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Facile, eco-friendly, catalyst-free synthesis of polyfunctionalized 2-aminopyrroles

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ABSTRACT

Simple and eco-friendly synthesis of polyfunctionalized 2-aminopyrroles from vinyl azides and α-cyano derivatives has been accomplished with a good to excellent yield. The reaction was performed in ethanol/water co-solvent system without catalyst and the workup was facile. A plausible mechanism has been proposed.

1. Introduction

Pyrroles are important heterocycles that display various biological activities[1] and are widely used in both organic chemistry and material science.[2] As the essential component of pyrroles, aminopyrroles have been found to show valuable and diverse biological properties.[3] Especially the 2-aminopyrrole fragments are part of many bioactive compounds[4] and have been used as precursors for the synthesis of purine analogues including pyrrolopyrimidines, pyrrolotriazines, and pyrrolopyridines.[5] In this regard, efficient and facile methodologies for constructing 2-aminopyrrole rings are valuable.

The use of vinyl azides with 1,3-dicarbonyl compounds has been reported as an efficient method for the synthesis of pyrroles.[6] During the past decades, a certain number of aminopyrrole syntheses have been reported.[7] Some of the common synthetic approaches either need a prolonged reaction time, expensive transition metal additives, complex substrates, or in unsatisfied yields.[8] In addition, pyrrole nitrate reduction methods result in low yields as well as isomers.[9] Furthermore, polyfunctionalized aminopyrroles are not readily available through general pyrrole ring-formation methods.

Herein, we report a novel, facile approach to provide polyfunctionalized 2-aminopyrroles using vinyl azides and α-cyano derivatives. An attractive feature of this protocol is that the desired product could be generated in a highly efficient and eco-friendly manner without catalyst.

2. Results and discussion

Initially, (*Z*)-ethyl-2-azido-3-(4-bromophenyl)acrylate and malononitrile were selected as the reagents to optimize the reaction condition. Firstly, a range of additives were screened. It was found that additive-free was favored for this reaction (Table 1, entry 3) and relatively high temperature could reduce the reaction time (Table 1, entries 10 and 11). With this condition in hand, we screened other aprotic and protic solvents (Table 1, entries 8 and 13–15). The result revealed that ethanol was the most efficient solvent and water could result in the transformation but with a lower yield. Next, we tried to utilize the co-solvent system to optimize this reaction. Different ratios of ethanol and water were tested. The best one verified by the conversion and isolated yield was EtOH:H_2O=1:1 (Table 1, entry 10). On the basis of this initial study, the most efficient and eco-friendly reactivity was obtained in a co-solvent of ethanol and water at 80 °C.

With the optimized reaction conditions in hand, the scope of the reaction was studied using a set of vinyl azides **1**, α-cyano derivatives with an electron-withdrawing group **2**. The α-azidovinylketones were readily prepared from the corresponding olefins by successive reaction with bromine then with sodium azide. And the α-azidovinylesters were prepared from the corresponding aldehydes with ethyl azidoacetate.[10,6a]

When α-azidovinylesters were applied in this reaction, almost all aryl groups could be tolerant in this approach (Table 2, **3a** to **3k**).

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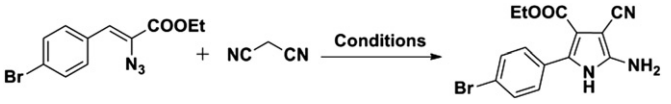
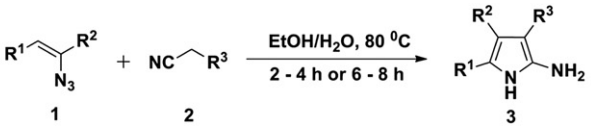
Table 1
Optimization of reaction conditions[a]

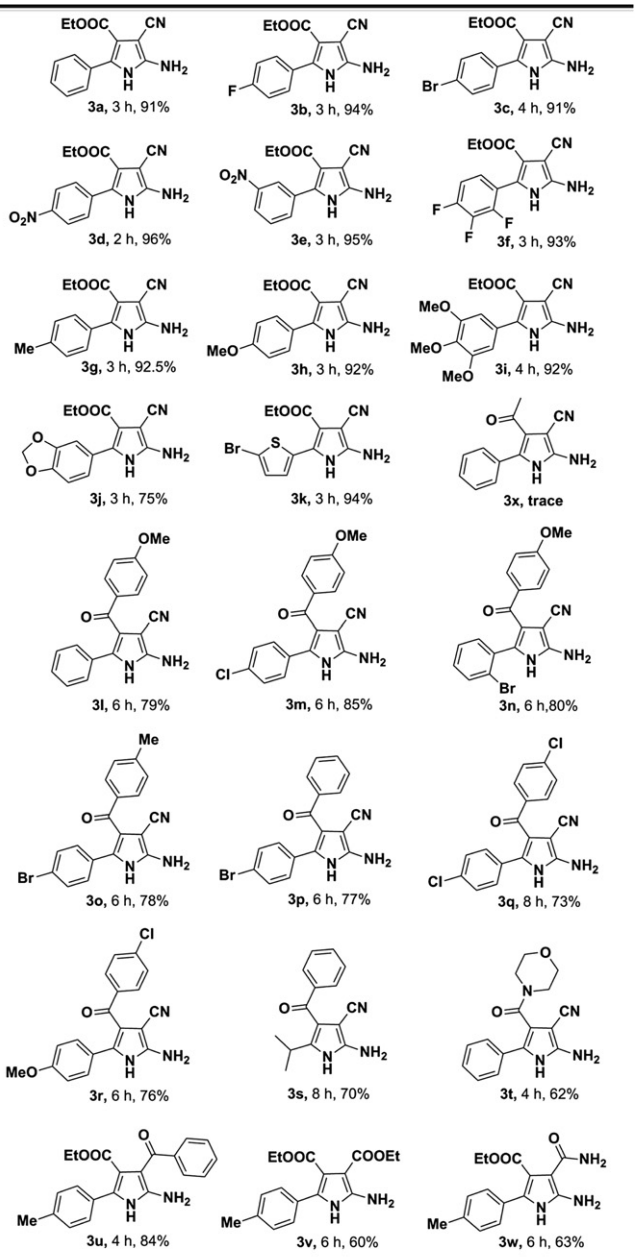


Entry	Additive	Solvent	T (°C)	t (h)	Conversion (%)[b]
1	$Mn(OAc)_2 \cdot 4H_2O$	EtOH	80	3	90
2	$Ni(OAc)_2 \cdot 4H_2O$	EtOH	80	3	94
3	—	EtOH	80	3	94 (85)[c]
4	AcOH	EtOH	80	3	91
5	K_2CO_3	EtOH	80	3	Trace
6	K_2CO_3	DMF	rt	12	Trace
7	DBU	DMF	rt	12	n.r.
8	—	H_2O	100	3	75
9	—	EtOH:H_2O=3:1	80	3	97 (80)[c]
10	—	**EtOH:H_2O=1:1**	**80**	**3**	**96 (91)**[c]
11	—	EtOH:H_2O=1:1	60	48	59
12	—	EtOH:H_2O=1:3	80	3	90 (78)[c]
13	—	*n*-Butanol	120	2	97[d]
14	—	1,4-Dioxane	80	3	93[d]
15	—	DMF	120	2	43

[a] Reaction conditions: α-azidovinylester (0.2 mmol, 1.0 equiv), malononitrile (0.24 mmol, 1.2 equiv), 2 mL of solvent.
[b] Determined by LC-MS, based on the disappearance of the starting α-azidovinylester.
[c] Isolated yields.
[d] Product could not precipitate from the reaction mixture. The most efficient entry is highlighted in bold.

Table 2
Synthesis of polyfunctionalized 2-aminopyrroles **3**[a,b,c]





[a] Reaction conditions: vinyl azides (0.4 mmol, 1.0 equiv.), α-cyano derivatives (0.48 mmol, 1.2 equiv.), 4 mL of solvent, 80 °C. [b] Reaction time. [c] Isolated yield.

The result reveals that not only electron-withdrawing groups, electron-donating groups, but also steric effects have no influence on the yields. While α-azidovinylesters seem in general to work efficiently in these conditions, α-azidovinylketones seem less efficient with decreased yields (compare **3a** to **3l**).

The scope of α-azidovinylketones examined in the reaction is summarized as follows. **1** with electron-withdrawing groups at the $\mathbf{R^1}$ position performed slightly better (**3p** compared to **3s**; **3m**, **3n** compared to **3l**). While at the $\mathbf{R^2}$ position, relatively strong electron-donating groups gave slight increases in yields (**3m** compared to **3q**). The morpholinylcarbonyl group and acetyl group at the $\mathbf{R^2}$ position were also utilized in this approach. Unfortunately, we could not get the desired product with an acetyl group at the $\mathbf{R^2}$ position (Table 2, **3x**). Meanwhile, the morpholinylcarbonyl substitution (Table 2, **3t**) resulted in a lower yield compared to **3a** and **3l**.

We also found that α-cyano derivatives **2** bearing a strong electron-withdrawing group on the $\mathbf{R^3}$ position were converted into the corresponding products with better efficiency (**3g** compared to **3u**, **3v**, **3w**), in a shorter time.

The structures of the polyfunctionalized 2-aminopyrroles **3** were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. The structure of **3** was proved by the 2D ^{1}H–^{1}H NOESY result of **3c**. Furthermore, the structure of **3i** was confirmed by X-ray crystal structure analysis as shown in Fig. 1.

On the basis of the results above, we proposed the following possible mechanism for this reaction, as shown in Scheme 1.

It is proposed that vinyl azides **1** could transform to the 2*H*-azirines **II** via the intermediate **I** under the heating condition.[6,10a,11] The 2*H*-azirines then reacted with the α-cyano derivatives **2** by a sequential domino cyclization to provide the intermediate **IV**. Subsequently, the reaction underwent an intramolecular electronic rearrangement to produce the desired product **3**.

3. Conclusion

In summary, we have developed a facile and catalyst-free strategy to prepare polyfunctionalized 2-aminopyrroles. This novel reaction can be realized in good yields via a domino process involving sequential cyclization and intramolecular rearrangement. Short reaction time, eco-friendly reaction conditions, and facile substituent variation are all notable aspects of this methodology. Furthermore, the synthesis is economical both in lost atom count and the reaction materials. This simple synthesis with the ability to incorporate multiple functional groups into a desired pyrrole ring system provides an attractive strategy for

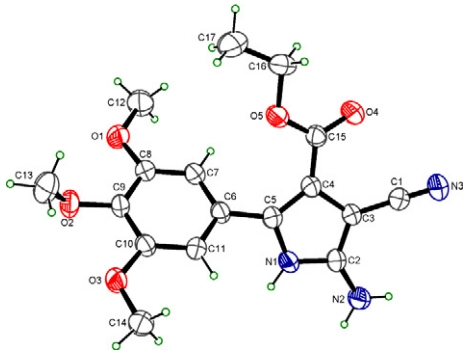
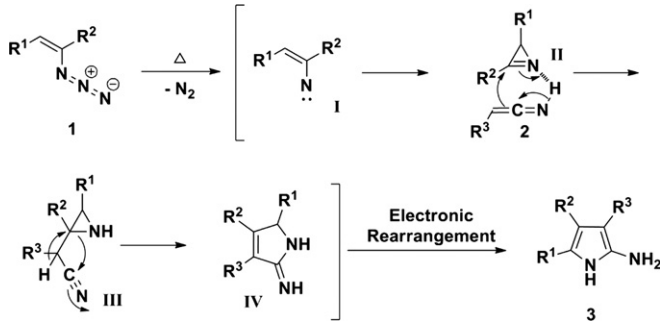


Fig. 1. X-ray crystal structure of **3i**.



Scheme 1. The proposed reaction mechanism.

pharmaceutical building blocks and medicinal chemistry applications.

4. Experimental section

4.1. General

All solvents were purified according to standard methods prior to use. Melting points were recorded on a BÜCHI B-540 melting point apparatus. NMR spectra were recorded for ^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz (compound **3c** was recorded for ^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz). For ^{1}H NMR, tetramethylsilane (TMS) served as internal standard (δ=0) and data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), and coupling constant(s) in Hertz. For ^{13}C NMR, TMS (δ=0) or DMSO (δ=40.45) was used as internal standard and spectra were obtained with complete proton decoupling. LC-MS and HRMS data was obtained using Agilent Technologies 6224 TOF LC/MS. Single-crystals of compound **3i** were measured on a Rigaku RAXIS-RAPID single-crystal diffractometer. The starting material vinyl azides **1a**–**t** were prepared according to literature methods. The starting material **2** were commercially available.

4.2. General procedure for the synthesis of 2-aminopyrroles

A mixture of α-azidovinylester or α-azidovinylketone **1** (0.4 mmol), α-cyano derivative **2** (0.48 mmol) was stirred in a co-solvent (ethanol 2 mL and water 2 mL) at 80 °C for several hours. After the completeness of the reaction, the reaction was diluted with water (16 mL). The crude product was filtered from the reaction mixture and purified by recrystallization (petroleum ether/diethyl ether=2:1) to afford **3**. The reaction mixture of compound **3s** or **3u** was extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated, and recrystallized in the same solvent.

*4.2.1. Ethyl 5-amino-4-cyano-2-phenyl-1H-pyrrole-3-carboxylate (**3a**).* White solid [R_f=0.5 (CH_2Cl_2/MeOH=15:1)]; mp: 216–217 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.26 (s, 1H), 7.50 (d, J=7.5 Hz, 2H), 7.40–7.33 (m, 3H), 5.84 (s, 2H), 4.10 (q, J=7.0 Hz, 2H), 1.15 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) δ 163.1, 149.5, 131.3, 130.9, 129.5, 128.4, 128.2, 117.4, 109.0, 71.9, 59.9, 14.3; HRMS (EI): found: m/z 255.1003. Calcd for $C_{14}H_{13}N_3O_2$ $(M)^+$: 255.1008.

*4.2.2. Ethyl 5-amino-4-cyano-2-(4-fluorophenyl)-1H-pyrrole-3-carboxylate (**3b**).* Light pink solid [R_f=0.3 (CH_2Cl_2/MeOH=15:1)]; mp: 194–195 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.30 (s, 1H), 7.58–7.51 (m, 2H), 7.25–7.22 (m, 2H), 5.86 (s, 2H), 4.10 (q, J=7.0 Hz, 2H), 1.15 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) δ 163.0, 162.3 (d, J=244), 149.5, 131.8 (d, J=8 Hz), 130.0, 127.8 (d, J=3 Hz), 117.3, 115.1 (d, J=21 Hz), 109.0, 71.7, 59.9, 14.3; HRMS (EI): found: m/z 273.0905. Calcd for $C_{14}H_{12}FN_3O_2$ $(M)^+$: 273.0914.

*4.2.3. Ethyl 5-amino-2-(4-bromophenyl)-4-cyano-1H-pyrrole-3-carboxylate (**3c**).* Light yellow solid [R_f=0.4 (CH_2Cl_2/MeOH=15:1)]; mp: 254–256 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.33 (s, 1H), 7.88 (d, J=8.8 Hz, 2H), 7.45 (d, J=8.4 Hz, 2H), 5.90 (s, 2H), 4.11 (q, J=7.2 Hz, 2H), 1.16 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ 162.9, 149.6, 131.4, 131.1, 130.3, 129.4, 121.5, 117.1, 109.4, 71.9, 59.9, 14.2; HRMS (EI): found: m/z 333.0121. Calcd for $C_{14}H_{12}BrN_3O_2$ $(M)^+$: 333.0113.

*4.2.4. Ethyl 5-amino-4-cyano-2-(4-nitrophenyl)-1H-pyrrole-3-carboxylate (**3d**).* Light yellow solid [R_f=0.4 (CH_2Cl_2/MeOH=15:1)]; mp: 227–229 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.58 (s, 1H), 8.24 (d, J=8.5 Hz, 2H), 7.78 (d, J=9.0 Hz, 2H), 6.11 (s, 2H), 4.16 (q, J=7.0 Hz, 2H), 1.19 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) δ 162.9, 150.4, 146.6, 137.6, 130.2, 127.7, 123.5, 116.9, 111.7, 73.2, 60.4, 14.3; HRMS (EI): found: m/z 300.0850. Calcd for $C_{14}H_{12}N_4O_4$ $(M)^+$: 300.0859.

*4.2.5. Ethyl 5-amino-4-cyano-2-(3-nitrophenyl)-1H-pyrrole-3-carboxylate (**3e**).* Light yellow solid [R_f=0.3 (CH_2Cl_2/MeOH=15:1)]; mp: 227–229 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.58 (s, 1H), 8.38 (t, J=2.0 Hz, 1H), 8.20–8.19 (m, 1H), 7.98–7.96 (m, 1H), 7.69 (t, J=8.5 Hz, 1H), 6.04 (s, 2H), 4.14 (q, J=7.5 Hz, 2H), 1.16 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) δ 162.9, 150.0, 147.7, 136.0, 132.6, 129.8, 127.9, 124.0, 122.9, 117.0, 110.6, 72.5, 60.3, 14.2; HRMS (EI): found: m/z 300.0853. Calcd for $C_{14}H_{12}N_4O_4$ $(M)^+$: 300.0859.

*4.2.6. Ethyl 5-amino-4-cyano-2-(2,3,4-trifluorophenyl)-1H-pyrrole-3-carboxylate (**3f**).* Light brown solid [R_f=0.3 (CH_2Cl_2/MeOH=15:1)]; mp: 224–226 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.48 (s, 1H), 7.41–7.36 (m, 1H), 7.33–7.29 (m, 1H), 6.07 (s, 2H), 4.07 (q, J=7.0 Hz, 2H), 1.09 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) δ 162.5, 149.9, 126.8–126.7 (m), 121.5 (d, J=2 Hz), 118.1–118.0 (m), 116.8, 112.6 (d, J=3 Hz), 112.9 (d, J=3 Hz), 112.0, 71.6, 60.0, 14.1; HRMS (EI): found: m/z 309.0718. Calcd for $C_{14}H_{10}F_3N_3O_2$ $(M)^+$: 309.0725.

*4.2.7. Ethyl 5-amino-4-cyano-2-(p-tolyl)-1H-pyrrole-3-carboxylate (**3g**).* Light yellow solid [R_f=0.3 (CH_2Cl_2/MeOH=15:1)]; mp: 218–219.5 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.16 (s, 1H), 7.40 (d, J=8.0 Hz, 2H), 7.19 (d, J=8.0 Hz, 2H), 5.78 (s, 2H), 4.10 (q, J=7.0 Hz, 2H), 2.33 (s, 3H), 1.16 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) δ 163.2, 149.4, 137.9, 131.1, 129.3, 128.8, 128.5, 117.4, 108.6, 71.8, 59.8, 21.3, 14.4; HRMS (EI): found: m/z 269.1167. Calcd for $C_{15}H_{15}N_3O_2$ $(M)^+$: 269.1164.

*4.2.8. Ethyl 5-amino-4-cyano-2-(4-methoxyphenyl)-1H-pyrrole-3-carboxylate (**3h**).* Light brown solid [R_f=0.4 (CH_2Cl_2/MeOH=15:1)];

mp: 200–202 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.15 (s, 1H), 7.45 (d, J=9.0 Hz, 2H), 6.95 (d, J=8.5 Hz, 2H), 5.78 (s, 2H), 4.10 (q, J=7.5 Hz, 2H), 3.78 (s, 3H), 1.17 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) δ 163.2, 159.5, 149.2, 131.2, 130.8, 123.7, 117.5, 113.7, 108.1, 71.5, 59.8, 55.6, 14.4; HRMS (EI): found: m/z 285.1107. Calcd for $C_{15}H_{15}N_3O_3$ $(M)^+$: 285.1113.

*4.2.9. Ethyl 5-amino-4-cyano-2-(3,4,5-trimethoxyphenyl)-1H-pyrrole-3-carboxylate (**3i**).* Light pink solid [R_f=0.5 (CH_2Cl_2/MeOH=15:1)]; mp: 197–199 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.15 (s, 1H), 6.85 (s, 2H), 5.80 (s, 2H), 4.12 (q, J=7.0 Hz, 2H), 3.79 (s, 6H), 3.69 (s, 3H), 1.17 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) δ 163.2, 152.6, 149.2, 138.0, 130.8, 126.6, 117.4, 108.9, 107.2, 72.0, 60.6, 59.9, 56.4, 14.4; HRMS (EI): found: m/z 345.1318. Calcd for $C_{17}H_{19}N_3O_5$ $(M)^+$: 345.1325.

*4.2.10. Ethyl 5-amino-2-(benzo[d][1,3]dioxol-5-yl)-4-cyano-1H-pyrrole-3-carboxylate (**3j**).* Light yellow solid [R_f=0.3 (CH_2Cl_2/MeOH=15:1)]; mp: 166–169 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.17 (s, 1H), 7.09 (d, J=1.5 Hz, 1H), 6.99–6.94 (m, 2H), 6.05 (s, 2H), 5.79 (s, 2H), 4.10 (q, J=7.0 Hz, 2H), 1.17 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) δ 163.1, 149.2, 147.5, 147.1, 130.8, 125.1, 123.3, 110.1, 108.2, 101.7, 99.7, 92.6, 71.6, 59.8, 14.3; HRMS (EI): found: m/z 299.0900. Calcd for $C_{15}H_{13}N_3O_4$ $(M)^+$: 299.0906.

*4.2.11. Ethyl 5-amino-2-(5-bromothiophen-2-yl)-4-cyano-1H-pyrrole-3-carboxylate (**3k**).* Light yellow solid [R_f=0.45 (CH_2Cl_2/MeOH=15:1)]; mp: 181–183 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.42 (s, 1H), 7.28 (d, J=4.0 Hz, 1H), 7.22 (d, J=4.0 Hz, 1H), 6.00 (s, 2H), 4.22 (q, J=7.5 Hz, 2H), 1.27 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) δ 163.0, 149.9, 133.9, 130.2, 127.4, 123.6, 117.0, 113.0, 109.2, 71.7, 60.4, 14.4; HRMS (EI): found: m/z 338.9681. Calcd for $C_{12}H_{10}BrN_3O_2S$ $(M)^+$: 338.9677.

*4.2.12. 2-Amino-4-(4-methoxybenzoyl)-5-phenyl-1H-pyrrole-3-carbonitrile (**3l**).* Light pink solid [R_f=0.35 (CH_2Cl_2/MeOH=15:1)]; mp: 214–217 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.26 (s, 1H), 7.60 (d, J=9.0 Hz, 2H), 7.22–7.12 (m, 5H), 6.81 (d, J=9.0 Hz, 2H), 5.92 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 189.7, 163.0, 149.6, 132.1, 131.3, 131.2, 128.6, 128.3, 128.1, 127.6, 119.0, 117.3, 113.9, 72.7, 55.9; HRMS (EI): found: m/z 317.1159. Calcd for $C_{19}H_{15}N_3O_2$ $(M)^+$: 317.1164.

*4.2.13. 2-Amino-5-(4-chlorophenyl)-4-(4-methoxybenzoyl)-1H-pyrrole-3-carbonitrile (**3m**).* Light yellow solid [R_f=0.3 (CH_2Cl_2/MeOH=15:1)]; mp: 262–264 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.36 (s, 1H), 7.62–7.59 (m, 2H), 7.27–7.25 (m, 2H), 7.19–7.17 (m, 2H), 6.86–6.84 (m, 2H), 6.01 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 189.6, 163.2, 149.7, 132.2, 132.1, 131.0, 130.1, 129.7, 128.6, 126.9, 119.5, 117.2, 114.0, 72.9, 55.9; HRMS (EI): found: m/z 351.0765. Calcd for $C_{19}H_{14}ClN_3O_2$ $(M)^+$: 351.0775.

*4.2.14. 2-Amino-5-(2-bromophenyl)-4-(4-methoxybenzoyl)-1H-pyrrole-3-carbonitrile (**3n**).* Light gray solid [R_f=0.25 (CH_2Cl_2/MeOH=15:1)]; mp: 260–262 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.28 (s, 1H), 7.47 (d, J=7.5 Hz, 3H), 7.19–7.11 (m, 3H), 6.69 (d, J=8.5 Hz, 2H), 5.97 (s, 2H), 3.70 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 188.6, 162.4, 149.4, 133.5, 133.0, 132.9, 131.6, 131.5, 130.4, 128.4, 127.6, 124.0, 120.6, 117.4, 113.3, 71.7, 55.8; HRMS (EI): found: m/z 395.0268. Calcd for $C_{19}H_{14}BrN_3O_2$ $(M)^+$: 395.0269.

*4.2.15. 2-Amino-5-(4-bromophenyl)-4-(4-methylbenzoyl)-1H-pyrrole-3-carbonitrile (**3o**).* Light yellow solid [R_f=0.4 (CH_2Cl_2/MeOH=15:1)]; mp: 287–289 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.38 (s, 1H), 7.50 (d, J=8.0 Hz, 2H), 7.37 (d, J=8.0 Hz, 2H), 7.10 (dd, J=7.0, 5.5 Hz, 4H), 6.01 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 190.5, 149.8, 143.2, 135.8, 131.5, 130.4, 130.2, 130.0, 129.2, 127.7, 120.8, 119.4, 117.2, 72.8, 21.5; HRMS (EI): found: m/z 379.0324. Calcd for $C_{19}H_{14}BrN_3O$ $(M)^+$: 379.0320.

*4.2.16. 2-Amino-4-benzoyl-5-(4-bromophenyl)-1H-pyrrole-3-carbonitrile (**3p**).* Light yellow solid [R_f=0.4 (CH_2Cl_2/MeOH=15:1)]; mp: 278–281 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.41 (s, 1H), 7.57–7.55 (m, 2H), 7.44 (t, J=7.5 Hz, 1H), 7.34 (d, J=8.5 Hz, 2H), 7.27 (t, J=7.5 Hz, 2H), 7.08 (d, J=8.5 Hz, 2H), 6.02 (s, 2H); ^{13}C NMR (125 MHz, DMSO) δ 190.7, 149.9, 138.6, 132.7, 131.4, 130.5, 130.3, 129.7, 128.7, 128.5, 121.0, 119.2, 117.2, 72.7; HRMS (EI): found: m/z 365.0157. Calcd for $C_{18}H_{12}BrN_3O$ $(M)^+$: 365.0164.

*4.2.17. 2-Amino-4-(4-chlorobenzoyl)-5-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile (**3q**).* Light yellow solid [R_f=0.25 (CH_2Cl_2/MeOH=15:1)]; mp: 295–297 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.48 (s, 1H), 7.55–7.53 (m, 2H), 7.33–7.31 (m, 2H), 7.25–7.23 (m, 2H), 7.17–7.15 (m, 2H), 6.06 (s, 2H); ^{13}C NMR (125 MHz, DMSO) δ 189.3, 150.0, 137.5, 137.3, 132.7, 131.5, 130.6, 129.8, 129.4, 128.6, 128.5, 118.8, 117.1, 72.4; HRMS (EI): found: m/z 355.0276. Calcd for $C_{18}H_{11}Cl_2N_3O$ $(M)^+$: 355.0279.

*4.2.18. 2-Amino-4-(4-chlorobenzoyl)-5-(4-methoxyphenyl)-1H-pyrrole-3-carbonitrile (**3r**).* Light yellow solid [R_f=0.4 (CH_2Cl_2/MeOH=15:1)]; mp: 263–265 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.31 (s, 1H), 7.50 (d, J=8.5 Hz, 2H), 7.27 (d, J=8.5 Hz, 2H), 7.07 (d, J=8.5 Hz, 2H), 6.73 (d, J=9.0 Hz, 2H), 5.94 (s, 2H), 3.68 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 189.2, 159.3, 149.7, 137.8, 136.8, 131.4, 130.5, 128.4, 123.4, 117.6, 117.5, 114.0, 71.8, 55.7; HRMS (EI): found: m/z 351.0770. Calcd for $C_{19}H_{14}ClN_3O_2$ $(M)^+$: 351.0775.

*4.2.19. 2-Amino-4-benzoyl-5-isopropyl-1H-pyrrole-3-carbonitrile (**3s**).* Light brown solid [R_f=0.3 (CH_2Cl_2/MeOH=15:1)]; mp: 115–118 °C; ^{1}H NMR (500 MHz, DMSO) δ 10.97 (s, 1H), 7.62–7.61 (m, 2H), 7.59–7.56 (m, 1H), 7.50–7.46 (m, 2H), 5.72 (s, 2H), 2.81–2.76 (m, 1H), 1.07 (d, J=7.0 Hz, 6H); ^{13}C NMR (125 MHz, DMSO) δ 189.9, 148.5, 140.1, 138.9, 131.7, 128.3, 128.1, 117.0, 116.1, 69.2, 25.3, 21.8; HRMS (EI): found: m/z 253.1207. Calcd for $C_{15}H_{15}N_3O$ $(M)^+$: 253.1215.

*4.2.20. 2-Amino-4-(morpholine-4-carbonyl)-5-phenyl-1H-pyrrole-3-carbonitrile (**3t**).* Light brown solid [R_f=0.2 (CH_2Cl_2/MeOH=15:1)]; mp: 244–247 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.03 (s, 1H), 7.39–7.36 (m, 2H), 7.34–7.32 (m, 2H), 7.25–7.22 (m, 1H), 5.90 (s, 2H), 3.55 (s, 4H), 3.20 (s, 4H); ^{13}C NMR (125 MHz, DMSO) δ 164.8, 149.3, 131.3, 129.2, 127.1, 125.7, 121.9, 117.2, 114.4, 71.5, 66.3; HRMS (EI): found: m/z 296.1264. Calcd for $C_{16}H_{16}N_4O_2$ $(M)^+$: 296.1273.

*4.2.21. Ethyl 5-amino-4-benzoyl-2-(p-tolyl)-1H-pyrrole-3-carboxylate (**3u**).* Light yellow solid [R_f=0.5 (CH_2Cl_2/MeOH=15:1)]; mp: 75–77 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.15 (s, 1H), 7.50 (d, J=7.0 Hz, 2H), 7.44–7.39 (m, 5H), 7.20 (d, J=7.5 Hz, 2H), 6.46 (s, 2H), 3.28 (t, J=7.5 Hz, 2H), 2.32 (s, 3H), 0.67 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) δ 189.6, 165.6, 149.6, 142.6, 137.4, 130.6, 129.2, 128.6, 128.5, 128.4, 128.3, 127.7, 110.6, 102.8, 59.9, 21.3, 13.8; HRMS (EI): found: m/z 348.1480. Calcd for $C_{21}H_{20}N_2O_3$ $(M)^+$: 348.1474.

*4.2.22. Diethyl 2-amino-5-(p-tolyl)-1H-pyrrole-3,4-dicarboxylate (**3v**).* Light yellow solid [R_f=0.5 (CH_2Cl_2/MeOH=15:1)]; mp: 44–46 °C; ^{1}H NMR (500 MHz, DMSO) δ 10.86 (s, 1H), 7.28 (d, J=8.5 Hz, 2H), 7.17 (d, J=8.0 Hz, 2H), 5.73 (s, 2H), 4.15 (q, J=7.0 Hz, 2H), 4.09 (q, J=7.0 Hz, 2H), 2.29 (s, 3H), 1.20 (q, J=7.0 Hz, 6H); ^{13}C NMR (125 MHz, DMSO) δ 167.3, 164.7, 147.7, 136.4, 129.6, 128.9,

125.9, 123.3, 111.6, 92.3, 60.7, 58.8, 21.1, 14.8, 14.4; HRMS (EI): found: *m*/*z* 316.1425. Calcd for $C_{17}H_{20}N_2O_4$ $(M)^+$: 316.1423.

*4.2.23. Ethyl 5-amino-4-carbamoyl-2-(p-tolyl)-1H-pyrrole-3-carboxylate (**3w**).* Light yellow solid [R_f=0.3 (CH_2Cl_2/MeOH=15:1)]; mp: 194–196 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.04 (s, 1H), 8.38 (s, 1H), 7.23 (d, *J*=7.0 Hz, 2H), 7.19 (d, *J*=7.0 Hz, 2H), 6.67 (s, 1H), 6.08 (s, 2H), 3.99 (q, *J*=6.5 Hz, 2H), 2.33 (s, 3H), 0.91 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) δ 168.2, 167.7, 148.0, 137.3, 132.2, 130.5, 129.4, 128.7, 106.5, 94.1, 60.3, 21.3, 13.9; HRMS (EI): found: *m*/*z* 287.1265. Calcd for $C_{15}H_{17}N_3O_3$ $(M)^+$: 287.1270.

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Supplementary data

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all products, the 2D ^{1}H–^{1}H NOESY spectra of **3c**, X-ray crystal data of **3i**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.11.041.

References and notes

1. (a) Lainton, J. A. H.; Hoffman, J. W.; Martin, B. R.; Compton, D. R. *Tetrahedron Lett.* **1995**, *36*, 1401; (b) De Leon, C. Y.; Ganem, B. *Tetrahedron* **1997**, *53*, 7731.
2. (a) Corvo, M. C.; Pereira, M. A. *Tetrahedron Lett.* **2002**, *43*, 455; (b) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J. *Chem. Rev.* **2008**, *108*, 264; (c) Heugebaert, T. S. A.; Roman, B. I.; Stevens, C. V. *Chem. Soc. Rev.* **2012**, *41*, 5626; (d) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491; (e) Pagani, G. A. *Heterocycles* **1994**, *37*, 2069; (f) Meyer, W. H.; Kiess, H.; Binggeli, B.; Meier, E.; Harbeke, G. *Synth. Met.* **1985**, *10*, 255.
3. (a) Yaroslavsky, C.; Bracha, P.; Glaser, R. *J. Heterocycl. Chem.* **1989**, *26*, 1649; (b) Howard, O. M. Z.; Oppenheim, J. J.; Melinda, M. G.; Covey, J. M.; Bigelow, J. *J. Med. Chem.* **1998**, *41*, 2184; (c) Smith, R. A.; Barbosa, J.; Blum, C. L.; Bobko, M. A.; Caringal, Y. V.; Dally, R.; Johnson, J. S.; Katz, M. E.; Kennure, N.; Kingery-Wood, J.; Lee, W.; Lowinger, T. B.; Lyons, J.; Marsh, V.; Rogers, D. H.; Swartz, S.; Walling, T.; Wild, H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2775.
4. (a) Cocco, M. T.; Congiu, C.; Onnis, V. *Bioorg. Med. Chem.* **2003**, *11*, 495; (b) Mohamed, M. S.; El-Domany, R. A.; El-Hameed, R. H. *Acta Pharm.* **2009**, *59*, 145; (c) Johnson, R. W.; Keenan, T. H.; Kosh, J. W.; Sowell, J. W., Sr.. *J. Pharm. Sci.* **1979**, *68*, 317; (d) Johnson, R. W.; Keenan, T. H.; Kosh, J. W.; Sowell, J. W., Sr.. *J. Pharm. Sci.* **1979**, *68*, 955; (e) Stephens, C. E.; Felder, T. M.; Sowell, J. W., Sr.; Andrei, G.; Balzarini, J.; Snoeck, R.; Clercq, E. D. *Bioorg. Med. Chem.* **2001**, *9*, 1123.
5. (a) Mohamed, M. S.; Kamel, R.; Fatahala, S. S. *Eur. J. Med. Chem.* **2010**, *45*, 2994; (b) Diana, P.; Barraja, P.; Lauria, A.; Montalbano, A.; Almerico, A. M.; Dattolo, G.; Cirrincione, G. *Bioorg. Med. Chem.* **2003**, *11*, 2371; (c) Diana, P.; Barraja, P.; Lauria, A.; Monotalbano, A.; Almerico, A. M.; Dattolo, G.; Cirrincione, G. *Eur. J. Med. Chem.* **2002**, *37*, 267; (d) Willemann, C.; Grunert, R.; Bednarski, P. J.; Troschutz, R.; Cocco, M. T.; Congiu, C.; Onnis, V. *Bioorg. Med. Chem.* **2009**, *17*, 4406; (e) Bennet, S. M.; Nguyen-Ba, N.; Ogilvie, K. K. *J. Med. Chem.* **1990**, *33*, 2162; (f) Krawczyk, S. H.; Nassiri, M. R.; Kucera, L. S.; Kern, E. R.; Ptak, R. G.; Wotring, L. L.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1995**, *38*, 4106; (g) Migawa, M. T.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **2005**, *48*, 3840; (h) Bookser, B. C.; Ugarkar, B. G.; Matelich, M. C.; Lemus, R. H.; Allan, M.; Tsuchiya, M.; Nakane, M.; Nagahisa, A.; Wiesner, J. B.; Erion, M. D. *J. Med. Chem.* **2005**, *48*, 7808; (i) Gangjee, A.; Jain, H. D.; Queener, S. F.; Kisliuk, R. L. *J. Med. Chem.* **2008**, *51*, 4589; (j) Lauria, A.; Bruno, M.; Diana, P.; Barraja, P.; Montalbano, A.; Cirrincione, G.; Dattolo, G.; Almerico, A. M. *Bioorg. Med. Chem.* **2005**, *13*, 1545.
6. (a) Chiba, S.; Wang, Y. F.; Lapointe, G.; Narasaka, K. *Org. Lett.* **2008**, *10*, 313; (b) Ng, E. P. J.; Wang, Y.; Hui, B. W.; Lapointe, G.; Chiba, S. *Tetrahedron* **2011**, *67*, 7728.
7. (a) Rosa, M. D.; Issac, R. P.; Houghton, G. *Tetrahedron Lett.* **1995**, *36*, 9261; (b) Wamhoff, H.; Wehling, B. *Synthesis* **1976**, 51; (c) Rosa, M. D.; Sellitto, I.; Issac, R. P.; Ralph, J.; Timken, M. D. *J. Chem. Res., Synop.* **1999**, 1433; (d) Lichitsky, B. V.; Dudinov, A. A.; Komogortsev, A. N.; Krayushkin, M. M. *Mendeleev Commun.* **2010**, *20*, 255; (e) Brouillette, Y.; Rombouts, F. J. R.; Lubell, W. D. *J. Comb. Chem.* **2006**, *8*, 117; (f) Chien, T.; Meade, E. A.; Hinkley, J. M.; Townsend, L. B. *Org. Lett.* **2004**, *6*, 2857; (g) Demir, A. S.; Emrullahoğlu, M. *Tetrahedron* **2005**, *61*, 10482; (h) Demir, A. S.; Emrullahoğlu, M. *Tetrahedron* **2006**, *62*, 1452.
8. (a) Wang, K.; Dömling, A. *Chem. Biol. Drug Des.* **2010**, *75*, 277; (b) Demir, A. S.; Emrullahoğlu, M.; Buran, K. *Chem. Commun.* **2010**, 8032; (c) Al-Mousawi, S. M.; Moustafa, M. S.; Meier, H.; Kolshorn, H.; Elnagdi, M. H. *Molecules* **2009**, *14*, 798; (d) Kanzian, T.; Nicolini, S.; Crescentini, L. D.; Attanasi, O. A.; Ofial, A. R.; Mayr, H. *Chem.—Eur. J.* **2010**, *16*, 12008; (e) Frolova, L. V.; Evdokimov, N. M.; Hayden, K.; Malik, I.; Rogelj, S.; Kornienko, A.; Magedov, I. V. *Org. Lett.* **2011**, *13*, 1118; (f) Jalani, H. B.; Pandya, A. N.; Baraiya, A. B.; Kaila, J. C.; Pandya, D. H.; Sharma, J. A.; Sudarsanam, V.; Vasu, K. K. *Tetrahedron Lett.* **2011**, *52*, 6331.
9. (a) Schmuck, C.; Dudaczek, J. *Tetrahedron Lett.* **2005**, *46*, 7101; (b) Moore, M. J. B.; Cuenca, F.; Searcey, M.; Neidle, S. *Org. Biomol. Chem.* **2006**, *4*, 3479; (c) Pantoş, G. D.; Rodríguez-Morgade, M. S.; Torres, T.; Lynch, V. M.; Sessler, J. L. *Chem. Commun.* **2006**, 2132; (d) Garabatos-Perera, J. R.; Rotsein, B. H.; Thompson, A. *J. Org. Chem.* **2007**, *72*, 7382; (e) Oda, H.; Hanami, T.; Iwashita, T.; Kojima, M.; Itoh, M.; Hayashizaki, Y. *Tetrahedron* **2007**, *63*, 12747.
10. (a) Gilchrist, T. L.; Mendonca, R. *ARKIVOC* **2000**, 769; (b) Liu, L.; Liebeskind, S. *J. Am. Chem. Soc.* **2008**, *130*, 6918; (c) Khazaei, M. A. *Synthesis* **2009**, *21*, 3672; (d) Kowalski, C. J.; Weber, A. E.; Fields, K. W. *J. Org. Chem.* **1982**, *47*, 5088.
11. (a) Law, K. W.; Lai, T.; Sammes, M. P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 111; (b) Knittel, D. *Synthesis* **1985**, 186; (c) Timén, Å. S.; Risberg, E.; Somfai, P. *Tetrahedron Lett.* **2003**, *44*, 5339.