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One-pot Conversion of 4-Aryl-3-Butenylazides into Benz[*f*]indoles by a Consecutive Staudinger Reaction / Aza Wittig Reaction / Intramolecular Diels-Alder Cycloaddition Process.

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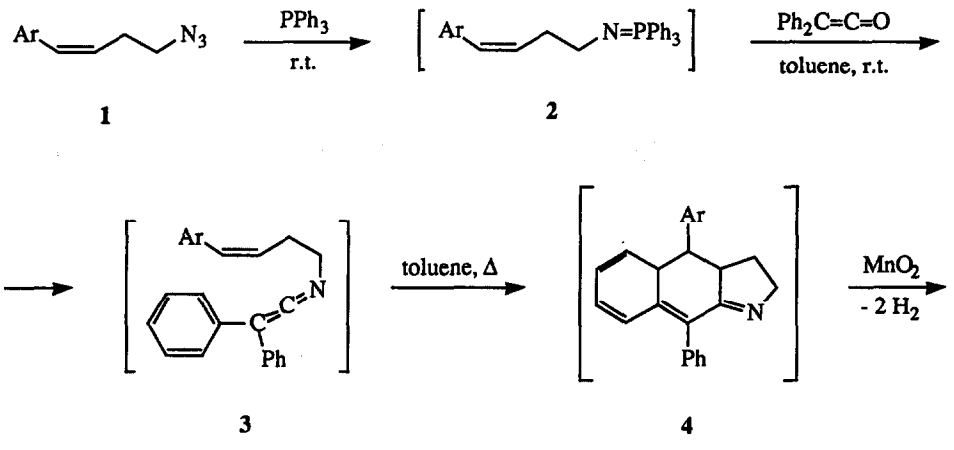
Abstract: *One-pot conversion of azides 1 into benz[f]indoles 5 based on the sequential treatment of azides 1 with triphenylphosphine, diphenyl ketene and further heating in the presence of activated manganese dioxide is reported.*

Although the benz[*f*]indole ring system constitutes the ABC rings of the potent antibiotics kinamycins, and some derivatives occur naturally[1], there are only a few reports dealing with the synthesis of such ring system. Most of the reported synthetic methods for linear benz[*f*]indole derivatives involve the pyrrole ring construction on a naphthalene derivative[2], and only two methods based on the central phenyl ring formation between a phenyl a pyrrole residue have been reported[3]. Recently, this ring system has been prepared by regioselective Diels-Alder reaction between an indole-4,7-dione derivative and 1-methoxy-1,3-cyclohexadiene[4]. However, synthesis of linear benz[*f*]indole derivatives involving the simultaneous formation of the pyrrole and the central phenyl ring has, to our knowledge, not been attempted.

The vinylketenimine variant of the intramolecular Diels-Alder (IMDA) cycloaddition in which the vinylketenimine serves as the diene component of the reaction has been applied to a convergent route of pyridocarbazole alkaloids[5]. In this context, we have reported[6] that ketenimines derived from the aza-Wittig reaction between o-butadienyl phenyliminophosphorane and ketenes undergo IMDA cycloaddition, whereby the arylketenimine moiety has functioned as the diene component using one cumulative carbon-carbon double bond and one carbon-carbon double bond of the aromatic ring.

In this communication, we wish to establish the efficacy of intramolecular cycloaddition of arylketenimines and styrene-like dienophiles that are linked with a flexible alkyl chain containing two carbon atoms. The process has been found to be useful in the simultaneous formation of pyrrole and phenyl rings in the synthesis of benz[*f*]indoles.

The starting azides[7] **1** were synthesized in 64-90% overall yields by the sequence: (a) reaction of triphenylphosphine with excess of 1,3-dibromopropane, (b) subsequent reaction with excess of sodium azide, (c) conversion



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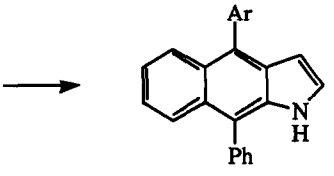

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a Ar= C_6H_5 (50%)

b Ar= 4-H_3CO-C_6H_4 (42%)

c Ar= 4-Cl-C_6H_4 (27%)

d Ar= 4-O_2N-C_6H_4 (45%)

e Ar= Ph-CH=CH (37%)

f Ar= 4-Pyridyl (38%)

g Ar= 3-Thienyl (59%)

Scheme

of the resulting phosphonium salt to the corresponding ylid by the action of potassium bis(trimethylsilyl)amide and (d) Wittig coupling with the appropriate aldehyde[8]. Staudinger reaction of azides **1** with triphenylphosphine in diethyl ether at room temperature for 2 h leads to the corresponding iminophosphoranes **2** (δ C-1= 34.9 ppm, $^2J_{PC}$= 17.12 Hz; δ C-2= 45.8 ppm, $^3J_{PC}$= 5.04 Hz; δ ^{31}P= 11.6 ppm) which were used without purification for the next step. Aza Wittig-type reaction of iminophosphoranes **2** with diphenylketene in toluene at room temperature for a short period of time leads to the corresponding ketenimine **3** which by treatment with activated manganese dioxide in toluene at reflux temperature for 2 h yielded the benz[*f*]indoles **5** in moderate yields[9] (27-59%). However, considering the number of steps involved in this one-pot reaction the yields could be considered as good. Efforts to improve the yield of the tricyclic compound **5** under a variety of conditions were unsuccessful, *e. g.* heating in toluene the intermediate ketenimine **3** led to a complex mixture in which the tricyclic compound **5** could be detected

as a minor component while in boiling nitrobenzene the benz[*f*]indoles **5** were obtained albeit in low yields (25-30%).

In spite of the moderate yields, this experimentally convenient sequence provides direct access to benz[*f*]indoles in one-pot process. In general this conversion proceeded without complications in a range of substrares and the Scheme presents some of the benz[*f*]indoles rendered readily available *via* this methodology.

The conversion **2** → **5** includes a initial formation of a ketenimine **3** (as evidenced by I.R. ν= 2016 cm^{-1}) as highly reactive intermediate which undergoes a [4+2] cycloadditon whereby the arylketenimine portion has functioned as a diene and the carbon-carbon double bond of the styryl portion has taken the role of the dienophile. A final oxidative aromatization of the cycloadduct **4** followed by a [1,3]-proton shift furnishes the benz[*f*]indole **5**.

In conclusion the present study demonstrate that the consecutive Staudinger reaction/aza Wittig reaction/ intramolecular Diels-Alder cycloaddition strategy afford a new entry to benzo[*f*]indoles[10]. Because of its simplicity, easy accessibility of starting materials and straightforward product isolation the investigated reaction provides a method for the preparation of benz[*f*]indoles which is competitive with known approaches to this ring system.

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7. ^{1}H NMR analysis at 300 MHz revealed the Z stereochemistry of the newly formed carbon-carbon double bond manifested itself in $^3J_{HaHb}$ values ranging from 10.6 to 11.7 Hz.
   Compound 1b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61 (dq, 2H, J= 1.83, 7.10 Hz, H-2), 3.35 (t, 2H, J= 7.1 Hz, H-1), 3.80 (s, 3H, CH_3O), 5.53 (dt, 1H, J= 7.1, 11.54 Hz, H-3), 6.49 (d, 1H, J= 11.5 Hz, H-4), 6.87 (d, 2H, J= 8.8 Hz, aromatics), 7.21 (d, 2H, J= 8.8 Hz, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3 (C-2), 51.2 (C-1), 55.3 (CH_3O), 113.7 (C_m), 126.0 (C-3), 129.6 (C_i), 129.9 (C_o), 131.1 (C-4), 158.6 (C_p). m/z (%) 203 (M^+, 12), 115 (100). I.R. ν (film) 2101 (-N_3) cm^{-1}.

Compound 1c: ^{1}H MNR (300 MHz, $CDCl_3$) δ 2.57 (dq, 2H, J=1.7, 6.7 Hz, H-2), 3.62 (t, 2H, J= 6.7 Hz, H-1), 5.66 (dt, 1H, J= 6.7, 11.54 Hz, H-3), 6.51 (d, 1H, J= 11.54 Hz, H-4), 7.18 (d, 2H, J= 8.43 Hz, aromatics), 7.31 (d, 2H, J= 8.43 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3 (C-2), 51.0 (C-1), 128.4 (C-3), 128.5 (C_m), 130.0 (C_o), 130.6 (C-4), 132.8 (C_p), 135.4 (C_i). m/z (%) 209 (M^++2, 6), 207 (M^+, 21), 115 (100). I.R. ν (film) 2098 (-N_3) cm^{-1}.

Compound 1f: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.62 (dq, 2H, J= 1.55, 7.0 Hz, H-2), 3.41 (t, 2H, J= 7.0 Hz, H-1), 5.84 (dt, 1H, J= 7.0, 11.71 Hz, H-3), 6.51 (d, 1H, J= 11.71 Hz, H-4), 7.17 (d, 2H, J= 5.9 Hz), 8.58 (d, 2H, J= 5.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4 (C-2), 50.8 (C-1), 123.3, 129.4 (C-3), 131.7 (C-4), 144.4 (q), 149.9. I.R. ν (film) 2101 (-N_3) cm^{-1}.

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9. **General Procedure**: To a solution of triphenylphosphine (0.72 g, 2 mmol) in dry diethyl ether (10 ml) was added dropwise a solution of the appropriate azide **1** in the same solvent and the reaction mixture was stirred at room temperature untill N_2 evolution was ceased (about 2 h). The solvent was removed under reduced pressure at room temperature and to the crude iminophosphorane **3** were added dry toluene (60 ml) and diphenylketene(0.39 g, 2 mmol). The resultant solution was stirred at room temperature for 5 min and then activated manganese dioxide (1.74 g, 20 mmol) was added. The resultant mixture was stirred at reflux temperature for 2 h. After cooling, the solvent was removed and the filtrate was concentrated to dryness. The crude product was chromatographed on silica gel column, eluting with diethyl ether / n-hexane (1:4) and recrystallized from chloroform / n-hexane (1:1) to afford **5** as brown crystals.

   Compound 5b (42%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3H, CH_3O), 6.47 (dd, 1H, J= 3.5, 1.8 Hz, H-3), 7.94 (s broad, 1H, NH), 7.10-8.00 (m, 14H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4 (CH_3O), 102.1 (C-3), 113.8, 118.9 (q), 122.5, 123.7, 125.0, 126.2, 127.0 (q), 127.8, 128.2, 128.5 (q), 128.6 (q), 129.2, 129.9 (q), 130.8, 131.5 (q), 132.1, 134.6 (C-9a), 137.1 (q), 158.8 (q).

   Compound 5e (37%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.99 (dd, 1H, J= 3.42, 2.2 Hz, H-3), 7.99 (s broad, 1H, NH), 7.01-8.39 (m, 17H, aromatics). ^{13}C NMR (50 MHz, $CDCl_3$) δ 102.4 (C-3), 119.7 (q), 122.9, 123.9, 128.5 (q), 128.6, 128.9, 129.2, 130.9, 135.1 (C-9a), 137.0, 138.2 (q).

   Compound 5g (59%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.53 (dd, 1H, J= 3.1, 1.9 Hz, H-3), 7.16-8.10 (m, 14H, aromatics + NH). ^{13}C NMR (50 MHz, $CDCl_3$) δ 102.2 (C-3), 119.3 (q), 122.7, 123.8, 124.4, 124.9 (q), 125.0 (q), 125.1, 125.2, 126.1, 127.2 (q), 127.8, 128.4, 128.5 (q), 129.2, 130.5, 130.8, 134.6 (C-9a), 137.0 (q), 139.3 (q).

10. Satisfactory ^{1}H, ^{13}C NMR, mass spectra and elemental analyses were obtained for all new compounds.

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