JOC Notes

Comparison of Benzene, Nitrobenzene, and Dinitrobenzene 2-Arylsulfenylpyrroles

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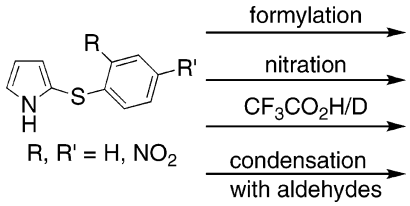

The effectiveness of the 2,4-dinitrobenzenesulfenyl and 4-nitrobenzenesulfenyl groups as masking and directing groups at the 2-position of pyrrole has been investigated and compared to that of 2-phenylthiopyrrole. The presence of the nitro group(s) enhances stability of the corresponding pyrrole toward acid and does not significantly decrease the ability of the pyrrolic unit to undergo electrophilic aromatic substitution reactions in the form of formylation, nitration, and condensation with aldehydes. The synthetic utility of 2-(2,4-dinitrobenzenesulfenyl)pyrrole was demonstrated through the synthesis of *meso*-substituted dipyrromethanes. The sulfoxides 2-(2,4-dinitrobenzenesulfinyl)pyrrole and 2-(4-nitrobenzenesulfinyl)pyrrole underwent neither formylation nor nitration, and the increasing presence of nitro groups within the moiety at the 2-position resulted in decreased stability under acidic conditions.

Pyrrolic molecules exhibit a wide variety of electronic and optical properties, and the pyrrolic unit is essential within the synthesis of many natural products, new materials, and improved pharmaceuticals.[1−5] As such, the preparation and manipulation of functionalized pyrroles is of increasing importance.[1,6−10] Many synthetic routes involving the pyrrolic unit require the controlled introduction of substituents via electrophilic substitution.[11] Success in this regard relies upon successful direction of incoming substituents and the ability to control the extent of reactivity. Such control has most commonly been achieved by the use of carboxylates at the 2-position which serve to both protect the pyrrolic unit, through their electron-withdrawing ability and formal carbamate character through resonance, and direct electrophilic substitution.[4,12] Although much practiced, removal of a carboxy moiety from the 2-position of pyrroles is often difficult and requires harsh conditions. In addressing the limitations of carboxylates as protecting groups for pyrroles, electron-rich sulfenyl groups have recently been demonstrated[13] to block the pyrrolic 2-position and activate, rather than protect, the pyrrolic ring. A variety of sulfenyl groups were investigated (Figure 1, R = CH_3, CH_2CH_3, $(CH_2)_9$, Ph), and the utility of the activated pyrroles in acylation reactions was established, as well as the removal of the sulfenyl group using Raney nickel. The realization that only blocking/masking the 2-position is necessary, rather than electronically protecting the N atom through the traditional use of electron-withdrawing groups, has highlighted the fact that synthetic pyrrole chemistry, although aged, is far from mastered.

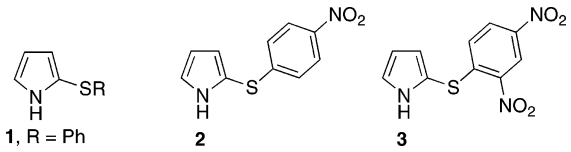

FIGURE 1. 2-(Arylsulfenyl)pyrroles.

We previously reported on the effectiveness of 2,4-dinitrobenzenesulfinyl and 2,4-dinitrobenzenesulfonyl units at the 2-position of pyrrole and demonstrated the removal of these substituents under mild deprotection conditions.[14] Following Lindsey's report concerning the activation and masking of pyrroles using 2-sulfenyl groups, we herein report the reactivity of **2** and **3**, pyrroles substituted at the 2-position by nitrobenzenesulfenyl groups. The nitro groups, although electron-withdrawing, do not significantly reduce the reactivity of pyrroles **2** and **3** compared to that of **1** and are found to impart stability in air and acid, as well as to increase crystallinity.

The reactivity of pyrroles **1**−**3** under Vilsmeier−Haack formylation[12] conditions was investigated to determine the

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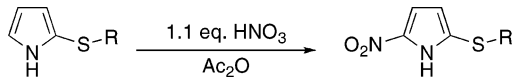
TABLE 1. Formylation of 2-Arylsulfenylpyrroles

pyrrole	selectivity[a]	yield (%)[b]
1	1:0	75
2	1:0	76
3	27:1	67

[a] Ratio of 2-substituted cf. 3-substituted product. [b] Isolated yields.

TABLE 2. Nitration of 2-Arylsulfenylpyrroles



pyrrole	*T* (°**C**)	time	yield (%)[a]
1	0	30 min	19
1	−5	30 min	28
2	rt	1 h	16
3	rt	1 h	35

[a] Isolated yields.

effects of the nitro substituents toward electrophilic aromatic substitution of the pyrroles. Although large excesses of reagents are often used for preparative electrophilic substitution reactions of pyrroles, only 1.5 equiv of the Vilsmeier−Haack reagent was used in our studies so that tangible differences in reactivity could be detected (Table 1). Interestingly, both 2-(4-nitrobenzenesulfenyl)pyrrole (**2**) and 2-(2,4-dinitrobenzenesulfenyl)pyrrole (**3**) gave formylation yields similar to that of 2-phenylthiopyrrole (**1**), revealing that the presence of the nitro group(s) does not significantly decrease the tendency of the corresponding 2-arylsulfenylpyrrole to undergo formylation. Only the 2-substituted (α-product) was observed for **1** and **2** (as determined by analysis of TLC and isolated products), and **3** yielded trace amounts of 3-formyl-5-(2,4-dinitrosulfenyl)pyrrole, assigned using two-dimensional NMR experiments (NOESY, HMQC, and HMBC). The excellent directing ability of the phenylsulfenyl, 4-nitrobenzenesulfenyl, and 2,4-dinitrobenzenesulfenyl groups for formylation at the vacant α-position is a useful feature of these masking groups.[11]

The 2-arylsulfinylpyrroles **4**−**6** (Figure 2), prepared by oxidation of **1**−**3** using *m*-CPBA, were completely unreactive under Vilsmeier−Haack formylation conditions (1.5 equiv). This is presumably due to the considerably greater electron-withdrawing nature of the sulfoxide functionality compared with that of the sulfide.[15]

To investigate the reactivity of pyrroles **1**−**6** toward nitration, these compounds were treated with 1.1 equiv of HNO_3 in Ac_2O. The reactivity trends observed for formylation were mirrored with the sulfides **1**−**3** giving similar yields for nitration (Table 2), and only the 5-nitration product was observed. Once again, the sulfoxides **4**−**6** were completely unreactive even after extended reaction times. As for other nitration reactions,[16,17] yields for the nitration of **1**−**3** were modest and the reactions did not proceed at all cleanly. Nevertheless, these results further

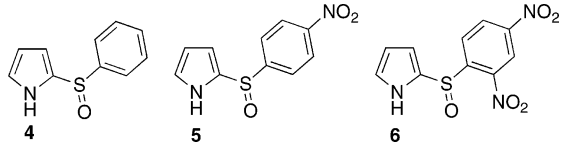


FIGURE 2. 2-(Arylsulfinyl)pyrroles.

demonstrate that the presence of the nitro group(s) does not cause significant reduction in reactivity.

Having established that the presence of the nitro group(s) does not diminish the reactivity of 2-arylsulfenylpyrroles toward electrophilic substitution reactions, we investigated the relative acid stabilities of **1**−**6**. The studies were carried out by adding a known amount of CF_3CO_2D to a stock solution of the appropriate pyrrole and 1,4-dichlorobenzene (internal standard) in CD_2Cl_2. Similar conditions, using CH_3CO_2D in place of CF_3CO_2D, have been previously used to investigate the extent of deuteration of 2-alkylsulfenyl- and 2-phenylsulfenyl-substituted pyrroles.[13] As 2-phenylthiopyrrole was reported to be poorly affected by deuterated acetic acid (very slow rates of deuteration), we turned to the stronger trifluoroacetic acid (deuterated) in order to assess the stability limits of arylsulfenylpyrroles bearing nitro groups: we felt that the nitro derivatives would be more stable to acidic conditions, hence our choice to use TFA instead of acetic acid. Equivalents of the deuterated acid were added at 30 min intervals to a maximum of 5.0 equiv, and ^{1}H NMR spectra were recorded 10 min after each addition. Comparison of the signal integrals to that of the internal standard, along with observations of new signals indicative of decomposition, revealed the degree of robustness of the pyrroles under acidic conditions. Interestingly, the nitro-substituted 2-arylsulfenylpyrroles **2** and **3** were still intact after the addition of 5.0 equiv of CF_3CO_2D, while **1** decomposed after the addition of 2.0 equiv, thereby supporting our laboratory observations regarding the stability of **1**. Indeed, in our hands, **1** was unstable in air and was thus protected as its *N*-tosyl derivative,[18] for ease of manipulation, and then deprotected with base immediately before use.[19] Furthermore, **1** was prepared from 2-thiocyanatopyrrole using phenyl magnesium bromide according to Campiani et al.,[20] and as indicated by Lindsey.[13] In our hands, 2-thiocyanatopyrrole decomposed very readily and was also extremely liable to pass through multiple layers of latex gloves to cause stains and discomfort of the skin. No such difficulties were encountered with the nitro derivatives **2** and **3** which were prepared by reaction of pyrrole with the corresponding sulfenyl chloride.[14] Evidently, the presence of electron-withdrawing nitro groups in the arylsulfenyl unit increases the stability of the pyrrolic core toward acidic conditions and supports the concept that basicity and nucleophilicity, although often correlated, are independent phenomena. For the 2-arylsulfinyl derivatives **4**−**6**, the opposite trend was observed compared to sulfides **1**−**3**. Indeed, **4** (no nitro groups, decomposition after 5.0 equiv of CF_3CO_2D added) was more resistant to acid-catalyzed decomposition than **6** (two nitro groups, decomposition after 2.0 equiv of CF_3CO_2D added).

To determine the nature of the observed acid-induced decomposition of **1**−**6**, and cognizant of the potential for

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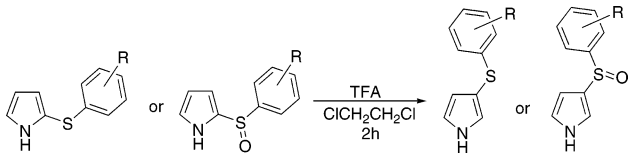
TABLE 3. Treatment of 1−6 with TFA



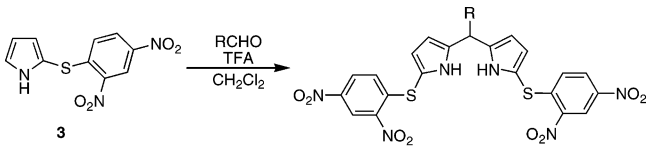
pyrrole	*T* (°C)	product ratio of 2- and 3-substituted pyrroles[a]
1	25	dec
1	84	dec
2	25	1:1
2	84	dec
3	84	1:4
4	25	1:0
4	84	dec
5	25	1:6
5	84	1:5
6	25	dec
6	84	dec

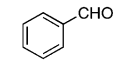
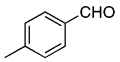
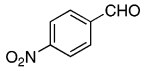
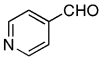
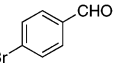
[a] Ratio determined from ^{1}H NMR spectra of crude reaction mixtures; dec = decomposed.

2-arylsulfenyl- and 2-arylsulfinylpyrroles to rearrange to their respective 3-substituted derivatives,[21,22] we investigated preparative-scale exposure of these compounds to TFA. Pyrroles **1**−**6** were thus mixed with a 1:1 mixture of TFA and DCE and stirred for 2 h at 25 or 84 °C (Table 3). Subsequent concentration to dryness and dissolution in deuterated DMSO, ensuring that all material was dissolved, allowed analysis of the crude reaction products by ^{1}H NMR spectroscopy. As observed during the NMR scale experiments described above, **1** was unstable under acidic conditions, even at 25 °C, and neither 2- nor 3-substituted pyrroles were apparent in the crude reaction mixture. The mononitro derivative **2** gave a 1:1 mixture of the 2- and 3-substituted products at 25 °C and only decomposed material at 84 °C. In contrast, the dinitro derivative **3** gave a 1:4 mixture of 2- and 3-(2,4-dinitrobenzene)sulfenylpyrroles, respectively, after treatment for 2 h at 84 °C. These results indicate that both the 2- and 3-substituted pyrroles show enhanced stability with increasing nitro substitution. The sulfinylpyrrole **4** was resistant to rearrangement at 25 °C, and only decomposition products were apparent after 2 h at 84 °C. The mononitrosulfinyl derivative **5** underwent significant rearrangement at both temperatures, and the dinitrosulfinyl analogue **6** only decomposed under acidic conditions, further supporting the determination that with increasing nitro substitution the sulfinylpyrroles become more unstable to acidic conditions. These preparative-scale experiments allowed a distinction to be made between rearrangement (2-substituted pyrroles to 3-substituted pyrroles) and general decomposition. However, whether decomposition is due to the instability of the 2-substituted starting material or the 3-substituted rearranged product is difficult to assess especially since we were unable to chromatographically separate the two.

The reactivity of **3** in the synthesis of *meso*-substituted dipyrromethanes, common precursors to porphyrinic compounds, was examined in order to further assess the synthetic utility of nitro-containing arylsulfenylpyrroles. Typically, the condensation was performed with a 2:1 ratio of **3**/benzaldehyde in CH_2Cl_2 containing TFA (0.05 M) at reflux temperature (Table 4), and dipyrromethanes were isolated in yields that are comparable to those reported using **1**.[13] With only stoichiometric amounts of **3** required for the preparation of reasonable yields of *meso*-substituted dipyrromethanes, the route is efficient in pyrrole and, again, the presence of the nitro groups does not significantly affect the nucleophilicity of the pyrrolic ring. However, pyrrole **3** did not react with the electron-rich aldehydes mesitaldehyde and *p*-anisaldehyde. All of the isolated dipyrromethanes were indefinitely stable to air and moisture. Deprotection of 1,9-bis(2,4-dinitrobenzenesulfenyl)-5-phenyldipyrromethane was achieved in 50% unoptimized yield by removal of the nitrobenzenesulfenyl groups through hydrodesulfurization with Raney nickel complex, akin to the literature method for the removal of alkyl- and arylsulfenyl masking groups.[13]

TABLE 4. Synthesis of Dipyrromethanes



RCHO	time (h)	yield (%)[a]
	24	59
	24	51
	48	65
	48	41
	24	52

[a] Isolated yields.

The studies reported herein further the scope of arylsulfenylpyrroles containing nitro groups. 2-(2,4-Dinitrobenzenesulfenyl)pyrrole and 2-(4-nitrobenzenesulfenyl)pyrrole are stable masked pyrroles that exhibit similar reactivity to 2-phenylthiopyrrole but with much enhanced stabilities toward acid and toward decomposition in air. Importantly, the presence of the nitro groups within the 2-arylsulfenyl moiety does not significantly diminish the nucleophilicity of the corresponding pyrrole. Furthermore, the presence of nitro groups significantly augments the crystallinity of 2-arylsulfenylpyrroles and generally enhances air stability and ease of isolation. Arylsulfinylpyrroles, both with and without nitro substituents, are unreactive toward formylation and nitration, and with increasing nitro substitution, these sulfoxides become less stable to acidic conditions.

Experimental Section

General Procedure for Formylation. To DMF (1.5 equiv) at 0 °C under N_2 was added $POCl_3$ (1.5 equiv) dropwise. After stirring at 100 °C for 15 min (to ensure the complete formation of the

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$POCl_3$−DMF complex), a solution of the pyrrole (1.0 equiv) in 1,2-dichloroethane was added at 0 °C. The reaction mixture was heated at reflux for the appropriate amount of time (1.0−1.5 h), and then hydrolysis was performed by the addition of an aqueous solution of NaOAc. The reaction mixture was then stirred at reflux temperature for 1 h, before being allowed to cool and then extracted three times with ether. The combined organic layers were washed three times with saturated Na_2CO_3 (aq) and once with brine, before being dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure, and the crude product was purified using column chromatography.

General Procedure for Nitration. A solution of the pyrrole (1.0 equiv) in Ac_2O was treated with a cold (0 °C) solution of 70% HNO_3 (1.1 equiv) in Ac_2O. After stirring at the appropriate temperature (0−25 °C) for the appropriate amount of time (0.5−1.0 h), the reaction mixture was poured onto ice and treated with solid Na_2CO_3 until pH 7. Extraction of the aqueous solution three times with ether followed by washing of the combined organic fractions with brine until pH 7, drying over $MgSO_4$, filtration, and removal of the solvent under reduced pressure gave the crude product which was purified using column chromatography.

General Procedure for Acid Stability Studies. Pyrrole (53 μmol) and 1,4-dichlorobenzene (20 μmol, 0.003 g) were dissolved in CD_2Cl_2 (600 μL). The solution was then transferred, with filtration if necessary, into an NMR tube, and ^{1}H NMR spectra were acquired every 30 min for a duration of 2.5 h. Following the acquisition of each of the first five spectra, CF_3CO_2D (4.1 μL, 53 μmol) was added to the tube, followed by thorough mixing via shaking.

General Procedure for Isomerization Experiments. A solution of the pyrrole (1.0 equiv) in a 1:1 mixture of TFA (37 equiv) and $ClCH_2CH_2Cl$ was stirred at the appropriate temperature (25 or 84 °C) for 2 h. After removal of the solvent in vacuo, analysis of the mixture using ^{1}H NMR spectroscopy gave the relative ratio of 2- and 3-isomers.

General Procedure for 1,9-Bis(2,4-dinitrobenzenesulfenyl)-dipyrromethanes. A solution of 2-(2,4-dinitrobenzenesulfenyl)-pyrrole (**3**) (2 equiv), aldehyde (1 equiv), and TFA in degassed CH_2Cl_2 was stirred at reflux temperature for the appropriate amount of time (20−48 h). To the resulting mixture, 0.1 N NaOH (50 mL) was added at 25 °C. The organic phase was washed with 0.1 N NaOH (3 × 50 mL) and H_2O (3 × 50 mL) before being dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude product which was purified using column chromatography.

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Supporting Information Available: Synthetic procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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