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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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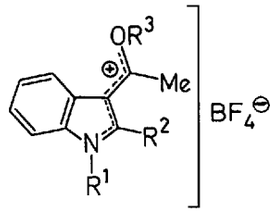
Abstract. The 3-indolyl(methyl)methoxycarbenium tetrafluoroborates **1a–d** were deprotonated with NaH to furnish *in situ* the highly reactive 3-indolyl enol ethers **2a** or their corresponding 3-indolyl enol ether anions **2b**. Subsequent trapping of the enol ethers **2** with dimethyl acetylenedicarboxylate 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.



(*E*)- and (*Z*)-rotamers

1	R^1	R^2	R^3
a	H	H	Me
b	H	Me	Me
c	Me	H	Me
d	Me	Me	Me
e	Me	H	Et

Introduction

2- and 3-Vinylindoles have now been established as a synthetically interesting class of compounds for the efficient construction of [*b*]anellated indoles, carbazoles, and alkaloids [1–7]. The key reaction involves a [4π + 2π] 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 dienophiles [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.

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Results and Discussion

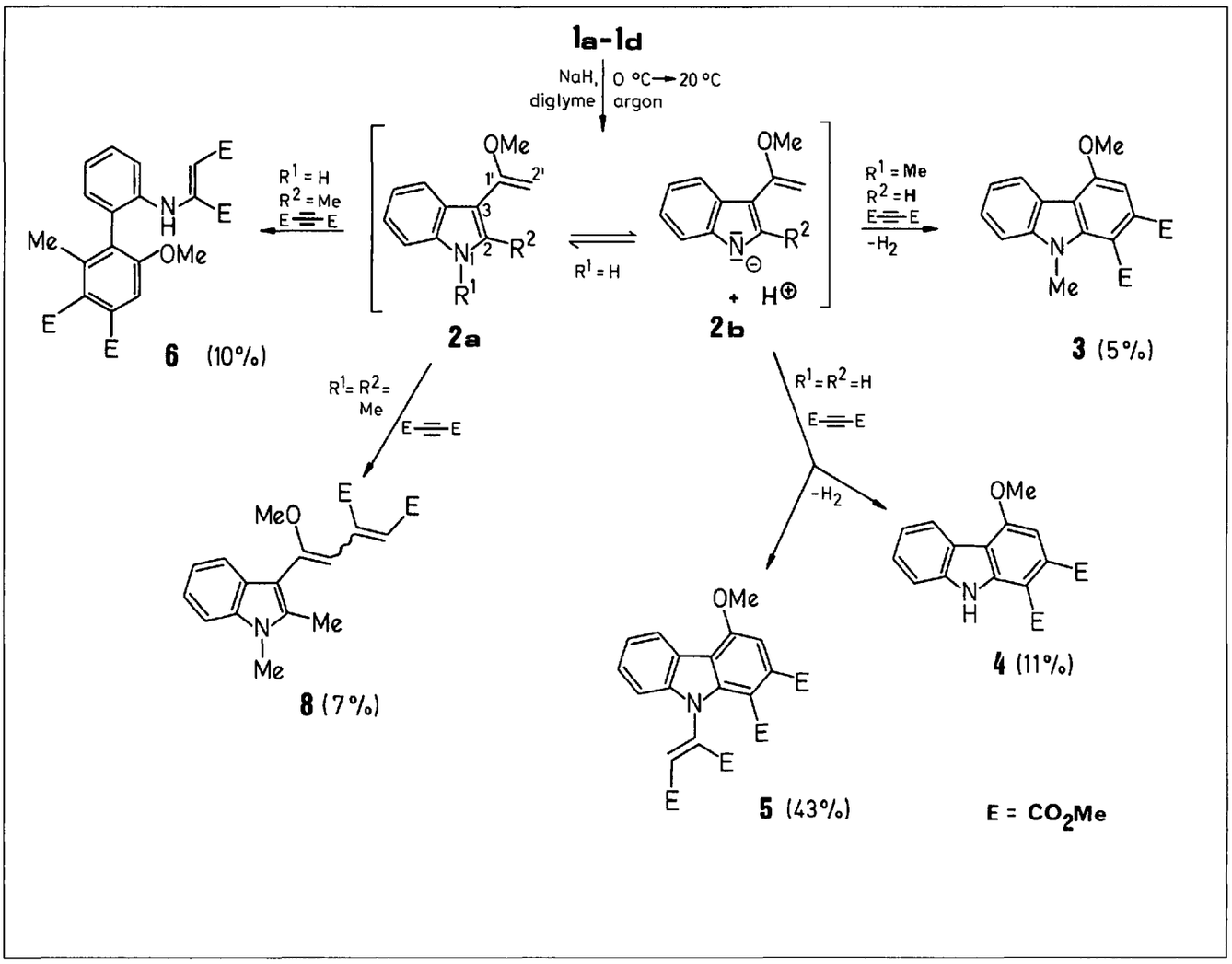
The ambident cations **1a–d**, readily obtainable from the corresponding indoles and methyl(dimethoxy)carbenium tetrafluoroborates [10][11], were deprotonated by treatment with NaH to generate the 3-indolyl methyl enol ethers of the type **2a**. In those cases where R^1 = H, the anion of the type **2b** also exists in equilibrium (detected by quenching with D_2SO_4 and subsequent ^{1}H-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) = 0.4606 (–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) = 0.5951 (–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.

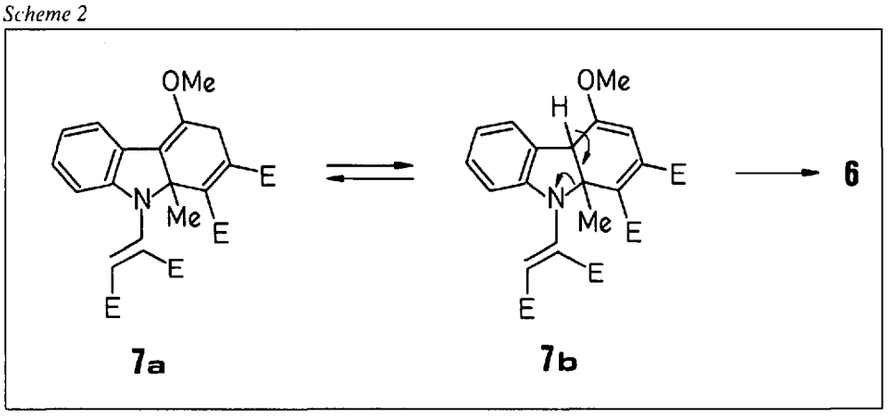
For example, **1c** reacted with dimethyl acetylenedicarboxylate *via* a [4+2] cycloaddition and H_2 elimination to furnish the carbazole **3** (m.p. 170°; a precursor of 9-methyl-3-demethoxycarbazomycin [5]). Similarly, **1a** reacted readily with the same dienophile to furnish the carbazole **4** (m.p. 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,C-*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.

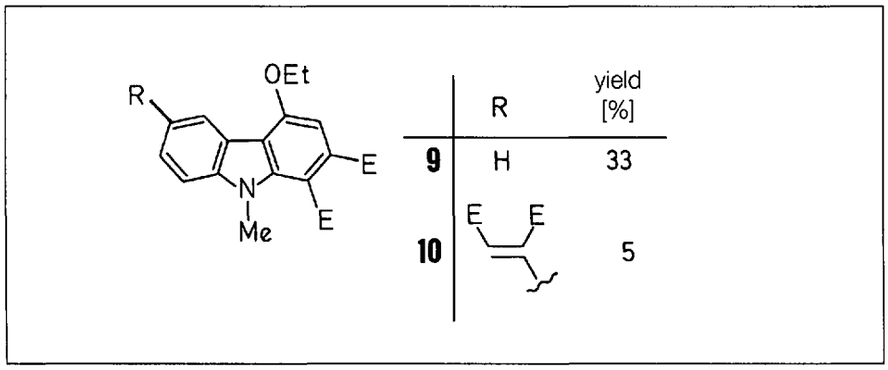
The salt **1d** reacted with the acetylene reagent to form an inseparable mixture ((*E*/*E*) and (*Z*/*E*), ratio 1:2) of the *Michael*-type adducts **8** (m.p. 106°). The configura-

Scheme 1



Scheme 2





tion (*E* or *Z*) of the vinylindole-alkene moiety of **8** has not yet been clarified unambiguously.

In addition, we have investigated the reactivity of **1e** 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-

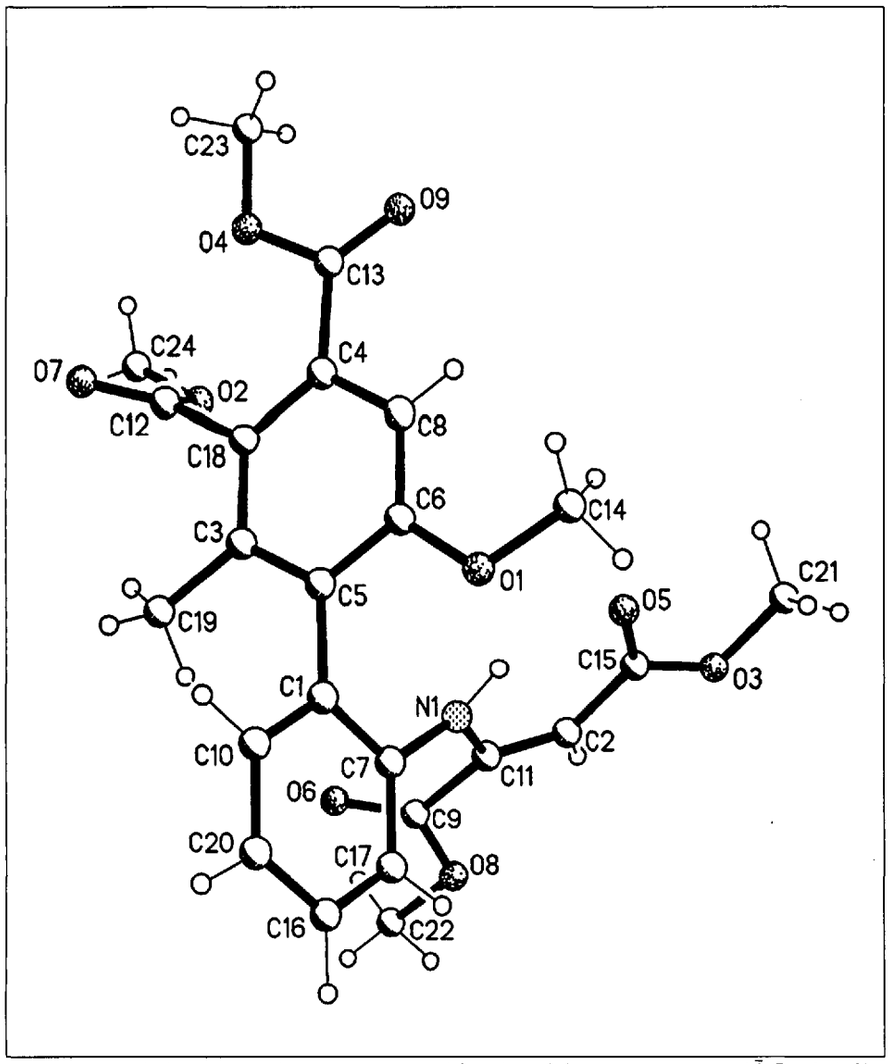


Figure. *Schakal plot of the molecular structure of* **6** *in the solid state* (space group $P\bar{1}$, $Z = 3$) [13]

rivative, and a 3-(butadienyl)indole. The carbazoles **3** and **4** represent potentially interesting building blocks for the synthesis of demethoxycarbazomycins exhibiting antibiotic activity.

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[12] For AM1 calculations, the quantum chemistry programme packet MOPAC 6.0 (QCPE 504) from Serena Software, Bloomington, IN, USA, was used.
[13] Full details of the X-ray crystallographic structure analysis will be provided in a full paper to be submitted to *Helv. Chim. Acta*.
[14] *Typical procedure for the synthesis of compounds* **4** *and* **5**: The indolyl(methoxy)carbenium 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, 54% HBF_4 in Et_2O) in 10 ml of CH_2Cl_2 was added dropwise to a soln. of 4.0 ml (31.3 mmol) of trimethyl orthoacetate in 10 ml of CH_2Cl_2 at −10°. After cooling to −70° and stirring, a colourless precipitate of methyl(dimethoxy)carbenium tetrafluoroborate was formed in the reaction vessel [16]. This precipitate was filtered, washed several times with Et_2O under Ar, and then dissolved in 10 ml of CH_2Cl_2 followed by cooling to 0°. A soln. of 7.4 g (20.5 mmol) of indole dissolved in 15 ml of CH_2Cl_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_2O under Ar, and then suspended in 30 ml of ethyleneglycol 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 ethyleneglycol 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_2O. The combined org. layers were dried ($MgSO_4$) and concentrated under reduced pressure. The products **4** and **5** were separated and purified by flash chromatography (*Merck*, silica gel *60*, 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 1* and for products **9** and **10** are based on the indole starting materials).
[15] *Selected ^{1}H-NMR data:* **4** (400 MHz, $CDCl_3$): 3.95, 3.96 (2*s*, CO_2CH_3); 4.12 (*s*, CH_3O); 6.75 (*s*, H–C(3)); 7.24–7.28 (*m*, 1 arom. H); 7.41–7.49 (*m*, 2 arom. H); 8.27 (*d*, ^3J = 7.8, H–C(5) or H–C(8)); 9.84 (br. *s*, NH). **5** (200 MHz, CD_2Cl_2): 3.64 (*s*, CH_3O); 3.89, 3.90, 3.92, 4.16 (4*s*, 4 CO_2CH_3); 6.75 (*s*, H–C(3')); 7.30–7.42 (*m*, 3 arom. H, including H–C(3) at 7.36); 7.51 (pseudo-*t*, ^3J = 7.68, 1 arom. H); 8.38 (*d*, ^3J = 7.45, H–C(5)).
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