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A New Access to 3-(2′-Aminovinyl)indoles and Their First Diels-Alder Reactions

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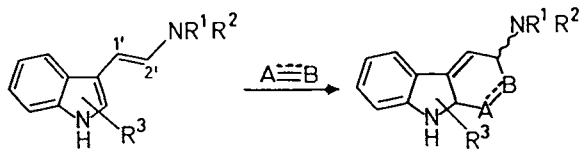
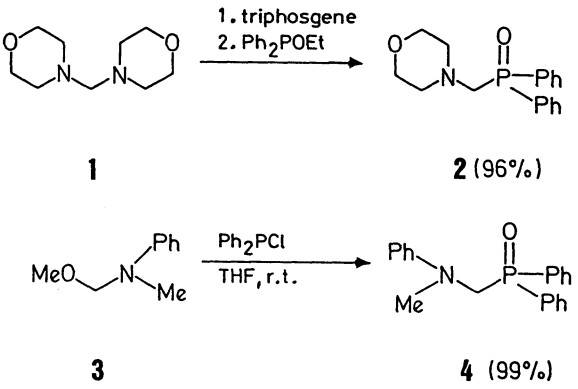
3-Acylindoles react with α-amino-α′-diphenylphosphinoyl-substituted carbanions to 3-(2′-aminovinyl)indoles (**7** and **12**) via carbinols. The electron-rich 3-vinylindoles **7** and **12** undergo Diels-Alder reactions with *N*-phenylmaleimide.

Diels-Alder reactions of 2- and 3-vinylindoles as 4π-electron components are versatile procedures for regio- and stereocontrolled syntheses of [*b*]annelated indoles and/or carbazoles, including alkaloids.[1-5] This concept also facilitates attractive new syntheses of heteroatom-functionalized carbazoles and annelated indoles, i.e. compounds selectively functionalized with alkoxy, alkylthio, or amino groups.[4-6] In this context, 3-(2′-aminovinyl)indoles **A** are of interest[6] since they possess the structural feature (indole-C-C-NR_2) of dehydrotryptamine and some alkaloids of *Aristotelia*.[7] On the other hand, indolylenamines **A** are also useful as building blocks for compounds exhibiting antidepressive and/or antitumor activity as well as indole alkaloids biogenetically derived from L-tryptophan/tryptamine.[7] On reactivity considerations, the two enamine functions in **A** can operate independently, in concert, or in opposition. Exemplarily performed π-SCF-MO and σ/π-charge calculations on (*E*)-3-[2′-(morpholin-4-yl)-vinyl]indole revealed[6] that **A** can, in principle, be involved both in HOMO(diene)-LUMO(dienophile)-controlled [4 + 2] cycloadditions to produce [*b*]annelated indoles **B** (Scheme 1) and in charge-controlled, simple, one-bond formations at C1′ (a Michael-type addition). However, syntheses of **A** from, e.g. indole-3-acetaldehyde and morpholine or pyrrolidine, are laborious. The relatively unstable species thus obtained are difficult to characterize and undergo polymerization rather than Diels-Alder reactions.[6,9]



Scheme 1.

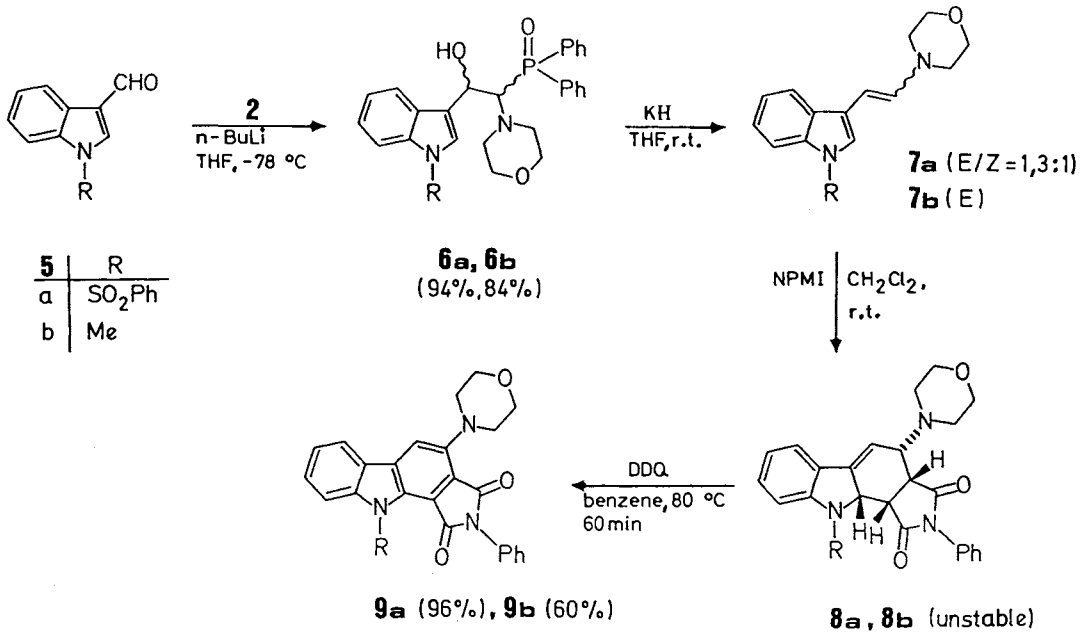
We now report on a new synthesis of three previously unknown 3-(2'-aminovinyl)indoles of type **A** starting from aminal or aminal ether substrates and their enophilic reactivity towards *N*-phenylmaleimide (NPMI). Diphenyl(*N*-morpholinomethyl)phosphine oxide (**2**)[10] was obtained by aminal cleavage[11] of **1** with phosgene (reagent used: triphosgene). Subsequent reaction with ethyl diphenylphosphinite[12] gave **2** (mp 160 °C; Scheme 2) in high yield. Analogously, the aminal ether **3**[13] was converted to **4** (mp 122 °C, 99%) by an Arbuzov reaction with chloro(diphenyl)phosphine.[14]



Scheme 2.

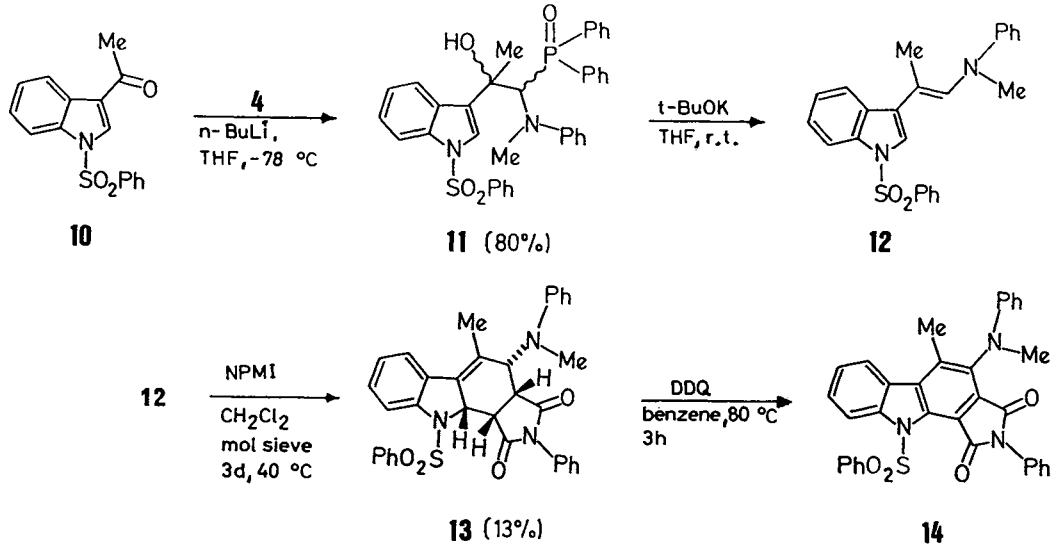
In the key step, a modified Horner-Wadsworth-Emmons reaction (Scheme 3), the indole-3-carbaldehydes **5a,b** each reacted with the *in situ* generated, reactive α-amino-α'-diphenylphosphinoyl carbanion derived from **2** to produce inseparable diastereoisomeric mixtures of the indole-3-carbinols **6a,b** (mp 189 °C). Potassium hydride-catalyzed 1,2-elimination of **6a,b** furnished the *N*-substituted 3-[2-(morpholin-4-yl)vinyl]indoles **7a,b** with a preference for (*E*)-stereoselectivity, but **7a,b** are unstable (like the *N*-unsubstituted indole analog)[6] and undergo rapid oligomerization and polymerization. The ^{1}H-NMR vinylic proton pattern is indicative for the constitution and stereochemistry of **7** [*E*-**7a**: δ = 5.86 and 6.64 ppm (d, J = 14.2 Hz), *Z*-**7a**: δ = 5.29 and 5.94 ppm (d, J = 9.2 Hz); *E*-**7b**: δ = 5.65 and 6.57 ppm (d, J = 14.2 Hz)]. Under nitrogen, however, freshly prepared **7a,b** undergo HOMO(diene)-LUMO(dienophile) controlled, stereoselective Diels-Alder reactions with NPMI to give the "endo"-cycloadduct **8a** (mp 198 °C) and the less stable and difficult to purify **8b**. ^{1}H-NMR configurational analyses of **8** showed retention of the "*E*"-stereochemistry of **7**. 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ)-catalyzed dehydrogenations of **8** gave the 14π-carbazoles **9a,b** (mp 112 °C and 131 °C) in good yields.

Similarly (Scheme 4), the 3-acetylindole **10** reacted with the *in situ* generated carbanion of **4** to furnish diastereomers of **11** (mp 192 °C and 175 °C, 80%). Potassium *t*-butoxide-induced 1,2-elimination stereoselectively furnished the oily *E*-3-vinylindole **12**. The electron-rich **12** exhibits the same instability as **7a,b**. However, freshly prepared **12** also



Scheme 3.

undergoes a Diels-Alder reaction with NPMI to give exclusively the "endo"-cycloadduct **13** (mp 219 °C). As outlined, DDQ-catalyzed dehydrogenation of **13** gave the unstable carbazole **14** (mp 252 °C; characterized by FD-MS).



Scheme 4.

The constitutions of **6**, **9**, **11** and the configurations of **7a,b**, **12**, **13** (**8b** was too unstable) were elucidated by 400 MHz ^{1}H-NMR and, in some cases, by 100.6 MHz ^{13}C-NMR as well as ^{1}H,^{1}H-NOE experiments.[15]

In summary, a new preparation some 3-(2'-aminovinyl)indoles and, above all, the first Diels-Alder reactions of this compound class are presented. The carbazoles **8** and **14** with a coplanar framework (chromophoric group) are of interest as antitumor active intercalators to human B-DNA.[16]

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References

1) U. Pindur, *Chimia*, **44**, 406 (1990); L. Pfeuffer and U. Pindur, *Helv. Chim. Acta*, **70**, 1419 (1987).
2) L. Pfeuffer and U. Pindur, *Helv. Chim. Acta*, **71**, 467 (1988).
3) U. Pindur and M.-H. Kim, *Heterocycles*, **27**, 967 (1988); U. Pindur and M. Eitel, *J. Org. Chem.*, **55**, 5368 (1990).
4) U. Pindur, M. Rogge, and W. Massa, *J. Org. Chem.*, in press; U. Pindur, C. Otto, W. Massa, and M. Molinier, *Helv. Chim. Acta*, **74**, 727 (1991).
5) M. Medio-Simon, C. Otto, and U. Pindur, *Tetrahedron Lett.*, **32**, 1771 (1991).
6) M. Medio-Simon and U. Pindur, *Helv. Chim. Acta*, **74**, 430 (1991).
7) J. E. Saxton, "Indoles, Part Four, The Monoterpenoid Indole Alkaloids," John Wiley & Sons, New York (1983).
8) C. H. Cashin, J. Fairhurst, D. C. Horwell, I. A. Pullar, S. Sutton, G. H. Timms, E. Wildsmith, and F. Wright, *Eur. J. Med. Chem.*, **13**, 495 (1987).
9) M. F. Schlecht and S. Giandinoto, *Heterocycles*, **25**, 485 (1987).
10) N. L. J. M. Broekhof, F. L. Jonkers, and A. van der Gen, *Tetrahedron Lett.*, **1979**, 2433.
11) H. Böhme, L. Koch, and E. Köhler, *Chem. Ber.*, **95**, 1849 (1962).
12) R. Rabinowitz and J. Pellon, *J. Org. Chem.*, **26**, 4623 (1961).
13) N. Azerbaev, Yu. G. Bosyakov, and S. D. Dzhailauov, *J. Gen. Chem. USSR*, **45**, 2349 (1975); cit. from *Chem. Abstr.*, **84**, 59669n (1976).
14) B. A. Arbuzov, *Pure Appl. Chem.*, **9**, 307 (1964).
15) Selected 400 MHz ^{1}H- and 100.6 MHz ^{13}C-NMR data. **8a**: ^{1}H-NMR ($CDCl_3$) δ = 2.4 (m, 2H, CH_2-morpholine), 2.91 (m, 3H, CH_2-morpholine and C4-H), 3.72 (dd, ^{3}J = 8.5 Hz, ^{3}J = 6.2 Hz, 1H, C3a-H), 3.83 (m, 4H, CH_2-morpholine), 4.15 (pseudo-t, ^{3}J = 8.4 Hz, ^{3}J = 7.4 Hz, 1H, C10b-H), 4.74 (dd, ^{3}J = 7.4 Hz, ^{4}J = 1.0 Hz, 1H, C10a-H), 6.19 (dd, ^{3}J = 8.5 Hz, ^{4}J = 1.0 Hz, 1H, C5-H), 6.9-7.9 (m, 14H, aromatic). ^{13}C-NMR ($CDCl_3$) δ = 28.4, 43.8, 52.9 (2 x CH_2), 61.33, 66.70 (2 x CH_2), 115.3, 115.8, 120.9, 124.1, 125.7, 126.4, 127.2, 128.4, 128.8, 129.3, 130.8, 131.6, 133.6, 136.3, 137.6, 144.9, 172.0 (CO), 173.1 (CO). **9a**: ^{1}H-NMR (CD_2Cl_2) δ = 3.37 (m, 4H, CH_2-morpholine), 4.01 (m, 4H, CH_2-morpholine), 7.30-7.60 (m, 10H, aromatic), 7.67 (s, 1H, C5-H), 7.84-7.95 (m, 2H, aromatic). **13**: ^{1}H-NMR (DMSO-d_6) δ = 1.85 (s, 3H, C5-CH_3), 3.07 (s, 3H, NCH_3), 4.00 (m, 1H, C3a-H), 4.18 (pseudo-t, ^{3}J = 8.05 Hz, ^{3}J = 7.2 Hz, 1H, C10b-H), 4.65 (d, ^{3}J = 5.18 Hz, 1H, C4-H), 5.26 (dd, ^{3}J = 7.2 Hz, ^{5}J = 1.9 Hz, 1H, C10a-H), 6.72-7.68 (m, 17H, aromatic), 8.0 (d, ^{3}J = 7.5 Hz, C2/6-H of phenyl-SO_2).
16) M. Sainsbury, "The Chemistry of Antitumor Agents," ed by D. E. V. Wilman, Blacky and Son, Ltd., Glasgow and London (1990), p. 140.

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