Diels–Alder Reactions of 2,3-Dimethylenepyrrole Analogues; a New Synthesis of Indoles†

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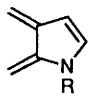
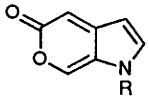
The pyrano[3,4-*b*]pyrrol-5(1*H*)-ones (**4**) are stable cyclic analogues of 2,3-dimethylenepyrrole, and undergo Diels–Alder reaction with a range of acetylenes, or acetylene equivalents, to give, after loss of carbon dioxide, indoles.

In the 120 years since Baeyer's first synthesis of indole,[1] this heteroaromatic compound has attracted much attention, not least because of the wide-ranging and potent biological activity of both synthetic and naturally occurring indoles. Research in indole chemistry continues unabated with many groups devoting considerable effort to developing new methods for the synthesis of, and functionalisation of, the indole ring system.[2] In continuation of our own interest in this area, we now report a new synthesis of indoles based on the Diels–Alder reaction of 2,3-dimethylenepyrroles (**1**).



(1)



(2)

Although 2,3-dimethyleneindoles and stable cyclic analogues thereof are now quite well described,[3] little is known about the corresponding pyrroles. Therefore, based on our previous experience with other heterocyclic analogues of orthoquinodimethane,[4] we chose to prepare the pyrrole-fused α-pyrone system, pyrano[3,4-*b*]pyrrol-5-(1*H*)-one, (**2**). Interestingly, highly substituted derivatives of this ring system have been prepared previously in poor yield by a multi-step sequence, although no Diels–Alder reactions were reported.[5] We found that the pyranopyrrolones (**4b–f**) could be prepared in modest yield (20–45%) simply by treating 1-phenylsulphonylpyrrol-3-yl-acetic acid[6] (**3c**) or its α-substituted derivatives (**3d**) with the appropriate carboxylic acid anhydride in the presence of boron trifluoride–diethyl ether. The α-substituted acids (**3d**) were prepared by alkylation of the ester[6] (**3a**), with lithium isopropylcyclohexylamide (LICA) as base, followed by hydrolysis (Scheme). The 'parent' pyranopyrrolone (**4a**) was prepared by

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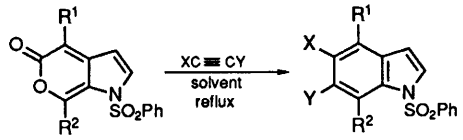
Table 1. Diels–Alder reactions of 1-phenylsulphonylpyrano[3,4-*b*]pyrrol-5(1*H*)-ones (4) with alkynes.

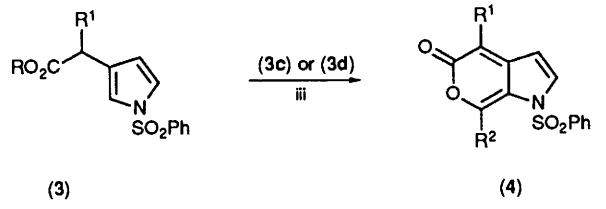


(4) (5)

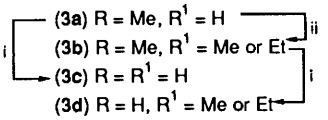
Compd. (4)	R^1	R^2	X	Y	Solvent	Yield (%)
a	H	H	H	CO_2Et	PhCl	61[a]
a	H	H	CO_2Me	CO_2Me	PhCl	58
a	H	H	$SiMe_3$	CO_2Et	PhCl	40[b]
b	H	Me	CO_2Me	CO_2Me	MeCN	70
b	H	Me	$SiMe_3$	CO_2Et	PhCl	53[c]
c	H	C_5H_{11}	CO_2Me	CO_2Me	PhBr	51
d	H	Pr^i	CO_2Me	CO_2Me	PhCl	59
e	Me	Me	CO_2Me	CO_2Me	PhCl	71
e	Me	Me	H	CO_2Et	PhCl	80[d]

[a] Formed as a 1:1 mixture with the other regioisomer, ethyl 1-phenylsulphonylindole-5-carboxylate. [b] Formed as a 2.5:1 mixture with the other regioisomer, ethyl 1-phenylsulphonyl-6-trimethylsilylindole-5-carboxylate. [c] Only one regioisomer detected by high field NMR spectroscopy. [d] Formed as a 1:1 mixture with the other regioisomer, ethyl 4,7-dimethyl-1-phenylsulphonylindole-5-carboxylate.

formylation of the ester (**3a**), using dichloromethyl methyl ether in the presence of tin(IV) chloride, which gave a 1:1 mixture of the 2- and 5-formyl derivatives, followed by hydrolysis, and cyclodehydration of the required 2-formylpyrrol-3-ylacetic acid derivative.



(3) (4)

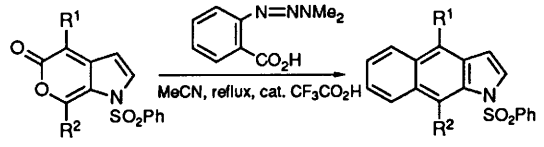


a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = Me$
c; $R^1 = H$, $R^2 = C_5H_{11}$
d; $R^1 = H$, $R^2 = Pr^i$
e; $R^1 = Me$, $R^2 = Me$
f; $R^1 = Et$, $R^2 = Me$

Scheme. *Reagents and conditions:* i, LiOH, aq. THF; ii, LICA, THF, −78 °C, then R^1I; iii, $(R^2CO)_2O$, $BF_3.Et_2O$. [(**4a**) prepared differently—see text.]

On heating with the electron-deficient alkyne, dimethyl acetylenedicarboxylate, the pyranopyrrolones (**4**) underwent Diels–Alder reaction to give, after loss of carbon dioxide, the indoles (**5**) (Table 1). As expected, the unsymmetrical acetylene, ethyl propiolate, was not regiospecific in its Diels–Alder reactions and gave inseparable mixtures of indole-5- and 6-esters. Ethyl 3-trimethylsilylpropynoate, however, underwent regioselective Diels–Alder reaction and gave the 5-trimethylsilyl indole-6-ester as the major product. The pyranopyrrolones (**4**) also reacted with benzyne, generated from 2-(3,3-dimethyltriazen-1-yl)benzoic acid, to give benz[*f*]indoles (**6**) in good yield (Table 2), and with the acetylene equivalent, phenyl vinyl sulphoxide, to give the 5,6-unsubstituted indoles (**7**) (Table 3). The *N*-phenylsulphonyl group, which appears to stabilise the pyrrole dienes (**4**), could be removed from the product indoles by alkaline hydrolysis or by reaction with lithium aluminium hydride. Alternatively the group could be left in place to facilitate further transformations of the indole ring such as 2-lithiation.

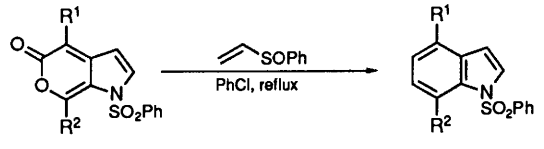
Table 2. Diels–Alder reactions of 1-phenylsulphonylpyrano[3,4-*b*]-pyrrol-5(1*H*)-ones (4) with benzyne.



(4) (6)

Compd. (4)	R^1	R^2	Compd. (6)	Yield (%)
a	H	H	**a**	49
b	H	Me	**b**	65
c	H	C_5H_{11}	**c**	77
e	Me	Me	**d**	60

Table 3. Diels–Alder reactions of 1-phenylsulphonylpyrano[3,4-*b*]-pyrrol-5(1*H*)-ones (4) with phenyl vinyl sulphoxide.



(4) (7)

Compd. (4)	R^1	R^2	Compd. (7)	Yield (%)
b	H	Me	**a**	60
c	H	C_5H_{11}	**b**	44
d	H	Pr^i	**c**	20
f	Et	Me	**d**	60

Pyrroles have been converted into indoles before, for example by intramolecular Friedel–Crafts reaction,[7] but the present Diels–Alder route is novel. The versatility of the cycloaddition approach should ensure that the route will enjoy wide applicability and constitute a useful new route to substituted indoles.

Experimental

Representative examples of preparations are given below.

7-Methyl-1-phenylsulphonylpyrano[3,4-b]*pyrrol-5*(1H)-one (**4b**).—Boron trifluoride–diethyl ether (0.2 ml) was added dropwise to a stirred, ice-cooled mixture of 1-phenylsulphonylpyrrol-3-ylacetic acid (**3c**) (360 mg, 1.35 mmol) and acetic anhydride (0.5 ml) in ether (3 ml). The mixture was stirred at room temperature for 6 h, diluted with ether, and filtered. The solid was washed with ether, aqueous sodium hydrogencarbonate, and water, and dried under vacuum to give the *title compound* (**4b**) (168 mg, 43%), m.p. 157–162 °C (Found: C, 58.1; H, 3.8; N, 4.8. $C_{14}H_{11}NO_4S$ requires C, 58.1; H, 3.8; N, 4.8%); ν_{max}(Nujol) 1 704 cm^{-1}; δ(270 MHz; $(CD_3)_2CO$) 7.84 (2 H, d, *J* 7 Hz), 7.79 (1 H, d, *J* 3.9 Hz), 7.72 (1 H, t, *J* 7.5 Hz), 7.62 (2 H, t, *J* 7.5 Hz), 6.50 (1 H, d, *J* 3.7 Hz), 5.83 (1 H, s), and 2.66 (3 H, s); *m/z* 289 (M^+, 18%), 148 (100), 77 (30), and 43 (39).

Dimethyl 7-Methyl-1-phenylsulphonylindole-5,6-dicarboxylate.—A mixture of the pyranopyrrolone (**4b**) (16 mg, 0.055 mmol), and dimethyl acetylenedicarboxylate (15 mg, 0.11 mmol) in acetonitrile (2 ml) was heated under reflux for 15 h. The solvent was evaporated and the residue chromatographed (silica gel, ether–light petroleum) to give the *title compound* (15 mg, 70%), m.p. 108–112 °C (Found: C, 58.8; H, 4.4; N, 3.5. $C_{19}H_{17}NO_6S$ requires C, 58.9; H, 4.4; N, 3.6%); ν_{max}(Nujol) 1 729, 1 278, and 1 188 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.11 (1 H, s), 7.92 (1 H, d, *J* 3.4 Hz), 7.66 (2 H, d, *J* 8 Hz), 7.57 (1 H, t, *J* 7.5 Hz), 7.47 (2 H, t, *J* 7.5 Hz), 6.76 (1 H, d, *J* 3.4 Hz), 3.92 (3 H, s), 3.88 (3 H, s), and 2.49 (3 H, s); *m/z* 387 (M^+, 34%), 356 (14), and 77 (100).

9-Methyl-1-phenylsulphonylbenz[f]*indole* (**6b**).—A mixture of the pyranopyrrolone (**4b**) (58 mg, 0.2 mmol), 2-(3,3-dimethyltriazen-1-yl)benzoic acid (116 mg, 0.6 mmol), and trifluoroacetic acid (1 drop) in acetonitrile (10 ml) was heated under reflux for 5 h. The solvent was evaporated and the residue chromatographed (silica gel, ether–light petroleum) to give the *title compound* (**6b**) (42 mg, 65%) (Found: C, 71.1; H, 4.7; N, 4.3. $C_{19}H_{15}NO_2S$ requires C, 71.0; H, 4.7; N, 4.4%); ν_{max}(film) 3 070, 1 583, 1 447, 1 364, 1 186, and 726 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.16 (1 H, d, *J* 8 Hz), 7.84 (1 H, d, *J* 8 Hz), 7.73 (1 H, s), 7.66 (1 H, d, *J* 3.9 Hz), 7.57–7.40 (5 H, m), 7.31–7.25 (2 H, m), 6.71 (1 H, d, *J* 3.9 Hz), and 3.05 (3 H, s); *m/z* 321 (M^+, 18%) and 180 (100).

7-Methyl-1-phenylsulphonylindole (**7a**).—A mixture of the pyranopyrrolone (**4b**) (90 mg, 0.31 mmol) and phenyl vinyl sulphoxide (142 mg, 0.93 mmol) in chlorobenzene (5 ml) was heated under reflux for 48 h. The solvent was evaporated and the residue chromatographed (silica gel, ether–light petroleum) to give the *title compound* (**7a**) (51 mg, 60%) (Found: C, 66.4; H, 4.9; N, 5.0. $C_{15}H_{13}NO_2S$ requires C, 66.4; H, 4.8; N, 5.2%), ν_{max}($CHCl_3$) 1 586, 1 446, 1 364, and 1 166 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.79 (1 H, d, *J* 3.8 Hz), 7.68–7.64 (2 H, m), 7.54–7.51 (1 H, m), 7.46–7.38 (3 H, m), 7.12 (1 H, t, *J* 7.8 Hz), 7.01 (1 H, d, *J* 6.8 Hz), 6.70 (1 H, d, *J* 3.7 Hz), and 2.52 (3 H, s); *m/z* 271 (M^+, 32%), 130 (100), and 77 (39).

Acknowledgements

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