JOC*Note*

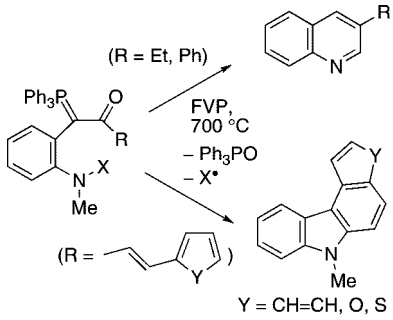
New Gas-Phase Cascade Reactions of Stabilized Phosphorus Ylides Leading to Ring-Fused Indoles and to Quinolines†

R. Alan Aitken* and Lorna Murray

School of Chemistry, University of St. Andrews, North Haugh, St. Andrews, Fife KY16 9ST, U.K.

raa@st-and.ac.uk

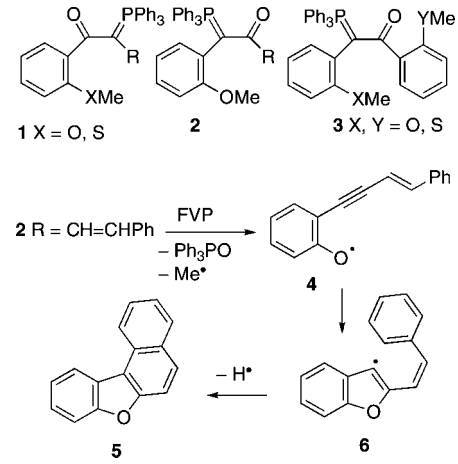
Received August 1, 2008



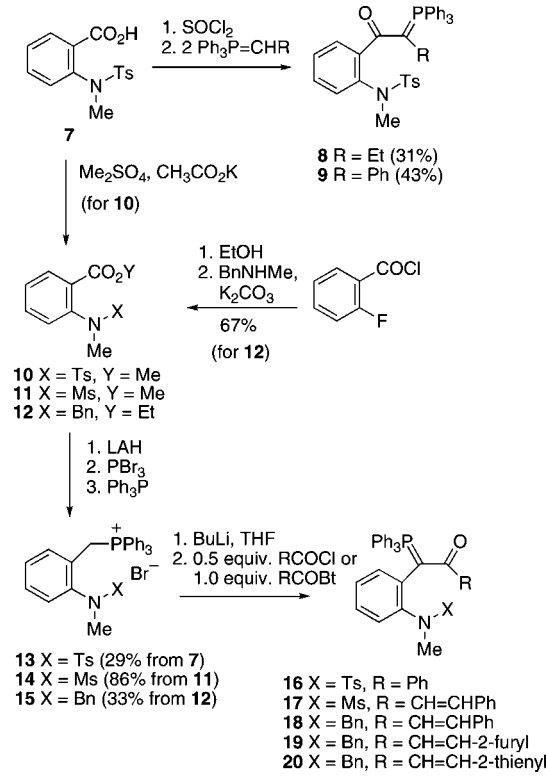
Gas-phase cyclization processes of stabilized phosphorus ylides bearing a suitably substituted 2-aminophenyl group lead efficiently either to 3-substituted quinolines or benzo[*c*]-carbazole and heterocyclic-fused analogues depending on the substituents present.

Cascade processes in which a series of functions are formed and immediately react with one another represent an attractive synthetic approach to complex target structures. In previous work, we showed that, under conditions of flash vacuum pyrolysis (FVP), thermal extrusion of Ph_3PO from ylides such as **1** to give an alkyne could be accompanied by a loss of Me• and cyclization leading to benzofurans and benzothiophenes.[1] The same process was also possible using precursors **2** with ylide and carbonyl functions interchanged,[2] and by choosing suitable R groups, including structures such as **3**, cascade processes leading to a variety of tetracyclic products were developed.[3−5] The key cyclization event in these sequences is illustrated by intermediate **4** derived from **2** (R = CH═CHPh) cyclizing to **6**, which then undergoes homolytic substitution with loss of H• to afford **5** (Scheme 1).[4] In this paper, we describe for the first time the extension of this approach to ylides with a nitrogen-based cyclizing group leading to the biologically and medicinally significant ring-fused indole products.

SCHEME 1



SCHEME 2



As a suitable thermally labile precursor for the required aminyl radical we first chose the *p*-toluenesulfonyl group and prepared the two model compounds **8** and **9** (Scheme 2). Sequential methylation[6] and tosylation[7] of anthranilic acid gave **7**, which was converted into its acid chloride and then reacted with 2 equiv of 1-propylidene- and benzylidenetriphenylphosphorane to give **8** and **9** in acceptable yields.

† This paper is dedicated to the memory of Professor A. I. Meyers.

(1) Aitken, R. A.; Burns, G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2455–2460.
(2) Aitken, R. A. *Arkivoc* **2000**, *v*, 798–805.
(3) Aitken, R. A.; Bradbury, C. K.; Burns, G.; Morrison, J. J. *Synlett* **1995**, 53–54.
(4) Aitken, R. A.; Burns, G.; Morrison, J. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3937–3941.
(5) Aitken, R. A.; Garnett, A. N. *Synlett* **2001**, 228–229.
(6) Houben, J.; Brassert, W. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 3233–3240.
(7) Schroetev, G. *Liebigs Ann. Chem.* **1919**, *418*, 161–257.

10.1021/jo801716z CCC: $40.75 © 2008 American Chemical Society
Published on Web 11/04/2008

TABLE 1. Synthesis of Ylides 16−20

ylide	salt	X	R	route[a]	yield (%)	^{31}P NMR δ
16	**13**	Ts	Ph	A	5	17.4
17	**14**	Ms	CH=CHPh	A	20	16.8
18	**15**	Bn	CH=CHPh	B	74	16.6
19	**15**	Bn	CH=CH-2-furyl	B	53	16.8
20	**15**	Bn	CH=CH-2-thienyl	B	44	16.6

[a] Key: A = 0.5 equiv of RCOCl; B = 1 equiv of RCOBt (Bt = 1-benzotriazolyl).

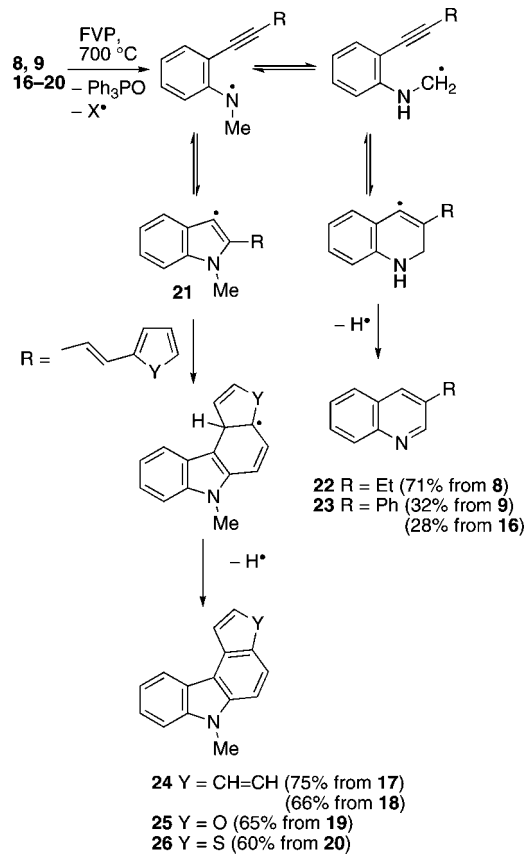
For greater flexibility in the synthesis of ylides with more complex groups, phosphonium salts containing the *o*-aminophenyl group were desirable. Thus, **7** was converted into its methyl ester **10**,[8] and a sequence of LAH reduction, bromination using PBr_3, and treatment of the crude bromide solution with Ph_3P afforded the salt **13** in reasonable overall yield. The corresponding *N*-methanesulfonylphosphonium salt **14** was prepared by a similar sequence of reactions starting from the ester **11**,[9] while the *N*-methyl-*N*-benzyl salt **15** was similarly prepared from the ethyl ester **12**, itself obtained in two steps from 2-fluorobenzoyl chloride.[10]

With the three salts **13**−**15** in hand, a range of ylides **16**−**20** were prepared (Table 1). The standard method for preparation of such acyl ylides involves treatment of the phosphonium salt with BuLi followed by an acid chloride, but this is rather wasteful since a 2:1 reacting ratio is needed and only half the salt ends up in the ylide. While compounds **16** and **17** were formed in low yield from **13** and **14** by this method, an improved method involving acylation with the corresponding *N*-acylbenzotriazoles[11] was used to convert salt **15** into ylides **18**−**20** in improved yield and with a 1:1 reacting ratio. It is of interest to note that the ylides showed broadening of the NMR signals attributable to the PPh groups and even at 55 °C not all signals could be observed as the usual sharp doublets.

The ylides were now subjected to flash vacuum pyrolysis (FVP), and 700 °C was found to be the optimum temperature, bringing about clean extrusion of Ph_3PO and loss of the leaving group X. For ylides **8** and **9**, the nitrogen-containing products were quite unexpectedly found to be the 3-substituted quinolines **22** and **23** which were readily recognized by the distinctive high-frequency doublets due to H-2 and H-4 in the ^{1}H NMR spectra. Thus, **8** gave 3-ethylquinoline **22**[12] (71%) while **9** gave 3-phenylquinoline **23**[13] (32%). The mechanism by which these products are formed seems likely, as shown in Scheme 3, to involve hydrogen atom transfer from CH_3 to N in the aminyl radical and cyclization to give the six-membered ring which then aromatizes with loss of a hydrogen atom. The compound **16**, isomeric with **9**, behaved in the same way giving **23** (28%) upon FVP.

When the ylide **17** with a pendant cinnamoyl group was examined, a complete change in behavior was noted. In this case, the desired cascade cyclization did occur, and the resulting *N*-methylbenzo[*c*]carbazole **24**[14] was obtained in 75% yield. The same pattern was followed for the other ylides **18**−**20** giving, respectively, **24** (66%), *N*-methylfuro[2,3-*c*]carbazole **25** (65%), and *N*-methylthieno[2,3-*c*]carbazole **26** (60%). These latter products are representatives of rather uncommon fused ring systems, but the furo[2,3-*c*]carbazole system is present in the natural product eustifoline D isolated from *Murraya euchrestifolia* Hayata, a shrub found in Taiwan,[15] and a synthesis of this natural product using the present approach is currently in progress.

SCHEME 3



The divergent thermal behavior of the two groups of ylides is apparently due to the reversibility of the various pathways open to the initially formed aminyl radical in the gas phase (Scheme 3).

For simple R groups such as Et or Ph, the intermediate **21** does not have any favorable route to produce a stable product and so the reaction is diverted to the quinoline products. In contrast, the further cyclization of **21** where R is a styryl group or heterocyclic analogue is highly favorable and is followed by irreversible aromatization giving entirely the carbazole products in these cases.

Experimental Section

[1-(2-*N*-Methyl-*N*-*p*-toluenesulfonylamino)benzoyl)benzylidene]-triphenylphosphorane (9). A suspension of benzyltriphenylphosphonium bromide (6.26 g, 16.1 mmol) in THF (50 mL) was stirred under nitrogen while a solution of BuLi (6.44 mL, 2.5 M, 16.1 mmol) in hexanes was added. The resulting brightly colored solution was stirred for 2 h, a solution of 2-(*N*-methyl-*N*-tosylamino)benzoyl chloride (2.60 g, 8.1 mmol) in THF (5 mL) was added, and the

(8) Chernova, N. I.; Ryabokobylko, Yu. S.; Brudz', V. G.; Bolotin, B. M. *Russ. J. Org. Chem. (Engl. Transl.)* **1971**, *7*, 1745–1751.
(9) Lombardino, J. G. *J. Heterocycl. Chem.* **1972**, *9*, 315–317.
(10) Léost, F.; Chantegrel, B.; Deshayes, C. *Tetrahedron* **1997**, *53*, 7557–7576.
(11) Katritzky, A. R.; Meher, N. K.; Singh, S. K. *J. Org. Chem.* **2005**, *70*, 7792–7794.
(12) O'Murchu, C. *Synthesis* **1989**, 880–882.
(13) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Tetrahedron* **1996**, *52*, 10225–10240.
(14) Grellmann, K. H.; Schmitt, U. *J. Am. Chem. Soc.* **1982**, *104*, 6267–6272.
(15) Ito, C.; Furukawa, H. *Chem. Pharm. Bull.* **1990**, *38*, 1548–1550.

mixture was stirred for a further 18 h. Water (50 mL) was added to the solution, and the mixture was extracted using ethyl acetate (2 × 50 mL). The combined extracts were washed with water, dried, and evaporated. The resulting solid was recrystallized (Et_2O/EtOAc) to give the title product (2.23 g, 43%) as pale yellow crystals: mp 213−214 °C; IR (Nujol) 1496 (CO), 1342 (SO_2), 1154 (SO_2) cm^{-1}; ^1H NMR δ 7.87−7.67 (m, 8H), 7.53−7.37 (m, 9H), 7.30 (d, J = 8 Hz, 2H), 7.20 (d, J = 8 Hz, 1H), 7.14 (d, J = 8 Hz, 2H), 6.99−6.88 (m, 2H), 6.87−6.74 (m, 3H), 6.43 (d, J = 8 Hz, 1H), 3.15 (s, 3H), 2.46 (s, 3H); ^{13}C NMR δ 184.2 (d, J = 6 Hz, C), 144.1 (d, J = 12 Hz, C), 142.9 (C), 139.5 (C), 137.4 (d, J = 12 Hz, C), 136.2 (C), 134.6 (d, J = 5 Hz, 2CH), 133.8 (d, J = 10 Hz, 6CH), 131.4 (d, J = 3 Hz, 3CH), 130.7 (CH), 129.3 (2CH), 128.5 (d, J = 12 Hz, 6CH), 128.2 (2CH), 127.6 (CH), 126.9 (3CH), 126.7 (d, J = 91 Hz, 3C), 126.4 (CH), 124.2 (d, J = 2 Hz, CH), 74.0 (d, J = 107 Hz, C), 41.1 (CH_3), 21.6 (CH_3); ^{31}P NMR δ 16.2; HRMS (ESI, M + Na ion) calcd for $C_{40}H_{34}NaNO_3PS$ 662.1895, found 662.1879.

FVP of Ylide 9 Giving 3-Phenylquinoline (23). Ylide **9** (0.690 g, 1.08 mmol) was subjected to FVP at 700 °C and 2−3 × 10^{-2} torr. NMR analysis of crude product showed a mixture of Ph_3PO, toluene, and 3-phenylquinoline. Purification by acid/base extraction gave 3-phenylquinoline (0.0704 g, 32%) as a brown solid: mp 49−50 °C (lit.[16] mp 49−52 °C); ^1H NMR δ 9.19 (d, J = 2 Hz, 1H), 8.32 (d, J = 2 Hz, 1H), 8.15 (d, J = 8 Hz, 1H), 7.90 (d, J = 8 Hz, 1H), 7.73 (d, J = 8 Hz, 2H), 7.63−7.49 (m, 4H), 7.45 (t, J = 8 Hz, 1H) (good agreement with ref 13).

2-(*N*-Benzyl-*N*-methylamino)benzyl Alcohol. Under a nitrogen atmosphere, a solution of **14** (19.92 g, 73.87 mmol) in dry THF (400 mL) was added dropwise to a stirred suspension of LAH (3.09 g, 81.34 mmol) in dry THF (80 mL), and the resulting mixture was stirred at room temperature for 18 h. To destroy the excess of LAH, water (3 mL) in THF (21 mL) was added to the mixture followed by 15% solution sodium hydroxide (3 mL) and finally water (9 mL). The suspension was stirred for 0.5 h, $MgSO_4$ was added, and the mixture was stirred overnight. The mixture was filtered, the solid was washed with ethyl acetate, and the combined filtrate and washings were evaporated to give the title product (14.08 g, 84%) as a yellow oil: ^1H NMR δ 7.33−7.18 (m, 8H), 7.09 (t, J = 8 Hz, 1H), 5.25 (br s, 1H, OH), 4.80 (s, 2H), 4.00 (s, 2H), 2.58 (s, 3H); ^{13}C NMR δ 151.2 (C), 137.4 (C), 135.7 (C), 128.8 (2CH), 128.3 (2CH), 128.3 (CH), 127.9 (CH), 127.2 (CH), 124.5 (CH), 121.2 (CH), 63.8 (CH_2), 61.6 (CH_2), 41.3 (CH_3); HRMS (ESI, M + Na ion) calcd for $C_{15}H_{17}NaNO$ 250.1208, found 250.1213.

2-(*N*-Benzyl-*N*-methylamino)benzyltriphenylphosphonium Bromide (15). A solution of 2-(*N*-benzyl-*N*-methylamino)benzyl alcohol (12.61 g, 55.3 mmol) in toluene (500 mL) was stirred with phosphorus tribromide (12.11 mL, 127.5 mmol) at room temperature for 18 h. The mixture was added to water (200 mL) and stirred for 0.5 h and the organic layer separated, washed with water (2 × 50 mL), and dried. The dried toluene solution was heated under reflux with triphenylphosphine (14.48 g, 55.3 mmol) for 8 h. The precipitate was filtered off, washed with diethyl ether, and oven-dried to give the title product (12.89 g, 39%) as a colorless solid: mp 206−207 °C; ^1H NMR δ 7.80−7.71 (m, 5H), 7.67−7.55 (m, 14H), 7.14−6.94 (m, 5H), 5.35 (br d, J = 15 Hz, 2H), 3.73 (br s, 2H), 2.04 (br s, 3H); ^{13}C NMR δ 153.5 (d, J = 6 Hz, C), 137.2 (C), 134.9 (d, J = 2 Hz, 3CH), 134.2 (d, J = 10 Hz, 6CH), 131.8 (d, J = 5 Hz, CH), 130.1 (d, J = 13 Hz, 6CH), 129.7 (d, J = 3 Hz, CH), 128.9 (2CH), 128.1 (2CH), 127.4 (CH), 125.0 (d, J = 3 Hz, CH), 123.2 (d, J = 8 Hz, C), 122.4 (d, J = 4 Hz, CH), 118.0 (d, J = 85 Hz, 3C), 62.1 (CH_2), 40.6 (CH_3), 25.5 (d, J = 47 Hz, CH_2); ^{31}P NMR δ 23.0. Anal. Calcd for $C_{33}H_{31}NPBr$: C, 71.74; H, 5.66; N, 2.54. Found: C, 71.59; H, 5.63; N, 2.59.

[(2-(*N*-Methyl-*N*-benzylamino)phenyl)(3-(2-furyl)propenoyl)-methylene]triphenylphosphorane (19). A suspension of salt **15** (1.00 g, 1.81 mmol) in THF (10 mL) was stirred under nitrogen while a solution of BuLi (0.80 mL, 2.25 M, 1.81 mmol) in hexanes was added. The resulting brightly colored solution was stirred for 2 h, a solution of 1-(3-(2-furyl)propenoyl)benzotriazole[17] (0.43 g, 1.81 mmol) in THF (5 mL) was added, and the mixture was stirred for a further 18 h. Water (20 mL) was added to the solution, and the mixture was extracted using ethyl acetate (2 × 20 mL). The combined extracts were washed with water, dried, and evaporated. The resulting solid was recrystallized (Et_2O/EtOAc) to give the title product (0.45 g, 53%) as yellow crystals: mp 188−189 °C; IR (Nujol) 1617 (C═C) cm^{-1}; ^1H NMR δ 7.46 (d, J = 8 Hz, 1H), 7.39−7.14 (m, 20H), 7.08−6.97 (m, 4H), 6.91 (d, J = 8 Hz, 1H), 6.41 (d, J = 8 Hz, 1H), 6.27 (dd, J = 6, 3 Hz, 1H), 6.21 (s, 1H), 4.40 (d, J = 14 Hz, 1H), 3.79 (d, J = 14 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR (55 °C) δ 178.8 (d, J = 6 Hz, C), 154.1 (d, J = 4 Hz, C), 153.4 (d, J = 2 Hz, C), 142.5 (CH), 138.5 (d, J = 5 Hz, CH), 136.9 (C), 133.8 (d, J = 10 Hz, 6CH), 132.0 (d, J = 10 Hz, C), 131.2 (d, J = 3 Hz, 3CH), 129.7 (2CH), 128.2 (d, J = 12 Hz, 6CH), 127.7 (2CH), 127.5 (d, J = 3 Hz, CH), 127.0 (d, J = 90 Hz, 3C), 126.8 (CH), 124.9 (d, J = 13 Hz, CH), 122.8 (d, J = 2 Hz, CH), 122.3 (d, J = 2 Hz, CH), 111.5 (CH), 110.8 (CH), 74.9 (d, J = 108 Hz, C), 60.0 (CH_2), 39.5 (CH_3); ^{31}P NMR δ 16.8; HRMS (ESI, M + 1 ion) calcd for $C_{40}H_{35}NO_2P$ 592.2405, found 592.2414.

FVP of Ylide 19 Giving *N*-Methylfuro[2,3-*c*]carbazole (25). Ylide **19** (0.56 g, 0.95 mmol) was subjected to FVP at 700 °C at 2−3 × 10^{-2} torr. NMR analysis of crude product showed a mixture of Ph_3PO, bibenzyl, and other products. The mixture was purified by preparative TLC (80:20 diethyl ether/hexane) to give the title product (0.136 g, 65%): mp 65−67 °C; ^1H NMR δ 8.20 (dt, J = 8, 1 Hz, 1H), 7.82 (dd, J = 2.4, 0.3 Hz, 1H), 7.65 (dd, J = 9, 1 Hz, 1H), 7.48 (dd, J = 6, 1 Hz, 1H), 7.47 (dd, J = 2.7, 1 Hz, 1H), 7.35 (dd, J = 9, 1 Hz, 1H), 7.325 (dd, J = 2.4, 1 Hz, 1H), 7.29 (ddd, J = 8, 6, 2.7 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR δ 150.3 (C), 145.4 (CH), 140.7(C), 137.2(C), 124.9 (CH), 122.3 (C), 121.1 (CH), 120.6 (C), 118.8 (CH), 114.2 (C), 109.3 (CH), 108.7 (CH), 105.37 (CH), 105.32 (CH), 29.5 (CH_3); HRMS (ESI, M + 1 ion) calcd for $C_{15}H_{12}NO$ 222.0919, found 222.0920.

Acknowledgment. We thank EPSRC (UK) for a studentship (L.M.).

Supporting Information Available: Full experimental procedures and characterization data for all compounds and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801716Z

(16) Cadogan, J. I. G. *J. Chem. Soc.* **1962**, 4257–4258.

(17) Katritzky, A. R.; Wang, M.; Zhang, S. *Arkivoc* **2001**, *ix*, 19–23.