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An effective new synthesis of 2-aminopyrrole-4-carboxylates

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Abstract—Efficient syntheses of 2-aminopyrroles are presented starting from β-dicarbonyl compounds, bromoacetonitrile, and amines. Alkylation of β-dicarbonyl compounds with bromoacetonitrile furnished α-cyanomethyl-β-dicarbonyl compounds. The condensation reaction of α-cyanomethyl-β-dicarbonyl compounds with amines catalyzed by *p*-TsOH affords the corresponding enamines in good yields. Base catalyzed cyclization via the addition of an amine moiety to the carbon–nitrogen triple bond of nitrile furnished 2-aminopyrroles in high yields.

1. Introduction

Pyrrole derivatives represent a class of compounds of great importance in heterocyclic chemistry primarily due to the fact that many pyrroles are subunits of natural products, pharmaceutical agents and polymers.[1] The valuable and diverse biological properties of pyrroles make the development of efficient methods for the preparation of these compounds, having a defined substitution pattern, a focus of considerable synthetic effort. β-Dicarbonyl compounds are versatile intermediates for the synthesis of pyrrole derivatives.[2] Pioneering work on the synthesis of pyrroles from β-dicarbonyl compounds was carried out by Hantzsch in 1890. Many studies have been published on the synthesis of pyrroles using the principle of Hantzsch's method starting from β-dicarbonyl compounds.[3] Aminopyrroles have been found to show interesting biological properties[4,5] or have been used as precursors[6] for known drugs, in which they have found use as synthetic precursors for acyclic nucleoside analogues of the pyrrolo[2,3-*d*]pyrimidine ring system.[7]

Aminopyrroles are not readily available through general pyrrole ring-formation methods.[8] Despite the large number of published methods for the elaboration of various pyrroles, relatively few examples have been reported for the preparation of simple 2-amino derivatives.

Most compounds of this type have been obtained by the reaction of a nitrogen-two-carbon compound with an appropriate two-carbon unit, for example, base-promoted condensation of an amino ketone[9] or a conjugated azoalkene[10] with a nitrile containing an active methylene group; 1,3-dipolar cycloaddition of conjugated azoalkenes with 1-propynyldiethylamine;[11] or base-induced 1,3-dipolar cycloaddition of 4,5-diaminothiazolium salts with electrophilic alkynes.[12] Recent access to 2-(alkylamino)- and 2-(arylamino)pyrroles by the addition of isocyanides to protonated 1-azabutadienes is described by Morel et al.[13] Other miscellaneous and limited methods were also described in the review by Trofimov et al.[14]

To continue our investigations that are directed towards the synthesis of substituted pyrroles[15] and related compounds,[16] we were especially interested in obtaining 2-amino-4-carboxyl- derivatives of pyrroles. These compounds are conformationally restricted GABA structure analogous (Fig. 1).

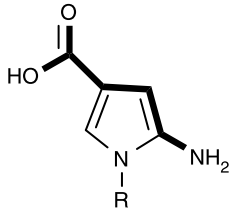

Figure 1.

2. Results and discussion

From a synthetic point of view, 2-aminopyrroles can be synthesized via a reaction sequence involving α-alkylation of β-dicarbonyl compounds with bromoacetonitrile,

Keywords: 2-Aminopyrroles; Amination; Cyclization; 1,3-Dicarbonyls.
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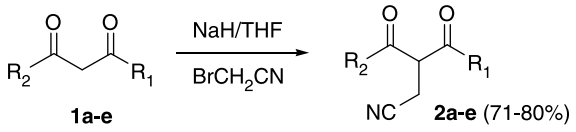
enamine formation, and finally a ring closure reaction. This seems like a very attractive route because a wide variety of substituents (R^1, R^2, and R^3) can be used, originating from readily accessible starting materials.

As shown in Scheme 1, α-cyanomethyl-β-dicarbonyl compounds **2a–e** were synthesized by alkylation of β-dicarbonyl compounds with bromoacetonitrile (NaH/THF and DBU/benzene) according to the literature procedure in 71–80% yields (Scheme 1).[17]



1a: R_1= Me, R_2= Me
1b: R_1= OEt, R_2= Me
1c: R_1= OEt, R_2= Et
1d: R_1= OEt, R_2= Ph
1e: R_1= OEt, R_2= 2-F-Ph

Scheme 1.

As shown in Scheme 2, the enamine derivatives **4a–i** were easily prepared from amines **3a–c** and α-cyanomethyl-β-dicarbonyl compounds **2a–e** in benzene at reflux with the addition of a catalytical amount of *p*-TsOH in 68–75% yields after purification of the crude products by column chromatography (Table 1). The formation of enamines by using ethyl 2-(cyanomethyl)-3-oxo-3-phenylpropanoate (**2d**) was not successful under the above described conditions. There are many general methods for the synthesis of β-amino-α,β-unsaturated carbonyl compounds, but as far as we know no convenient procedure is described in the literature for the formation of enamines starting from 2-alkyl-3-aryl-1,3-dicarbonyl compounds. Various reaction conditions were applied in order to find a convenient procedure for the formation of enamine **4j** (ethyl-3-(benzylamino)-2-cyanomethyl-3-phenylacrylate) with benzylamine as described below:

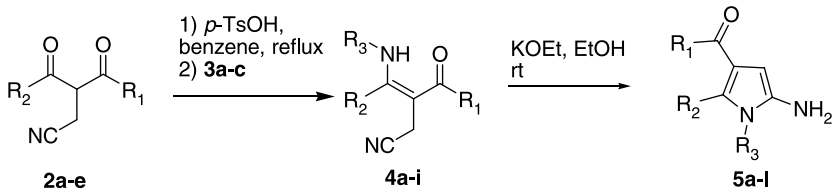
1. *p*-TsOH–Benzene (or Toluene), azeotropic removal of water. (1 equiv **2d**, 2 equiv **3c**, 10 ml solvent, 48 h): product was obtained in very low yield.
2. TFA–Benzene (1 equiv **2d**, 2 equiv diketone, 10 ml solvent, 48 h): trace amount of product formation (GC–MS).
3. BF_3–Et_2O, Toluene (1 equiv **2d**, 2 equiv **3c** 10 ml solvent): no product formation.
4. Al_2O_3 supported reaction[18] (1 equiv **2d**, 1.5 equiv **3c**, Al_2O_3, at 70 °C): no product formation.
5. Al_2O_3 supported microwave reaction (1 equiv **2d**, 1.5 equiv **3c**, Al_2O_3): starting material and unidentified side products.
6. *p*-TsOH, silica gel or K-10 Montmorillonitrite clay supported microwave reaction[19] (1 equiv **2d**, 1.5 equiv **3c**): product was observed, but in low yield (5–7%).
7. Stefani et al.[20] described the preparation of enaminones from β-ketoesters or β-diketones and primary amines in water. Application of this procedure to **2d** (1 equiv **2d**, 2 equiv **3c**, 5 ml H_2O, stirred at room temperature for 3 h) furnished the decarboxylation product **6** in 10% yield (Scheme 3).
8. Five equivalents **3c** was neutralized with 5 equiv acetic acid added to 1 equiv **2d** solution refluxed in ethanol for 24 h:[21] product formed with very low yield, but was not reproducible.
9. Finally the highest yield (46%) was achieved from **2d** and **3c** without a solvent and excess amine. This reaction was carried out at 140 °C for 4 h. Increasing temperature increases the amount of side products, which could not be identified. This reaction was also carried out under microwave conditions without heat and solvent, in which the product was obtained in 40% yield.

After many trials, we found that the latter procedure was the best choice for the conversion of **2d–e** to enamine **4j–l**.

The cyanomethyl substituted enamines **4a–l** were also assumed to be obtained starting from β-dicarbonyl compounds **1a–e** and amines, by the formation of enamine followed by alkylation with bromoacetonitrile. In a representative reaction, **1b** was reacted with aniline in benzene at reflux with the addition of a catalytical amount of *p*-TsOH to give enamine **7** in 79% yield. Deprotonation of the enamine with NaH in THF followed by alkylation with bromoacetonitrile furnished trace amount of the desired product. This method was not suitable for the synthesis of enamines **4a–l**.

Simple and efficient conditions were found for the cyclization of enamines to pyrroles. This condition involved the treatment of enamines **4a–l** with potassium ethoxide in ethanol at room temperature, in which the pyrrole derivatives **5a–l** were obtained in excellent yields in a short reaction time (5–10 min; for aryl substituted enamines 20–30 min) (Scheme 2).

In addition to the above described experiments, many attempts were made for the direct- one pot synthesis of pyrroles starting with; (a) β-dicarbonyl compound, bromoacetonitrile and amine, (b) starting from enamine, bromoacetonitrile, heating in benzene in the presence of catalytical amount of *p*-TsOH or TFA, but none of the reactions were successful.



Scheme 2.

Table 1. Synthesis of substituted 2-aminopyrroles

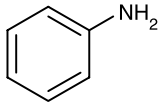
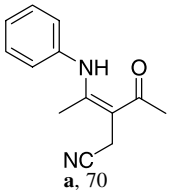
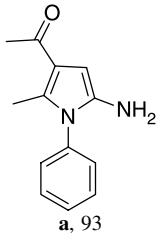
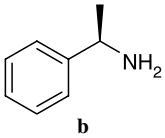
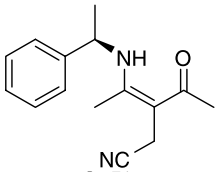
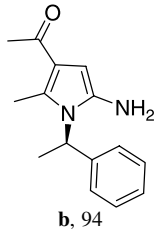
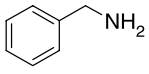
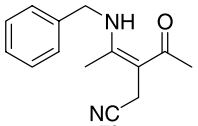
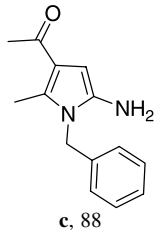
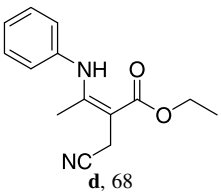
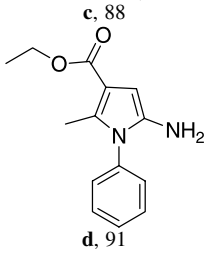
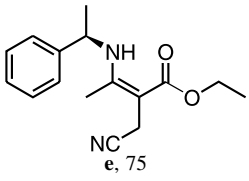
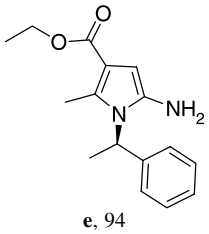
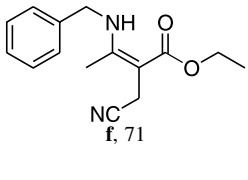
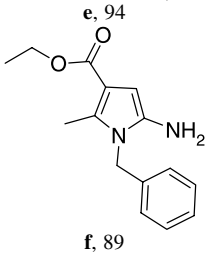
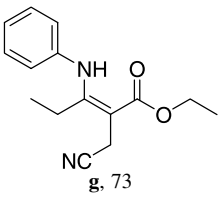
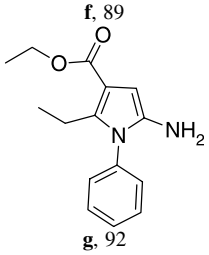
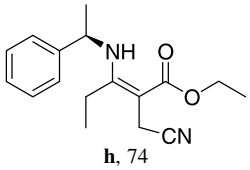
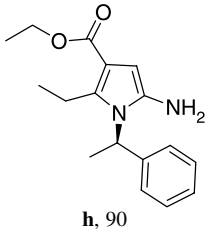
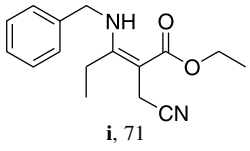
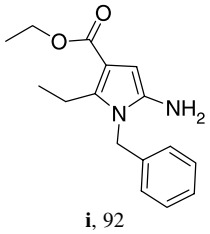
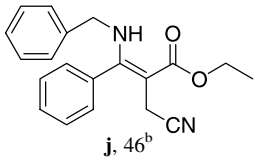
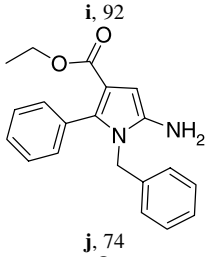
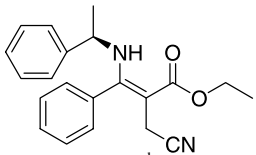
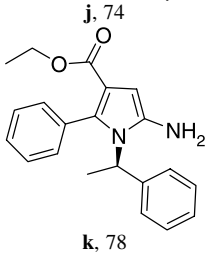
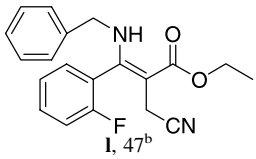
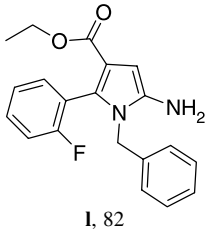
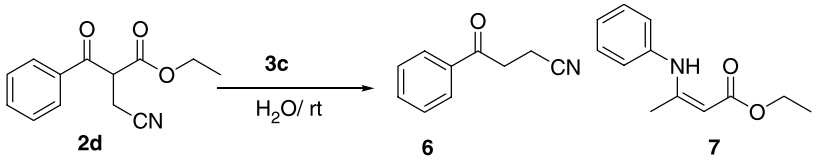
Entry	Dicarbonyl compound **2**	Amine **3**	Enamine **4**, Yield (%)[a]	Pyrrole **5**, Yield (%)[a]
1	**a**	 **a**	 **a**, 70	 **a**, 93
2	**a**	 **b**	 **b**, 71	 **b**, 94
3	**a**	 **c**	 **c**, 73	 **c**, 88
4	**b**	**a**	 **d**, 68	 **d**, 91
5	**b**	**b**	 **e**, 75	 **e**, 94
6	**b**	**c**	 **f**, 71	 **f**, 89
7	**c**	**a**	 **g**, 73	 **g**, 92

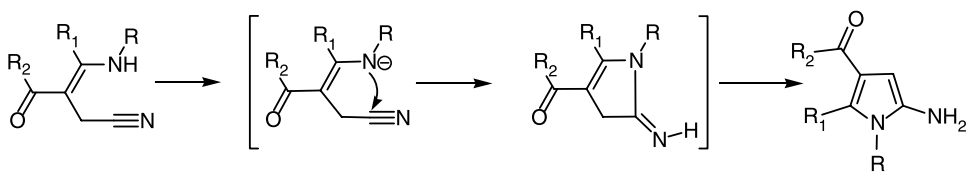
Table 1 (*continued*)

Entry	Dicarbonyl compound **2**	Amine **3**	Enamine **4**, Yield (%)[a]	Pyrrole **5**, Yield (%)[a]
8	**c**	**b**	 **h**, 74	 **h**, 90
9	**c**	**c**	 **i**, 71	 **i**, 92
10	**d**	**c**	 **j**, 46[b]	 **j**, 74
11	**d**	**b**	 **k**, 49[b]	 **k**, 78
12	**e**	**c**	 **l**, 47[b]	 **l**, 82

[a] Isolated yield.
[b] Synthesized by solvent-free heating of α-cyanomethyl-β-dicarbonyl compounds with amines.



Scheme 3.



Scheme 4.

All of the pyrrole derivatives were identified by spectroscopic methods and all spectroscopic data are in agreement with the given structures.

The mechanism is assumed to involve the deprotonation of the enamine, then the addition of the amine moiety to the carbon–nitrogen triple bond to afford the cyclic intermediate (Scheme 4). This is followed by a rearrangement to afford pyrrole **5**. The attack of nitrogen to the carbon–nitrogen triple bond is activated by the potassium ion. This mechanism is consistent with the generally accepted mechanism of the nucleophilic addition to metal-activated carbon–carbon multiple bonds.[22]

3. Conclusions

This investigation has resulted in the elaboration of a convenient procedure for the preparation of 2-aminopyrrole derivatives. The condensation reaction of α-cyanomethyl-β-dicarbonyl compounds with amines catalyzed by *p*-TsOH affords the corresponding enamines in good yields. Base catalyzed cyclization via the addition of an amine moiety to the carbon–nitrogen triple bond furnished 2-aminopyrroles in high yields.

4. Experimental

4.1. Materials and methods

NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^{1}H: $\delta=7.27$), $CDCl_3$ (^{13}C: $\delta=77.0$) and CCl_4 (^{13}C: $\delta=96.4$) as internal standards. IR spectra were recorded on a Perkin Elmer 1600 FTIR series instrument.

Column chromatography was conducted on silica gel 60 (40–63 μm). TLC was carried out on aluminum sheets pre-coated with silica gel $60F_{254}$ (Merck), and the spots were visualized with UV light ($\lambda=254$ nm). Optical rotations were measured with a Krüss P3002RS automatic polarimeter.

4.2. General procedure for alkylation of β-dicarbonyl compounds

NaH (1.5 mmol) was added slowly to a stirred solution of β-dicarbonyl compound (1 mmol) in THF at room temperature under argon. The reaction mixture was stirred for 1 h and then a solution of bromoacetonitrile (1.2 mmol) in THF (15 ml) was added slowly and stirred for 4 h. The reaction was monitored by TLC. Water was added, the mixture extracted with ethyl acetate and the combined organic layers were dried over $MgSO_4$. After the evaporation of the solvent under reduced pressure, the crude product was purified on silica gel to afford **2a–e** (hexane–ethyl acetate (4–1)).

4.2.1. 3-Acetyl-4-oxopentanenitrile (2a). Yield: (105 mg, 76%); yellow oil. IR (neat): 2333, 2976, 1723 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.25$ (s, 6H), 2.73 (d, 2H, $J=7.1$ Hz), 4.02 (t, 1H, $J=7.1$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=15.7$, 23.5, 30.0, 62.9, 117.7, 191.5, 200.1. Anal. Calcd for $C_7H_9NO_2$ (139.15): C, 60.42; H, 6.52; N, 10.07. Found: C, 60.23; H, 6.35; N, 9.83.

4.2.2. Ethyl 2-(cyanomethyl)-3-oxobutanoate (2b). Yield: (181 mg, 71%); yellow oil. IR (neat): 2331, 2978, 1725 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.27$ (t, 3H, $J=7.1$ Hz), 2.32 (s, 3H), 2.73–2.79 (m, 2H), 3.75 (t, 1H, $J=7.2$ Hz), 4.23–4.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.4$, 15.8, 29.6, 55.5, 62.6, 117.4, 166.6, 198.6. Anal. Calcd for $C_8H_{11}NO_3$ (169.7): C, 56.80; H, 6.55; N, 8.28. Found: C, 56.66; H, 6.73; N, 7.92.

4.2.3. Ethyl 2-(cyanomethyl)-3-oxopentanoate (2c). Yield: (146 mg, 80%); yellow oil. IR (neat): 2326, 2975, 1720 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.05$ (t, 3H, $J=7.2$ Hz), 1.23 (t, 3H, $J=7.1$ Hz), 2.43–2.67 (m, 2H), 2.74 (d, 2H, $J=7.2$ Hz), 3.77 (t, 1H, $J=7.2$ Hz), 4.18 (q, 2H, $J=7.1$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=12.7$, 14.7, 22.4, 30.1, 52.5, 62.2, 116.7, 192.4, 198.1. Anal. Calcd for $C_9H_{13}NO_3$ (183.2): C, 59.00; H, 7.15; N, 7.65. Found: C, 58.82; H, 7.33; N, 7.39.

4.2.4. Ethyl 2-(cyanomethyl)-3-oxo-3-phenylpropanoate (2d). Yield: (198 mg, 78%); colorless oil. IR (neat): 2978, 2249, 1736, 1689 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.20$ (t, 3H, $J=7.1$ Hz), 3.07 (dd, 1H, $J=5.4$, 17.0 Hz), 3.12 (dd, 1H, $J=6.9$, 17.0 Hz), 4.20 (q, 2H, $J=7.1$ Hz), 4.66 (t, 1H, $J=7.2$ Hz), 7.53–8.05 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.3$, 16.1, 49.7, 62.0, 116.4, 128.3, 128.5, 133.7, 134.5, 166.0, 190.4. Anal. Calcd for $C_{13}H_{13}NO_3$ (231.25): C, 67.52; H, 5.67; N, 6.06. Found: C, 67.38; H, 5.33; N, 5.71.

4.2.5. Ethyl 2-(cyanomethyl)-3-(2-fluorophenyl)-3-oxopropanoate (2e). Yield: (199 mg, 80%); yellow oil. IR (neat): 2954, 2212, 1732, 1679 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.17$ (t, 3H, $J=7.0$ Hz), 2.93 (dd, 1H, $J=7.2$, 16.8 Hz,), 3.05 (dd, 1H, $J=6.7$, 16.8 Hz), 4.17 (q, 2H, $J=7.0$ Hz), 4.62 (t, 1H, $J=7.0$ Hz), 7.14–7.94 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.3$, 15.8, 53.2, 61.7, 95.7, 116.1 (d, $J=23$ Hz), 123.6 (d, $J=11$ Hz), 124.3 (d, $J=3$ Hz), 130.8, 135.1 (d, $J=9$ Hz), 161.3 (d, $J=253$ Hz), 166.2, 189.0. Anal. Calcd for $C_{13}H_{12}FNO_3$ (249.24): C, 62.65; H, 4.85; N, 5.62. Found: C, 62.41; H, 4.76; N, 5.31.

4.3. General procedure for enamine formation

Alkylated β-dicarbonyl compound (1 mmol) was dissolved in benzene (10 ml). Corresponding amine (1.2 mmol) together with catalytic amount of PTSA was added to the stirring mixture and heated at 80 °C for 6–10 h using a Dean-Stark trap. Reaction was monitored by TLC. The reaction mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure and the crude product purified by column chromotography.(hexane–ethyl acetate (4–1)).

4.3.1. (*Z*)-3-acetyl-4-(phenylamino)pent-3-enenitrile (4a). Yield: (149 mg, 70%); brown oil. IR (neat): 2987, 2242, 1592, 1570 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.03$ (s, 3H), 2.22 (s, 3H), 3.29 (s, 2H), 7.09–7.19 (m, 5H), 13.51 (s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=19.0$,

20.5, 30.4, 98.3, 120.6, 128.0, 128.8, 131.6, 140.6, 163.0, 196.7. Anal. Calcd for $C_{13}H_{14}N_2O$ (214.26): C, 72.87; H, 6.59; N, 13.07. Found: C, 72.62; H, 6.45; N, 12.75.

4.3.2. (*R*)-(*Z*)-4-(1-phenylethylamino)-3-acetylpent-3-enenitrile (4b). Yield: (171 mg, 71%); white solid, mp = 105–106 °C, $[\alpha]_D^{22}$ −586 (1.2, $CHCl_3$). IR (in $CHCl_3$): 3441, 2962, 2921, 2357, 2240, 1598 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.48 (d, 3H, J = 6.7 Hz), 1.84 (s, 3H), 2.14 (s, 3H), 3.11 (d, 1H, J = 18.6 Hz), 3.19 (d, 1H, J = 18.6 Hz), 4.60–4.65 (m, 1H), 7.17–7.44 (m, 5H), 12.56 (d, 1H, J = 7.1 Hz, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 18.4, 25.2, 28.3, 54.1, 94.7, 118.8, 125.8, 127.8, 129.3, 144.2, 163.0, 193.8. Anal. Calcd for $C_{15}H_{18}N_2O$ (242.32): C, 74.35; H, 7.49; N, 11.56. Found: C, 74.11; H, 7.22; N, 11.33.

4.3.3. (*Z*)-3-acetyl-4-(benzylamino)pent-3-enenitrile (4c). Yield: (166 mg, 73%); brown oil. IR (neat): 3436, 3028, 2917, 2346, 2240, 1599 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.92 (s, 3H), 2.10 (s, 3H), 3.17 (s, 2H), 4.37 (d, 2H, J = 5.9 Hz), 7.11–7.21 (m, 5H), 12.32 (s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.6, 18.5, 28.3, 47.5, 119.0, 127.0, 127.9, 129.2, 137.7, 163.7, 193.8. Anal. Calcd for $C_{14}H_{16}N_2O$ (228.90): C, 73.66; H, 7.06; N, 12.27. Found: C, 73.46; H, 7.24; N, 11.88.

4.3.4. (*Z*)-ethyl 2-(cyanomethyl)-3-(phenylamino)but-2-enoate (4d). Yield: (166 mg, 68%); colorless oil. IR (neat): 3214, 3135, 2981, 2933, 2245, 1606 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, 3H, J = 7.1 Hz), 2.02 (s, 3H), 3.29 (s, 2H), 4.17 (q, 2H, J = 7.1 Hz), 6.96–7.11 (m, 5H), 11.16 (s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9, 16.6, 17.9, 31.5, 60.2, 86.1, 118.0, 118.7, 119.0, 125.8, 126.1, 129.5, 130.1, 139.1, 159.0, 168.9. Anal. Calcd for $C_{14}H_{16}N_2O_2$ (244.29): C, 68.83; H, 6.60; N, 11.47. Found: C, 68.78; H, 6.57; N, 11.15.

4.3.5. (*R*)-(*Z*)-ethyl 3-(1-phenylethylamino)-2-(cyanomethyl)but-2-enoate (4e). Yield: (203 mg, 75%); yellow oil, $[\alpha]_D^{22}$ −278 (2.1, $CHCl_3$). IR (neat): 3492, 2981, 2363, 2243, 1653 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, 3H, J = 7.1 Hz), 1.46 (d, 3H, J = 6.7 Hz), 1.81 (s, 3H), 3.07 (d, 1H, J = 17.9 Hz), 3.28 (d, 1H, J = 17.9 Hz), 4.01–4.11 (m, 2H), 4.49–4.57 (m, 1H), 7.13–7.22 (m, 5H), 9.88 (d, 1H, J = 5.6 Hz, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0, 16.0, 16.5, 25.4, 53.8, 59.8, 83.4, 119.4, 125.7, 127.6, 129.3, 144.9, 161.3, 169.2. Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.34): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.41; H, 7.32; N, 10.02.

4.3.6. (*Z*)-ethyl 3-(benzylamino)-2-(cyanomethyl)but-2-enoate (4f). Yield: (183 mg, 71%); yellow oil. IR (neat): 3254, 2980, 2357, 2242, 1646, 1597 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, 3H, J = 7.0 Hz), 1.90 (s, 3H), 3.20 (s, 2H), 4.07 (q, 2H, J = 7.0 Hz), 4.31 (d, 2H, J = 6.0 Hz), 7.11–7.21 (m, 5H), 9.82 (s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9, 15.6, 16.6, 47.5, 59.8, 83.6, 119.5, 125.7, 127.3, 127.9, 128.5, 129.3, 138.5, 161.7, 169.1. Anal. Calcd for $C_{15}H_{18}N_2O_2$ (258.32): C, 69.74; H, 7.02; N, 10.84. Found: C, 69.61; H, 6.91; N, 10.62.

4.3.7. (*Z*)-ethyl 2-(cyanomethyl)-3-(phenylamino)pent-2-enoate (4g). Yield: (188 mg, 73%); colorless oil. IR (neat): 3489, 2967, 2360, 2253, 1646 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, 3H, J = 7.6 Hz), 1.29 (t, 3H, J = 7.2 Hz), 2.37 (q, 2H, J = 7.6 Hz), 3.27 (s, 2H), 4.18 (q, 2H, J = 7.2 Hz), 7.01–7.11 (m, 5H), 10.99 (s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 14.5, 16.0, 22.0, 59.8, 84.7, 119.0, 126.2, 126.3, 129.2, 138.9, 164.2, 169.1. Anal. Calcd for $C_{15}H_{18}N_2O_2$ (258.32): C, 69.74; H, 7.02; N, 10.84. Found: C, 69.61; H, 7.17; N, 10.61.

4.3.8. (*R*)-(*Z*)-ethyl 3-(1-phenylethylamino)-2-(cyanomethyl)pent-2-enoate (4h). Yield: (211.5 mg, 74%); yellow oil, $[\alpha]_D^{22}$ 365 (1.7, $CHCl_3$). IR (neat): 3321, 3127, 2978, 2142, 1423 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, 3H, J = 7.6 Hz), 1.28 (t, 3H, J = 7.1 Hz), 1.47 (d, 3H, J = 6.8 Hz), 2.13–2.26 (m, 2H), 3.11 (d, 1H, J = 17.8 Hz), 3.21 (d, 1H, J = 17.8 Hz), 4.09–4.21 (m, 2H), 4.48–4.62 (m, 1H), 7.21–7.25 (m, 5H), 9.87 (s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 14.6, 15.8, 22.2, 25.3, 53.0, 59.5, 82.5, 119.3, 125.3, 127.3, 128.9, 144.9, 165.5, 169.3. Anal. Calcd for $C_{17}H_{22}N_2O_2$ (286.37): C, 71.30; H, 7.74; N, 9.78. Found: C, 71.12; H, 7.71; N, 9.57.

4.3.9. (*Z*)-ethyl 3-(benzylamino)-2-(cyanomethyl)pent-2-enoate (4i). Yield: (193 mg, 71%); yellow oil. IR (neat): 3456, 3123, 2903, 2344, 1599 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (t, 3H, J = 7.7 Hz), 1.25 (t, 3H, J = 7.1 Hz), 2.34 (q, 2H, J = 7.7 Hz), 3.22 (s, 2H), 4.08 (q, 2H, J = 7.1 Hz). 7.19–7.22 (m, 5H), 9.80 (s, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 14.6, 15.9, 21.9, 46.8, 59.5, 82.6, 119.3, 126.2, 127.6, 128.9, 138.2, 165.8 169.2. Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.34): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.34; H, 7.32; N, 9.88.

4.3.10. (*Z*)-ethyl 3-(benzylamino)-2-(cyanomethyl)-3-phenylacrylate (4j). Yield: (146 mg, 46%) brown oil. IR (neat): 3496, 3321, 2765, 2346, 1587 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, 3H, J = 7.1 Hz), 2.78 (s, 2H), 3.99 (d, 2H, J = 6.3 Hz), 4.12 (q, 2H, J = 7.1 Hz), 7.18–7.22 (m, 10H), 9.63 (br s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 17.8, 30.7, 48.5, 59.7, 84.9, 119.3, 126.7, 127.3, 127.6, 129.1, 129.4, 133.5, 138.5, 163.9, 169.0. Anal. Calcd for $C_{20}H_{20}N_2O_2$ (320.38): C, 75.42; H, 6.63; N, 8.38. Found: C, 75.35; H, 6.58; N, 7.92.

4.3.11. (*R*)-(*Z*)-ethyl 3-(1-phenylethylamino)-2-(cyanomethyl)-3-phenylacrylate (4k). Yield: (168 mg, 49%); brown oil, $[\alpha]_D^{22}$ −420 (2.0, $CHCl_3$). IR (neat): 3436, 3028, 2917, 2240, 1587 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, 3H, J = 7.6 Hz), 1.37 (d, 3H, J = 6.8 Hz), 2.69 (d, 1H, J = 17.4 Hz), 2.80 (d, 1H, J = 17.4 Hz), 4.00–4.06 (m, 1H), 4.18–4.23 (m, 2H), 6.65–7.51 (m, 10H), 9.69 (d, 1H, J = 8.8 Hz, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 17.6, 24.6, 29.7, 54.3, 59.8, 84.8, 119.6, 125.5, 127.0, 127.2, 127.8, 128.5, 128.7, 129.0, 129.3, 133.7, 144.5, 163.4, 169.2. Anal. Calcd for $C_{21}H_{22}N_2O_2$ (334.4): C, 75.42; H, 6.63; N, 8.38. Found: C, 75.38; H, 6.40; N, 8.12.

4.3.12. (*Z*)-ethyl 3-(benzylamino)-2-(cyanomethyl)-3-(2-fluorophenyl)acrylate (4l). Yield: (158 mg, 47%); yellow oil. IR (neat): 3412, 3123, 2923, 2221, 1598 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, 3H, J = 7.1 Hz), 2.65 (d, 1H, J = 18.2 Hz), 3.03 (d, 1H, J = 18.2 Hz), 3.92–4.09 (m, 2H),

4.12–4.21 (m, 2H), 7.01–7.31 (m, 9H), 9.61 (br s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.5, 17.6, 48.6, 59.9, 85.5, 116.3 (d, J=20 Hz), 118.8, 120.1, 124.9, 126.9, 127.4, 128.6, 130.0, 131.7, 137.9, 157.8, 161.2 (d, J=252 Hz), 168.7. Anal. Calcd for $C_{20}H_{19}FN_2O_2$ (338.38): C, 70.99; H, 5.66; N, 8.28. Found: C, 70.83; H, 5.61; N, 7.92.

4.4. General procedure for base catalyzed cyclization

Enamine (1 mmol) was added to potassium ethoxide in ethanol solution (5 ml, 24 wt%) and stirred for 5–30 min at room temperature. The reaction was monitored by TLC. Then water was added and the mixture extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude pruduct was purified by column chromotography. (hexane–ethyl acetate (4–1)).

4.4.1. 1-(5-Amino-2-methyl-1-phenyl-1*H*-pyrrol-3-yl) ethanone (5a). Yield: (199 mg, 93%); brown oil. IR (neat); 3370, 2989, 1644 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.20 (s, 3H), 2.28 (s, 3H), 2.95 (s, 2H, NH_2), 5.65 (s, 1H), 7.17–7.30 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.1, 28.9, 92.3, 128.7, 129.1, 130.0, 130.9, 135.2, 136.2, 194.7. Anal. Calcd for $C_{13}H_{14}N_2O$ (214.26): C, 72.87; H, 6.59; N, 13.07. Found: C, 72.76; H, 6.40; N, 12.78.

4.4.2. (*R*)-1-(5-amino-2-methyl-1-(1-phenylethyl)-1*H*-pyrrol-3-yl)ethanone (5b). Yield: (201 mg, 94%); oil, $[\alpha]_D^{22}$ 33 (0.7, $CHCl_3$). IR (neat): 3418, 2901, 2924, 2355, 1645 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.80 (d, 3H, J=7.0 Hz), 2.21 (s, 3H), 2.40 (s, 3H), 2.60 (s, 2H, NH_2), 5.53 (q, 1H, J=7.0 Hz), 5.61 (s, 1H), 7.14–7.23 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.1, 18.2, 50.8, 59.5, 110.4, 126.3, 127.4, 129.3, 131.3, 134.7, 141.2, 166.2. Anal. Calcd for $C_{15}H_{18}N_2O$ (242.32): C, 74.35; H, 7.49; N, 11.56. Found: C, 74.21; H, 7.23; N, 11.35.

4.4.3. 1-(5-Amino-1-benzyl-2-methyl-1*H*-pyrrol-3-yl) ethanone (5c). Yield: (200 mg, 88%); brown oil. IR (neat): 3388, 3007, 2917, 2849, 1656 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.27 (s, 3H), 2.41 (s, 3H), 2.82 (s, 2H, NH_2), 4.99 (s, 2H), 5.76 (s, 1H), 7.15–7.29 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.1, 28.9, 30.1, 45.5, 119.4, 126.1, 127.9, 129.3, 131.1, 133.8, 137.4, 194.6. Anal. Calcd for $C_{14}H_{16}N_2O$ (228.18): C, 73.66; H, 7.06; N, 12.27. Found: C, 73.55; H, 7.25; N, 11.88.

4.4.4. Ethyl 5-amino-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylate (5d). Yield: (222 mg, 91%); yellow oil. IR (neat); 3315, 2982, 2926, 2336, 1687 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.24 (t, 3H, J=7.1 Hz), 2.18 (s, 3H), 2.93 (s, 2H, NH_2), 4.18 (q, 2H, J=7.1 Hz), 5.68 (s, 1H), 7.13–7.30 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 12.59, 15.0, 59.4, 92.2, 96.5, 128.8, 128.9, 129.9, 131.3, 135.2, 136.6, 165.7. Anal. Calcd for $C_{14}H_{16}N_2O_2$ (244.12): C, 68.83; H, 6.60; N, 11.47. Found: C, 68.76; H, 6.64; N, 11.24.

4.4.5. (*R*)-ethyl 5-amino-2-methyl-1-(1-phenylethyl)-1*H*-pyrrole-3-carboxylate (5e). Yield (255 mg, 94%); yellow oil, $[\alpha]_D^{22}$ 332 (1.0, $CHCl_3$). IR (neat); 3243, 2923, 2854, 2342, 1688 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.24 (t, 3H, J=7.1 Hz), 1.81 (d, 3H, J=6.7 Hz), 2.40 (s, 3H), 2.67 (s, 2H, NH_2), 4.18 (q, 2H, J=7.1 Hz), 5.51–5.59 (m, 1H), 5.76 (s, 1H), 7.13–7.28 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.2, 14.9, 18.3, 51.8, 59.5, 110.5, 126.3, 127.7, 129.1, 131.6, 134.8, 141.3, 166.2. Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.34): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.52; H, 7.34; N, 9.92.

4.4.6. Ethyl 5-amino-1-benzyl-2-methyl-1*H*-pyrrole-3-carboxylate (5f). Yield: (229 mg, 89%); yellow oil. IR (neat); 3305, 2980, 2933, 2343, 1683 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.24 (t, 3H, J=7.1 Hz), 2.34 (s, 3H), 2.82 (s, 2H, NH_2), 4.13 (q, 2H, J=7.1 Hz), 4.95 (s, 2H), 5.78 (s, 1H), 7.09–7.21 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.6, 15.0, 45.6, 59.3, 96.1, 110.3, 126.2, 127.7, 129.2, 131.4, 134.0, 137.7, 165.8. Anal. Calcd for $C_{15}H_{18}N_2O_2$ (258.32): C, 69.74; H, 7.02; N, 10.84. Found: C, 69.61; H, 7.05; N, 10.58.

4.4.7. Ethyl 5-amino-2-ethyl-1-phenyl-1*H*-pyrrole-3-carboxylate (5g). Yield: (263 mg, 92%); colorless oil. IR (neat): 3375, 2970, 2913, 2340, 1681 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.91 (t, 3H, J=7.3 Hz), 1.27 (t, 3H, J=7.2 Hz), 2.59 (q, 2H, J=7.3 Hz), 2.86 (br s, 2H, NH_2), 4.20 (q, 2H, J=7.2 Hz), 5.70 (s, 1H), 7.28–7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.5, 19.0, 29.7, 58.9, 92.0, 109.9, 114.9, 128.7, 129.4, 134.6, 136.3, 137.3, 165.0. Anal. Calcd for $C_{15}H_{18}N_2O_2$ (286.37): C, 69.74; H, 7.02; N, 10.84; O. Found: C, 69.68; H, 7.01; N, 10.61.

4.4.8. (*R*)-ethyl 5-amino-2-ethyl-1-(1-phenylethyl)-1*H*-pyrrole-3-carboxylate (5h). Yield: (257 mg, 90%); colorless oil, $[\alpha]_D^{22}$ 197 (1.4, $CHCl_3$). IR (neat): 3298, 2934, 2984, 2323, 1645 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.08 (t, 3H, J=7.4 Hz), 1.26 (t, 3H, J=6.9 Hz), 1.86 (d, 3H, J= 7.0 Hz), 2.52 (br s, 2H, NH_2), 2.95 (q, 2H, J=7.4 Hz), 4.17 (q, 2H, J=7.0 Hz), 5.45 (q, 1H, J=7.0 Hz), 5.67 (s, 1H), 7.10–7.19 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.6, 15.0, 18.1, 18.7, 51.3, 58.8, 95.4, 109.4, 125.9, 127.3, 128.8, 134.1, 137.0, 141.2. Anal. Calcd for $C_{17}H_{22}N_2O_2$ (286.37): C, 71.30; H, 7.74; N, 9.78. Found: C, 71.33; H, 7.68; N, 9.59.

4.4.9. Ethyl 5-amino-1-benzyl-2-ethyl-1*H*-pyrrole-3-carboxylate (5i). Yield: (244 mg, 92%); yellow oil. IR (neat): 3323, 2979, 2934, 2334, 1675 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.02 (t, 3H, J=7.4 Hz), 1.27 (t, 3H, J=7.1 Hz), 2.81 (br s, 2H, NH_2), 2.86 (q, 2H, J=7.1 Hz), 4.21 (q, 2H, J=7.4 Hz), 5.12 (s, 2H), 5.72 (s, 1H), 6.81–7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.6, 18.7, 29.6, 45.1, 58.8, 96.01, 109.3, 125.6, 127.3, 127.3, 133.3, 137.6, 137.6, 165.0. Anal. Calcd for $C_{16}H_{20}N_2O_2$ (286.37): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.53; H, 7.29; N, 9.95.

4.4.10. Ethyl 5-amino-1-benzyl-2-phenyl-1*H*-pyrrole-3-carboxylate (5j). Yield: (236 mg, 74%); yellow oil. IR (neat): 3312, 2978, 2923, 2332, 1679 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.03 (t, 3H, J=7.1 Hz), 2.87 (br s, 2H, NH_2), 4.01 (q, 2H, J=7.1 Hz), 4.84 (s, 2H), 5.93 (s, 1H), 6.84–7.28 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 14.2, 46.4, 58.9, 95.7, 111.7, 125.7, 127.3, 127.9, 127.9,

128.8, 130.8, 132.2, 132.9, 133.9, 135.0, 137.8, 164.5. Anal. Calcd for $C_{20}H_{20}N_2O_2$ (320.15): C, 74.98; H, 6.29; N, 8.74. Found: C, 74.80; H, 6.21; N, 8.51.

4.4.11. (*R*)-ethyl 5-amino-2-phenyl-1-(1-phenylethyl)-1*H*-pyrrole-3-carboxylate (5k). Yield: (260 mg, 78%); yellow oil, $[\alpha]_D^{22}$ 413 (3.0, $CHCl_3$). IR (neat): 3298, 2976, 2943, 2321, 1675 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta=$ 1.08 (t, 3H, $J=7.1$ Hz), 1.84 (d, 3H, $J=7.0$ Hz), 2.65 (br s, 2H, NH_2), 4.06 (q, 2H, $J=7.1$ Hz), 5.21 (q, 1H, $J=7.0$ Hz), 5.85 (s, 1H), 7.21–7.38 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.2$, 17.8, 52.5, 58.9, 95.3, 111.5, 126.0, 127.3, 127.7, 128.0, 128.8, 130.9, 132.8, 133.8, 135.6, 141.1, 164.5. Anal. Calcd for $C_{21}H_{22}N_2O_2$ (334.17): C, 75.42; H, 6.63; N, 8.38. Found: C, 75.24; H, 6.55; N, 8.12.

4.4.12. Ethyl 5-amino-1-benzyl-2-(2-fluorophenyl)-1*H*-pyrrole-3-carboxylate (5l). Yield: (277 mg, 82%); yellow oil. IR (neat): 3294, 2985, 2934, 2234, 1656 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.02$ (t, 3H, $J=7.1$ Hz), 2.93 (br s, 2H, NH_2), 3.98–4.05 (m, 2H), 4.71 (d, 1H, $J=16.3$ Hz), 4.88 (d, 1H, $J=16.3$ Hz), 5.97 (s, 1H), 6.76–7.21 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.7$, 46.6, 50.4, 59.1, 92.6, 113.3, 115.4 (d, $J=22$ Hz), 120.1, 123.4, 126.0, 126.3, 127.2, 127.5, 128.4, 128.8, 130.1 (d, $J=8$ Hz), 133.1, 137.0, 138.9, 139.9, 161.1 (d, $J=253$ Hz), 164.3. Anal. Calcd for $C_{20}H_{19}FN_2O_2$ (338.38): C, 70.99; H, 5.66; N, 8.28. Found: C, 70.91; H, 5.54; N, 8.11.

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References and notes

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