[4+2] CYCLOADDITION REACTION OF *N*-ETHOXYCARBONYL-2-[(1-TRIMETHYLSILOXY)VINYL]PYRROLE WITH ACETYLENIC CARBOXYLATES

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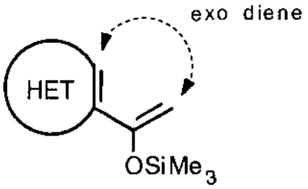
Abstract– The title reaction resulted in the formation of functionalized indoles through rearomatization via ene reaction followed by elimination reaction or via competitive air oxidation reaction. Under an atmosphere of oxygen the latter process predominated to give majorly 7-hydroxy substituted indoles.

Heteroaromatic silyl enol ethers were demonstrated to be useful diene components to access bi- and tricyclic heteroaromatic compounds by means of [4+2] cycloaddition reactions.[1,2] Skeletons such as benzofuran and -thiophene as well as indole and carbazole were constructed starting from acetylfuran, -thiophene, -pyrrole and -indole, in which various rearomatization processes were observed.



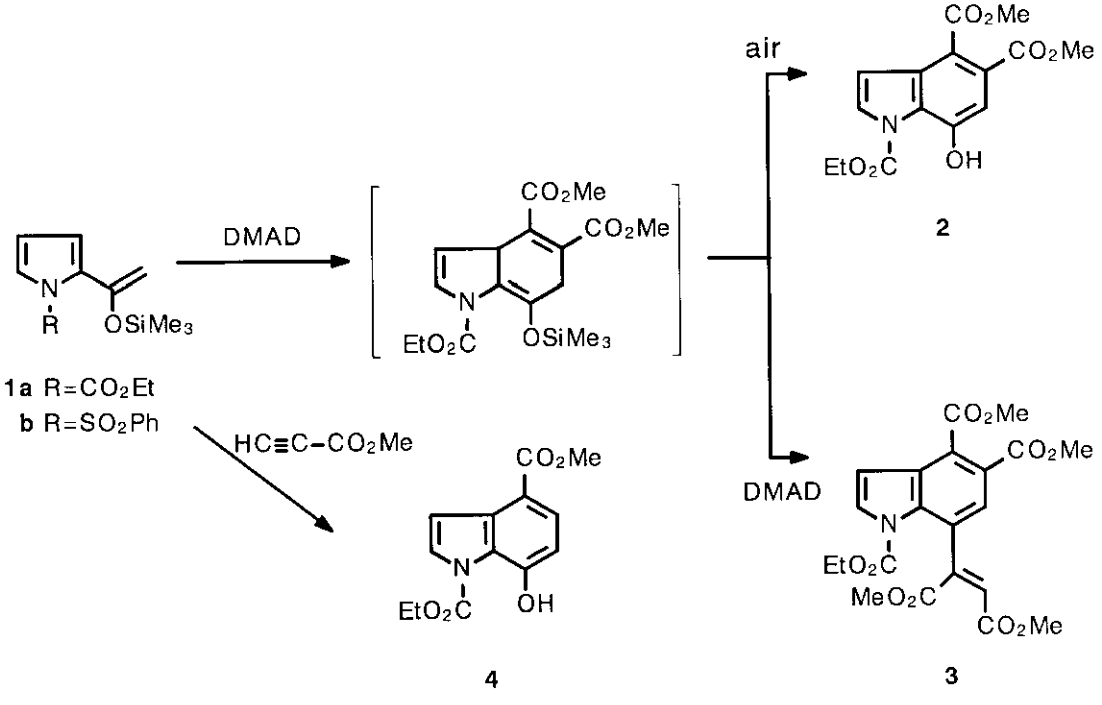
HET: Furan, Thiophene, Pyrrole

and Their Benzo Analogs

These cycloaddition reactions with acetylenic carboxylates[3-7] involved the rearomatization process via ene reaction for the furan and thiophene cases and via air oxidation for the indole case. In the continuous work[8] we wish to report the result of those for the pyrrole case.

Silyl enol ethers (**1a** and **1b**) were prepared by *N*-protection and in turn by silylation with triethylamine/trimethylsilyl chloride/zinc chloride (catalytic amount)/acetonitrile or lithium diisopropylamide/trimethylsilyl chloride, respectively.

The cycloaddition reaction of **1a** was carried out by heating with dimethyl acetylenedicarboxylate (DMAD) in toluene under an atmosphere of argon. The reaction mixture was then exposed to air together with *p*–toluenesulfonic acid. Separation by chromatogrphy gave two types of cycloadducts (4.6:5.4) in 35% yield. The minor cycloadduct was characterized as 7–hydroxyindole–1,4,5–tricarboxylate (**2**) which arised by air oxidation; the mass spectral and elemental analyses primarily supported to be a 1:1 cycloadduct, and the ir spectrum showed the presence of hydroxyl and ester groups. Furthermore, the ^{1}H–nmr spectrum indicated the indole structure by the appearance of aromatic signals at δ 7.00 and 7.62 (*d*, C_2– and C_3–H) and 7.15 (*s*, C_6–H). The major cycloadduct was characterized as the 7–vinylindole (**3**), 1:2 cycloadduct. This was resulted from rearomatization via ene reaction of the primary cycloadduct with another DMAD followed by elimination of trimethylsilanol. The structure was deduced similarly by spectroscopic analyses; in addition to a peak at m/z 447 (M^+) in the mass spectrum, signals due to four ester methyl groups and a vinylic proton appeared reasonably in the ^{1}H– nmr spectrum.



Interestingly, atmospheric change caused the reversal of the ratio of **2**/**3** (7.2:2.8); when the reaction was carried out without a solvent under an atmosphere of oxygen, the enhancement in the oxidative process lead to the predominant formation of **2**.

With this result in hand, the reaction with methyl propiolate was performed in the same manner, and the regiospecific cycloadduct, 7-hydroxyindole-1,4-dicarboxylate (**4**), was obtained in 17% yield; ^{1}H-nmr spectrum clearly indicated that a methoxycarbonyl group was located at C_5 because of $J_{5,6}$=8.6 Hz.

The similar cycloaddition reaction using *N*-phenylsulfonylpyrrole (**1b**) was attempted. It might afford a *N*-unsubstituted indole derivative if the same deprotective rearomatization as previouly reported[8] was followed. However, the reaction with DMAD formed a highly complex mixture, and isolation of the desired product failed.

In conclusion, the silyl enol ether (**1a**) of 1-ethoxycarbonyl-2-acetylpyrrole cycloadded to DMAD including both rearomatization processes via ene and air oxidation reactions, in which the latter became preferential under an atmosphere of oxygen. In any event the present reaction provides a simple method for preparing functionalized indole derivatives.

EXPERIMENTAL

Melting points were uncorrected. Ir spectra were recorded on a JASCO A-100. ^{1}H-Nmr spectra were determined at 200 MHz with Varian GEMINI-200 and mass spectra at 70eV with ESCO EDM-058. Chromatographic separations were carried out on silica gel column (Fuji-Davison BW-300) eluted with the solvent noted.

Synthesis of Silyl Enol Ether 1a. This was prepared according to ref. 8. Spectral data are as follows: Ir ($CHCl_3$) 3120, 2970, 1750, 1625, 1250, 850 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 0.11 (9 H, s, $SiCH_3$), 1.36 (3 H, t, J=7.0 Hz, $COOCH_2C\underline{H}_3$), 4.36 (2 H, q, J=7.0 Hz, $COOC\underline{H}_2CH_3$), 4.42 and 4.52 (each 1 H, d, J=0.8 Hz, $C=CH_2$), 6.08 (1 H, dd, J=3.2, 3.4 Hz, C_4-H), 6.24 (1 H, dd, J=1.8, 3.4 Hz, C_3-H), 7.20 (1 H, dd, J=1.8, 3.2 Hz, C_5-H).

Cycloaddition Reaction of 1a with DMAD. A solution of **1a** (127 mg, 0.5 mmol) and DMAD (142 mg, 1 mmol) in dry toluene (2 ml) was heated in a rubber-sealed glass cylinder at 115°C for 37 h under an atmosphere of argon. After evaporation of the solvent, the residue was dissolved in ether (2 ml) including *p*-toluenesulfonic acid monohydrate (95 mg, 0.5 mmol), and the solution was stirred overnight at room temperature, while being exposed to air. The mixture was poured into water, and the products were extracted with ether and dried over sodium sulfate. After evaporation of the solvent, the resulting residue was chromatograhed with hexane/ethyl acetate (v/v 3/1) to give the cycloadduct (**2**) (22 mg, 16%); mp 95-100°C; ir ($CHCl_3$) 3150, 2990, 2955, 1720, 1710, 1585, 1435 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.49 (3 H, t, J=7.0 Hz, $COOCH_2C\underline{H}_3$), 3.92 and 3.93 (each 3 H, s, $COOCH_3$), 4.55 (2 H, q, J=7.0 Hz, $COOC\underline{H}_2CH_3$), 7.00 and 7.62 (each 1 H, d, J=4.0 Hz, C_2- and C_3-H), 7.15 (1 H, s, C_6-H), 11.16 (1 H, s, OH); ms, m/z (relative intensity)

321(M^+, 100), 290(33), 246(27), 218(87), 166(33), 138(40). Anal. Calcd for $C_{15}H_{15}NO_7$: C, 56.08; H, 4.71; N, 4.36. Found: C, 55.95; H, 5.00; N, 4.36.

Successive elution with the same solvent gave the other cycloadduct (**3**) (35 mg, 19%) as a pasty oil: Ir ($CHCl_3$) 3000, 2965, 1730, 1640, 1580, 1440 cm^{-1}; ^1H-nmr ($CDCl_3$) δ 1.39 (3 H, t, J=7.2 Hz, $COOCH_2C\underline{H}_3$), 3.70, 3.89, 3.93 and 4.01 (each 3 H, s, $COOCH_3$), 4.46 (2 H, q, J=7.2 Hz, $COOC\underline{H}_2CH_3$), 6.36 (1 H, s, C=CH), 6.78 and 7.77 (each 1 H, d, J=3.8 Hz, C_2– and C_3–H), 7.79 (1 H, s, C_6–H); ms, m/z (relative intensity) 447(M^+, 95), 416(24), 375(19), 358(18), 344(86), 328(19), 312(57), 284(100). Anal. Calcd for $C_{21}H_{21}NO_{10}$: C, 56.38; H, 4.73; N, 3.13. Found: C, 56.27; H, 4.73; N, 3.13.

Under the same conditions except for heating for 2.5 h without a solvent under an atmosphere of oxygen, **2** and **3** were obtained in 28% and 11% yield, respectively.

Cycloaddition Reaction of 1a with Methyl Propiolate. A mixture of **1a** (117 mg, 0.5 mmol) and methyl propiolate (84 mg, 1 mmol) was heated at 90°C for 16 h under an atmosphere of oxygen. The same work up as above and chromatography [hexane/ethyl acetate (v/v 4/1)] gave the cycloadduct (4) (22mg, 17%): mp 94–95°C; ir ($CHCl_3$) 3360, 1705, 1600, 1440 cm^{-1}; ^1H-nmr ($CDCl_3$) δ 1.49 (3 H, t, J=7.2 Hz, $COOCH_2C\underline{H}_3$), 3.93 (3 H, s, $COOCH_3$), 4.54 (2 H, q, J=7.2 Hz, $COOC\underline{H}_2CH_3$), 6.87 and 7.94 (each 1 H, d, J=8.6 Hz, C_5– and C_6–H), 7.42 and 7.62 (each 1 H, d, J=3.8 Hz, C_2 and C_3–H), 11.32 (1 H, s, OH); ms, m/z (relative intensity) 263(M^+, 96), 232(35), 204(46), 191(51), 160(100). Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.20; H, 5.02; N, 5.31.

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