Cyclodimerization of indol-2-ylacetylenes. An example of intermolecular enyne–alkyne cycloaddition

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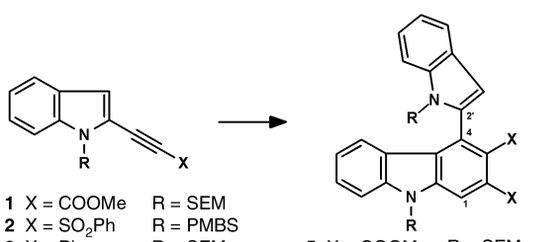
Received (in Cambridge, UK) 29th September 2000, Accepted 14th November 2000
First published as an Advance Article on the web 14th December 2000

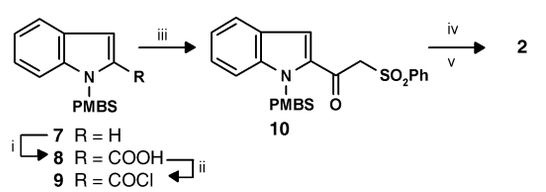
Cyclodimerization of methyl 3-(indol-2-yl)propiolate **1** and 2-(indol-2-yl)-1-(phenylsulfonyl)acetylene **2** proceeds through an enyne–alkyne cycloaddition to give 4-(indol-2-yl)carbazoles.

The enediynes and the enyne–allene cyclizations are receiving great attention because of their involvement as key steps in the activation of some natural antibiotics[1] and show promise as methods for the synthesis of polycyclic systems.[2] Recently intramolecular [4 + 2]π cyclization of 1-en-3-ynes with alkynes has been reported,[3] and it provided a useful tool for the ready construction of polycyclic aromatics. A small number of intermolecular cycloadditions of enynes with alkynes has been described in the review literature.[4]

Here we describe a cyclodimerization of indol-2-ylacetylenes that could be considered an example of an enyne–alkyne [4 + 2]π cyclization. We discovered this type of reaction when we studied the reactivity in Diels–Alder cycloaddition reactions of methyl indol-2-ylpropiolate.[5] In the reaction of **1** (SEM is



trimethylsilylethoxymethyl) with different dienophiles none of the expected products were detected but only a compound whose molecular weight induced us to take a dimeric structure into account. The ^{1}H NMR spectrum suggested a structure incorporating two indole systems. The ^{1}H–^{1}H COSY permitted us to assign the signals at δ 7.70 (d), 7.65 (d), 7.31 (t), 7.22 (t) and 6.63 (s) to the 2-substituted indole moiety. The correlation of the signals at δ 8.32 (s), 7.57 (d), 7.43 (t), 6.98 (t) and 6.80 (d) confirmed not only the presence of a 2,3-disubstituted indole but also of a carbazole portion. The presence of the signal at δ 8.32 (s) indicated the 2,3,4-trisubstituted carbazole structure. A complete spectroscopic analysis confirmed the structure **5** as deriving from the homocycloaddition of methyl indolylpropiolate that reacts as enyne and alkyne at the same time. The formation of the product was observed when the reaction temperature was raised to 100 °C and the starting material was completely undetectable after 12 h. Then we prepared 2-(indol-2-yl)-1-(phenylsulfonyl)acetylene **2** (PMBS is *p*-methoxyphenylsulfonyl) where the electron-withdrawing sulfone group was expected to improve the cyclodimerization rate, by activation of the dienophile, providing a common and easily removable functional group for further transformations. Compound **2** was obtained by a conventional procedure based on the *in situ* elimination reaction of enol phosphate derived from a β-oxo sulfone (Scheme 1). The acyl chloride **9**[9] was converted into



Scheme 1 *Reagents and conditions*: i: BuLi, −78 °C, CO_2 (Ref. 6); ii: $SOCl_2$, 40 °C; iii: $C_6H_5SO_2CHLi_2$, −30 °C; iv: NaH, $(EtO)_2POCl$, rt; v: *t*-BuOK, −78 °C.

β-oxo sulfone **10** by reaction with the dianion of methyl phenyl sulfone[7] at −30 °C. Reaction of **10** with NaH in THF followed by addition of diethyl chlorophosphate,[8] gave the corresponding enol phosphate.[9] The *in situ* addition of a solution of *t*-BuOK in THF at −78 °C leads to the elimination product, 2-indol-2-yl-1-(phenylsulfonyl)acetylene **2** in 55% yield. Compound **2** spontaneously underwent benzoannulation just in the course of its purification affording the binary compound **6**. Heating compound **2** in toluene at 75 °C for 1 h we obtained **6** in 60% yield after purification. The NMR spectra of **6** appeared complex but the spin systems of indole and carbazole were easily detected.

To clarify the influence of the nature of the group present on the acetylenic portion, compounds **3** and **4** were prepared.[5] Compounds **3** and **4** did not give any cyclization products by heating in toluene at 100 °C for 60 h. We deduced that the presence of an electron-withdrawing group is necessary to obtain products deriving from *homo*-benzoannulation.

We have described a particular behaviour of indolylacetylenes **1** and **2** bearing an electron-withdrawing group. By cyclodimerization they produce 4-indolylcarbazoles **5** and **6** and even if they appear as byproducts, their formation represents one of the few interesting examples of enyne–alkyne intermolecular cycloaddition. Moreover the development of new methods for the synthesis of functionalized carbazoles is currently attracting chemists due to the discovery of many carbazole alkaloids with varied biological activity.[10]

Experimental[5]

N-(2-Trimethylsilylethoxymethyl)-2,3-dimethoxycarbonyl-4-[*N*-(2-trimethylsilylethoxymethyl)indol-2-yl]carbazole (5)

A mixture of **1** (100 mg, 0.3 mmol) and toluene (10 ml) were heated at 100 °C for 12 h. After removal of the solvent and

DOI: 10.1039/b009154p

purification by chromatography (AcOEt–hexane 1:5) compound **5** was isolated (65 mg, 65%). Oil. R_f 0.2 (AcOEt–hexane 1:5). ^{1}H-NMR ($CDCl_3$) δ 8.32 (1H, s), 7.70 (1H, d, J = 7.5 Hz), 7.65 (1H, d, J = 7.5 Hz), 7.57 (1H, d, J = 7.5 Hz), 7.43 (1H, t, J = 7.5 Hz), 7.31 (1H, t, J = 7.5 Hz), 7.22 (1H, t, J = 7.5 Hz), 6.98 (1H, t, J = 7.5 Hz), 6.80 (1H, d, J = 7.5 Hz), 6.63 (1H, s), 5.84 (2H, s), 5.25 (2H, s), 4.00 (3H, s), 3.64 (3H, s), 3.60 (2H, t, J = 7 Hz), 3.15 (2H, t, J = 7 Hz), 0.92 (2H, t, J = 7 Hz), 0.45 (2H, t, J = 7 Hz), 0.00 (9H, s), −0.30 (9H, s). ^{13}C-NMR ($CDCl_3$) δ 169.1 (CO), 166.5 (CO), 142.4 (C), 139.5 (C), 137.6 (C), 134.6 (C), 129.5(C) , 128.4 (C), 127.9 (CH), 126.5 (C), 125.2 (C), 124.9 (C), 123.0 (CH), 122.4 (CH), 122.0 (C), 121.7 (CH), 121.0 (CH), 120.4 (CH), 112.1 (CH), 111.0 (CH), 109.5 (CH), 104.4 (CH), 74.1 (CH_2), 72.6 (CH_2), 66.5 (CH_2), 66.0 (CH_2), 52.7 (CH_3), 52.4 (CH_3), 17.8 (CH_2), 17.6 (CH_2), −1.4 ($3CH_3$), −1.7 ($3CH_3$). FABMS: 659 (M + 1). Anal. calcd for $C_{36}H_{46}N_2O_6Si_2$: C 65.62, H 7.08, N 4.25. Found: C 65.74, H 7.23, N 4.33%.

N-(*p*-Methoxyphenylsulfonyl)-2,3-bis(phenylsulfonyl)-4-[*N*-(*p*-methoxyphenylsulfonyl)indol-2-yl]carbazole (6)

A mixture of **2** (100 mg, 0.22 mmol) and toluene (10 ml) were heated at 75 °C for 1 h. After removal of the solvent and purification by chromatography (AcOEt–hexane 3:2) compound **6** was isolated (60 mg, 60%). Oil. R_f 0.3 (hexane–AcOEt 2:3). ^{1}H-NMR ($CDCl_3$) δ 9.80 (1H, s), 8.30 (1H, d, J = 7.5 Hz), 8.10 (1H, d, J = 7.5 Hz), 8.00–7.91 (3H, m), 7.98 (1H, d, J = 7.5 Hz), 7.68 (2H, d, J = 7 Hz), 7.60–7.51 (4H, m), 7.46–7.30 (4H, m), 7.22 (2H, d, J = 7 Hz), 7.10 (2H, d, J = 8 Hz), 6.92 (2H, d, J = 8 Hz), 6.62 (1H, t, J = 7.5 Hz), 6.26 (1H, s), 6.19 (2H, d, J = 8 Hz), 5.90 (1H, d, J = 7.5 Hz), 3.80 (3H, s), 3.60 (3H, s). ^{13}C-NMR ($CDCl_3$) δ 164.6, 163.4, 143.9, 142.3, 141.0, 140.2, 140.0, 139.6, 138.5, 136.4, 135.9, 132.9, 132.4, 131.5, 130.2, 129.3 (4C), 129.2 (2C), 129.5, 129.0, 128.7 (2C), 128.6, 128.3 (2C), 128.1, 126.6, 125.3, 124.4, 123.9, 123.4, 122.9, 121.5, 120.5, 114.9 (2C), 114.6, 114.2, 113.4 (2C), 111.4, 55.8, 55.4. FABMS: 903 (M + 1). HREIMS calcd. for $C_{46}H_{34}N_2O_{10}S_4$ 902.1096. Found 902.1123.

1-[*N*-(2-Trimethylsilylethoxymethyl)indol-2-yl]-2-phenylacetylene (3)

2-Iodo-*N*-SEMindole (460 mg, 1.2 mmol) was dissolved in CH_3CN (10 ml). CuI (10 mg, 0.053 mmol), $Pd(PPh_3)_4$ (32 mg, 0.028 mmol), phenylacetylene (0.154 ml, 1.4 mmol) and Et_3N (1.5 ml) were added. The solution was stirred for 6 h at 40 °C and for 12 h at room temperature. The mixture was poured into a saturated NaCl solution and extracted with AcOEt. The crude mixture was purified by flash chromatography (CH_2Cl_2–hexane 1:5). Yield: 42%. Oil. ^{1}H-NMR ($CDCl_3$) δ 7.60 (1H, d, J = 7.5 Hz), 7.58–7.54 (2H, m), 7.49 (1H, d, J = 7.5 Hz), 7.42–7.36 (3H, m), 7.28 (1H, t, J = 7.5 Hz), 7.17 (1H , t, J = 7.5 Hz), 6.87 (1H, s), 5.71 (2H, s), 3.61 (2H, t, J = 8 Hz), 0.92 (2H, t, J = 8 Hz), −0.08 (9H, s). ^{13}C-NMR ($CDCl_3$) δ 132.0, 126.2, 123.5, 123.3, 122.7, 118.4 (2C), 117.5, 116.8, 115.8 (3C), 105.3, 103.8, 90.4, 75.8, 68.0, 60.6, 12.7, −1.5 (3C).

3-[*N*-(2-Trimethylsilylethoxymethyl)indol-2-yl]prop-2-ynyl-*N*,*N*-dimethylamine (4)

2-Iodo-*N*-SEMindole (460 mg, 1.2 mmol) was dissolved in CH_3CN (10 ml). CuI (10 mg, 0.053 mmol), $Pd(PPh_3)_4$ (32 mg, 0.028 mmol), 1-dimethylaminoprop-2-yne (0.150 ml, 1.4 mmol) and Et_3N (1.5 ml) were added. The solution was stirred for 6 h at 40 °C and for 12 h at room temperature. The mixture was poured into a saturated NaCl solution and extracted with AcOEt. The crude mixture was purified by flash chromatography (hexane–AcOEt 1:1). Yield: 38%. Oil. ^{1}H-NMR ($CDCl_3$) δ 7.57 (1H, d, J = 7.5 Hz), 7.47 (1H, d, J = 7.5 Hz), 7.28 (1H, t, J = 7.5 Hz), 7.15 (1H, t, J = 7.5 Hz), 6.77 (1H, s), 5.63 (2H, s), 3.60 (2H, s), 3.55 (2H, t, J = 7.5 Hz), 2.43 (6H, s), 0.91 (2H, t, J = 7.5 Hz), −0.05 (9H, s). ^{13}C-NMR (CH, CH_2, CH_3) ($CDCl_3$) δ 123.3, 120.7 (2C), 110.3, 108.7, 73.1, 65.6, 48.6, 44.1 (2C), 17.8, −1.5 (3C).

N-(*p*-Methoxyphenylsulfonyl)indole-2-carboxylic acid (8)

1-(*p*-Methoxyphenylsulfonyl)indole **7** (2 g, 7 mmol) was dissolved in THF (20 ml). The solution was cooled at −78 °C and BuLi (3.62 ml, 9 mmol) was added dropwise. The reaction mixture was maintained at rt for 5 min and then cooled at −78 °C. Solid CO_2 (1.5 eq.) was added. The solution was then allowed to reach room temperature. The mixture was poured into aqueous $NaHCO_3$; the organic phase was separated and the aqueous phase was acidified (HCl 5 M) and extracted with CH_2Cl_2. Amorphous solid. Yield: 62%. ^{1}H-NMR ($CDCl_3$) δ 8.17 (1H, d, J = 8 Hz), 8.02 (2H, AA′ part of AA′BB′ system), 7.60 (1H, d, J = 8 Hz), 7.48 (1H, t, J = 8 Hz), 7.37 (1H, s), 7.31 (1H, t, J = 8 Hz), 6.93 (2H, BB′ part of AA′BB′ system), 3.80 (3H, s). ^{13}C-NMR ($CDCl_3$) δ 163.8, 163.6, 138.7, 131.1, 130.3, 129.8 (2C), 127.9, 127.2, 124.1, 122.6, 118.5, 115.5, 114.1 (2C), 55.6. Anal. calcd. for $C_{16}H_{13}NO_5S$: C 58.00, H 3.96, N 4.23. Found: C 58.19, H 4.01, N 4.31%.

1-[*N*-(*p*-Methoxyphenylsulfonyl)indol-2-yl]-2-(phenylsulfonyl)-ethanone (10)

Carboxylic acid **8** (1.4 g, 4.3 mmol) was dissolved in $SOCl_2$ (2 ml). After 4 hours at 40 °C the excess of $SOCl_2$ was removed under reduced pressure and the product **9** was directly used for the subsequent step. Methyl phenyl sulfone (625 mg, 4 mmol) was dissolved in THF (5 ml). The mixture was cooled to −30 °C and BuLi (3.6 ml, 9 mmol) was added dropwise. After 30 min a solution of **9** (1.28 g, 3.7 mmol) in THF was added. After 1 h the solution was poured into a saturated solution of NH_4Cl and extracted with CH_2Cl_2. The organic phase was washed with brine. The crude β-keto sulfone was purified by flash chromatography (hexane–AcOEt 2:1). Amorphous solid. Yield: 50%. R_f 0.28 (hexane–AcOEt 2:1). IR ($CHCl_3$) ν/cm^{-1} 3040, 1685, 1590. ^{1}H-NMR ($CDCl_3$) δ 8.02 (1H, d, J = 8 Hz), 7.85 (2H, AA′ part of AA′BB′ system), 7.65–7.20 (8H, m), 7.10 (1H, s), 6.75 (2H, BB′ part of AA′BB′ system), 4.80 (2H, s), 3.75 (3H, s). ^{13}C-NMR ($CDCl_3$) δ 181.9, 164.3, 139.1, 133.5, 132.9, 131.5, 131.4, 129.2, 128.9 (3C), 127.5 (3C), 127.2, 124.5, 123.2, 121.5, 116.0, 114.0 (2C), 66.9, 55.7. Anal. calcd. for $C_{23}H_{19}NO_6S_2$: C 58.83, H 4.08, N 2.98. Found: C 58.91, H 4.18, N 3.01%.

1-[*N*-(*p*-Methoxyphenylsulfonyl)indol-2-yl]-2-phenylsulfonylacetylene (2)

NaH (40 mg, 1.1 mmol) was suspended in THF (5 ml). A solution of **10** (400 mg, 0.92 mmol) in THF (10 ml) was added dropwise at rt. After 30 minutes, diethyl chlorophosphate (0.12 ml, 1.1 mmol) was added dropwise. After 4 h the solution was cooled at −78 °C and *t*-BuOK (134 mg, 1.2 mmol) in THF (5 ml) was added slowly. The mixture was poured into aqueous NH_4Cl and extracted with AcOEt. The crude product **2** (228 mg, 55%) was purified by flash chromatography (hexane–AcOEt 1:1). Yellow oil. R_f 0.4 (hexane–AcOEt 1:1). IR ($CHCl_3$) ν/cm^{-1} 3060, 2100, 1590, 1375, 1165; ^{1}H-NMR ($CDCl_3$) δ 8.22 (1H, d, J = 8 Hz), 8.20–7.43 (5H, m), 7.80 (2H, AA′ part of AA′BB′ system), 7.65 (1H, d, J = 8 Hz), 7.50 (1H, t, J = 8 Hz), 7.28 (1H, t, J = 8 Hz), 7.16 (1H, s), 6.85 (2H, BB′ part of AA′BB′ system), 3.80 (3H, s). ^{13}C-NMR ($CDCl_3$) δ 163.4, 139.9, 137.3, 135.9, 134.3, 131.4, 129.3 (2C), 129.9 (2C), 129.0 (2C), 128.0, 127.6, 127.0, 124.3, 122.2, 114.8, 114.6 (2C), 85.1, 65.3, 55.3. HREIMS calcd. for $C_{23}H_{17}NO_5S_2$: 451.0548. Found 451.1165.

Acknowledgements

This work was supported by Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST).

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