New [4 + 2] Cycloadditions of in situ Generated Indolyl Enol Ethers and Their Anions with Dimethyl Acetylenedicarboxylate: A One-Pot Access to 4-Alkoxy-Substituted Carbazoles

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Abstract. The 3-indolyl(methyl) methoxycarbeneium tetrafluoroborates 1a–d were deprotonated with NaH to furnish in situ the highly reactive 3-indolyl enol ethers 2a or their corresponding 3-indolyl enol ether anions 2b. Subsequent trapping of the enol ethers 2 with dimethyl acetylenedicarboxylate gave rise to 4-methoxy-functionalised carbazole derivatives in a HOMO(diene)-LUMO(dienophile)-controlled [4+2] cycloaddition. After variation of the 3-indolyl(alkoxy)carbenium tetrafluoroborates 1, Michael-type adducts and a ring-opened, biaryl product 6 were formed additionally.

Introduction

2- and 3-Vinylindoles have now been established as a synthetically interesting class of compounds for the efficient construction of [6]annulated indoles, carba-zoles, and alkaloids [1–7]. The key reaction involves a \([4 \pi + 2 \pi]\) cycloaddition, the regio- and stereoselectivity of which can, in most cases, be predicted by the frontier-molecular-orbital concept [6]. However, only little information is so far available about the reactions of in situ generated vinylindoles and their trapping reactions with dipheniophiles [8]. In continuation of our investigations on pericyclic 6-electron processes with indole derivatives [9], we now report our new results on the reactivity of some indolyl enol methyl or ethyl ethers and their anions, generated in situ from the readily accessible indolyl(alkoxy)carbenium tetrafluoroborates upon exposure to hydride ion, towards an acetylenic dienophile.

Results and Discussion

The ambient cations 1a–d, readily obtainable from the corresponding indoles and methyl(dimethoxy)carbenium tetrafluoroborates [10][11], were deprotonated by treatment with NaH to generate the 3-indolyl methyl enol ethers of the type 2a. The anions of the type 2b also exist in equilibrium (detected by quenching with \(D_2SO_4\) and subsequent \(^1H\)-NMR spectroscopy) (Scheme 1). The reactive 3-vinylindoles 2a, b underwent HOMO(diene)-LUMO(dienophile)-controlled Diels-Alder reactions with dimethyl acetylenedicarboxylate (Scheme 1), in accordance with the results of AM1 calculations [12] (E(HOMO) from 2a \((R^1, R^2 = H) = -8.1235\) eV; HOMO coefficients (charge): at \(N(1) = -0.3489\) \((-0.21)\), at \(C(2) = 0.3616\) \((-0.05)\), at \(C(3) = 0.4066\) \((-0.12)\), at \(C(1') = -0.1983\) \((0.13)\), at \(C(2') = -0.4396\) \((-0.35)\); E(HOMO) of the respective anion \(=-3.2704\) eV; HOMO coefficients (charge): at \(N(1') = -0.3579\) \((-0.24)\), at \(C(2) = 0.1799\) \((-0.08)\), at \(C(3) = 0.3951\) \((-0.29)\), at \(C(1') = -0.0449\) \((0.20)\), at \(C(2') = -0.4226\) \((-0.47)\). However, some dealkylation of 1 to 3-acetylindole as well as uncontrollable polymerisation reactions diminished the yields of the characterisable products in all cases. Even so, the product spectra obtained so far are of considerable interest.

For example, 1c reacted with dimethyl acetylenedicarboxylate via a [4+2] cycloaddition and \(H_2\) elimination to furnish the carbazole 3 (m.p. 170°; a precursor of 9-methyl-3-demethoxycarbazomycin [5]). Similarly, 1a reacted readily with the same dienophile to furnish the carbazole 4 (m.p. 130–131°; a precursor of 3-demethoxycarbazomycin [5]) together with the \(N\)-substituted carbazole 5 (m.p. 225°). Product 5 is probably the result of an N-Michael-type reaction of the anion of 4 generated in the reaction medium. It is interesting to note that the reaction of 1b with dimethyl acetylenedicarboxylate furnished the tri-ortho-substituted biaryl derivative 6 (m.p. 158°; see Fig. for constitution and preferred conformation in the solid state) as the only characterisable product beside the 3-acetyl-2-methylindole. As a rationalisation for this process, we assume the intermediate formation of the primary Diels-Alder adduct 7a which undergoes equilibration with 7b by a formal 1,3-H shift (Scheme 2). Subsequent ring opening of 7b then gives rise to the more stable biaryl derivative 6; driving force for this reaction is the loss of strain energy and the gain in aromatisation energy, respectively.

The salt 1d reacted with the acetylene reagent to form an inseparable mixture \((\{E/E\} and \{Z/E\}, \text{ratio }1:2)\) of the Michael-type adducts 8 (m.p. 106°). The configura-
In addition, we have investigated the reactivity of 1 towards dimethyl acetylenedicarboxylate. Under the same conditions as mentioned above, the dehydrogenated Diels-Alder product 9 (m.p. 162–163°) and the substitution product 10 (m.p. 134–136°) were obtained.

The constitutions and/or configurations at the alkene groups of all new compounds mentioned (with the exception of 8) were clarified above all by 400-MHz $^1$H,$^1$H-NOE measurements and $^{13}$C-APT techniques. Furthermore, the constitution and preferred conformation in the solid state of compound 6 were unequivocally confirmed by an X-ray crystallographic analysis [13] (see Fig.).

For some preparative details and NMR data, see [14][15]. In summary, the trapping of the in situ generated indolyl alkyl enol ethers of the type 2 by an acetylenic dienophile provides a one-pot procedure for the preparation of a variety of novel, alkoxy-functionalised carbazole derivatives, a tri-ortho-substituted biphenyl de-
Figure. Schakal plot of the molecular structure of 6 in the solid state (space group P1, Z = 3) [13].

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[10] For AM1 calculations, the quantum chemistry programme packet MOPAC 6.0 (QCPE 504) from Software, Bloomington, IN, USA, was used.
[11] Full details of the X-ray crystallographic structure analysis will be provided in a full paper to be submitted to Helv. Chim. Acta.
[12] Typical procedure for the synthesis of compounds 4 and 5: The indolylmethoxycarbanium tetrafluoroborate 1a was prepared in a special apparatus developed in our group (see [16]). Solvents of the highest purity standards were used and all reactions were performed under an Ar atmosphere. A soln. of 4.1 ml of HBF$_4$ (30.0 mmol, 34% HBF$_4$ in Et$_2$O) in 10 ml of CH$_2$Cl$_2$ was added dropwise to a soln. of 4.0 ml (31.3 mmol) of trimethyl orthoacetate in 10 ml of CH$_2$Cl$_2$ at -10°. After cooling to ~70° and stirring, a colourless precipitate of methyl(dimethoxy)carbanium tetrafluoroborate was formed in the reaction vessel [16]. This precipitate was filtered, washed several times with Et$_2$O under Ar, and then dissolved in 10 ml of CH$_2$Cl$_2$ followed by cooling to 0°. A soln. of 7.4 g (20.5 mmol) of indole dissolved in 15 ml of CH$_2$Cl$_2$ was added rapidly with vigorous stirring to the above carbenium salt soln. After 45 min, an orange precipitate of 1a had separated. This precipitate was filtered, washed several times with Et$_2$O under Ar, and then suspended in 30 ml of ethynyleglycol diethyl ether. Dimethyl acetylenedicarboxylate (4.0 ml, 32.7 mmol) was then added, the suspension was cooled to ~10°, and a suspension of 700 mg (29.2 mmol) of NaH in 20 ml of ethynyleglycol dimethyl ether was added dropwise over a period of 30 min. The mixture was stirred for a further 40 min, then allowed to warm to r.t., and filtered. The filtrate was poured onto ice and the aq. layer was extracted three times with Et$_2$O. The combined org. layers were dried (MgSO$_4$) and concentrat- ed under reduced pressure. The products 4 and 5 were separated and purified by flash chromatography (Merck, silica gel60, grain size 0.040-0.063 mm, eluent hexane/AcOEt 3:2). Yield of 4: 0.56 g (11%); yield of 5: 3.2 g (43%). These yields as well as those given in Scheme I and for products 9 and 10 are based on the indole starting material.

[15] Selected $^1$H-NMR data: 4 (400 MHz, CDCl$_3$): 3.95, 3.96 (2H, CO$_2$CH$_3$); 4.12 (s, CH$_3$O); 6.75 (s, H–C(3)); 7.24–7.28 (m, 1 atom. H); 7.41–7.49 (m, 2 atom. H); 8.27 (d, $^2J = 7.8$, H–C(5) or H–C(8)); 9.84 (br. s, NH). 5 (200 MHz, CDCl$_3$): 3.64 (s, CH$_3$O); 3.89, 3.90, 3.92, 4.16 (4s, 4CO$_2$CH$_3$); 6.75 (s, H–C(3)); 7.30–7.42 (m, 3 atm. H, including H–C(3) at 7.36); 7.51 (pseudo-t, $^3J = 7.68$, 1 atm. H); 8.38 (d, $^3J = 7.45$, H–C(5)).