Synthesis of Substituted Pyrroles via Ultrasound Assisted Three-component Coupling Reaction of Amines, α,β-Unsaturated Aldehydes and Nitroalkanes

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An efficient synthesis of substituted pyrroles via ultrasound-assisted three-component coupling reaction of amines with α,β-unsaturated aldehydes and nitroalkanes is reported.

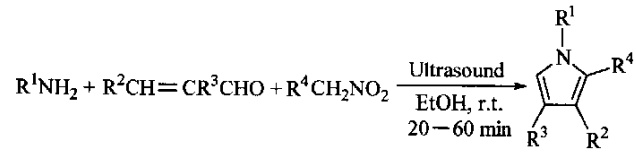
Keywords amine, pyrrole, ultrasound, α,β-unsaturated aldehyde, nitroalkane, one-pot synthesis

Introduction

Pyrroles are important synthetic targets since they are applied as precursors to many useful classes of organic compounds such as porphyrins and alkloids.[1] Several substituted pyrroles have potential application as fungicids and bactericides and as active components of nonsteroidal *anti*-inflammatory drugs inhibiting human cyclooxygenase.[2,3] In addition, amino acids such as proline and hydroxyproline also contain the hydrogenated pyrrole ring that is a pyrrolidine framework. Although there are a number of potentially useful methods for the synthesis of pyrroles,[4] the Knorr's method is used frequently.[5] Recently, Ishii *et al*. have reported the synthesis of pyrroles via samarium-catalyzed three-component coupling reaction of aldehydes, amines and nitroalkanes,[6] and the lanthanide-catalyzed synthesis of alkylpyrroles from imines and nitroalkenes.[7] Ranu *et al*.[8] have also reported the synthesis of pyrroles on the surface of silica gel and alumina under microwave irradiation.[8] However, these one-step procedures are not satisfactory with regard to reaction conditions, yield, generality and scope of substitution at the ring. Thus, it is necessary to develop a simple, efficient and more general method for the synthesis of this useful heterocyclic nucleus.

Ultrasound has been utilized in organic synthesis for its lower reaction temperature and simple operation as compared with the conventional heating method.[9] Most of the observed phenomena are due to cavitation: the formation, growth and collapse of bubbles in an irradiated liquid. Cavitation induces very high local temperatures and pressures inside the bubbles and will enhance mass transfer and turbulency form in the liquid. In the course of our study on the ultrasound chemistry, it was found that ultrasound could promote the three-component coupling of amines, α,β-unsaturated aldehydes and nitroalkanes to give the corresponding pyrroles in good yields under mild conditions (Scheme 1).

Scheme 1



1a—1h **2a—2c** **3a—3c** **4a—4m**

Results and discussion

As shown in Scheme 1, under the ultrasound-assisted condition, a mixture of *n*-butylamine (**1a**, 1.0 mmol), 2-ethyl-2-hexenoic aldehyde (**2a**, 1.0 mmol) and nitroethane (**3a**, 1.5 mmol) in ethanol (5 mL) was allowed to react at room temperature for 20 min to give **4a** in 90% yield. Ishii's method[6,7] generally requires prolonged the reaction time (17 h) and high temperature (60 ℃). In our case, however, the reaction could complete in 20 min at room temperature. This result prompted us to examine the reactions of other amines, α,β-unsaturated aldehydes and nitroalkanes.

The results are summarized in Table 1. The three-component coupling of nitroethane (**3a**) with α,β-unsaturated aldehydes (**2a—2c**) and a variety of aliphatic or aromatic amines (**1a—1h**) afforded the corresponding pyrroles **4** in good yields (Entries 1, 4—7 and 9—11). However, the reaction using nitromethane (**3b**) and nitropropane (**3c**) under the same conditions gave pyrroles **4** in lower yields (Entries 2 and 3). The bulky amines (**1d** and **1h**) also resulted in lower yields even in a prolonged reaction time (Entries 8, 12 and 13). It is interesting to note that the coupling reaction of amines (**1**) with α,β-unsaturated aldehydes (**2**) and nitroalkanes (**3**) takes place in the absence of any catalysts. On the basis of these results, a possible reaction path for the formation of pyrroles is shown in Scheme 2.

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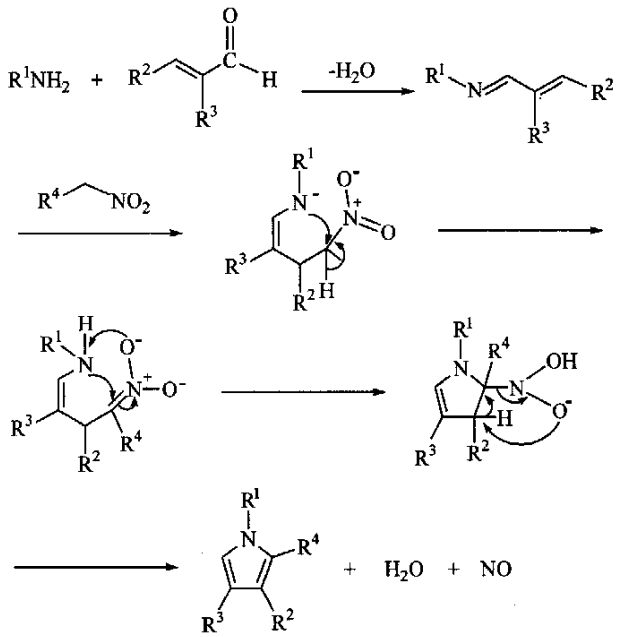
Scheme 2



Conclusion

In conclusion, the present ultrasound-assisted one-pot procedure provides an efficient method for the synthesis of highly substituted pyrroles from easily available starting materials by a simple three-component coupling reaction of amines, α,β-unsaturated aldehydes and nitroalkanes. The notable advantages of this procedure are: (a) reasonably good yields, (b) fast reaction, (c) choice of appropriate substituents on the pyrrole ring, (d) general applicability and (e) mild reaction conditions. Therefore, it is believed that our procedure would find important applications in the synthesis of pyrroles to meet the needs of academy as well as pharmaceutical industries.

Experimental

General

^{1}H NMR and ^{13}C NMR spectra were detected on a Bruker Avance spectrometer (400 MHz) in $CDCl_3$ solutions with TMS as internal standard. IR spectra (KBr) were measured on a Bruker Veitor 22 spectrometer. Mass spectra were recoded on an HP MS 5989B mass spectrometer (70 eV). Melting points were determined on a glass disk with an electrical bath and were uncorrected. Ultrasound was performed in KQ-100 ultrasonic cleaner (40 kHz, 100 W, made in Qunshan). The reaction flask was located at the maximum energy area in the cleaner. Ethanol was distilled over magnesium before use. Ethyl acetate and hexane were purified by distillation.

General procedure for the synthesis of pyrroles

To a solution of amines (**1**) (1.0 mmol) in ethanol (5 mL) was added α,β-unsaturated aldehydes (**2**) (1.0 mmol) and nitroalkanes (**3**) (1.5 mmol). The mixture was irradiated in the water bath of an ultrasonic cleaner (frequency: 40 kHz, nominal power: 100 W) at room temperature for 20—60 min. The solvent was removed under reduced pressure, and the products were purified by silica gel column. The known compounds (**4a**—**4c**, **4e**—**4f** and **4h**) were identified by comparison of spectral data with that reported. The spectra of all new compounds are presented below in order of their entries.

N-n-Butyl-4-ethyl-2-methyl-3-n-propylpyrrole (**4a**)

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.31 (s, 1H), 3.70 (t, J = 7.4 Hz, 2H), 2.43 (q, J = 7.6 Hz, 2H), 2.32 (t, J = 7.8 Hz, 2H), 2.10 (s, 3H), 1.68—1.62 (m, 2H), 1.47—1.43 (m, 2H), 1.36—1.30 (m, 2H), 1.17 (t, J = 7.4 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 124.3, 123.3, 118.3, 115.2, 46.3, 33.6, 26.9, 24.7,

Table 1 Pyrroles prepared by ultrasound reaction via Scheme 1

Entry	Comp. **4**	R^1	R^2	R^3	R^4	Time (min)	Yield (%)
1	**4a**	*n*-Bu	*n*-Pr	Et	Me	20	90
2	**4b**	*n*-Bu	*n*-Pr	Et	H	20	64
3	**4c**	*n*-Bu	*n*-Pr	Et	Et	20	72
4	**4d**	*n*-Bu	*n*-Pent	H	Me	20	83
5	**4e**	*n*-Bu	Ph	H	Me	20	80
6	**4f**	Bn	*n*-Pr	Et	Me	20	89
7	**4g**	CH(Me)Ph	*n*-Pr	Et	Me	20	86
8	**4h**	*t*-Bu	*n*-Pr	Et	Me	60	61
9	**4i**	CH_2COOEt	*n*-Pr	Et	Me	20	85
10	**4j**	CH(Me)COOEt	*n*-Pr	Et	Me	20	83
11	**4k**	CH_2CH_2OH	*n*-Pr	Et	Me	20	92
12	**4l**	$CH(CH_2OH)CH(OH)(p\text{-}NO_2C_6H_4)$	*n*-Pr	Et	Me	60	78
13	**4m**	$CH(CH_2OH)CH(OH)(p\text{-}NO_2C_6H_4)$	*n*-Pent	H	Me	60	75

20.1, 18.5, 14.7, 14.3, 13.8, 9.7; IR (neat) ν: 2960, 1549, 1463, 1386, 1261, 1098, 804 cm^{-1}; MS (70 eV) m/z (%): 207 (M^+, 26), 178 (100), 136 (57). Anal. calcd for $C_{14}H_{25}N$: C 81.16, H 12.08, N 6.76; found C 81.13, H 12.09, N 6.78.

N-n-Butyl-3-ethyl-4-n-propylpyrrole (**4b**) Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.35 (s, 2H), 3.74 (t, J = 7.3 Hz, 2H), 2.42 (q, J = 7.5 Hz, 2H), 2.36 (t, J = 7.8 Hz, 2H), 1.76—1.61 (m, 2H), 1.61—1.45 (m, 2H), 1.39—1.21 (m, 2H), 1.17 (t, J = 7.4 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 124.1, 122.2, 117.8, 117.1, 49.1, 33.7, 27.6, 23.7, 20.1, 18.5, 14.6, 14.3, 13.7; IR (neat) ν: 2959, 1532, 1463, 1372, 1159, 767 cm^{-1}; MS (70 eV) m/z (%): 193(M^+, 30), 164 (100), 122 (57). Anal. calcd for $C_{13}H_{23}N$: C 80.83, H 11.92, N 7.25; found C 80.58, H 11.87, N 7.55.

N-n-Butyl-2,4-diethyl-3-n-propylpyrrole (**4c**) Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.23 (s, 1H), 3.63 (t, J = 7.8 Hz, 2H), 2.45 (q, J = 7.6 Hz, 2H), 2.35 (q, J = 7.6 Hz, 2H), 2.25 (t, J = 8.0 Hz, 2H), 1.68—1.57(m, 2H), 1.44—1.35(m, 2H), 1.32—1.24 (m, 2H), 1.10 (t, J = 7.8 Hz, 3H), 1.04 (t, J = 7.4 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 130.4, 123.4, 117.8, 115.0, 46.0, 33.9, 27.1, 25.2, 20.2, 18.5, 17.4, 15.5, 14.5, 14.3, 13.8; IR (neat) ν: 2960, 1707, 1525, 1463, 1385, 1190, 725 cm^{-1}; MS (70 eV) m/z (%): 221 (M^+, 20), 192 (100), 150 (57). Anal. calcd for $C_{15}H_{27}N$: C 81.45, H 12.22, N 6.33; found C 81.36, H 12.40, N 6.24.

N-n-Butyl-2-methyl-3-n-pentylpyrrole (**4d**) Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.49 (d, J = 2.7 Hz, 1H), 5.93 (d, J = 2.7 Hz, 1H), 3.74 (t, J = 7.4 Hz, 2H), 2.36 (t, J = 7.6 Hz, 2H), 2.11 (s, 3H), 1.68—1.64 (m, 2H), 1.55—1.48 (m, 2H), 1.36—1.30 (m, 6H), 0.93 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 124.4, 122.9, 118.8, 109.7, 46.2, 33.3, 26.2, 22.6, 20.2, 18.5, 14.1, 13.8, 12.2, 9.8; IR (neat) ν: 2927, 1547, 1463, 1356, 774 cm^{-1}; MS (70 eV) m/z (%): 207 (M^+, 35), 150 (100), 108 (32). Anal. calcd for $C_{14}H_{25}N$: C 81.16, H 12.08, N 6.76; found C 81.19, H 12.10, N 6.71.

N-n-Butyl-2-methyl-3-phenylpyrrole (**4e**) Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40—7.18 (m 5H), 6.62 (d, J = 3.0 Hz, 1H), 6.25 (d, J = 2.4 Hz, 1H), 3.83 (t, J = 7.4 Hz, 2H), 2.34 (s, 3H), 1.75—1.71 (m, 2H), 1.42—1.36 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR($CDCl_3$) δ: 137.7, 128.2, 128.0, 125.0, 124.6, 121.9, 119.6, 107.6, 46.8, 33.4, 20.1, 13.8, 10.8; IR (neat) ν: 2958, 1602, 1501, 1350, 702 cm^{-1}; MS (70 eV) m/z (%): 213 (M^+, 64), 170 (100), 156 (20), 128 (18). Anal. calcd for $C_{15}H_{19}N$: C 84.51, H 8.92, N 6.57; found C 84.36, H 8.84, N 6.80.

N-Benzyl-4-ethyl-2-methyl-3-n-propylpyrrole (**4f**) Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.30—7.22 (m, 3H), 6.98 (d, J = 7.3 Hz, 2H), 6.37 (s, 1H), 4.95 (s, 2H), 2.44 (q, J = 7.5 Hz, 2H), 2.35 (t, J = 7.4 Hz, 2H), 2.02 (s, 3H), 1.49—1.45 (m, 2H), 1.17 (t, J = 7.6 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 139.0, 128.6, 127.0, 126.3, 124.8, 123.9, 119.1, 116.2, 50.2, 26.9, 24.7, 18.5, 14.7, 14.1, 9.7; IR (neat) ν: 2960, 1694, 1454, 1389, 731 cm^{-1}; MS (70 eV) m/z (%): 241 (M^+, 22), 212 (100), 77 (32). Anal. calcd for $C_{17}H_{23}N$: C 84.65, H 9.54, N 5.81; found C 84.56, H 9.60, N 5.84.

N-α-Methylbenzyl-4-ethyl-2-methyl-3-n-propylpyrrole (**4g**) Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.27—7.19 (m, 3H), 6.92 (d, J = 7.4 Hz, 2H), 6.54 (s, 1H), 5.20 (q, J = 7.1 Hz, 1H), 2.47 (q, J = 7.5 Hz, 2H), 2.34 (t, J = 7.4 Hz, 2H), 1.95 (s, 3H), 1.76 (d, J = 7.1 Hz, 3H), 1.47—1.43 (m, 2H), 1.20 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 144.8, 128.7, 127.1, 125.9, 125.4, 123.7, 119.3, 112.5, 55.0, 27.0, 24.9, 22.7, 19.0, 15.1, 14.4, 10.2; IR (neat) ν: 2954, 1696, 1451, 1367, 699 cm^{-1}; MS (70 eV) m/z (%): 255 (M^+, 39), 226 (30), 122 (100), 105 (63), 77 (21). Anal. calcd for $C_{18}H_{25}N$: C 84.71, H 9.80, N 5.49; found C 84.83, H 9.91, N 5.26.

N-tert-Butyl-4-ethyl-2-methyl-3-n-propylpyrrole (**4h**) Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.67 (s, 1H), 2.59 (q, J = 7.6 Hz, 2H), 2.48(t, J = 7.9 Hz, 2H), 2.47 (s, 3H), 1.72 (s, 9H), 1.63—1.59 (m, 2H), 1.35 (t, J = 7.6 Hz, 3H), 1.09 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 124.8, 121.6, 120.9. 113.2, 55.3, 30.8, 27.0, 24.5, 18.6, 14.4, 14.3, 13.4; IR (neat) ν: 2961, 1526, 1463, 1367, 1216, 912 cm^{-1}; MS (70 eV) m/z (%): 207 (M^+, 26), 178 (100), 136 (19). Anal. calcd for $C_{14}H_{25}N$: C 81.16, H 12.08, N 6.76; found C 81.23, H 12.09, N 6.68.

N-(Ethoxycarbonylmethyl)-4-ethyl-2-methyl-3-n-propylpyrrole (**4i**) Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.30 (s, 1H), 4.47 (s, 2H), 4.21 (q, J = 7.1 Hz, 2H), 2.43 (q, J = 7.5 Hz, 2H), 2.33 (t, J = 7.8 Hz, 2H), 2.06 (s, 3H), 1.49—1.43 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.5 Hz, 3H) , 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 169.4, 125.1, 124.6, 119.4, 116.5, 61.4, 48.4, 26.9, 24.5, 18.5, 14.5, 14.2, 14.1, 9.6; IR (neat) ν: 2960, 1740, 1528, 1457, 1375, 1184, 860 cm^{-1}; MS (70 eV) m/z (%): 237 (M^+, 62), 208 (100), 180 (57). Anal. calcd for $C_{14}H_{23}NO_2$: C 70.89, H 9.70, N 5.95; found C 70.78, H 9.75, N 5.87.

DL-N-(Ethoxycarbonylethyl)-4-ethyl-2-methyl-3-n-propylpyrrole (**4j**) Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.45 (s, 1H), 4.68 (q, J = 7.2 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.43 (q, J = 7.3 Hz, 2H), 2.33 (t, J = 7.7 Hz, 2H), 2.09 (s, 3H), 1.66 (d, J =

7.2 Hz, 3H), 1.49—1.43(m, 2H), 1.23 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 171.9, 124.9, 124.4, 119.0, 112.6, 61.3, 53.5, 26.8, 24.5, 18.7, 17.8, 14.5, 14.1, 9.8; IR (neat) ν: 2961, 1742, 1530, 1459, 1375, 1184, 799 cm^{-1}; MS (70 eV) m/z (%): 251 (M^+, 54), 222 (100), 194 (27). Anal. calcd for $C_{15}H_{25}NO_2$: C 71.71, H 9.96, N 5.58; found C 71.66, H 10.01, N 5.77.

N-(2-*Hydroxyethyl*)-4-*ethyl*-2-*methyl*-3-*n*-*propylpyrrole* (**4k**) Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.36 (s, 1H), 3.88 (t, J = 5.7 Hz, 2H), 3.76 (t, J = 5.4 Hz, 2H), 3.61(s, 1H), 2.41 (q, J = 7.5 Hz, 2H), 2.31 (t, J = 7.8 Hz, 2H), 2.12 (s, 3 H), 1.44—1.43 (m, 2H), 1.17 (t, J = 7.5 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 123.9, 122.4, 118.1, 113.9, 62.3, 49.5, 32.7, 26.3, 24.1, 18.6, 14.7, 9.8; IR (neat) ν: 3367, 2963, 1736, 1696, 1550, 1450, 1325, 1059 cm^{-1}; MS (70 eV) m/z (%): 195 (M^+, 35), 177 (19), 166 (100). Anal. calcd for $C_{12}H_{21}NO$: C 73.85, H 10.77, N 7.18; found C 73.74, H 10.68, N 7.34.

N-2-[(1*S*, 2*S*)-(+)-1-(4-*nitrophenyl*)-1, 3-*propanediol*]-4-*ethyl*-2-*methyl*3-*n*-*propylpyrrole* (**4l**) Yellow solid, m.p. 118—120 ℃, $[\alpha]_D^{21}$ + 28.1 (c 2.67, acetone), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 6.60 (s, 1H), 5.12 (d, J = 5.7 Hz, 1H), 4.13 (q, J = 5.7 Hz, 1H), 3.91 (d, J = 6.1 Hz, 2H), 3.58 (s, 1H), 2.65 (s, 1H), 2.43 (q, J = 7.5 Hz, 2H), 2.26(t, J = 7.2 Hz, 2H), 1.77 (s, 3H), 1.38—1.36 (m, 2H), 1.19 (t, J = 7.5 Hz, 3H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 147.9, 147.8, 127.6, 126.4, 125.9, 123.6, 118.9, 112.5, 73.8, 62.6, 62.2, 31.7, 26.5, 24.4, 18.6, 14.0, 9.8; IR (KBr) ν: 3491, 3385, 2959, 1605, 1512, 1460, 1353, 1081, 855 cm^{-1}; MS (70 eV) m/z (%): 346 (M^+, 18), 317 (8), 194 (100). Anal. calcd for $C_{19}H_{26}N_2O_4$: C 65.90, H 7.51, N 8.09; found C 65.85, H 7.56, N 8.13.

N-2-[(1*S*,2*S*)-(+)-1-(4-*nitrophenyl*)-1,3-*propanediol*]-2-*methyl*-3-*n*-*pentylpyrrole* (**4m**) Yellow solid, m.p. 117—118 ℃, $[\alpha]_D^{21}$ + 30.0 (c 3.33, acetone), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 2.9 Hz, 1H), 6.05 (d, J = 2.9 Hz, 1H), 5.16 (d, J = 5.3 Hz, 1H), 4.16 (q, J = 5.7 Hz, 1H), 3.91 (d, J = 6.1 Hz, 2H), 3.58 (s, 1H), 2.65(s, 1H), 2.28 (t, J = 7.4 Hz, 2H), 1.73 (s, 3H), 1.45—1.41 (m, 2H), 1.32—1.22 (m, 4H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 147.9, 147.8, 127.6, 125.7, 123.6, 120.5, 116.2, 109.2, 73.7, 62.8, 62.2, 31.6, 30.9, 26.2, 22.6, 14.1, 9.5; IR (KBr) ν: 3491, 3385, 2927, 1603, 1511, 1456, 1353, 1081, 856 cm^{-1}; MS (70 eV) m/z (%): 346 (M^+, 18), 317 (8), 194 (100). Anal. calcd for $C_{19}H_{26}N_2O_4$: C 65.90, H 7.51, N 8.09; found C 65.78, H 7.47, N 8.26.

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