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Microwave-Assisted Protection of Primary Amines as 2,5-Dimethylpyrroles and Their Orthogonal Deprotection

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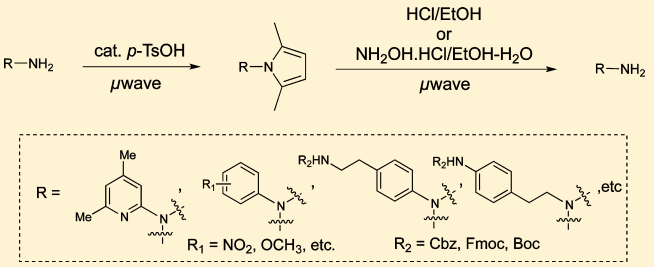
Supporting Information

ABSTRACT: Primary amines can be readily doubly protected as *N*-substituted 2,5-dimethylpyrroles. Although this protecting group is stable toward strong bases and nucleophiles, long reaction times are required for both the protection and deprotection steps, generally resulting in low deprotection yields. By employing microwave irradiation, protection and deprotection reaction times are dramatically reduced. Furthermore, deprotection with dilute hydrochloric acid in ethanol increases reaction yields. Diverse deprotection conditions have been developed in conjunction with microwave irradiation, so that protection as an *N*-substituted 2,5-dimethylpyrrole can be orthogonal to other standard amine protecting groups, such as *tert*-butyloxycarbonyl (Boc), carbobenzyloxy (Cbz), and 9-fluorenylmethyloxycarbonyl (Fmoc).



INTRODUCTION

Protection and deprotection of reactive amino groups are fundamental strategies in multistep syntheses of amine-containing molecules; various protecting groups have been essential for the synthesis of target molecules without interference with other functionalities.[1] The use of carbamates, such as *tert*-butyloxycarbonyl (Boc[2]), carbobenzyloxyl (Cbz[3]), and 9-fluorenylmethyloxycarbonyl (Fmoc[4]), as protecting groups for amines has been significant because of the efficiency in the protection and deprotection with short reaction times as well as chemoselectivity in the deprotection. They have proven to be relatively successful in protecting both aliphatic and aromatic amines, although they are not sufficient to protect amines from strong basic conditions, such as BuLi and LDA, because a monocarbamate protected amine can be deprotonated and undergo nucleophilic addition reactions.

During the course of our syntheses of selective inhibitors of neuronal nitric oxide synthase (nNOS), a protecting group for amines that was stable under basic conditions was essential.[5,6] Since 2-aminopyridine derivatives have proven viable as selective NOS inhibitors, blockage of both hydrogens of the amino group has been critical for efficient synthesis of the target molecules.[7] Our initial protection attempts with *N*-diBoc protected 2-aminopyridine-containing compounds were not successful under either acidic or basic conditions. Other double protection attempts, such as *N*-benzyl-*N*-(*t*-butyl)carbamate required additional reaction steps, and phthalimide[8] protection strategy was not successful under strongly basic conditions. Our previous nNOS inhibitor syntheses[9] and syntheses from other research groups[10] (Figure 1) have confirmed the use of 2,5-dimethylpyrrole,[11] generated from acetonylacetone, as an alternative doubly protected amine strategy that is non-ionizable, stable to strong bases, stable to strong reducing agents, and removed via treatment with hydroxylamine hydrochloride (Scheme 1).[12]

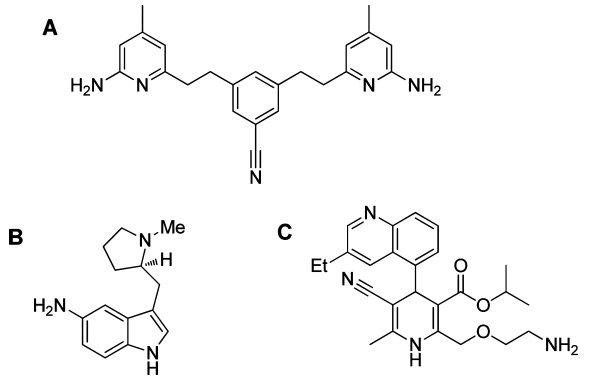


Figure 1. Examples of molecules using the 2,5-dimethylpyrrole protection/deprotection strategy.

However, current methods of protection and deprotection of amines as 2,5-dimethylpyrroles require long reaction times and proceed with low yields. The conventional method of protection with acetonylacetone requires more than 24 h reflux in toluene, and deprotection of the 2,5-dimethylpyrrole requires excess hydroxylamine and reflux with alcohol and water for over 24 h.[13] Furthermore, the deprotected amine is usually water-soluble, which makes the separation of the product from excess hydroxylamine (also water-soluble) difficult.

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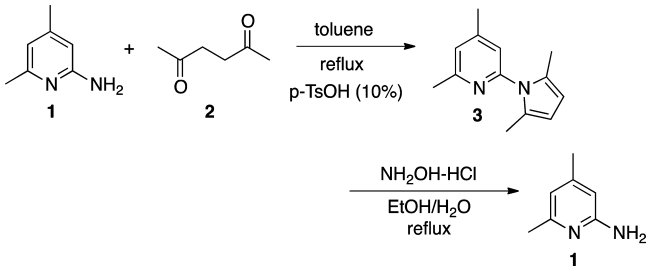
Scheme 1. Paal–Knorr Synthesis of 2,5-Dimethylpyrrole As an Amine Protecting Group



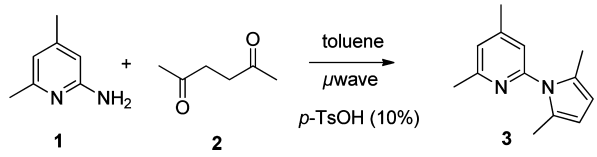
Our aim was to develop a method to reduce the reaction time and retain high yields for the protection reaction and reduce reaction time and increase yields for the deprotection reaction. We sought to reduce the reaction time of the protection by employing microwave irradiation[14] rather than conventional heating. Furthermore, we anticipated that microwave irradiation would also reduce the reaction time for deprotection under various conditions. Mechanistically, the deprotection reaction can occur by protonation of the pyrrole ring and nucleophilic addition by hydroxylamine[16] or by acid-catalyzed hydrolysis in protic solvents. By controlling the pH of the aqueous solvent system to adjust the concentration of protons using either hydrochloric acid or hydroxylamine HCl salt, we hoped to reduce the reaction time for deprotection under mild conditions.[15,16] Additionally, we explored diverse deprotection conditions for the 2,5-dimethylpyrrole moiety for use with other amine protecting groups, such as Fmoc, Cbz, and Boc. We anticipated orthogonal deprotection of the 2,5-dimethylpyrrole group in the presence of acid-labile protecting groups (e.g., Boc) using hydroxylamine conditions; in the presence of acid-stable protecting groups (Cbz and Fmoc), we anticipated that hydrochloric acid conditions could be used.

RESULTS AND DISCUSSION

Microwave-Assisted 2,5-Dimethylpyrrole Protection of Primary Amines. We assumed that nucleophilic attack of the primary amino group in **1** (Scheme 1) on the activated carbonyl in **2** could be accelerated by employing microwave irradiation. Because microwaves are known to accelerate a variety of organic reactions in toluene,[17] and microwave-assisted reactions with *p*-toluene sulfonic acid have been reported,[18] we decided to determine the efficiency of microwaves to reduce the reaction time for protection of **1** with **2** (Scheme 1). The overall sequence required the addition of the primary amine (1 equiv), acetonylacetone (1.2 equiv), and *p*-toluene sulfonic acid (0.1 equiv) to toluene in a sealed microwave reaction vessel. After screening a variety of reaction times and conditions, we determined that heating the reaction mixture containing 3–5 mmol of the primary amine in toluene and 10% *p*-toluenesulfonic acid for 60 min at 150 °C under microwave irradiation provided the best yields for protection (Table 1). By microwave irradiation, we were able to reduce the reaction time significantly (Table 1: experiments 7–9) yet retain high yields.

Microwave-Assisted Deprotection of Substituted 2,5-Dimethylpyrroles under Various Conditions. Initially, we used the most prevalent condition for deprotection in the literature of hydroxylamine hydrochloride in aqueous ethanol. Without microwave irradiation (Table 2: experiment 1), reaction times were long and yields were moderate. With microwave irradiation (Table 2: experiments 2–6), reaction times decreased 40-fold, although the yields did not improve; microwave irradiation was able to provide sufficient energy for reaction rate acceleration.[13] Earlier literature showed that the use of trifluoroacetic acid and water for deprotection reduced the reaction time;[19] therefore, deprotection of 2,5-dimethylpyrrole was investigated under a variety of acidic conditions with and without microwave irradiation (Table 2: experiments 7–13). We first used an acetic acid and hydrochloric acid mixture (9:1; Table 2: experiment 8), which worked well for deprotection of the pyrrole ring in **3**, but these conditions were too harsh for many other compounds. We slightly reduced the acidity of the reaction conditions by using a combination of ethanol and hydrochloric acid (9:1; Table 2: experiments 9–13), which gave comparable yields to that with HCl in AcOH and increased the reaction rate 30-fold over the reaction that was not microwave irradiated (Table 2: experiment 9). The

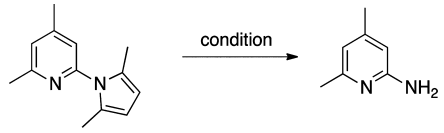
Table 1. Optimization of the Protection Conditions



#	acetonylacetone (equiv)	temp (°C)	time (min)	yield[a] (%)
1	1.2	111	12 h	75[b]
2	1.0	100	60	58
3	1.0	120	60	61
4	1.2	100	60	60
5	1.2	120	60	67
6	1.2	140	60	71
7	1.2	150	45	61
8	1.2	150	60	78[c]
9	1.2	170	45	68[d]

[a]Isolated yield. [b]Reflux without microwave irradiation. [c]2-Amino-4,6-dimethylpyridine was consumed (determined by TLC and ninhydrin stain). [d]2,5-Hexanedione was consumed (determined by TLC and PMA stain).

Table 2. Optimization of the Deprotection Conditions



#	conditions	temp (°C)	time (min)	yield[a] (%)	microwave
1	$NH_2OH{\cdot}HCl$[b]	100	20 h	66	no
2	$NH_2OH{\cdot}HCl$[b]	100	60	68	yes
3	$NH_2OH{\cdot}HCl$[b]	110	40	67	yes
4	$NH_2OH{\cdot}HCl$[b]	120	30	68	yes
5	$NH_2OH{\cdot}HCl$[b]	120	40	65	yes
6	$NH_2OH{\cdot}HCl$[b]	130	40	54	yes
7	90% TFA in H_2O	100	8 h	62	no
8	10% conc HCl in AcOH	100	10	82	yes
9	10% conc HCl in EtOH	100	5 h	74	no
10	10% conc HCl in EtOH	100	30	76	yes
11	10% conc HCl in EtOH	110	20	76	yes
12	10% conc HCl in EtOH	120	10	84	yes
13	10% conc HCl in EtOH	130	10	68	yes

[a]Isolated yield. [b]10 equiv; 33% H_2O in EtOH.

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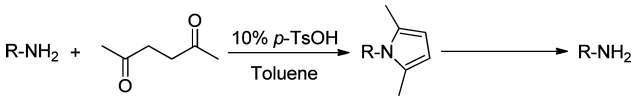
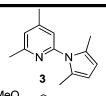
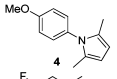
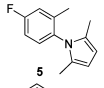
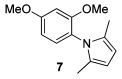
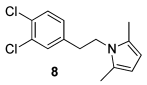
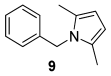
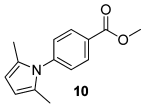
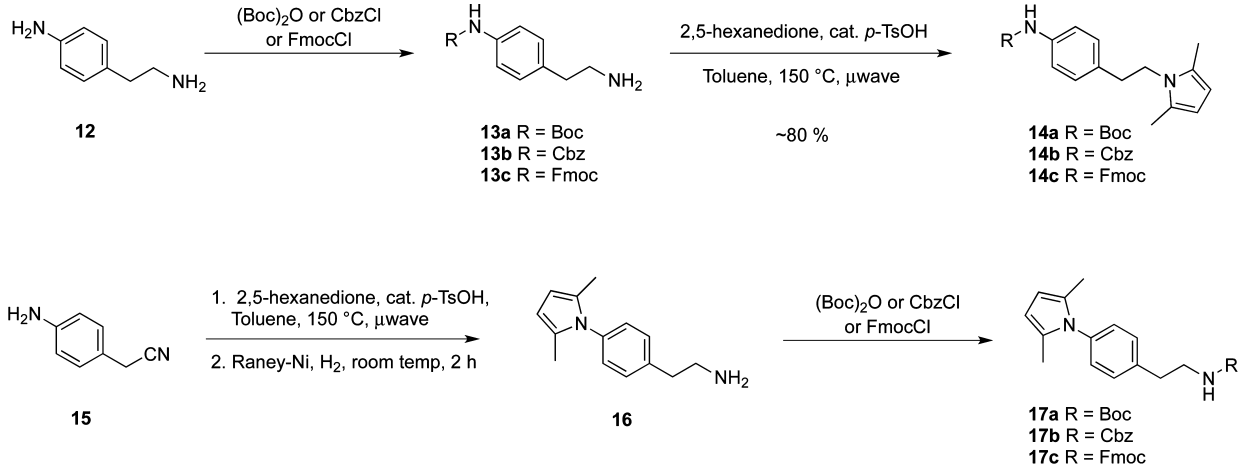
Table 3. Scope of Enhanced Deprotection and Protection Conditions



entry	protected amine	protection		deprotection	
		conventional[a] yield	μwave[b] yield	conventional[c] yield	μwave[d] time, yield
1	 3	66%	78%	64%	20 min, 88%
2	 4	84%	89%	59%	15 min, 71%
3	 5	78%	84%	59%	15 min, 81%
4	 6	73%	72%	61%	20 min, 78%
5	 7	82%	81%	56%	30 min, 91%
6	 8	78%	81%	54%	10 min, 68%
7	 9	81%	88%	58%	10 min, 76%
8	 10	82%	84%	51%	20 min, 72%[e]
9	 11	74%	88%	48%	30 min, 52%

[a]111 °C, 36 h. [b]150 °C, 60 min. [c]10 equiv of NH_2OH·HCl, reflux, 36 h. [d]10% conc HCl in EtOH, 120 °C. [e]10% conc HCl in MeOH, 120 °C.

Scheme 2. Preparation of Diamine with Boc, Cbz, or Fmoc and 2,5-Dimethylpyrrole



modified acid media used also increased the reaction yields compared with those with trifluoroacetic acid.

With the microwave conditions for protection (Table 1) and deprotection (Table 2) optimized, we then surveyed the reaction scope as a function of the type of primary amine, including aromatic and aliphatic amines (Table 3), using the optimal conditions reported in the literature and our optimal conditions with microwave irradiation. The yields and reaction rates for all of the deprotection steps with microwave irradiation were considerably greater than those without microwave irradiation. The reaction rates for protection with microwave irradiation were 35−40 times greater than without microwave irradiation; the yields were comparable or greater with microwave irradiation. Acid-catalyzed transesterification occurred when deprotecting methyl 4-aminobenzoate (**10**), producing ethyl 4-aminobenzoate. This complication was

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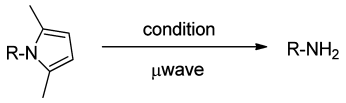
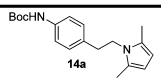
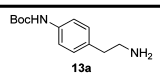
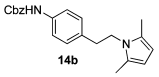
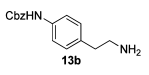
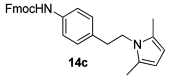
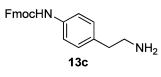
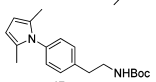
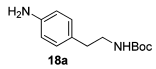
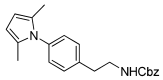
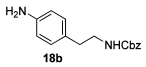
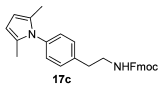
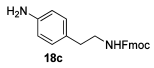
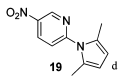
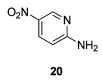
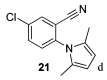
Table 4. Scope of Enhanced Deprotection Conditions for Diamines and Acid-Sensitive Compounds



entry	protected amine	deprotected amine	Deprotection conditions	Deprotection Time (min)	yield[a] (%)
1	 14a	 13a	$NH_2OH{\cdot}HCl$[c]	30	56
2	 14b	 13b	HCl in EtOH[b]	30	66
3	 14c	 13c	HCl in EtOH[b]	30	64
4	 17a	 18a	$NH_2OH{\cdot}HCl$[c]	30	67
5	 17b	 18b	HCl in EtOH[b] $NH_2OH{\cdot}HCl$[c]	20 60	77 69
6	 17c	 18c	HCl in EtOH[b] $NH_2OH{\cdot}HCl$[c]	20 60	78 53
7	 19 d	 20	$NH_2OH{\cdot}HCl$[c]	20 30	74 71
8	 21 d	 22	$NH_2OH{\cdot}HCl$[c]	30	76

[a]Isolated yield. [b]10% conc HCl in EtOH, 120 °C. [c]10 equiv of $NH_2OH{\cdot}HCl$ in 2:1 EtOH:H_2O, 120 °C. [d]These compounds are acid sensitive.

resolved by replacing ethanol with methanol in our new dilute hydrochloric acid conditions (Table 3: experiment 8).

Because the hydrochloric acid and ethanol conditions were not applicable to compounds with acid-sensitive functional groups, we developed a separate set of conditions for those compounds. The reagent had to be acidic enough to protonate the pyrrole ring, yet unreactive to acid-sensitive functional groups. By employing the conventional hydroxylamine method with the assistance of microwave irradiation, we attained the yields of the conventional deprotection method with a reduction in reaction time from 36 h to 30 min (Table 2: experiment 4).

Once conditions for both acid-labile and base-labile functional groups were optimized, we could take advantage of applying these methods for orthogonal protection and deprotection of diamines protected with Boc, Cbz, and Fmoc groups. On the basis of reactions described in the literature, we were able to selectively protect aromatic amines in the presence of aliphatic amines.[20] We first protected the aromatic amine of 4-aminophenethylamine with Boc, Cbz, or Fmoc and then protected the aliphatic amine with acetonylacetone under our optimized microwave irradiation conditions (Scheme 2, **14a–c**). After both amines were protected, we selectively deprotected the 2,5-dimethylpyrrole. For the acid-sensitive Boc group, hydroxylamine with microwave irradiation proved effective at removing the 2,5-dimethylpyrrole protecting group without affecting the Boc group. Since the Cbz and Fmoc protecting groups are less acid-sensitive, they were stable under the HCl/EtOH with microwave irradiation conditions for deprotection of the 2,5-dimethylpyrrole group (Table 4).

The same diamine, 4-aminophenethylamine, was further studied by protecting the aliphatic amine with Boc, Cbz, or Fmoc and subsequently protecting the aromatic amine as 2,5-dimethylpyrrole (Scheme 2, **17a–c**). Selective deprotection of the 2,5-dimethylpyrrole was achieved in good yields (Table 4). Product purification was also simpler because of a significantly nonpolar product compared to the aliphatic amine in the first selective deprotection. For aromatic and aliphatic 2,5-dimethylpyrroles in the presence of an N-Boc protecting group (Table 4: entries 1, 5), selective deprotection with hydroxylamine proceeded in lower yields because of its acid lability. Additionally, selective deprotection of 2,5-dimethylpyrrole with Cbz and Fmoc was much faster and produced higher yields when using HCl/EtOH rather than hydroxylamine. No significant side-products were produced when using HCl/EtOH, which made separations rather simple (Table 4). The deprotection yields for the aromatic carbamates (Table 4: entries 1–3) were lower than those for the aliphatic carbamates (Table 4: entries 4–6), presumably because of the relative instability of aromatic carbamates under the reaction conditions.

■ CONCLUSION

The 2,5-dimethylpyrrole protecting group has the advantage over common protecting groups, such as Boc, Cbz, and Fmoc, of being able to doubly protect a primary amine, leaving no acidic proton to hamper other base reactions. However, reaction times for installing and removing the protecting group are long and often with low yields. Here we have shown

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that reaction times for primary amine protection with acetonylacetone to give the corresponding 2,5-dimethylpyrrole can be dramatically shortened with the use of microwave irradiation. Because 2,5-dimethylpyrrole is a stable aromatic system, protonation of the pyrrole nitrogen is low. By lowering the pH of the reaction medium, higher yields and shorter reaction times for deprotection were realized; reaction times for deprotection were further dramatically reduced by microwave irradiation. When acid-sensitive functional groups, including Boc-protected amines, are present elsewhere in the molecule, the conventional hydroxylamine conditions can be used, but the reaction times can be significantly reduced with microwave irradiation. This allows for orthogonal protection of primary amines as a 2,5-dimethylpyrrole in the presence of other amines protected with a Boc group. Likewise, using the acid conditions developed here, the 2,5-dimethylpyrrole protecting group also becomes orthogonal to Cbz- and Fmoc-protecting groups. Often it is desirable to doubly protect primary amines, and 2,5-dimethylpyrrole can now be used in the presence of acid- or base-sensitive groups without hesitation.

EXPERIMENTAL SECTION

General Methods for Synthesis and Structural Characterization. All reagents and solvents were purchased from commercial sources and were used without further purification. Microwave irradiation was performed in a Biotage Initiator Microwave with 2−5 mL Biotage reaction vials. Flash column chromatography was performed using prepacked silica cartridges with a flash purification system. Reaction progress was monitored by thin-layer chromatography (TLC) carried out on silica gel plates (2.5 cm × 7.5 cm, 250 μm thick, 60 F254) and visualized by using UV (254 nm). ^{1}H NMR and ^{13}C NMR spectra were recorded in the indicated solvent on a 500 and 126 MHz for ^{1}H and ^{13}C, respectively, spectrometer. MS was performed on a system consisting of an electrospray ionization (ESI) source in a LCQ mass spectrometer. High resolution mass spectra were obtained using an LC-TOF spectrometer. Melting points were measured in open capillaries on a melting point analyzer.

General Procedure for Conventional Protection. To a solution of an amine (10 mmol) in toluene (50 mL) was added acetonylacetone (1.23 mL, 10.5 mmol) and *p*-TsOH (19 mg, 10%). The reaction mixture was heated to reflux in a Dean−Stark apparatus for 36 h. After being cooled to room temperature, the mixture was concentrated by rotary evaporation, and the resulting brown oil was purified by flash column chromatography (EtOAc/hexanes, 1:19−1:9) to give the protected amine.

General Procedure for Conventional Deprotection. To a solution of the protected amine (0.5 mmol) in EtOH (10 mL) was added hydroxylamine hydrochloride (NH_2OH·HCl, 340 mg, 5 mmol) followed by H_2O (5 mL). The reaction mixture was heated at 100 °C for 24 h. After being cooled to room temperature, the reaction mixture was partitioned between Et_2O (50 mL) and 2 N aqueous NaOH (25 mL). The aqueous layer was extracted with Et_2O (2 × 25 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the resulting yellow oil was purified by flash chromatography (5−10% MeOH in CH_2Cl_2).

General Procedure for Protection Using Microwave Irradiation. Method A. To a dry 5 mL microwave vial equipped with a magnetic stir bar was added the amine (1.1 mmol) dissolved in toluene (4 mL). Acetonylacetone (0.126 g, 1.1 mmol) and *p*-toluenesulfonic acid (0.203 g, 10%) were then added, and the vial was capped with a rubber septum. The vial was shaken vigorously and then heated in the microwave irradiator for 60 min at 150 °C (as recorded via the IR sensor of the microwave instrument). After heating, the vessel was cooled, diluted with methanol, and concentrated under reduced pressure. After being cooled to room temperature, the mixture was concentrated by rotary evaporation, and the resulting brown oil was purified by flash column chromatography using a 25 g silica gel cartridge to give the protected amine.

General Procedure for Deprotection Using Microwave Irradiation. Method B. To a dry 5 mL microwave vial equipped with a magnetic stir bar was added the protected amine (1.1 mmol) dissolved in ethanol (2.7 mL). Concentrated hydrochloric acid (0.3 mL) was added dropwise to the reaction mixture. The vial was shaken vigorously and then heated in the microwave irradiator for 20 min at 120 °C (as recorded via the IR sensor of the microwave instrument). After heating, the vessel was cooled, diluted with water (5 mL) and partitioned between Et_2O (10 mL) and 2 N aqueous NaOH (5 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the resulting yellow oil was purified by flash column chromatography (5−10% MeOH in CH_2Cl_2).

Compounds **3**−**11**, **14a**−**c**, **19**, and **21** were synthesized using General Method A.

2-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-4,6-dimethylpyridine (3). Yield 443 mg (78%): pale yellow solid; R_f = 0.4 (EtOAc/hexanes, 1:19−1:9); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.84 (s, 1H), 5.7 (s, 2H), 2.54 (s, 3H), 2.37 (s, 3H), 2.12 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 151.4, 149.4, 128.4, 122.9, 119.7, 106.6, 76.8, 24.2, 21.0, 13.2; LRMS (ESI) m/z = 201.13 $[M + H]^+$. The data were in accordance with those previously reported.[5]

1-(4-Methoxyphenyl)-2,5-dimethyl-1*H*-pyrrole (4). Yield 532 mg (89%): yellow crystals; mp 57−59 °C; R_f = 0.4 (EtOAc/hexanes, 1:19−1:9); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15−7.10 (m, 1H), 6.99−6.94 (m, 1H), 5.89 (s, 1H), 3.86 (s, 1H), 2.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 131.8, 129.3, 129.2, 114.3, 105.3, 55.6, 13.1; LRMS (ESI) m/z = 202.12 $[M + H]^+$. The data were in accordance with those previously reported.[21]

1-(4-Fluoro-2-methylphenyl)-2,5-dimethyl-1*H*-pyrrole (5). Yield 545 mg (84%): yellow oil; mp 84−86 °C; R_f = 0.4 (EtOAc/hexanes, 1:19−1:9); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16−7.11 (dd, J = 8.5, 5.5 Hz, 1H), 7.05−7.01 (dd, J = 9.2, 2.8 Hz, 1H), 7.00−6.93 (td, J = 8.3, 2.9 Hz, 1H), 5.90 (s, 2H), 1.92 (s, 3H), 1.91 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.1 (d, J = 247.0 Hz), 139.5 (d, J = 8.5 Hz), 134.0 (d, J = 3.0 Hz), 130.3 (d, J = 9.0 Hz), 128.3, 117.3 (d, J = 22.2 Hz), 113.5 (d, J = 22.5 Hz), 105.4, 17.3, 12.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{15}FN$ 204.1183, found 204.1188.

2,5-Dimethyl-1-phenyl-1*H*-pyrrole (6). Yield 376 mg (72%): pale brown crystals; mp 49−51 °C; R_f = 0.3 (EtOAc/hexanes, 1:19−1:9); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.37 (m, 3H), 7.24−7.19 (m, 2H), 5.91 (s, 2H), 2.04 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2, 129.3, 129.1, 128.5, 127.9, 105.8, 13.3; LRMS (ESI) m/z = 172.11 $[M + H]^+$. The data were in accordance with those previously reported.[22]

1-(2,4-Dimethoxyphenyl)-2,5-dimethyl-1*H*-pyrrole (7). Yield 607 mg (81%): pale yellow oil; R_f = 0.4 (EtOAc/hexanes, 1:19−1:9); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.68 (d, J = 2.7 Hz, 1H), 6.63 (dd, J = 8.5, 2.7 Hz, 1H), 5.99 (s, 2), 3.94 (s, 3H), 3.84 (s, 3H), 2.10 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 156.7, 130.4, 129.2, 120.5, 104.9, 104.1, 99.4, 55.6, 55.5, 12.5; LRMS (ESI) m/z = 232.13 $[M + H]^+$. The data were in accordance with those previously reported.[23]

1-(3,4-Dichlorophenethyl)-2,5-dimethyl-1*H*-pyrrole (8). Yield 791 mg (81%): yellow crystals; mp 96−99 °C; R_f = 0.5 (EtOAc/hexanes, 1:19−1:9); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 8.2 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 6.85 (dd, J = 8.2, 2.0 Hz, 1H), 5.79 (s, 2H), 4.12 (q, J = 7.2 Hz, 1H), 3.95−3.89 (m, 2H), 2.95−2.75 (m, 2H), 2.12 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6, 132.5, 130.9, 130.7, 130.5, 128.4, 127.3, 105.6, 44.6, 36.6, 12.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{15}Cl_2N$ 268.0654, found 268.0641.

1-Benzyl-2,5-dimethyl-1*H*-pyrrole (9). Yield 440 mg (88%): white crystals; mp 43−45 °C; R_f = 0.4 (EtOAc/hexanes, 1:19−1:9); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.21 (m, 3H), 6.89−6.88 (m, 2H), 5.86 (s, 2H), 5.01 (s, 2H), 2.17 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.7, 128.8, 128.2, 127.1, 125.8, 105.5, 46.8, 12.6; LRMS (ESI) m/z = 186.12 $[M + H]^+$. The data were in accordance with those previously reported.[24]

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Methyl 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)benzoate (10). Yield 344 mg (81%): white crystals; mp 106−108 °C; R_f = 0.4 (EtOAc/hexanes, 1:19−1:9); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 5.93 (s, 2H), 3.96 (s, 3H), 2.05 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 143.2, 130.6, 129.4, 128.8, 128.2, 106.6, 52.5, 13.2; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{16}NO_2$ 230.1176, found 230.1182.

2-(2,5-Dimethyl-1*H*-pyrrol-1-yl)thiazole (11). Yield 321 mg (88%): colorless oil; R_f = 0.2 (EtOAc/hexanes, 1:19−1:9); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 3.6 Hz, 1H), 7.36 (d, J = 3.6 Hz, 1H), 5.92 (s, 2H), 2.23 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 140.6, 129.9, 119.7, 107.8, 13.2; LRMS (ESI) m/z = 179.06 [M + H]$^+$. The data were in accordance with those previously reported.[25]

***tert*-Butyl (4-(2-(2,5-dimethyl-1*H*-pyrrol-1-yl)ethyl)phenyl)carbamate (14a).** Yield 362 mg (78%): yellow oil; R_f = 0.15 (EtOAc/hexanes, 1:7−1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 8.0 Hz, 2H), 7.02 (m, 2H), 6.55 (s, 1H), 5.78 (s, 2H), 3.93 (m, 2H), 2.84 (m, 2H), 2.15 (s, 6H), 1.54 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.8, 146.8, 137.0, 133.1, 129.4, 127.4, 118.7, 105.2, 85.3, 80.5, 45.4, 36.9, 28.4, 27.5, 12.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{19}H_{26}N_2NaO_2$ 337.1886, found 337.1889.

Benzyl (4-(2-(2,5-dimethyl-1*H*-pyrrol-1-yl)ethyl)phenyl)carbamate (14b). Yield 331 mg (78%): colorless oil; R_f = 0.2 (EtOAc/hexanes, 1:7−1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.31 (m, 7H), 7.09−7.02 (m, 2H), 6.75 (s, 1H), 5.82 (s, 2H), 5.25 (s, 2H), 3.99−3.91 (m, 2H), 2.94−2.84 (m, 2H), 2.18 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.4, 136.4, 136.1, 133.7, 129.5, 128.7, 128.4, 128.4, 127.4, 118.9, 105.2, 67.06, 45.3, 36.9, 12.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{25}N_2O_2$ 349.1911, found 349.1898.

(9*H*-Fluoren-9-yl)methyl (4-(2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-ethyl)phenyl)carbamate (14c). Yield 421 mg (79%): pale white solid; mp 227−229 °C; R_f = 0.2 (EtOAc/hexanes, 1:7−1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86−7.71 (m, 2H), 7.68−7.56 (m, 2H), 7.49−7.36 (m, 2H), 7.40−7.29 (m, 4H), 7.01 (d, J = 7.9 Hz, 2H), 6.62 (s, 1H), 5.76 (s, 2H), 4.54 (d, J = 6.6 Hz, 2H), 4.44 (d, J = 6.6 Hz, 1H), 3.91 (t, J = 7.6 Hz, 2H), 2.84 (t, J = 7.6 Hz, 2H), 2.13 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.8, 143.7, 141.4, 129.5, 127.8, 127.6, 127.4, 127.1, 127.0, 124.9, 120.1, 119.9, 105.2, 66.9, 47.1, 45.3, 36.8, 12.4; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{29}H_{29}N_2O_2$ 437.2224, found 437.2224.

2-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-5-nitropyridine (19). Yield 145 mg (82%): yellow crystals; mp 206−208 °C; R_f = 0.4 (EtOAc/hexanes, 1:19−1:9); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.63 (d, J = 8.8 Hz, 1H), 7.40 (d, J = 8.7 Hz, 1H), 6.00 (s, 2H), 2.25 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.1, 145.1, 142.1, 133.2, 129.1, 120.7, 109.3, 13.8; LRMS (ESI) m/z = 218.09 [M + H]$^+$. The data were in accordance with those previously reported.[26]

5-Chloro-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)benzonitrile (21). Yield 66.9 mg (78%): yellow crystals; mp 106−108 °C; R_f = 0.3 (EtOAc/hexanes, 1:19−1:9); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 2.4 Hz, 1H), 7.68 (dd, J = 8.5, 2.4 Hz, 1H), 7.30 (d, J = 8.5 Hz, 1H), 5.97 (s, 2H), 2.02 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.6, 134.6, 134.0, 133.1, 131.3, 128.8, 114.9, 114.7, 107.5, 12.8; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_{11}ClN_2Na$ 253.0503, found 253.0506.

Compounds **13a−c** were synthesized by a procedure described in Perron et al.[20] for selective protection of an aromatic amine.

***tert*-Butyl (4-(2-aminoethyl)phenyl)carbamate (13a).** Yield 405 mg (78%): white solid; mp 88−91 °C; ^{1}H NMR (500 MHz, MeOD) δ 7.38 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 2.84 (t, J = 7.2 Hz, 2H), 2.69 (t, J = 7.2 Hz, 2H), 1.52 (s, 9H); ^{13}C NMR (126 MHz, MeOD) δ 155.4, 138.9, 134.9, 130.2, 120.1, 80.7, 44.1, 39.0, 28.9; LRMS (ESI) m/z = 259.15 [M + Na]$^+$. The data were in accordance with those previously reported.[19]

Benzyl (4-(2-aminoethyl)phenyl)carbamate (13b). Yield 438 mg (81%): pale yellow solid; mp 151−153 °C; ^{1}H NMR (500 MHz, CD_3OD) δ = 7.30−7.42 (m, 7H), 7.13 (d, J = 8.6 Hz, 2H), 5.16 (s, 2H), 2.87 (t, J = 6.8 Hz, 2H), 2.72 (t, J = 7.0 Hz, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ 155.9, 142.7, 138.5, 138.2, 135.4, 130.2, 129.6, 129.4, 129.1, 129.0, 128.3, 128.0, 120.2, 67.5, 65.3, 44.1, 39.1; LRMS (ESI) m/z = 271.14 [M + H]$^+$. The data were in accordance with those previously reported.[19]

(9*H*-Fluoren-9-yl)methyl (4-(2-aminoethyl)phenyl)-carbamate (13c). Yield 472 mg (79%): white solid; mp 207−209 °C; H NMR (500 MHz, DMSO-d_6) δ 7.92−8.05 (m, 2H), 7.89 (d, J = 7.6 Hz, 2H), 7.73 (d, J = 7.4 Hz, 2H), 7.31−7.43 (m, 4H), 7.13 (d, J = 8.2 Hz, 2H), 4.45 (d, J = 6.7 Hz, 2H), 4.28 (t, J = 6.5 Hz, 1H), 2.93−2.97 (m, 2H), 2.78−2.82 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d6) δ 153.47, 143.66, 140.73, 137.54, 131.25, 128.97, 127.72, 127.13, 125.09, 120.14, 118.57, 66.28, 46.54, 32.19, 21.03; LRMS (ESI) m/z = 359.17 [M + H]$^+$. The data were in accordance with those previously reported.[19]

2-(4-(2,5-Dimethyl-1*H*-pyrrol-1-yl)phenyl)ethanamine HCl (16). Using method B, starting material **15** was converted to the intermediate 2-(4-(2,5-dimethyl-1*H*-pyrrol-1-yl)phenyl)acetonitrile. The data were in accordance with those previously reported.[27] Yield 862 mg (86%): white crystal, mp 102−104 °C; R_f = 0.6 (EtOAc/hexanes, 1:8); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 5.95 (s, 2H), 3.87 (s, 2H), 2.06 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.91, 129.42, 128.95, 128.80, 128.75, 117.64, 106.06, 23.38, 13.07. After mixing this intermediate (0.210 g, 1 mmol) with Raney Nickel (0.1 mL, 50% in water) in ethanol (30 mL), the mixture was stirred under hydrogen balloon at room temperature for 2 h. The reaction mixture was filtered by using membrane filter (25 mm, 0.22 μm PVDF), and the filtrate was concentrated in a vacuum to give colorless oil. This oil was dissolved in hydrochloric acid in methanol and reconcentrated in a vacuum to give **16** as pale yellow HCl salt. (93%). This amine HCl salt was used directly in the next step without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (bs, 3H), 7.36 (d, J = 7.9 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 5.91 (s, 2H), 3.45−3.29 (m, 2H), 3.27−3.15 (m, 2H), 2.05 (s, 6H) ; ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 135.4, 129.5, 128.8, 105.9, 41.1, 33.4, 13.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{19}N_2$ 215.1548, found 215.1540.

Compounds **17a−c** were synthesized using following method from compound **16**.

To a dry 25 mL round-bottom flask equipped with a magnetic stir bar was added compound **16** (0.200 g, 1 mmol) dissolved in dichloromethane (15 mL). Boc_2O (0.23 mL, 1.2 mmol), CbzCl (0.143 mL, 1.2 mmol), or Fmoc-OSu (0.337 g, 1.2 mmol) were added to the mixture depending on if **17a**, **17b**, or **17c** was desired, respectively. Triethylamine (0.028 mL, 1.2 mmol) was also added dropwise to the reaction mixture to deprotonate the HCl salt. The reaction mixture was stirred at room temperature for 4 h and then concentrated by rotary evaporation. The resulting yellow oil was purified by flash column chromatography using a 25 g silica gel cartridge to give the protected amine.

***tert*-Butyl 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)-phenethylcarbamate (17a).** Yield 249 mg (79%): white crystals; mp 170−172 °C; R_f = 0.3 (EtOAc/hexanes, 1:15−1:6); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 5.90 (s, 2H), 4.71 (m, 1H), 3.49−3.35 (m, 2H), 2.92−2.80 (m, 2H), 2.04 (s, 6H), 1.52−1.42 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 138.6, 137.2, 129.4, 128.8, 128.3, 105.6, 79.3, 41.7, 36.0, 28.5, 13.1; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{19}H_{26}N_2NaO_2$ 337.1886, found 337.1893.

Benzyl 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)phenethylcarbamate (17b). Yield 280 mg (86%): clear oil; R_f = 0.3 (EtOAc/hexanes, 1:15−1:6); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.35 (m, 5H), 7.32−7.25 (m, 2H), 7.21−7.14 (m, 2H), 5.94 (s, 2H), 5.15 (s, 2H), 4.90 (m, 1H), 3.58−3.49 (q, J = 6.8 Hz, 2H), 2.96−2.87 (t, J = 7.0 Hz, 2H), 2.06 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 138.2, 137.4, 136.5, 129.4, 128.9, 128.6, 128.4, 128.3, 128.2, 105.6, 66.8, 42.1, 35.8, 13.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{25}N_2O_2$ 349.1911, found 349.1905.

(9*H*-Fluoren-9-yl)methyl 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)-phenethylcarbamate (17c). Yield 243 mg (84%): white crystals; mp 215−218 °C; R_f = 0.3 (EtOAc/hexanes, 1:15−1:6); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85−7.78 (d, J = 7.6 Hz, 2H), 7.67−7.60 (d, J = 7.4 Hz, 2H), 7.48−7.42 (t, J = 7.4 Hz, 2H), 7.40−7.32 (t, J = 7.4 Hz, 2H),

7.31−7.24 (d, J = 6.7 Hz, 2H), 7.18 (s, 1H), 5.95 (s, 2H), 4.90 (s, 1H), 4.49 (d, J = 6.7 Hz, 2H), 4.27 (t, J = 6.6 Hz, 1H), 3.54 (q, J = 6.6 Hz, 2H), 2.91 (t, J = 6.9 Hz, 2H), 2.11 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 143.9, 141.4, 138.3, 137.4, 129.5, 128.9, 128.3, 127.8, 127.1, 125.0, 120.0, 105.6, 66.5, 47.3, 42.2, 35.9, 13.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{29}H_{29}N_2O_2$ 437.2224, found 437.2226.

Compounds **18a−c** were synthesized by General Method B.

***tert*-Butyl 4-aminophenethylcarbamate (18a).** Yield 56.4 mg (67%): clear oil; R_f = 0.3 (EtOAc/hexanes, 1:15−1:6); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (d, J = 7.9 Hz, 2H), 6.64 (d, J = 7.9 Hz, 2H), 4.68 (bs, 1H), 3.56 (bs, 2H), 3.32 (q, J = 6.7 Hz, 2H), 2.68 (t, J = 7.2 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 144.9, 129.6, 128.8, 115.4, 79.1, 42.1, 35.2, 28.5; LRMS (ESI) m/z = 259.09 $[M + Na]^+$. The data were in accordance with those previously reported.[28]

Benzyl 4-aminophenethylcarbamate (18b). Yield 56.6 mg (77%): clear oil; R_f = 0.3 (EtOAc/hexanes, 1:15−1:6); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.33 (m, 5H), 6.99 (d, J = 8.0 Hz, 2H), 6.62 (d, J = 8.0 Hz, 2H), 5.13 (s, 2H), 3.63 (bs, 2H), 3.42 (m, 2H), 2.72 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.5, 145.1, 136.8, 129.7, 128.6, 128.5, 128.2, 127.9, 115.4, 66.6, 42.6, 35.2; LRMS (ESI) m/z = 293.13 $[M + Na]^+$. The data were in accordance with those previously reported.[29]

(9*H*-Fluoren-9-yl)methyl 4-aminophenethylcarbamate (18c). Yield 78.2 mg (78%): colorless oil; R_f = 0.3 (EtOAc/hexanes, 1:10−1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 7.5 Hz, 2H), 7.58 (d, J = 7.5 Hz, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.32 (m, 2H), 6.96 (d, J = 7.7 Hz, 2H), 6.64 (d, J = 7.8 Hz, 2H), 4.39 (d, J = 6.9 Hz, 2H), 4.23 (d, J = 7.2 Hz, 1H), 3.61 (bs, 2H), 3.40 (d, J = 6.5 Hz, 2H), 2.72 (t, J = 7.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 144.0, 141.3, 129.7, 128.6, 127.7, 127.0, 125.1, 120.0, 115.4, 66.5, 53.5, 47.3, 42.5, 35.2; LRMS (ESI) m/z = 381.20 $[M + Na]^+$. The data were in accordance with those previously reported.[30]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C spectra giving spectroscopic data for the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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