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ULTRASOUND-MEDIATED ONE-POT SYNTHESIS OF THE FULLY FUNCTIONALIZED *N,N′*-(1,3-PROPANE)BISPYRROLES

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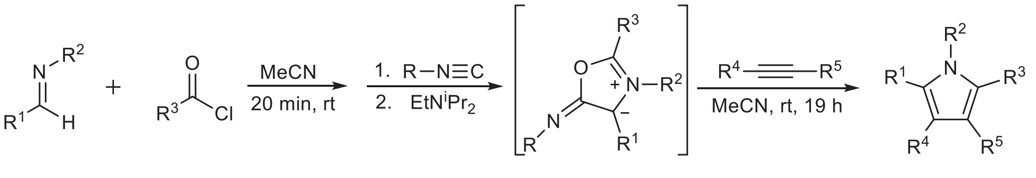
Abstract – Five fully functionalized *N,N′*-(1,3-propane)bispyrroles were synthesized by the *tert*-butyl isocyanide-mediated one-pot reaction of bisimines, aroyl chloride and dimethyl acetylenedicarboxylate under ultrasonic irradiation in good yield. The structures of *N,N′*-(1,3-propane)bispyrroles were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy.

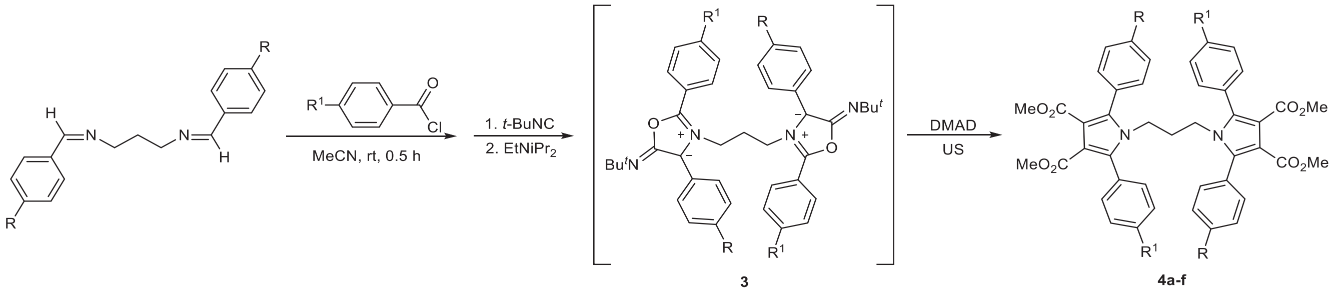
N,N′-(1,3-Propane)bispyrrole and their derivatives has received much attention from the research group due to wide range of biological and materials science applications.[1] As a consequence, much attention has been paid to their preparation by classical methods such as the Knorr reaction,[2] Paal–Knorr reaction,[3] *C–N* cross-coupling reaction,[4] Michael addition reaction,[5] Hantzsch pyrrole synthesis,[6] 1,3-dipolar cycloaddition reaction.[7]

In 2015, we reported a new approach for synthesis of bispyrrole by using the ability of alkynes to undergo the double 1,3-dipolar cycloaddition-extrusion to bis(1,3-oxazolium-5-oxides (Münchnones)).[8] While bismünchnones are typically prepared in situ from bisglycine derivatives, an inadequate aspect is that can themselves require a multistep synthesis. In 2007, a new isocyanide-mediated reaction of imines and acid chlorides generating the mono-oxazolium salt **1** was discovered by Arndtsen and co-workers.[9] **1** were trapped by alkynes to form mono-pyrroles **2** (**Scheme 1**).



Scheme 1. Synthesis of monopyrroles by isocyanide-mediated reaction

As such, we became interested in developing routes to construct bispyrroles. The advantage of ultrasound irradiation to promote organic reactions includes shorter reaction time and high-yields.[10] We describe herein that this assembly of fully functionalized *N*,*N′*-(1,3-propane)bispyrroles can be obtained via isocyanide-mediated reaction under ultrasonic irradiation.



Scheme 2. Synthesis of *N*,*N′*-(1,3-propane)bispyrrole derivatives **4a-f**

As shown in Scheme 2, target products **4** were synthesized by the three step one-pot method under ultrasonic irradiation, First, at room temperature, bisimines were treated by aroyl chloride for 0.5 h, then, *tert*-butyl isocyanide was added, stirring for 0.5 h; The second, EtN^iPr_2 was dropped slowly to the above mixture yield yellow-blue color bis-oxazolium salts **3a, 3b, 3d** (when 4-nitrobenzoyl chloride was used, yield violet color bis-oxazolium salts **3c, 3e, 3f**); Last, surprisingly, the addition of dimethyl acetylenedicarboxylate (DMAD) to **3** leads to the generation of the corresponding bispyrrole **4** over the course of 2 h (Table 1, entries 3 and 5 for 3 h) under ultrasonic irradiation and the bright and charming colors have vanished. Compound **4f** has not been successfully obtained by this method (Table 1, entry 6).

Table 1. Yield of *N*,*N′*-(1,3-propane)bispyrrole derivatives **4a-f**

Entry	R	R^1	Compound	Method A		Method B		Method C[7]	
				Time (US) / h	Yield (%)[a]	Time / h	Yield (%)[a]	Time / h	Yield (%)[a]
1	H	H	**4a**	2	72.5	24	59.0	72	30.0
2	H	OMe	**4b**	2	74.6	24	61.2	-	-
3	H	NO_2	**4c**	3	69.0	24	45.3	72	18.0
4	OMe	OMe	**4d**	2	77.7	24	62.1	-	-
5	OMe	NO_2	**4e**	3	62.5	24	46.4	-	-
6	NO_2	NO_2	**4f**	3	0.0	24	0.0	-	-

[a] Isolated yields.

We carried out the reaction under conventional conditions (Method B) and compared the results with those obtained under ultrasound conditions (Method A). Thus application of ultrasound not only prevents side products but also reduces reaction time. The yields of products under both ultrasound and room temperature conditions are shown in Table 1. In terms of yield and reaction time, method A is more advantageous than method C (Table 1, entries 1and 3).

The structures of compounds **4a**-**e** were determined on the basis of their elemental analyses, ^{1}H NMR, ^{13}C NMR spectroscopic data. In the ^{1}H NMR spectra of **4a**-**e**, the proton of methylene possessed *N* showed triplet at 3.10–3.30 ppm, and it is noteworthy that in the ^{1}H NMR spectra of all bispyrrole esters, the proton of methyl possessed ester group (–CO_2Me) showed resonances at 3.6–3.7 ppm, the single peak of **4a** (**4d**) is observed at 3.61 ppm (3.62 ppm), the two single peak of **4b** (**4c**, **4e**) are observed at 3.60 and 3.62 ppm (**4c** 3.62 and 3.63 ppm, **4e** 3.62 and 3.64 ppm), the proton of possessed aryl group showed resonances at > 6 ppm. ^{13}C NMR spectra of compounds **4a**-**4e** showed resonances at 51–52 ppm (a carbon of methyl of CO_2Me); 114–116 ppm (carbon of pyrrole with methoxycarbonyl group) and 164–165 ppm (carbon of carbonyl group of CO_2Me), both consistent with the presence of the heterocyclic ring.

In conclusion, polysubstituted *N*,*N'*-(1,3-propane)bispyrroles were successfully synthesized utilizing the *tert*-butyl isocyanide-mediated stepwise fashion one-pot of bisimines, aroyl chloride, dimethyl acetylenedicarboxylate under ultrasonic irradiation in short time, simultaneously providing a modular method to construct these bisheterocycles with facile diversity and high atom economy.

EXPERIMENTAL

Melting points were recorded on a Yanaco hot-stage melting point apparatus and uncorrected. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra were recorded at 100 MHz using a JEOL ECA 400 or ECX 400 spectrometer. Chemical shifts were reported in parts per million (δ) relative to tetramethylsilane (TMS). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration). Elemental analyses were performed with a Yanaco MT-5 CHN-Corder. All high resolution mass spectra were obtained on a micro TOF-QII 10203 spectrometer. Ultrasonication was done in a KQ5200DE and a frequency of 40 kHz ultrasound clear with an out power 200 W. All of the organic solvents used in this study were dried over appropriate drying agents.

Starting Materials

Bisimine were prepared by previously reported procedures,[11] and used directly without purification. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of Compounds 4a-e

Method A: A 25 mL two-neck round bottom flask equipped with a magnetic bar was charged the bisimine (0.1 mmol, 1 equiv.) and MeCN (2 mL), and stirring. Aroyl chloride (0.22 mmol, 2.2 equiv.) was injected by syringe. After 0.5 h at room temperature, *tert*-butyl isocyanide (0.22 mmol, 2.2 equiv.) was injected. After 0.5 h at room temperature, diisopropylethylamine (0.22 mmol, 2.2 equiv.) was injected. After 0.5 h at room temperature, DMAD (0.22 mmol, 2.2 equiv.) was injected and the reaction was carried out under ultrasonic irradiation for 2 or 3 h. The solution was concentrated *in vacuo*, the crude products were purified by silica gel chromatography using CH_2Cl_2/EtOAc acetate ($V : V = 4 : 1$) as eluent. The corresponding product was obtained.

Method B: A 25 mL two-neck round bottom flask equipped with a magnetic bar was charged the bisimine (0.1 mmol, 1 equiv.) and MeCN (2 mL), and stirring. Aroyl chloride (0.22 mmol, 2.2 equiv.) was injected by syringe. After 0.5 h at room temperature, *tert*-butyl isocyanide (0.22 mmol, 2.2 equiv.) was injected. After 0.5 h at room temperature, diisopropylethylamine (0.22 mmol, 2.2 equiv.) was injected. After 0.5 h at room temperature, DMAD (0.22 mmol, 2.2 equiv.) was injected and the reaction was carried out at room temperature for 24 h. The solution was concentrated *in vacuo* to give the crude product which was purified by silica gel chromatography using CH_2Cl_2/EtOAc ($V : V = 4 : 1$) as eluent. The corresponding product was obtained.

Tetramethyl 1,1′-(propane-1,3-diyl) bis(2,5-diphenyl-1*H*-pyrrole-3,4-dicarboxylate) (4a): Colorless solid, yield: 72.5%. mp 119–121 °C. $R_f = 0.75$. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.06$–1.12 (m, 2H, CH_2), 3.16–3.20 (t, $J = 7.6$ Hz, 4H, CH_2), 3.61 (s, 12H, CH_3), 7.06–7.09 (d, $J = 8.4$ Hz, 8H, ArH), 7.33–7.42 (m, 12H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 31.5$, 41.6, 51.6, 114.7, 128.5, 128.9, 130.2, 130.3, 136.0, 166.1. HRMS (ESI$^+$) calcd for $C_{43}H_{38}N_2O_8$ (MH$^+$) 711.7768, found 711.7766. Anal. Calcd for $C_{43}H_{38}N_2O_8$: C, 72.66; H, 5.39; N, 3.94%. Found: C, 72.43; H, 5.43; N, 3.81.

Tetramethyl 1,1′-(propane-1,3-diyl) bis[2-phenyl-5-(4-methoxy-phenyl)-1*H*-pyrrole-3,4-dicarboxylate] (4b): Colorless solid, yield: 74.6%. mp 82–85 °C, $R_f = 0.67$. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta =$ 1.07–1.15 (m, 2H, CH_2), 3.16–3.20 (t, $J = 8.0$ Hz, 4H, CH_2), 3.60 (s, 6H, CH_3), 3.62 (s, 6H, CH_3), 3.87 (s, 6H, CH_3), 6.87–6.89 (d, $J = 8.8$ Hz, 4H, ArH), 7.00–7.02 (d, $J = 8.8$ Hz, 4H, ArH), 7.06–7.08 (d, $J = 6.8$ Hz, 4H, ArH), 7.30–7.42 (m, 6H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 31.6$, 41.6, 51.6, 55.3, 113.9, 114.5, 114.6, 122.3, 128.5, 128.8, 130.2, 130.4, 131.5, 135.7, 135.9, 159.9, 165.2, 165.3. HRMS (ESI$^+$) calcd for $C_{45}H_{42}N_2O_{10}$ (MH$^+$) 771.8286, found 771.8285. Anal. Calcd for $C_{45}H_{42}N_2O_{10}$: C, 70.12; H, 5.49; N, 3.63%. Found: C, 69.75; H, 5.57; N, 3.87.

Tetramethyl 1,1′-(propane-1,3-diyl) bis[2-phenyl-5-(4-nitrophenyl)-1*H*-pyrrole-3,4-dicarboxylate] (4c): Yellow solid, yield: 69%. mp 199–201 ºC. $R_f = 0.70$. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.96–1.04$ (m, 2H, CH_2), 3.23–3.27 (t, $J = 7.6$ Hz, 4H, CH_2), 3.62 (s, 6H, CH_3), 3.63 (s, 6H, CH_3), 7.12–7.14 (t, $J = 7.6$ Hz, 4H, ArH), 7.24–7.26 (d, $J = 8.8$ Hz, 4H, ArH), 7.37–7.47 (m, 6H, ArH), 8.19–8.21 (d, $J = 8.8$ Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 29.7$, 41.8, 51.9, 53.5, 115.7, 116.0, 123.7, 128.7, 129.4, 129.6, 130.1, 131.2, 133.4, 136.7, 136.8, 147.8, 164.3, 164.8. HRMS (ESI$^+$) calcd for $C_{43}H_{36}N_4O_{12}$ (MH$^+$) 801.7720, found 801.7716. Anal. Calcd for $C_{43}H_{36}N_4O_{12}$: C, 64.50; H, 4.53; N, 7.00%. Found: C, 65.09; H, 5.17; N, 6.50.

Tetramethyl 1,1′-(propane-1,3-diyl) bis[2,5-di(4-methoxy-phenyl)-1*H*-pyrrole-3,4-dicarboxylate] (4d): Colorless solid, yield: 77.7%. mp 261–262 ºC. $R_f = 0.70$. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta =$ 1.11–1.19 (m, 2H, CH_2), 3.16–3.20 (t, $J = 7.6$ Hz, 4H, CH_2), 3.62 (s, 12H, CH_3), 3.87 (s, 12H, CH_3), 6.87–6.89 (d, $J = 8.8$ Hz, 8H, ArH), 7.00–7.02 (d, $J = 8.4$ Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 31.7, 41.5, 51.6, 55.3, 113.9, 114.4, 122.4, 131.5, 135.7, 159.9, 165.4. HRMS (ESI$^+$) calcd for $C_{47}H_{46}N_2O_{12}$ (MH$^+$) 831.8804, found 831.8800. Anal. Calcd for $C_{47}H_{46}N_2O_{12}$: C, 67.94; H, 5.58; N, 3.37%. Found: C, 67.94; H, 5.77; N, 3.37.

Tetramethyl 1,1′-(propane-1,3-diyl) bis[2-(4-methoxyphenyl)-5-(4-nitrophenyl)-1*H*-pyrrole-3,4-dicarboxylate] (4e): Yellow solid, yield: 62.5%. mp 98–101 ºC. $R_f = 0.55$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.01–1.09 (m, 2H, CH_2), 3.22–3.26 (t, $J = 7.6$ Hz, 4H, CH_2), 3.62 (s, 6H, CH_3), 3.64 (s, 6H, CH_3), 3.89 (s, 6H, CH_3), 6.92–6.94 (d, $J = 8.8$ Hz, 4H, ArH), 7.07–7.09 (d, $J = 8.8$ Hz, 4H, ArH), 7.23–7.25 (d, $J = 7.6$ Hz, 4H, ArH), 8.19–8.21 (d, $J = 8.0$ Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 31.5$, 41.8, 51.9, 55.4, 113.9, 114.1, 115.6, 115.7, 121.5, 123.6, 131.2, 131.5, 133.1, 136.7, 136.9, 147.9, 160.3, 164.5, 164.9. HRMS (ESI$^+$) calcd for $C_{45}H_{40}N_4O_{14}$ (MH$^+$) 862.8317, found 862.8317. Anal. Calcd for $C_{45}H_{40}N_4O_{14}$: C, 62.79; H, 4.68; N, 6.51%. Found: C, 62.55; H, 5.06; N, 6.15.

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