Diastereoselective Synthesis of Nicotine Derivatives *via* 1,3-Dipolar Cycloaddition Reactions

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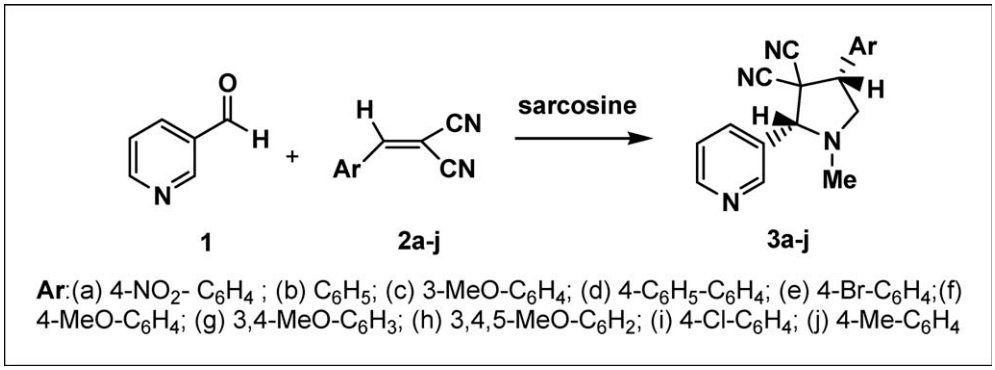

A simple diastereoselective route to nicotine derivatives is presented. The one-pot three component 1,3-dipolar cycloaddition reaction of the Knöevenagel adducts of a number of aromatic aldehydes and malononitrile with an azomethine ylide derived *in situ* from pyridine-3-carbaldehyde and sarcosine give access to nicotine derivatives in good yields.

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INTRODUCTION

(S)-Nicotine is present together with a number of minor alkaloids in tobacco and a wide variety of other plants (Fig. 1). Dried leaves of the tobacco plants *Nicotiana rustica* and *N. tabacum* contain as much as 2–8% of (S)-nicotine [1]. A large scale application of nicotine was its use as an insecticide, as ~2800 tons of (S)-nicotine was used as a crop protectant per year [2]. Aqueous solutions of nicotine sulfate are still used throughout the world as insecticides. (S)-Nicotine has drawn a lot of interest in the last few decades due to its potential role in therapeutics for the central nervous system (CNS) [1]. In particular, (S)-nicotine may have beneficial effects in the treatment of Parkinson's disease (PD), Alzheimer's disease (AD), Tourette's syndrome, anxiety, schizophrenia, uterative colitis, and other disorders [3]. Detrimental effects including actions on both the cardiovascular and gastrointestinal systems, sleep disturbance, and at higher doses, neuromuscular effects and seizures limit the use of nicotine as a therapeutic reagent [4]. These side effects are due to subtype selectivity, or a lack thereof, among the various *n*AChRs [5]. Hence, there has been a need to synthesize nicotine derivatives that are more selective in their binding to ACh sites to minimize side effects while retaining beneficial activity.

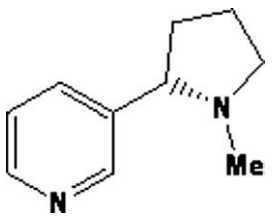
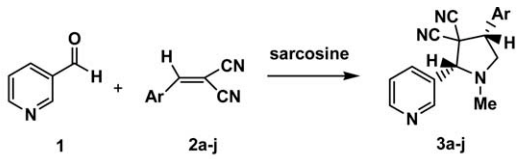


Figure 1. (S)-Nicotine.

RESULTS AND DISCUSSION

Considerable attention has been given to the synthesis of nicotine derivatives that would exhibit the beneficial biological properties at lower toxicity [6]. Most of the approaches have been directed toward the synthesis of nicotine [3] and nicotine analog derivatives [7] with modification on the pyridine ring. 1,3-Dipolar cycloaddition reactions of azomethine ylides with various alkenes and alkynes represent an efficient and convergent method for the construction of pyrrolidine and pyrrolizine units [8]. To the best of our knowledge, a few reports are present in literature for the preparation of nicotine derivatives with modification at the pyrrolidine ring *via* cycloaddition of azomethine ylides to chalcones. 1,3-Dipolar cycloaddition of phenylvinyl sulfone with azomethine ylide generated based on the

Scheme 1. Synthesis of Nicotine derivatives **3**.



Ar:(a) 4-NO_2- C_6H_4 ; (b) C_6H_5; (c) 3-MeO-C_6H_4; (d) 4-C_6H_5-C_6H_4; (e) 4-Br-C_6H_4;(f) 4-MeO-C_6H_4; (g) 3,4-MeO-C_6H_3; (h) 3,4,5-MeO-C_6H_2; (i) 4-Cl-C_6H_4; (j) 4-Me-C_6H_4

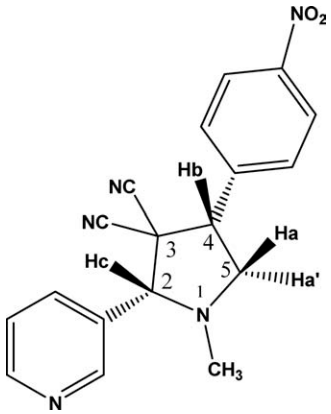
in situ, fluorine-mediated desilylation of cyanoaminosilane afforded 3-benzensulfonylnicotine [9]. Recently, Zhai and his coworkers utilized the azomethine ylide–alkene [3+2] cycloadditions toward the synthesis of conformationally restricted nicotine derivatives [10]. Herein, we describe a simple diastereoselective synthesis of nicotine derivatives *via* one-pot three component 1,3-dipolar cycloaddition reaction of the Knöevenagel adducts of a number of aromatic aldehydes and malononitrile with an azomethine ylide derived *in situ* from pyridine-3-carbaldehyde and sarcosine in refluxing toluene.

The Knöevenagel adducts **2a**–**j** were prepared from the condensation of malononitrile with a series of aromatic aldehydes *via* the previously reported procedure [8c]. These adducts were subsequently treated with pyridine-3-carbaldehyde **1** and sarcosine in refluxing toluene for 3 h (Scheme 1). After evaporation of solvent under reduced pressure, methanol was added, and the solid products were filtered and recrystallized from methanol resulting in nicotine derivatives **3a**–**j**.

Identification of the products was carried out by spectroscopic methods. The ^{1}H NMR spectrum of **3a** (Scheme 2) exhibited a singlet at δ 2.42 for N—CH_3, a doublet of doublets appears as a triplet at δ 3.26 (J = 10.3 Hz, Ha′), a doublet of doublets at δ 3.83 (J = 10.3, 5.7 Hz, Ha), a singlet at δ 4.15 (Hc), a doublet of doublets at δ 4.25 (J = 10.3, 5.7 Hz, Hb), a multiplet at δ 7.46 (pyridine-*m*-H), a doublet at δ 7.76 (J = 8.6 Hz, Ar-*m*-2H), a broad doublet at δ 7.98 (pyridine-*p*-H), a doublet at δ 8.34 (J = 8.6 Hz, Ar-*o*-2H), a broad doublet at δ 8.76 (pyridine-*o*-H), and a singlet at δ 8.82 (pyridine-*o*-H). The ^{13}C NMR spectrum of **3a** showed 16 signals at δ 39.8, 50.4, 52.2, 58.6, 76.5, 111.7, 114.2, 124.4, 124.8, 128.8, 130.0, 136.3, 142.5, 148.9, 150.4, and 152.2. The MS (EI) spectrum revealed the molecular ion peak at *m*/*z* 333 corresponding to the molecular weight of **3a**.

The relative configuration of the stereocenters in **3a** was assigned using X-ray crystallographic study of its single crystal (Fig. 2), which implied a cis (syn diastereomer) arrangement between C-2 and C-4 [11]. On the basis of this result, we propose a transition-state model to account for the diastereoselectivity of the reaction (Scheme 3). Hence, the structure of the azomethine ylides generated *in situ* may be represented as *E* and *Z* diastereomers. These two can approach the chalcone *via* **I**, **II**, and **I**′, **II**′ structures, respectively. **I** and **I**′ are sterically favored relative to **II** and **II**′ since the latter two experience more steric hindrance from aryl and methyl groups which are eclipsed to each other (Scheme 3). The formation of the 2,4-syn diastereomer as the sole product in most cases reveals that the azomethine ylide with the structure of **I***E* configuration has been implicated in the reaction pathway. Since **3c** and **3h** are generated as a mixture of dl, and identified as syn and anti with the ratios of 3:2 and 2:1, respectively, the involvement of both **I***E* and **II***E* azomethine configurations in reaction should be taken into consideration. We believe that **2c** and **2h** albeit have different number of methoxy substituents, behave similarly since the electron withdrawing effect of the 5-methoxy group of **2h** on the Michael addition rate of zomethine ylide to ArCH=$C(CN)_2$ roughly offsets the electron donating effect of the 4-methoxy group. Therefore, the disfavored steric effect present in **II***E* in retarding the reaction rate of **2h** seems to be compensated by rate enhancement

Scheme 2. Strucure of derivative **3a**.



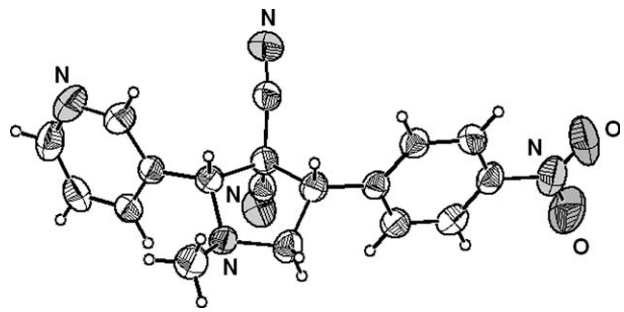
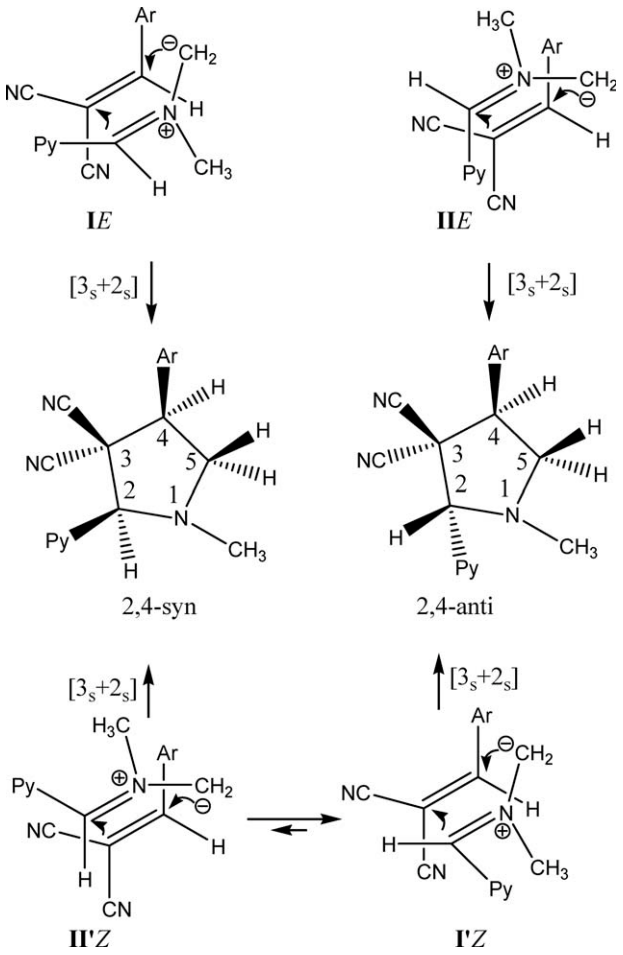


Figure 2. ORTEP diagram of **3a**.

Scheme 3. Transition state models evoked to account for reaction diastereoselectivities.

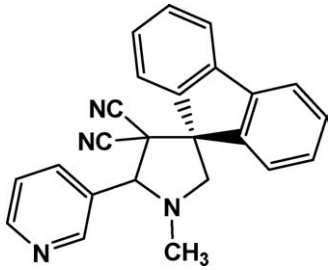


due to the favored electronic effect of the 3-methoxy group.

Under similar conditions, utilization of the Knöevenagel adduct of fluorenone with malononitrile afforded the corresponding 4-spironicotine derivative **3k** in 75% yield (Scheme 4). This reaction exhibits the diversity of the method in applying different chalcones.

In summary, a range of nicotine derivatives have been synthesized *via* the one-pot three component 1,3-dipolar cycloaddition reaction of the Knöevenagel adducts of a number of aromatic aldehydes and malononitrile with an azomethine ylide derived *in situ* from sarcosine and pyridine-3-carbaldehyde.

Scheme 4. Structure of derivative **3k**.



EXPERIMENTAL

All commercially available chemicals and reagents were used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer; in cm^{-1}. ^1H and ^{13}C NMR Spectra: Bruker DRX-500-AVANCE spectrometer at 500 (^1H) and 125.7 MHz (^{13}C); $CDCl_3$ solns.; δ in ppm, *J* in Hz. Mass spectra of the products were obtained with a HP (Agilent technologies) 5937 Mass Selective Detector. Elemental analyses were carried out by a CHN-O-Rapid Heraeus elemental analyzer (Wellesley, MA).

General procedure for the synthesis of *N*-methyl-4-(X-substituted)-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3a–k). A mixture of sarcosine (2.0 mmol), pyridine-3-carbaldehyde (2.0 mmol), and chalcone (2.0 mmol) in dry toluene (20 mL) containing molecular sieves 4 Å (1000 mg) was refluxed with stirring for 3 h. The progress of the reaction was followed by TLC. After completion, the solvent was removed under reduced pressure. After addition of methanol (1 mL), the resulting solid was filtered and recrystallized from methanol to afford a crystalline product (Table 1).

***N*-methyl-4-(4-nitrophenyl)-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3a).** Yellow crystals; Yield: 70%; mp 188–189°C; IR (KBr): 2250 cm^{-1}; ^{1}PH NMR: 2.42 (s, 3H), 3.26 (t, *J* = 10.3, 1H), 3.83 (dd, *J* = 10.3, 5.7, 1H), 4.15 (s, 1H), 4.25 (dd, *J* = 10.3, 5.7, 1H), 7.46 (m, 1H), 7.76 (d, *J* = 8.6, 2H), 7.98 (bd, 1H), 8.34 (d, *J* = 8.6, 2H), 8.76 (bd, 1H), 8.82 (s, 1H); ^{13}C NMR: 39.8, 50.4, 52.2, 58.6, 76.4, 111.7, 114.2, 124.4, 124.8, 128.8, 130.0, 136.3, 142.6, 148.9, 150.4, 152.2; MS: *m*/*z* = 333 [M^+]; Anal. Calcd. For $C_{18}H_{15}N_5O_2$: C, 64.86; H, 4.50; N, 21.02%. Found: C, 64.39; H, 4.38; N, 20.69%.

***N*-methyl-4-phenyl-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3b).** White crystals; Yield: 72%; mp 127–128°C; IR

Table 1

Results of synthesized nicotine derivaties.

Entry	Ar	Product	Yield (%)
1	4-Nitrophenyl	**3a**	70
2	Phenyl	**3b**	72
3	3-Methoxyphenyl[a]	**3c**	65
4	Biphenyl	**3d**	75
5	4-Bromophenyl	**3e**	73
6	4-Methoxyphenyl	**3f**	64
7	3,4-Methoxyphenyl	**3g**	70
8	3,4,5-Methoxyphenyl[a]	**3h**	68
9	4-Chlorophenyl	**3i**	77
10	4-Methylphenyl	**3j**	75

[a] Obtained as a mixture of dr, identified as 3:2 and 2:1 of anti:syn, respectively, by ^1H NMR.

(KBr): 2250 cm^{-1}; ^{1}PH NMR: 2.39 (s, 3H), 3.20 (t, J = 10.2, 1H), 3.85 (dd, J = 10.2, 6.6, 1H), 4.14 (m, 2H), 7.44–7.57 (m, 6H), 8.00 (bd, 1H), 8.74 (bd, 1H), 8.83 (s, 1H); ^{13}C NMR: 39.9, 50.9, 52.8, 58.4, 76.4, 112.0, 114.6, 124.3, 128.8, 129.4, 129.6, 129.7, 135.0, 136.4, 150.4, 151.9; MS: m/z = 288 [M^+]; Anal. Calcd. For $C_{18}H_{16}N_4$: C, 74.97; H, 5.59; N, 19.43%. Found: C, 74.56; H, 5.23; N, 19.72%.

N-methyl-4-(3-methoxyphenyl)-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3c). White crystals; Yield: 75%; IR (KBr): 2248 cm^{-1}; ^{1}PH NMR (syn/anti): 2.37 (s, 3H)/2.38 (s, 3H), 3.17 (t, J = 10.2, 1H)/3.05 (t, J = 10.2, 1H), 3.84 (dd, J = 10.2, 7.0, 1H)/3.73 (dd, J = 10.2, 7.0, 1H), 3.86 (s, 3H)/3.85, s, 3H), 4.12 (dd, J = 10.2, 7.0, 1H)/4.10 (dd, J = 10.2, 7.0, 1H), 4.14 (s, 1H)/4.04 (s, 1H), 6.93–6.96 (m, 2H)/7.00–7.03 (m, 2H), 7.13 (bd, 1H)/7.01 (bd, 1H), 7.36–7.39 (m, 2H)/7.41–7.45 (m, 2H), 7.99 (bd, 1H)/7.92 (bd, 1H), 8.73 (bd, 1H)/8.72 (bd, 1H), 8.82 (s, 1H)/8.79 (s, 1H); ^{13}C NMR (syn and anti mixture): 39.9, 49.4, 50.8, 52.7, 53.9, 55.8, 58.3, 60.1, 67.3, 76.9, 112.1, 113.8, 114.6, 114.6, 114.8, 114.9, 115.0, 115.2, 121.0, 121.1, 124.3, 124.3, 129.4, 130.6, 130.7, 130.8, 136.0, 136.4, 136.4, 136.5, 150.3, 150.4, 151.8, 151.9, 160.4, 160.49; MS: m/z = 318 [M^+]; Anal. Calcd. For $C_{19}H_{18}N_4O$: C, 71.66; H, 5.70; N, 17.60%. Found: C, 71.15; H, 6.10; N, 17.14%.

N-methyl-4-biphenyl-2-(pyridine-3-yl) pyrrolidine-3,3-dicarbonitrile (3d). White crystals; Yield: 77%; mp 152–153°C; IR (KBr): 2246 cm^{-1}; ^{1}PH NMR: 2.42 (s, 3H), 3.23 (t, J = 10.2, 1H), 3.88 (dd, J = 10.2, 6.6, 1H), 4.17 (s, 1H), 4.19 (dd, J = 10.2, 6.6, 1H), 7.39–7.53 (m, 4H), 7.64 (bd, 4H), 7.71 (bd, 2H), 8.03 (bd, 2H), 8.76 (bd, 1H), 8.82 (s, 1H); ^{13}C NMR: 39.9, 50.9, 52.6, 58.4, 76.3, 112.1, 114.6, 124.3, 127.6, 128.2, 128.3, 129.3, 129.3, 129.4, 129.5, 133.8, 136.4, 136.4, 140.6, 142.6, 150.4, 152.0; MS: m/z = 364 [M^+]; Anal. Calcd. For $C_{24}H_{20}N_4$: C, 79.12; H, 5.49; N, 15.38%. Found: C, 78.69; H, 5.51; N, 15.27%.

N-methyl-4-(4-bromophenyl)-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3e). White crystals; Yield: 73%; mp 154–155°C; IR (KBr): 2250 cm^{-1}; ^{1}PH NMR: 2.37 (s, 3H), 3.19 (t, J = 10.2, 1H), 3.77 (dd, J = 10.2, 6.3, 1H), 4.09 (dd, J = 10.2, 6.3, 1H), 4.12 (s, 1H), 7.42–7.46 (m, 3H), 7.60 (bd, 2H), 7.98 (bd, 1H), 8.74 (bd, 1H), 8.80 (s, 1H); ^{13}C NMR: 39.8, 50.7, 52.2, 58.4, 76.3, 112.0, 114.4, 124.0, 124.3, 129.2, 130.5, 130.6, 132.9, 134.2, 136.3, 150.4, 151.9, 152.0; MS: m/z = 367 [M^+]; Anal. Calcd. For $C_{18}H_{15}N_4Br$: C, 58.85; H, 4.11; N, 15.25%. Found: C, 58.36; H, 3.89; N, 15.05%.

N-methyl-4-(4-methoxyphenyl)-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3f). White crystals; Yield: 64%; mp 138–139°C; IR (KBr): 2248 cm^{-1}; ^{1}PH NMR: 2.37 (s, 3H), 3.17 (t, J = 10.2, 1H), 3.78 (dd, J = 10.2, 6.7, 1H), 3.84 (s, 3H), 4.10 (dd, J = 10.2, 6.7, 1H), 4.12 (s, 1H), 6.98 (d, J = 8.6, 2H), 7.42 (m, 1H), 7.47 (d, J = 8.6, 2H), 7.99 (bd, 1H), 8.72 (bd, 1H), 8.82 (s, 1H); ^{13}C NMR: 39.9, 51.2, 52.4, 55.8, 58.4, 76.2, 112.2, 114.7, 115.0, 124.3, 126.8, 129.6, 130.0, 136.3, 150.4, 151.9, 160.7; MS: m/z = 318 [M^+]; Anal. Calcd. For $C_{19}H_{18}N_4O$: C, 71.66; H, 5.70; N, 17.60%. Found: C, 71.33; H, 5.42; N, 17.47%.

N-methyl-4-(3,4-methoxyphenyl)-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3g). White crystals; Yield: 70%; mp 111–112°C; IR (KBr): 2252 cm^{-1}; ^{1}PH NMR: 2.37 (s, 3H), 3.18 (t, J = 10.2, 1H), 3.80 (dd, J = 10.2, 7.0, 1H), 3.91 (s, 3H), 3.95 (s, 3H), 4.08 (dd, J = 10.2, 7.0, 1H), 4.12 (s, 1H), 6.92 (d, J = 8.2, 2H), 7.06 (s, 1H), 7.10 (d, J = 8.2, 2H), 8.72 (bd, 1H), 8.81 (s, 1H); ^{13}C NMR: 39.9, 51.2, 52.9, 56.3, 56.5, 58.3, 76.1, 111.7, 111.8, 112.3, 114.6, 121.4, 124.3, 127.0, 129.4, 136.3, 149.8, 150.3, 150.3, 151.8; MS: m/z = 348 [M^+] Anal. Calcd. For $C_{20}H_{20}N_4O_2$: C, 68.93; H, 5.79; N, 16.08%. Found: C, 68.35; H, 5.29; N, 15.83%.

N-methyl-4-(3,4,5-methoxyphenyl)-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3h). White crystals; Yield: 64%; IR (KBr): 2245 cm^{-1}; ^{1}PH NMR (syn/anti): 2.38 (s, 3H)/2.39 (s, 3H), 3.18 (t, J = 10.3, 1H)/3.03 (t, J = 10.3, 1H), 3.80 (dd, J = 10.3, 7.0, 1H)/3.70 (dd, J = 10.3, 7.0, 1H), 3.91 (s, 9H)/3.89 (s, 9H), 4.07 (dd, J = 10.3, 7.0, 1H)/4.04 (dd, J = 10.3, 7.0, 1H), 4.13 (s, 1H)/4.05 (s, 1H), 6.75 (s, 2H)/6.62 (s, 2H), 7.46 (bd, 1H)/7.43 (bd, 1H), 7.99 (bd, 1H)/7.91 (bd, 1H), 8.73 (bd, 1H)/8.72 (bd, 1H), 8.82 (s, 1H)/8.79 (s, 1H); ^{13}C NMR (syn and anti mixture): 39.9, 40.0, 49.3, 51.0, 53.3, 54.5, 56.7, 56.8, 58.3, 60.1, 61.3, 61.3, 76.1, 106.0, 106.3, 112.2, 114.1, 114.6, 114.8, 124.3, 124.3; MS: m/z = 378 [M^+]; Anal. Calcd. For $C_{21}H_{22}N_4O_3$: C, 66.63; H, 5.86; N, 14.80%. Found: C, 66.76; H, 6.12; N, 14.73%.

N-methyl-4-(4-chlorophenyl)-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3i). White crystals; Yield: 77%; mp 147–148°C; IR (KBr): 2250 cm^{-1}; ^{1}PH NMR: 2.38 (s, 3H), 3.19 (t, J = 10.2, 1H), 3.77 (dd, J = 10.2, 6.3, 1H), 4.11 (m, 2H), 7.37–7.50 (m, 5H), 7.98 (bd, 1H), 8.74 (bd, 1H), 8.82 (s, 1H); ^{13}C NMR: 39.8, 50.8, 52.2, 58.5, 76.3, 112.0, 114.4, 124.3, 129.2, 129.9, 129.9, 130.2, 130.3, 133.6, 135.8, 136.3, 150.4, 152.0; MS: m/z = 322 [M^+]; Anal. Calcd. For $C_{18}H_{15}N_4Cl$: C, 66.96; H, 4.68; N, 17.36%. Found: C, 66.85; H, 4.94; N, 17.23%.

N-methyl-4-(4-methylphenyl)-2-(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3j). White crystals; Yield: 75%; mp 146–147°C; IR (KBr): 2250 cm^{-1}; ^{1}PH NMR: 2.38 (s, 3H), 2.40 (s, 3H), 3.18 (t, J = 10.2, 1H), 3.83 (dd, J = 10.2, 6.7, 1H), 4.11 (dd, J = 10.2, 6.7, 1H), 4.13 (s, 1H), 7.28 (d, J = 8.0, 1H), 7.43 (m, 1H), 7.45 (d, J = 8.0, 1H), 8.00 (bd, 1H), 8.73 (bd, 1H), 8.83 (s, 1H); ^{13}C NMR: 21.6, 39.9, 51.9, 52.6, 58.3, 76.2, 112.2, 114.7, 124.3, 128.7, 128.9, 129.6, 130.3, 131.9, 136.4, 139.6, 150.4, 151.9; MS: m/z = 302 [M^+]; Anal. Calcd. For $C_{19}H_{18}N_4$: C, 75.46; H, 6.00; N, 18.53%. Found: C, 74.96; H, 6.38; N, 18.26%.

Spiro[9,4]-1-N-methyl-2(pyridine-3-yl)pyrrolidine-3,3-dicarbonitrile (3k). White crystals; Yield: 75%; mp 222–223°C; IR (KBr): 2243 cm^{-1}; ^{1}PH NMR: 2.46 (s, 3H), 3.28 (d, J = 10.3, 1H), 3.78 (d, J = 10.3, 1H), 4.44 (s, 1H), 7.45–7.56 (m, 5H), 7.71 (d, J = 7.5, 1H), 7.76 (d, J = 7.3, 1H), 7.80 (d, J = 7.4, 1H), 8.01 (d, J = 7.4, 1H), 8.01 (d, J = 7.8, 1H), 8.77 (d, J = 3.6, 1H), 8.96 (s, 1H); ^{13}C NMR: 39.9, 53.8, 60.8, 65.9, 77.4, 113.1, 113.3, 120.7, 121.1, 124.4, 125.9, 126.6, 128.4, 128.6, 129.6, 130.2, 130.5, 136.8, 140.6, 141.2, 144.6, 145.4, 150.6, 152.0; MS: m/z = 362 [M^+]; Anal. Calcd. For $C_{24}H_{18}N_4$: C, 79.56; H, 4.97; N, 15.47%. Found: C, 79.34; H, 4.63; N, 15.48%.

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[11] Crystallographic data for **3a** have been deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 748115. Copies of these data can be obtained free of charge *via* www.ccdc.ca-m.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk).