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Synthesis of 1,2′- and 1,3′-bipyrroles from 2- and 3-nitropyrroles

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Abstract

1,2′- and 1,3′-Bipyrroles, which are attractive precursors for the synthesis of bipyrrole-based natural products, are synthesized in one-pot from 2- and 3-nitropyrroles by a sequential nitro group reduction—Paal–Knorr pyrrole synthesis.

Keywords: Bipyrroles; Nitropyrroles; Reduction; Paal–Knorr pyrrole synthesis

Bipyrroles are attractive precursors for the synthesis of the various polyhalogenated 2,2′- and 1,2′-bipyrroles found in marine organisms (Fig. 1), which are ubiquitous in the marine environment.[1,2] Previous syntheses of 2,2′-bipyrroles include coupling of 2-halopyrroles;[3] for example, phenyliodine bis(trifluoroacetate),[4] palladium,[5] nickel,[6] and other methods.[7] However, no general method is available for the preparation of 1,2′- and 1,3′-bipyrroles and only a few syntheses are known.[8,9]

Our recent reductive acylation of 3-nitroindoles[10a] and 2- and 3-nitropyrroles[10b] prompted us to explore the use of 2- and 3-nitropyrroles as a simple route to 1,2′- and 1,3′-bipyrroles. We now describe the results of this study.

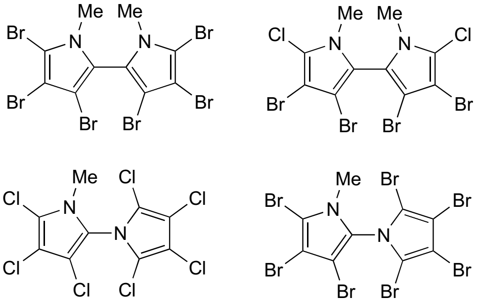
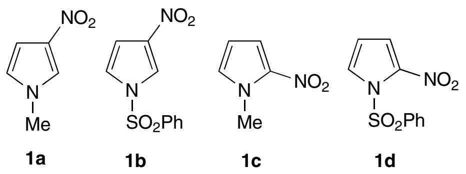


Fig. 1. Representative marine bipyrrole natural products.

We selected the readily available[10b] 1-methyl-3-nitropyrrole (**1a**), 3-nitro-1-(phenylsulfonyl)pyrrole (**1b**), 1-methyl-2-nitropyrrole (**1c**), and 2-nitro-1-(phenylsulfonyl)pyrrole (**1d**) as substrates (Scheme 1).

Thus, 3-nitro-1-(phenylsulfonyl)pyrrole (**1b**) was treated with indium or tin and 2,5-dimethoxy-2,5-dihydrofuran in acetic acid at 60 °C under nitrogen to afford a low yield (22%) of the desired bipyrrole **2b**. No improvement was seen when the solvent was changed to toluene, benzene, dichloroethane, or methanol. Similarly, 2-nitro-1-(phenylsulfonyl)pyrrole (**1d**) gave bipyrrole **2d** in only 20% yield (Scheme 2).

However, the use of 1,4-dicarbonyl compounds, which are widely employed in the Paal–Knorr synthesis of pyrroles from primary amines,[11] was more productive (Scheme 3). Thus, exposing 1-methyl-3-nitropyrrole (**1a**) to a mixture of tin, acetonylacetone, and acetic acid in methanol,



Scheme 1.

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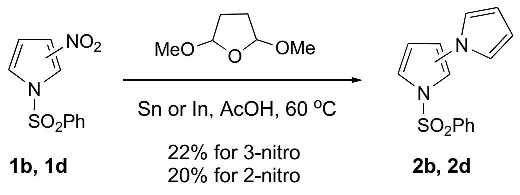


Scheme 2.

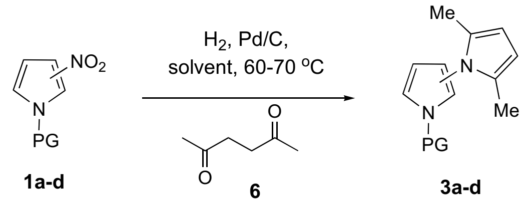
provides the desired bipyrrole **3a**[12] in 86% yield after column chromatography (Table 1, entry 1). Similarly, an 87% yield of **3b**[14] was obtained from nitropyrrole **1b** (Table 1, entry 2). In contrast, 2-nitropyrrole **1d** affords **3d**[14] in only 45% yield.

Likewise, 2-nitropyrrole **1c** gives **3c**[14] in 42% yield in a solvent mixture of methanol and dichloroethane.

To possibly circumvent the low yield observed with 2,5-dimethoxy-2,5-dihydrofuran, we prepared and utilized in its place, succindialdehyde, readily available from 2,5-dimethoxy-2,5-dihydrofuran.[15] To our delight, under these conditions 3-nitro-1-(phenylsulfonyl)pyrrole (**1b**) gives the desired bipyrrole **2b**[14] in 91% yield after column chromatography (Table 1, entry 6). The use of succindialdehyde also affords bipyrroles **2a**, **2c**, and **2d**[14] but in 35–65% yields.

Acetonylacetophenone and dibenzoylethane also undergo this sequential reduction—Paal–Knorr sequence. Thus, 3-nitropyrroles **1a** and **1b** with acetylacetophenone furnish bipyrroles **4a**[14] and **4b**[14] in 91% and 70% yields, respectively (Table 1, entries 9 and 10). Similarly, bipyrrole **5a**[14] is isolated in 62% yield from the reaction of 3-nitropyrrole **1a** and dibenzoylethane (Table 1, entry 11). However, bipyrrole **5b** could not be isolated in several attempts (entry 12).

We also explored catalytic reduction in place of the tin conditions in this sequence (Scheme 4). In the event, the treatment of 3-nitropyrrole **1a** with H_2, Pd/C, and acetonylacetone in methanol gives the desired bipyrrole **3a**[13] in 91% yield following column chromatography (Table 2,

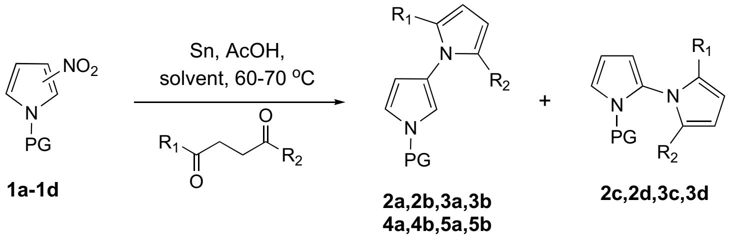


Scheme 4.

Table 2
Catalytic reductive pyrrolylation of nitropyrroles with acetonylacetone (**6**)

Entry	Nitropyrrole	Solvent	Product	Yield[a] (%)
1	**1a**	MeOH	**3a**	91
2	**1b**	MeOH	**3b**	92
3	**1c**	AcOH $(CH_2Cl)_2$	**3c**	15
4	**1d**	AcOH $(CH_2Cl)_2$	**3d**	43

[a] Yield after column chromatography.



Scheme 3.

Table 1
Sn-mediated reductive pyrrolylation of nitropyrroles with dicarbonyl compounds

Entry	Nitropyrrole	PG	R_1 & R_2	Solvent	Product	Yield[a] (%)
1	**1a**	Me	$R_1 = R_2 = Me$	MeOH	**3a**	86
2	**1b**	SO_2Ph	$R_1 = R_2 = Me$	MeOH	**3b**	87
3	**1c**	Me	$R_1 = R_2 = Me$	MeOH, $(ClCH_2)_2$	**3c**	42
4	**1d**	SO_2Ph	$R_1 = R_2 = Me$	MeOH	**3d**	45
5	**1a**	Me	$R_1 = R_2 = H$	MeOH	**2a**	39
6	**1b**	SO_2Ph	$R_1 = R_2 = H$	MeOH	**2b**	91
7	**1c**	Me	$R_1 = R_2 = H$	MeOH, $(ClCH_2)_2$	**2c**	35
8	**1d**	SO_2Ph	$R_1 = R_2 = H$	MeOH	**2d**	65
9	**1a**	Me	$R_1 = Me, R_2 = Ph$	MeOH	**4a**	91
10	**1b**	SO_2Ph	$R_1 = Me, R_2 = Ph$	MeOH	**4b**	70
11	**1a**	Me	$R_1 = R_2 = Ph$	MeOH	**5a**	62
12	**1b**	SO_2Ph	$R_1 = R_2 = Ph$	MeOH	**5b**	0

[a] Yield after column chromatography.

entry 1). Similarly, **3b**[14] is obtained in 92% yield from 3-nitropyrrole **1b** (Table 2, entry 2). Whereas neither 2-nitropyrrole **1c** or **1d** leads to their corresponding bipyrroles in methanol, a mixture of acetic acid and dichloroethane provides a low yield of bipyrrole **3c**[14] and a 43% yield of bipyrrole **3d**,[14] respectively (entries 3 and 4).

In summary, we describe the first general synthesis of N-protected 1,2′- and 1,3′-bipyrroles from 2- and 3-nitropyrroles that features a simple in situ reduction—Paal–Knorr pyrrole annulation sequence. The application of this method to naturally occurring bipyrroles is underway.

Acknowledgments

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12. *Representative procedure* (**3a**) (*Procedure I*): 1-Methyl-3-nitropyrrole (**1a**) (100 mg, 0.80 mmol) and tin (470 mg, 4.0 mmol) in MeOH (5 mL) were added to acetic acid (1 mL) and acetonylacetone (271 mg, 2.4 mmol). The resulting mixture was heated to 70 °C under nitrogen for 0.5 h. The reaction mixture was cooled to room temperature and transferred into a beaker. Saturated NaHCO$_3$ was added carefully until the solution was no longer acidic. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with saturated NaHCO$_3$ (20 mL), brine (20 mL), and dried over Na$_2$SO$_4$. The removal of solvent and column chromatography over hexane–EtOAc (16:1 and 4:1) gave product **3a** (120 mg, 0.69 mmol) as a white solid in 87% yield: mp 46–47 °C; ^{1}H NMR (CDCl$_3$): δ = 6.62–6.65 (m, 2H), 6.13 (dd, 1H), 5.93 (s, 2H), 3.76 (s, 3H), 2.17 (s, 6H); ^{13}C NMR (CDCl$_3$): δ = 130.0, 123.0, 121.0, 118.7, 108.1, 105.0, 37.0, 13.3; MS (EI): m/z (%) = 174 ([M$^+$], 100), 159, 132, 118, 94, 81; HRMS (EI): m/z calcd for C$_{11}$H$_{14}$N$_2$: 174.1157. Found: 174.1156.

13. *Representative procedure* (**3a**) *(Procedure II)*: To a solution of 1-methyl-3-nitropyrrole (**1a**) (59 mg, 0.47 mmol) and acetonylacetone (160 mg, 1.4 mmol) in anhydrous methanol (3 mL) was added 10% palladium on carbon (12 mg). The atmosphere of the flask was replaced by hydrogen gas and the reaction was cooled to −78 °C. After three vacuum/hydrogen cycles to remove air from the reaction flask, the reaction mixture was heated to 70 °C under atmospheric pressure for 1.5 h, having the hydrogen atmosphere maintained by a balloon. The catalyst was removed by filtration through Celite. The filtrate was evaporated and the crude product was purified by column chromatography (hexane–EtOAc = 16:1) to give the desired product (**3a**) (73 mg, 90%) as a white solid which was identical with the sample prepared above by ^{1}H NMR, ^{13}C NMR, and TLC.
14. *Compound* **3b**: white solid; mp 91–92 °C; ^{1}H NMR ($CDCl_3$): δ = 7.89 (m, 2H), 7.64–7.67 (m, 1H), 7.54–7.57 (m, 2H), 7.21 (dd, 1H), 7.14 (t, 1H), 6.27 (dd, 1H), 5.85 (s, 2H), 2.00 (s, 6H); ^{13}C NMR ($CDCl_3$): δ = 138.8, 134.5, 129.8, 129.3, 128.0, 127.0, 120.7, 117.3, 114.0, 106.2, 13.1; MS (EI): *m*/*z* (%) = 300 ($[M^+]$), 272, 257, 242, 229, 206, 191, 159 (100), 143, 125, 111, 97, 71; HRMS (EI): *m*/*z* calcd for $C_{16}H_{16}N_2O_2S$: 300.0933. Found: 300.0929. Compound **3c**: yellow oil; ^{1}H NMR ($CDCl_3$): δ = 6.67 (dd, 1H), 6.20 (dd, 1H), 6.12 (dd, 1H), 5.92 (s, 2H), 3.23 (s, 3H), 2.01 (s, 6H); ^{13}C NMR ($CDCl_3$): δ = 130.7, 126.9, 120.4, 106.9, 106.4, 106.0, 32.4, 12.7; MS (EI): *m*/*z* (%) = 174 ($[M^+]$, 100), 159, 132, 118, 94, 81; HRMS (EI): *m*/*z* calcd for $C_{11}H_{14}N_2$: 174.1157. Found: 174.1156. Compound **3d**: white solid; mp 105–106 °C; ^{1}H NMR ($CDCl_3$): δ = 7.60–7.63 (m, 1H), 7.56 (m, 2H), 7.41–7.45 (m, 3H), 6.32 (t, 1H), 6.15 (dd, 1H), 5.80 (s, 2H), 1.57 (s, 6H); ^{13}C NMR ($CDCl_3$): δ = 138.0, 134.4, 131.7, 129.3, 128.5, 127.3, 121.8, 113.7, 110.1, 106.6, 12.3; MS (EI): *m*/*z* (%) = 300 ($[M^+]$), 272, 257, 229, 191, 175, 159 (100), 131, 117, 91, 77; HRMS (EI): *m*/*z* calcd for $C_{16}H_{16}N_2O_2S$: 300.0933. Found: 300.0933. Compound **2a**: column chromatography over Al_2O_3; yellowish oil (solid upon standing); ^{1}H NMR ($CDCl_3$): δ = 6.90 (dd, 2H), 6.67 (m, 1H), 6.53 (dd, 1H), 6.25 (dd, 2H), 6.20 (dd, 1H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 128.0, 121.2, 120.4, 112.1, 108.8, 102.2, 36.9; MS (EI): *m*/*z* (%) = 146 ($[M^+]$, 100), 131, 118, 104, 91, 78; HRMS (EI): *m*/*z* calcd for $C_9H_{10}N_2$: 146.0844. Found: 146.0844. Compound **2b**: white solid; mp 77–78 °C; ^{1}H NMR ($CDCl_3$): δ = 7.89 (m, 2H), 7.62–7.65 (m, 1H), 7.52–7.55 (m, 2H), 7.17 (m, 2H), 6.89 (m, 2H), 6.43 (dd, 1H), 6.27 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 138.8, 134.4, 131.9, 129.8, 127.1, 121.3, 119.6, 110.3, 108.5, 108.1; MS (EI): *m*/*z* (%) = 272 ($[M^+]$), 236, 207, 191, 177, 149, 131 (100), 104, 87, 77; HRMS (EI): *m*/*z* calcd for $C_{14}H_{12}N_2O_2S$: 272.0620. Found: 272.0622. Compound **2c**: column chromatography over Al_2O_3; yellow oil; ^{1}H NMR ($CDCl_3$): δ = 6.78 (t, 2H), 6.59 (t, 1H), 6.32 (t, 2H), 6.14 (m, 2H), 3.39 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 123.4, 119.8, 109.1, 106.4, 104.1, 103.7, 27.5; HRMS (EI): *m*/*z* calcd for $C_9H_{10}N_2$: 146.0844. Found: 146.0842. Compound **2d**: yellowish oil; ^{1}H NMR ($CDCl_3$): δ = 7.57 (m, 1H), 7.47 (m, 2H), 7.38–7.42 (m, 2H), 7.35 (dd, 1H), 6.49 (t, 2H), 6.28 (t, 1H), 6.17 (m, 3H); ^{13}C NMR ($CDCl_3$): δ = 137.8, 134.2, 130.4, 129.4, 127.8, 125.2, 121.3, 111.4, 110.3, 109.3; MS (EI): *m*/*z* (%) = 272 ($[M^+]$), 207, 191, 149, 131 (100), 104, 77; HRMS (EI): *m*/*z* calcd for $C_{14}H_{12}N_2O_2S$: 272.0620. Found: 272.0622. Compound **4a**: yellow oil; ^{1}H NMR ($CDCl_3$): δ = 7.35 (m, 2H), 7.25–7.29 (m, 2H), 7.17–7.20 (m, 1H), 6.59 (t, 1H), 6.49 (m, 1H), 6.41 (d, 1H), 6.14 (d, 1H), 6.12 (dd, 1H), 3.64 (s, 3H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 134.8, 134.4, 132.9, 128.1, 127.9, 125.8, 123.5, 121.0, 118.9, 108.6, 108.1, 106.9, 36.9, 13.6; MS (EI): *m*/*z* (%) = 236 ($[M^+]$, 100), 221, 194, 180, 159, 132, 118, 81; HRMS (EI): *m*/*z* calcd for $C_{16}H_{16}N_2$: 236.1314. Found: 236.1313. Compound **4b**: white solid; mp 109–110 °C; ^{1}H NMR ($CDCl_3$): δ = 7.75–7.77 (m, 2H), 7.67 (m, 1H), 7.50–7.53 (m, 2H), 6.99–7.13 (m, 7H), 6.28 (d, 1H), 6.19 (dd, 1H), 6.05 (dd, 1H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 139.0, 134.6, 134.3, 133.4, 132.1, 129.7, 128.5, 128.1, 128.0, 127.0, 126.1, 120.6, 117.5, 114.3, 109.0, 107.9, 13.3; MS (EI): *m*/*z* (%) = 362 ($[M^+]$), 260, 238, 219, 206, 191, 169, 155, 141, 125, 105, 71; HRMS (EI): *m*/*z* calcd for $C_{21}H_{18}O_2N_2S$: 362.1089. Found: 362.1088. Compound **5a**: white solid; mp 175–176 °C; ^{1}H NMR ($CDCl_3$): δ = 7.19–7.34 (m, 10H), 6.49 (m, 3H), 6.35 (t, 1H), 5.95 (dd, 1H), 3.58 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 136.7, 134.0, 128.7, 127.9, 126.3, 123.4, 120.8, 119.3, 109.3, 109.2, 36.9; MS (EI): *m*/*z* (%) = 298 ($[M^+]$, 100), 283, 254, 243, 220, 194, 178, 167, 149, 115, 105, 77; HRMS (EI): *m*/*z* calcd for $C_{21}H_{18}N_2$: 298.1470. Found: 298.1469.

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