Synthesis of Isoquinolines by Intramolecular Aza-Wittig Reaction

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Isoquinolines (**3**) and (**5**) are formed under mild neutral conditions by intramolecular aza-Wittig reactions of iminophosphoranes, readily derived from azides (**1**) and (**4**) with triethyl phosphite; the azafluoranthene (**7**) can also be prepared from the isolable iminophosphoranes (**8**), (**9**), and (**10**).

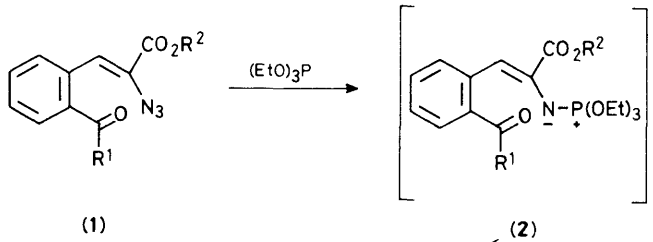
Compounds containing the isoquinoline nucleus are widely distributed in nature, and since the isolation of isoquinoline itself in 1885 considerable effort has been devoted to the synthesis of this bicyclic aromatic system.[1,2] However, the most widely used methods of isoquinoline synthesis involve harsh acid or dehydrating conditions to effect ring closure, and since they usually involve electrophilic attack on a benzene ring, the reaction is greatly facilitated by the presence of electron donating substituents. Indeed, ring closure to systems lacking such substituents often fails. We now report a solution to the problem[3] based on the intramolecular aza-Wittig reaction, which enables ring closure to occur under mild, neutral conditions. Although a few examples of this reaction are known,[4—8] it has not been applied to the synthesis of isoquinolines before.

The substrates for the intramolecular aza-Wittig reaction are azidocinnamates (**1**) containing *ortho*-carbonyl substituents. Azides (**1a**) and (**1b**) were prepared from 2-(1,3-dioxolan-2-yl)- and 2-(2-methyl-1,3-dioxolan-2-yl)-benzaldehyde respectively, by condensation of the aldehyde with methyl azidoacetate followed by acid cleavage of the dioxolane ring. Direct condensation of ethyl azidoacetate with 2-formylbenzophenone[9] and commercially available 2-formylbenzoic acid gave the azides (**1c**) and (**1d**). Esterification of the acid (**1d**) with ethanol containing hydrogen chloride gave the ester (**1e**).

Treatment of the azidocinnamate (**1a**) with triethyl phosphite (TEP) (1.1 equiv.) in benzene at room temperature gave methyl isoquinoline-3-carboxylate (**3a**)[10] (91%) as the sole product after aqueous work-up to remove triethyl phosphate. The ketones (**1b**) and (**1c**) behaved similarly on reaction with TEP, and gave the corresponding isoquinolines (**3b**) and (**3c**) in high yield (Table 1). The intermediate iminophosphoranes (**2**) were not detected, intramolecular attack on the carbonyl group presumably being very rapid. That the intramolecular aza-Wittig reaction is particularly favoured in these systems was further demonstrated by the fact that even less reactive ester and carboxylic acid carbonyls both readily participate. Thus the acid (**1d**) and the ester (**1e**) cyclised on treatment with TEP to give isoquinolone (**3d**)[11] (74%), and the 1-ethoxyisoquinoline (**3e**) (90%) respectively.

The scope of the reaction is not limited to simple bicyclic isoquinolines. The azide (**4**), prepared in four steps from 8-bromo-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-one,[12] gave the tricyclic isoquinoline (**5**) (91%), m.p. 122—123 °C, on treatment with excess of TEP in benzene at room temperature. In this case an orange intermediate, presumably the iminophosphorane, was detected by t.l.c. but was rapidly converted into (**5**) on work-up.

Attempts to extend the reaction to the preparation of the tetracyclic azafluoranthene (**7**) were initially unsuccessful. Reaction of the azide (**6**), prepared from 9-oxofluorene-1-carbaldehyde,[13] with TEP gave the isolable iminophosphorane (**8**) as an orange oil, and with triphenylphosphine gave the analogous ylide (**9**) (99%) as an orange solid, m.p. 206—210 °C. Although the ylides [(**8**) and (**9**)] were recovered after heating in xylene, they were both converted into the desired azafluoranthene (**7**) on melt pyrolysis (300—350 °C) albeit in low yield (12 and 19%, respectively). The yield of (**7**) was improved by the use of 1,2,5-triphenylphosphole in place of TEP or triphenylphosphine. Thus, the iminophosphole (**10**),



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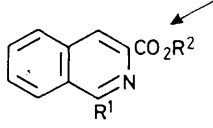

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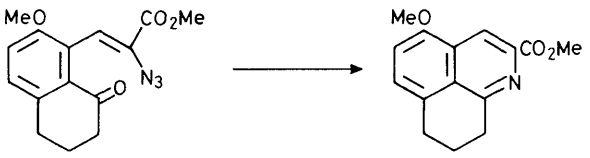
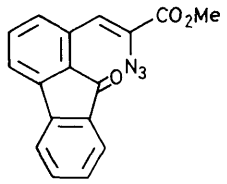


(4) (5)



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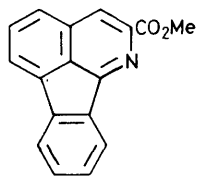

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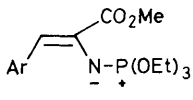
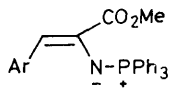
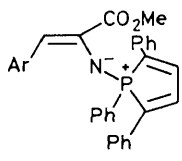


(8)



(9)



(10)

Ar = 9-oxofluoren-1-yl.

Table 1

(1)—(3)	R^1	R^2	Solvent	Temp.	Time (h)	Yield (%)	M.p. (°C)
a	H	Me	Benzene	Room	21	91	88—89[a]
b	Me	Me	Benzene	Room	4.5	93	104—105
c	Ph	Et	Cyclohexane	35 °C	2	94	100—101
d	OH	Et	Tetrahydrofuran	Room	16	74	146.5—148.5[b]
e	OEt	Et	Benzene	50 °C	0.5	90	93—94

[a] Lit.,[10] m.p. 86—88 °C. [b] Exists as the isoquinolone; lit.,[11] m.p. 147—148 °C.

prepared (71%) from the azide (**6**) and 1,2,5-triphenylphosphole, gave the azafluoranthene (**7**) (34%) on melt pyrolysis (300 °C, 2 min). Such iminophospholes from 1,2,5-triphenylphosphole are known to decompose faster than the corresponding iminophosphoranes derived from triphenylphosphine.[14] Clearly intramolecular attack on the carbonyl by iminophosphoranes derived from the azide (**6**) is disfavoured, presumably by the additional steric constraint imposed by the rigid fluorenone system, and therefore the ring closure to the azafluoranthene (**7**) requires more forcing conditions. In contrast, the electronically similar, but more flexible, benzophenone derivative (**1c**) cyclises readily at 35 °C.

Thus, in the absence of severe steric strain, the intramolecular aza-Wittig reaction of iminophosphoranes derived from azidocinnamates bearing *ortho*-carbonyl substituents constitutes a new isoquinoline synthesis in which the ring closure step occurs under exceptionally mild conditions. Although in its present form the method gives isoquinolines bearing an ester at the 3-position, the synthetic versatility of the ester substituent ensures that this is not a serious limitation.

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