The Reactivity of Imide Carbonyl Groups in the Intramolecular Aza-Wittig Reaction. An Efficient Route to Iminolactam Derivatives

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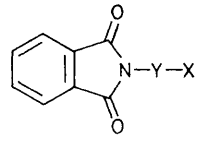
Treatment of *N*-(ω-azidoalkyl)imides with triphenylphosphine in toluene or xylene under reflux gave the corresponding iminolactam derivatives in good yields *via* the Staudinger reaction followed by the intramolecular aza-Wittig reaction.

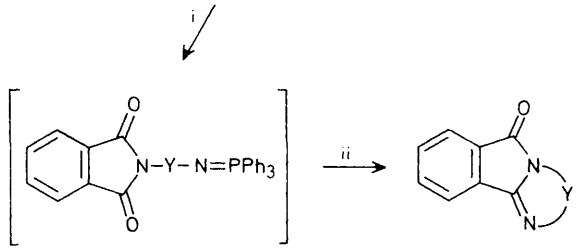
The intramolecular aza-Wittig reaction has attracted considerable attention recently because of its high potential for synthesis of nitrogen heterocycles.[1—3] The ready and clean generation of iminophosphoranes from azides, and their aza-Wittig type reaction with carbonyl groups provides a regiospecific synthesis of imines.[1,2] Several interesting applications of the intramolecular version of the above sequence have appeared recently.[3] However, the reactivity criteria for these aza-Wittig reactions seems so far to be ambiguous compared with the Wittig olefination reactions.[4] Ester carbonyl groups are unreactive generally in intermolecular aza-Wittig reactions but they react in the intramolecular version to afford the corresponding iminocyclisation products, at least for 5-membered ring formation.[5] The intermolecular reaction of phthalic anhydride with iminophosphoranes has been reported recently to afford phthalimides and iminophthalic anhydrides.[6] We report here the reactivity of imide carbonyl groups in the intramolecular aza-Wittig reactions, thus providing an efficient route to iminolactam derivatives.

The starting *N*-(ω-azidoalkyl)imides (**2a—e**) were readily obtained from the corresponding bromides (**1a—e**) by treatment with sodium azide (2.5 fold excess) in a benzene–water two-phase system using a phase-transfer catalyst (Adogen 464 or Aliquat 336) (Table 1).† The reaction of (**2**) with an equimolar amount of triphenylphosphine (TPP) in toluene occurred spontaneously at room temperature (nitrogen gas evolution by the Staudinger reaction) and ceased during 1 h; however, the cyclisation to give the iminolactams (**3**) by the aza-Wittig reaction required heating (Scheme 1). For example, (**3a**)[7] was obtained in 35% yield by heating at 80 °C for 15 h after preparative TLC (silica gel, $CHCl_3$–AcOEt). The yield of (**3a**) increased to 58% on heating at 110 °C for 2 h, and to 93% on heating at 140 °C for 4 h. Azides (**2b—c**) were treated similarly with TPP in toluene, followed by heating to reflux for 2—4 h. Usual work-up and chromatography (silica gel, $CHCl_3$–AcOEt or hexane–AcOEt) afforded the corresponding iminolactams (**3b—e**) in the yields summarised in Table 1. The iminocyclisation depended on the Y moiety of (**2**). For example, (**2c**) having a longer azidoalkyl chain gave only a 22% yield of (**3c**) under the above conditions, while (**2d**) and (**2e**) having *o*-azidomethyl-phenyl and -benzyl groups respectively gave better yields of the cyclisation products (**3d,e**) than the corresponding simple alkyl azides. This could be ascribable to the restricted conformation of the side chain in (**2d,e**), that should be entropically favourable for the cyclisation. The yields of (**3c,e**) improved to 59 and 89%, respectively by reaction in xylene under reflux for 4 h (Table 1).

The above one-pot iminocyclisation of the *N*-azidoalkylphthalimides could be extended to succinimide and glutarimide systems (Scheme 2). The azides (**4a,b**) similarly prepared from the bromides were treated with TPP in xylene at room temperature for 1 h, followed by heating to reflux for 2 h to provide the corresponding iminolactams (**5a,b**), m.p. 151—153 °C and 116—120 °C, respectively, both in 92% yield.



(**1**) X = Br
(**2**) X = N_3



(**3**)

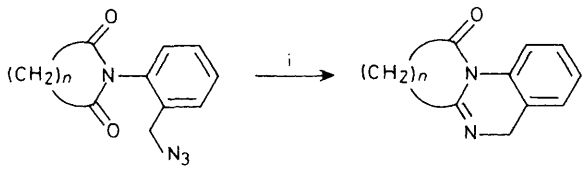
Scheme 1. For Y, see Table 1. *Reagents and conditions*: i, Ph_3P in toluene, room temperature; ii, heat.

Table 1. Yields of azides (**2**) and iminolactams (**3**).

	Y	(**2**), %	(**3**), %	M.p. of (**3**), *t*/°C
a	$-(CH_2)_2-$	65	93	156—157[b]
b	$-(CH_2)_3-$	98	84	77.5—79
c	$-(CH_2)_4-$	98	22(59)[a]	114—116.5
d	$-o-CH_2C_6H_4-$	95	99	182—185.5
e	$-o-CH_2C_6H_4CH_2-$	87	52(89)[a]	188.5—191

[a] In parentheses reaction in xylene under reflux for 4 h. [b] Lit.[7] 139—141 °C.

† All new compounds described here had spectral and microanalytical properties in agreement with the assigned structures.



(**4**) (**5**)

a; $n = 2$
b; $n = 3$

Scheme 2. *Reagents and conditions*: i, Ph_3P in xylene, room temperature, 1 h, heat to reflux, 2 h.

Iminolactams are useful intermediates for further modifications of the nitrogen heterocycles. Simple derivatives of (**3a**) are known as antidepressants.[8]

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