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SYNTHESIS OF 4-ACYLINDOLES VIA 2-(2-PHENYLSULFINYLVINYL)PYRROLE.[1]

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SUMMARY: 4-Acylindoles are readily obtained by the [4π + 2π] cycloaddition of 1-triisopropylsilyl-trans-2-(2-phenylsulfinylvinyl)-pyrrole with electron deficient acetylenes followed by N-desilylation of the cycloadducts with fluoride ion.

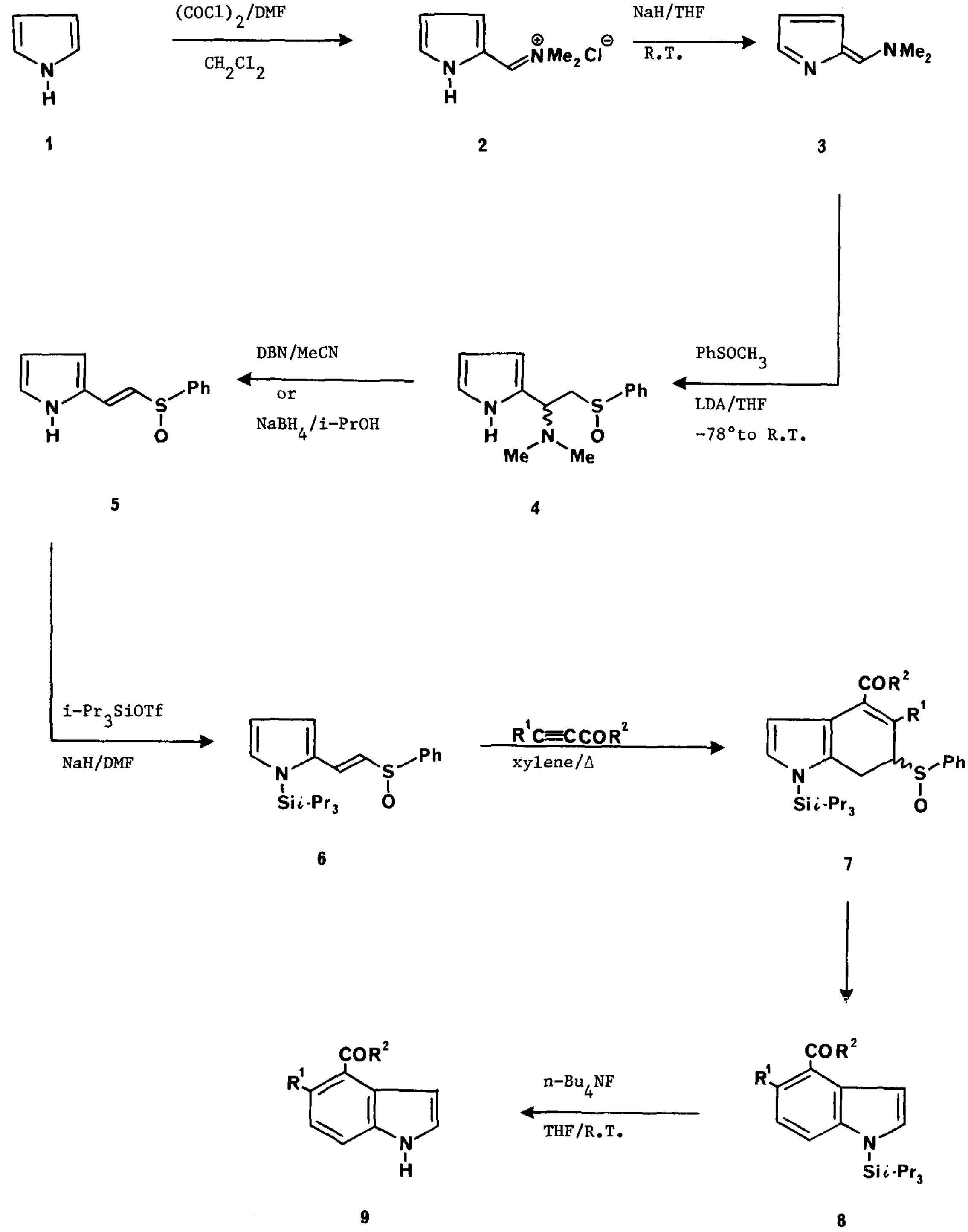
Indoles substituted at C-4 are of considerable interest as starting materials for the synthesis of a variety of important natural products and medicinal agents. In the past, access to such indoles was usually gained via the Reissert[3] synthesis, but this has now been largely supplanted by that due to Leimgruber and Batcho[4]. The [4π + 2π] cycloaddition of 2-vinylpyrroles with electron deficient acetylenes, followed by dehydrogenation of the dihydroindoles formed thereby is, in principle, an attractive route to 4-substituted indoles. In practice, however, it is limited to N-substituted-2-vinylpyrroles and dimethyl acetylenedicarboxylate; methyl propiolate unexpectedly gives the indole-4,7-dicarboxylate[5]. This publication shows that the Diels-Alder reaction of 2-vinylpyrroles with π-electron poor acetylenes is, in fact, particularly suited to the synthesis of 4-acylindoles when the olefinic terminus of the diene bears a phenylsulfinyl group.

The preparation of the required diene system 6 was based on the notable susceptibility of 1-azafulvenes to nucleophilic addition at C-6.[6] Thus, addition of a THF solution of lithium phenylsulfinyl carbanion to a suspension of 6-dimethylamino-1-azafulvene (3, generated in situ by deprotonation of the Vilsmeier-Haack product 2 with sodium hydride) in the some solvent (-78°C to r.t.), gave a 2:1 mixture of isomeric sulfoxides 4 (mp 128-130 °C) in over 80% yield.[7] The elimination of dimethylamine from 4 was effected, in ca. 95% yield, either with an equimolar amount of DBN in boiling acetonitrile (24 h) or with sodium borohydride (0.5 mol) in 2-propanol at reflux temperature (14 h).[8] In both cases, the sulfoxide 5 [mp 182-184 °C; δ($CDCl_3$) 6.70(d, 1H, J= 15.5 Hz), 7.26(d, 1H, J= 15.5 Hz)] is considered to arise by thermal isomerization of an initially formed 1-azafulvene.[8,9] Reaction of 5 with triisopropylsilyltrifluoromethane sulfonate (NaH/DMF/0 °C) gave the N-protected diene 6 (mp 96-97 °C; 66%). This protection serves to obviate conjugate addition of the starting material and the product to the acetylenic dienophile[11] and to impose a favorable cisoid conformation on the diene system of 6 for the cycloaddition process.[12] When a solution of 6 and dimethyl acetylenedicarboxylate (2 mol) was heated in p-xylene at reflux temperature for 22 h, the oily 4,5-bis-methoxycarbonyl indole derivative 8a was formed directly in 90% yield (see Table). Monitoring of this reaction by tlc showed no evidence of an intermediate, thus the dihydroindole 7 presumably aromatized spontaneously under the reaction conditions. The phenylsulfenic acid formed in this process is, at least in part, trapped by the excess dienophile, as demonstrated by the isolation of dimethyl 2-phenylsulfinyl-2-butenedioate (46%, oil, stereochemistry unknown). Ethyl propiolate and ethyl phenylpropiolate also gave the expected indoles 8b and 8c under the conditions described above (see Table) while propiolic aldehyde (10 equiv.) produced the indole-4-aldehyde derivative 8d [δ 1.15(d, 18H, J = 7.5 Hz), 1.72(sept, 3H, J = 7.5 Hz), 7.30(dd, H-6, J = 7.4 Hz), 7.46(dd, H-3, $J_{2,3}$ = 3.2 Hz, $J_{3,7}$ = 0.8 Hz[13]), 7.48(d, H-2, $J_{2,3}$ = 3.2 Hz), 7.64(dd, H-5, $J_{5,6}$ = 7.3 Hz, $J_{5,7}$ = 0.8 Hz), 7.78 (dt, H-7, $J_{6,7}$ = 7.5 Hz, $J_{5,7}$ = $J_{3,7}$ = 0.8 Hz), 10.26(s, CHO)] even in boiling chloroform. Unactivated dienophiles, such as phenylacetylene, as yet, have not been found to react under any conditions. Desilylation of 8a-d to the 4-acylated indoles 9a-d was effected with tetra-n-butylammonium fluoride[14] in THF at 0 °C (ca. 10 min). The methodology described herein thus constitutes a new and viable route to such compounds and the applicability of this annulation sequence to the synthesis of other aromatic systems is currently being studied.

Table. Synthesis of 4-Substituted Indoles

	Compound				
no.	R^1	R^2	react time	% yield	mp °C
8a	CO_2Me	OMe	22 h	90	oil
8b	H	OEt	24 h	91	oil
8c	Ph	OEt	3 d	22	oil
8d	H	H	20 h	84	oil
9a	CO_2Me	OMe		56	125-128
9b	H	OEt		88	68-70[a]
9c	Ph	OEt		74	205-206[b]
9d	H	H		84	139-140[c]

[a] lit.,[15] mp 70-71 °C. [b] Mp of carboxylic acid obtained by saponification of 9c. [c] Lit.,[16] mp 140-142 °C.


1
(COCl)2/DMF
CH2Cl2
2
NaH/THF
R.T.
3
PhSOCH3
LDA/THF
-78° to R.T.
4
DBN/MeCN
or
NaBH4/i-PrOH
5
i-Pr3SiOTf
NaH/DMF
6
R1C≡CCOR2
xylene/Δ
7
8
n-Bu4NF
THF/R.T.
9

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References and Notes

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2. Syntex Research Post-Doctoral Fellow, 1985-1986.
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