

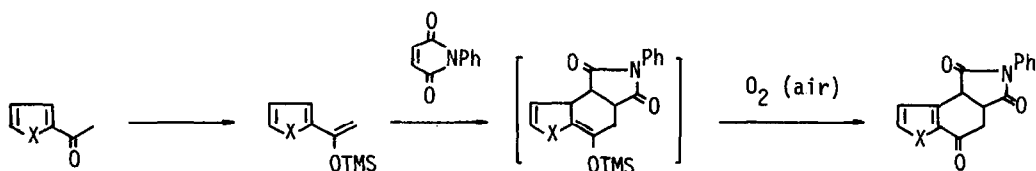
DIVERSE PROCESS IN [4+2]CYCLOADDITION REACTION OF SILYL ENOL ETHERS
OF *N*-SUBSTITUTED 2-ACETILPYRROLES TO AN INDOLE SKELETON

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Summary: The title reaction occurred with the diverse rearomatization process depending on the *N*-substituent: Air oxidation (*N*-ethoxycarbonyl), elimination of PhSO₂ and Me₃Si groups (*N*-phenylsulfonyl), or ene reaction with another dienophile (*N*-methyl).

The utility of a silyl enol ether has expanded enormously in organic synthesis.¹ Cycloaddition reactions, not exceptionally, are advanced by this functionality. Typically, the electron-rich nature has allowed to use it straightforwardly as an electronically favored 4π-component in the Diels-Alder reaction.² Thus, the combination of a silyl enol ether with a variety of unsaturated bonds constructs fruitful diene components.² A unique application lies in a diene system where a silyl enol ether is conjugated with one of the double bonds in an aromatic ring.³ In our previous paper,^{3a} such a cycloaddition reaction was reported for the silyl enol ethers of 2-acetylfuran and -thiophene and their benzo analogs as well as 3-acetylimidole, in which the formal oxidative [4+2]cycloaddition reaction was observed.



X=O,S

TMS=trimethylsilyl

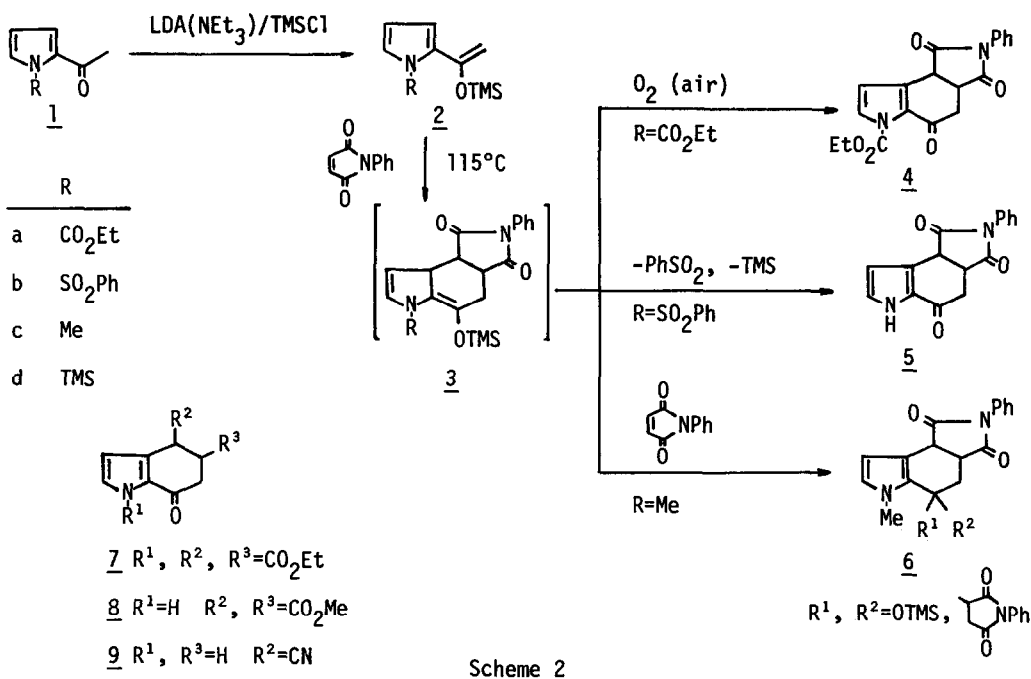
Scheme 1

The above strategy involves a useful method for the formation of polycyclic heteroaromatics. We now wish to report the case of *N*-substituted 2-acetylpyrroles leading to a indole skeleton. Attempted were

N-ethoxycarbonyl, *N*-phenylsulfonyl, *N*-methyl and *N*-trimethylsilyl derivatives 1a-d. These substituents scarcely effected the Diels-Alder reactivity except for 1d, but altered the rearomatization process at the second stage; especially interesting was 2b, which gave a *N*-unsubstituted cycloadduct as a result of deprotection during the reaction through elimination of PhSO₂ and Me₃Si groups.

Starting silyl enol ethers 2a-d were obtained by the standard procedure.⁴ For the [4+2]cycloaddition reaction of the prepared 2a-d, *N*-phenylmaleimide was a reagent of choice as a dienophile, and these reactants in toluene were heated at 115°C in a sealed tube under an atmosphere of argon for an appropriate time (Table). The products were separated by silica gel column chromatography and characterized by spectral inspections. The reaction of *N*-ethoxycarbonyl-substituted 2a occurred in the same manner as shown in Scheme 1; when the reaction mixture was exposed to air, smooth oxidation gave rise to a cycloadduct, 7-oxo-4,5,6,7-tetrahydroindole 4. The similar reaction with diethyl fumarate also afforded 7. This rearomatization process is a remarkable feature in a heteroaryl silyl enol ether,^{2a} compared with that 1,3 hydrogen shift often seen in 2-vinylfuran, -thiophene and -pyrrole.⁵ *N*-Phenylsulfonyl-substituted 2b showed different chemical behavior; the structure of the product obtained was characterized as 5, free from a substituent on the ring nitrogen. This result indicated that the rearomatization, after the cycloaddition reaction, was accomplished by elimination of PhSO₂ and Me₃Si groups,⁶ This novel process seems interesting from a synthetic viewpoint; a *N*-unsubstituted cycloadduct is obtainable without a hydrolytic treatment for deprotection. Similarly, with dimethyl fumarate and acrylonitrile, the expected deprotective [4+2]cycloaddition reaction afforded 8 and 9 albeit in low yields. Noted here is the regioselectivity observed in 9; a cyano group was oriented to be located at C₄.⁷

In contrast to these electron-withdrawing substituents, a methyl-substituent effected the rearomatization process in the other way; 2c reacted with *N*-phenylmaleimide to give a 1:2 adduct 6, as a result of the ene reaction of the primary cycloadduct 3 with another molecule of the dienophile. Silylated 2d did not react at all under the same conditions. This might be attributed to a steric effect; a model study suggested that the bulkiness of a trimethylsilyl group suppressed a requisite cisoid conformation.⁸ To overcome this disadvantage, intramolecular Si-bridging to both an acetyl oxygen and a ring nitrogen was attempted; however, the aimed synthesis from 2-acetylpyrrole and dichlorodimethylsilane failed.



Scheme 2

Table Cycloaddition Reaction of 2

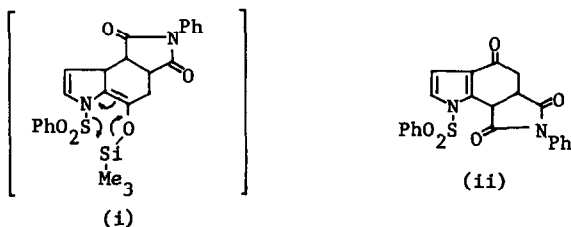
Diene	Dienophile ^a	Time (hr)	Product	Yield (%)	m.p. (°C)
<u>2a</u>	<i>N</i> -Phenylmaleimide	17	<u>4</u>	43	55-58
<u>2b</u>	<i>N</i> -Phenylmaleimide	27	<u>5</u>	49 ^b	222-225
<u>2c</u>	<i>N</i> -Phenylmaleimide	22	<u>6</u>	34	125-129
<u>2a</u>	Diethyl fumarate	45	<u>7</u>	14	oil
<u>2b</u>	Dimethyl fumarate	48	<u>8</u>	17 ^b	159-162
<u>2b</u>	Acrylonitrile	100	<u>9</u>	22 ^b	128-130

(a) 2 eq. for *N*-phenylmaleimide and dialkyl fumarate, and 10 eq. for acrylonitrile.(b) The yield based on 1b.

The structures of the above [4+2]cycloadducts were deduced primarily by mass spectral and elemental analyses, being supported by the ¹H NMR spectra; a characteristic ABX₂ pattern was always observed for C₄-, C₅- and C₆-H, and a simple doublet or double doublet for C₂- and C₃-H at the aromatic region. The appearance of these signals resembled those of furan and thiophene adducts indicated in Scheme 1.^{3a, 9}

References and Notes

- (1) (a) Weber, W. P.: "Silicon Reagents for Organic Synthesis", Springer Verlag, Berlin, 1983. (b) Pawlenko, S.: "Organosilicon Chemistry", Walter de Gruyter, Berlin, 1986.
- (2) Brownbridge, P. Synthesis (1983) 85. See also ref. 1a.
- (3) (a) Sasaki, T.; Ishibashi, Y.; Ohno, M. J. Chem. Research (1984) (S)218, (M) 1972. (b) Kita, Y.; Okunaka, R.; Honda, T.; Shindo, M.; Tamura, O. Tetrahedron Lett. (1989) 30 3995 and ref. cited therein.
- (4) The silylation was achieved according to the reported procedure; for 2a, treatment of 1a with $\text{NEt}_3/\text{TMSCl}/\text{ZnCl}_2$ (cat. amount) in CH_3CN at r.t. overnight and purification by trap-to-trap distillation [110°C (oven temp.)/2 mmHg] gave 2a in 85% yield. [cf. Brownbridge, P.; Chan, T.H. Tetrahedron Lett. (1980) 21 3423.] For 2b-d, treatment of 1b-d with LDA (2 eq.) in THF at -78°C for 3 hr and then with TMSCl (4 eq.) at r.t. for 3 hr and purification by trap-to-trap distillation [2c: 100°C (oven temp.)/2 mmHg, 2d: 120°C (oven temp.)/2 mmHg] gave 2c in 93% yield and 2d in 85% yield; 2b was used without distillation for the next cycloaddition reaction.
- (5) (a) Paul, R. Bull. Soc. Chim. Fr. (1943) 163. (b) Scully, J. F.; Brown, E. W. J. Am. Chem. Soc. (1953) 75 6329. (c) Jones, R. A.; Marriott, M. T. P.; Resental, W. P.; Arques, J. S. J. Org. Chem. (1980) 45 4515.
- (6) The elimination observed might proceed *via* a cyclic transition state (i), followed by consecutive hydrogen shift; because the same reaction using the silyl enol ether of isomeric 1-phenylsulfonyl-3-acetylpyrrole in which the above situation is not allowed, resulted in the formation of phenylsulfonyl group-retained (ii) along the line with air oxidation of 3.



- (7) This fact coincided with the reported regiochemistry of 2-vinylpyrrole^{5c}; possibly, this tendency was enhanced by *para*-directing effect due to a siloxy group.
- (8) Hwu, J. R.; Wang, N. Chem. Rev. (1989) 89 1599.
- (9) All new compounds satisfied microanalytical data. Typical spectral data are as follows:
- 4 IR (CHCl_3) 1720, 1680 cm^{-1} . ^1H NMR (CDCl_3) 1.42 (3 H, t, $J=7.0$ Hz), 2.98 and 3.36 (each 1 H, dd, $J=16.8, 8.4$ Hz and $J=16.8, 3.2$ Hz, respectively), 3.74 (1 H, ddd, $J=8.4, 8.2, 3.2$ Hz), 4.34 (1 H, d, $J=8.2$ Hz), 4.46 (2 H, q, $J=7.0$ Hz), 6.57 and 7.55 (each 1 H, d, $J=3.2$ Hz), 7.21-7.50 (5 H, m).
- MS (relative intensity) 352 (M^+ , 19), 280 (37), 148 (47), 132 (100).