.157, 127.45, 128.45, 129.189, 130.30, 130.95, 132.8, 135.8, 136.2, 137.1, 145.7, and 159.9. Anal. calcd. for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13%. Found: C, 78.31; H, 4.49; N, 17.11%. Mass *m/z* (EI, 30 eV): *m/z* = 245 (M^+).

2-Amino-5-formylpyridine-3-carbonitrile (2h). Yield: 78%; yello-white solid; mp = 127–129°C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.06 (s, 2H), 8.18 (d, H, *J* = 2.3 Hz), 9.21(d, H, *J* = 2.3 Hz), 9.95 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ = 97.31, 115.38, 123.24, 142.19, 154.92, 168.84, and 192.45. Anal. calcd. for $C_7H_5N_3O$: C, 57.14; H, 3.43; N, 28.56%. Found: C,57.11; H, 3.41; N, 28.53%. Mass *m/z* (EI, 30 eV): *m/z* = 147 (M^+).

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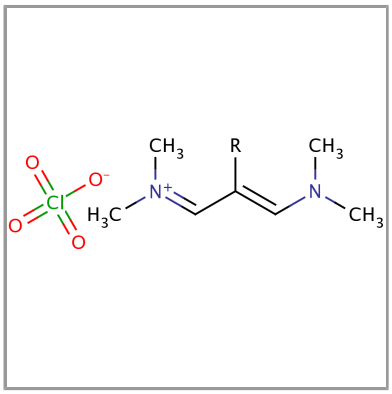

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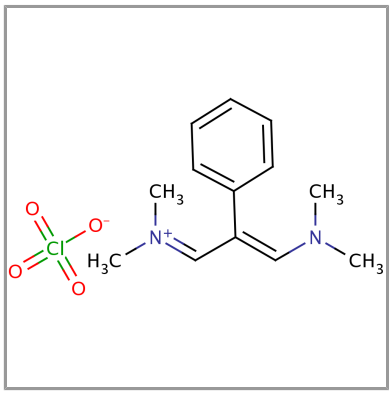

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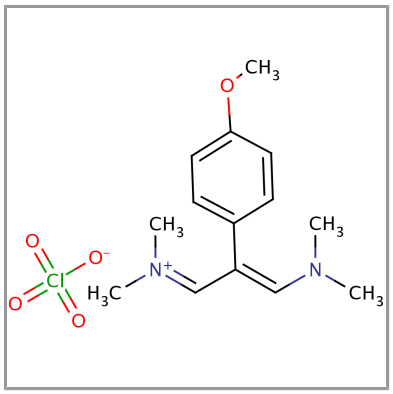

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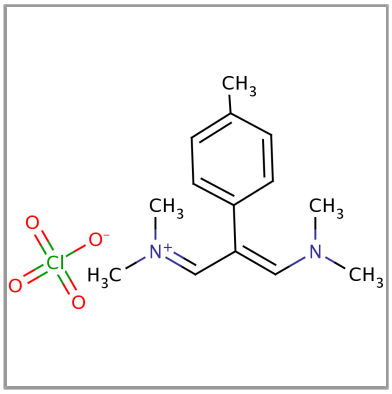

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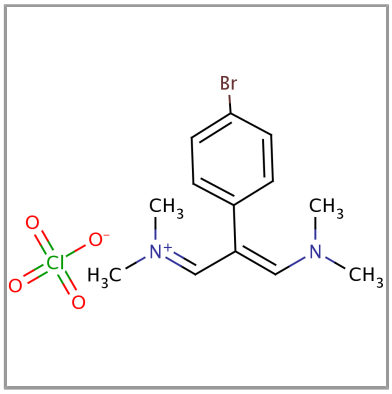

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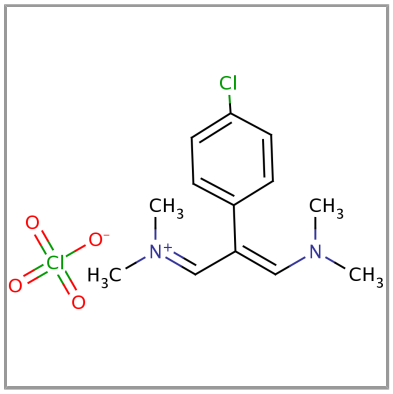

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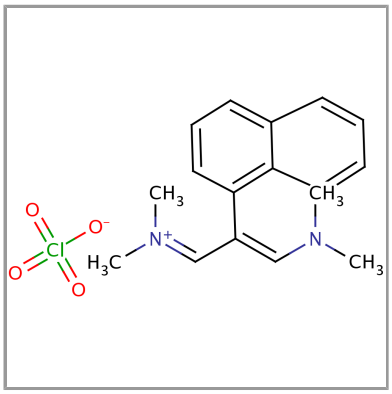

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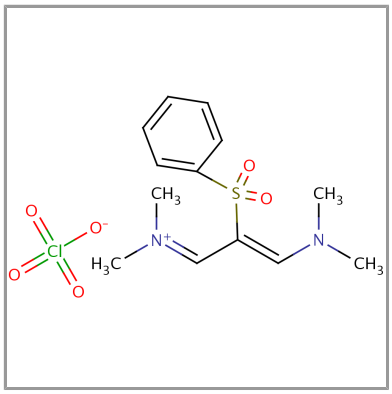

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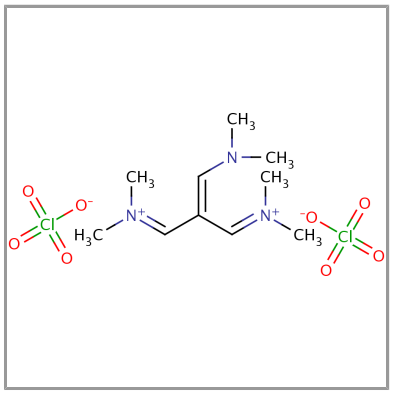

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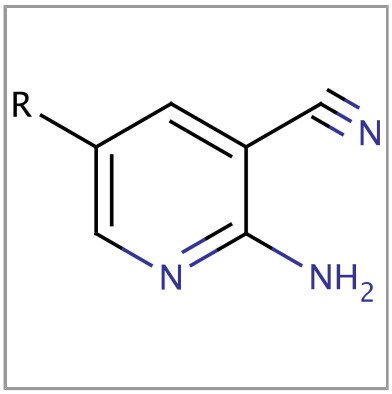

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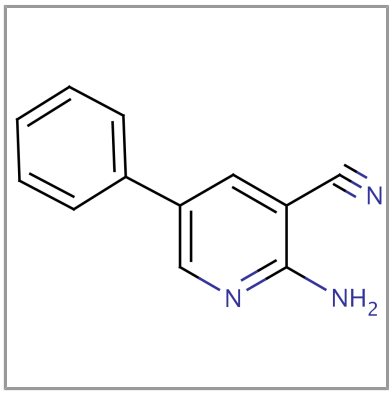

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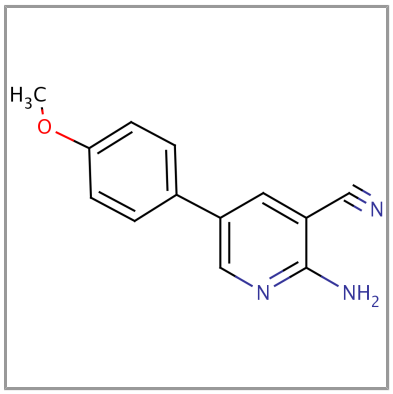

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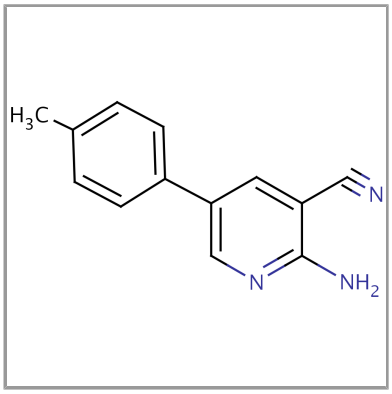

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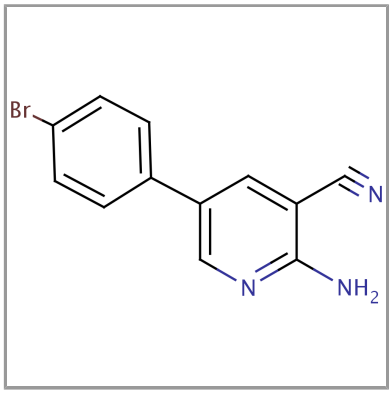

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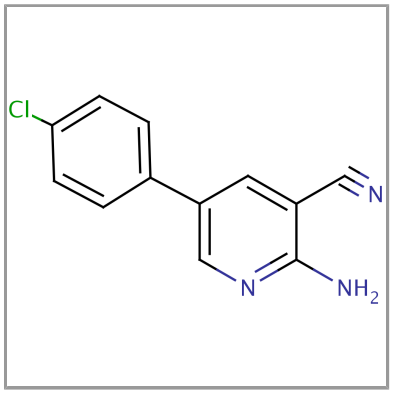

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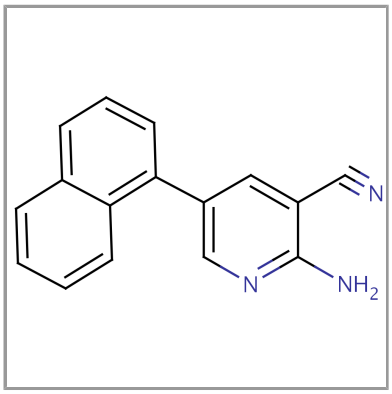

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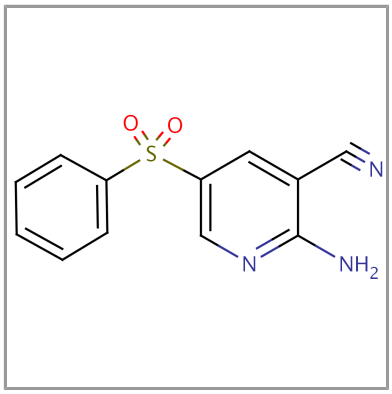

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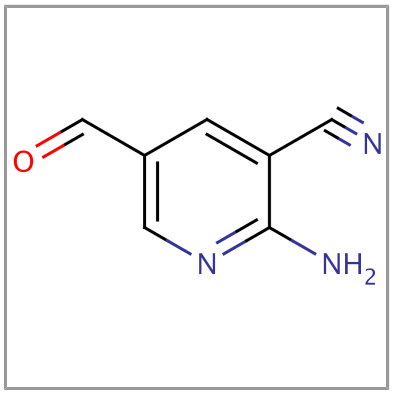

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