Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 2779–2794

Aza-Wittig reaction of fluoroalkylated *N*-vinylic phosphazenes with carbonyl compounds. Usefulness of 2-azadienes for the preparation of fluoroalkyl pyridine derivatives

Francisco Palacios,* Concepción Alonso, Gloria Rubiales and Maite Villegas

Departamento de Química Orgánica I, Facultad de Farmacia, Universidad del País Vasco, Apartado 450, 01080, Spain

Received 25 November 2004; revised 18 January 2005; accepted 20 January 2005

Abstract—A method for the preparation of 3-fluoroalkyl substituted 2-aza-butadienes **6** by aza-Wittig reaction of 3-fluoroalkyl-*N*-vinylic phosphazenes **4** and aldehydes **5** is reported. [4+2] Cycloaddition reaction of these heterodienes **6** with enamines **9** gives fluoroalkyl substituted pyridine **15**, **16**, **24**–**27** and isoquinoline **12**–**14**, **20** derivatives.

1. Introduction

Functionalized 2-azabutadiene systems have proved to be efficient key intermediates in organic synthesis for the preparation of heterocycles[1,2] although the great majority of 2-azadienes studied are substituted with electron-donating groups and are excellent reagents in normal Diels–Alder reactions with electron-poor dienophiles.[1–3] In this context, we have described new methods for the preparation of heterocycles,[4] as well as for the synthesis of neutral azadienes **I** (Fig. 1)[5] and of electron-poor 2-aza-1,3-butadienes derived from α- and β-amino esters **II** (Fig. 1)[6] and we have also reported their use in the preparation of nitrogen heterocyclic compounds.[4–6]

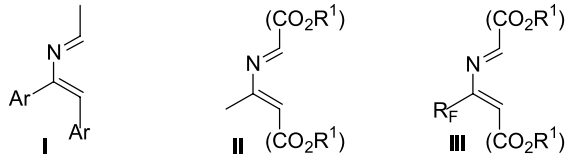


Figure 1.

Moreover, special interest has been focused on developing synthetic methods for the preparation of fluorinated building blocks since they are used for the efficient and/or selective preparation of fluorine-containing molecules with biological activity[7] and commercial applications.[8] Direct fluorination is the simplest way to prepare fluorinated heterocyclic compounds,[9] but usually the use of fluorinated precursors has been of more interest due to the easy formation of the products and to the regioselectivity of the fluorine substituents on the heterocyclic ring.[10] In this context, fluoroalkyl substituted 2-aza-1,3-butadienes **III** ($R_F = CF_3$, C_2F_5, … Fig. 1), despite their potential interest as synthons in organic synthesis for the construction of more complex fluoro-containing acyclic and cyclic compounds, have not received much attention, probably owing to the lack of general methods of synthesis of these compounds. Moreover, the presence of carboxylic groups in position 1 and 4 in compounds **III** (Fig. 1) may open new entries to the formation of heterodienes derived from α- and β-amino-acids. However, as far as we know, there has only been synthesis of 4-alkoxy-1,4-disilyloxy-1-trifluoromethyl-,[11a] 1,1-bis-(trifluoromethyl-),[11b] 4,4-difluoro- and 3-trifluoromethyl-2-aza-1,3-butadienes[11c] and reactions of 4-alkoxy-1,4-disilyloxy-1-trifluoromethyl-2-aza-1,3-butadienes with carbonyl compounds[12a] and 1,1-bis-(trifluoromethyl)-2-aza-1,3-butadiene with bromide, amines, mercaptans,[12b] diazomethane[12c] and phosphines[12d] have been described. As a continuation of our work on the design of new building blocks, we report herein an easy and versatile method for the synthesis of fluoroalkyl substituted 2-azadienes **III** involving aza-Wittig reaction[13] of *N*-vinylic phosphazenes **IV** with aldehydes and the use of these substrates as starting materials for the construction of fluoroalkyl functionalized heterocycles (Fig. 2).[14]

Keywords: *N*-vinylic phosphazenes; Aza-Wittig reaction; 2-Aza-1; 3-butadienes; Fluoroalkyl derivatives; Heterocycles.
* Corresponding author. Tel.: +34 945013103; fax: +34 945013049; e-mail: qoppagaf@vc.ehu.es

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.01.080

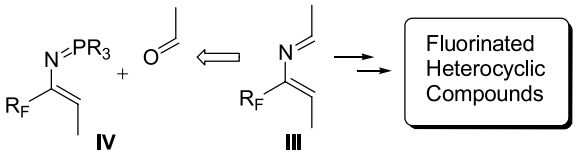
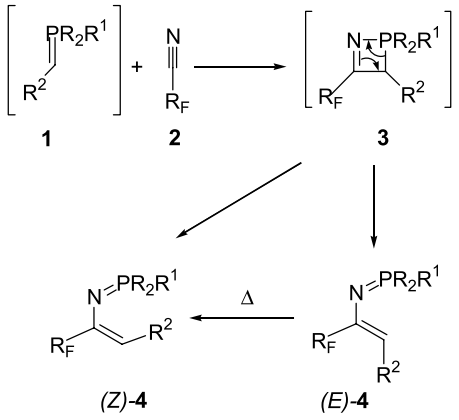


Figure 2.



Scheme 1.

2. Results and discussion

2.1. Synthesis of *N*-vinylic phosphazenes

Fluoroalkyl substituted *N*-vinylic phosphazenes **4** were prepared by reaction of phosphorus ylides and perfluoroalkyl nitriles.[15] Gas nitriles **2a** ($R_F=CF_3$) and **2b** ($R_F=C_2F_5$) were freshly generated[16] and bubbled through a solution of phosphorus ylides **1** (R^2=Ph, CO_2Me, CN),[17] affording the corresponding *N*-vinylic phosphazenes **4a**, **4b**, **4d**, **4e**, **4g**, **4i**, **4l** and **4m** (Scheme 1) in good yields (Table 1, entries 1, 2, 4, 5, 7, 9, 12 and 13). Commercially available nitrile **2c** ($R_F=C_7F_{15}$) was also used for the synthesis of phosphazenes **4c**, **4f**, **4h**, **4j**, **4k**, **4n** (Table 1, entries 3, 6, 8, 10, 11 and 14). Inorganic salts were eliminated by filtration and some phosphazenes were crystallized from ethyl acetate and isolated. However, other phosphazenes were less stable and, for this reason, were used without isolation (Table 1, entries 6–11) from the crude mixtures.

Crystalline compounds **4** were characterized on the basis of their spectroscopic data as *E* or *Z* isomers. Phosphazenes **4a–c** with a phenyl group (R^2=Ph) were exclusively obtained as *E* isomers (Table 1, entries 1–3), while phosphazenes **4d–h** derived from methoxycarbonyl ylides ($R^2=CO_2Me$) afforded phosphazenes whose HOESY ^{19}F–^{1}H experiments showed cross signals between fluorinated groups and vinylic protons, suggesting the formation of *Z* isomers (Table 1, entries 4–8).

However, when ylides containing a cyan substituent were employed (R^2=CN) either only *E* isomers (Table 1, entries 10, 11 and 14) or mixtures of *E* and *Z* isomers (Table 1, entries 9, 12 and 13) with a higher proportion of *E* isomers were obtained. Formation of conjugated phosphazenes **4** can be explained through [2+2] cycloaddition of phosphorus ylides **1** and nitriles **2** followed by ring opening of the unstable four-membered cyclic compounds **3**[5b,18] (Scheme 1). In this context, it is noteworthy that, isomerization of *E* isomer towards *Z* isomer was observed during purification (recrystallization or column chromatography) or thermal treatment.

For instance, spectroscopic analysis confirmed the total thermal isomerization to the new *Z* isomers when only the *E* isomers (phosphazenes **4a–c** and **4n**) as well as mixtures of *E*- and *Z*-isomers (phosphazenes **4i**, **4l** and **4m**) were heated at 110 °C in toluene. For example, ^{1}H NMR monitoring of *E*-phosphazene **4a** upon heating showed a singlet at δ_H 6.23 ppm for the vinylic proton of *Z*-phosphazene **4a**, instead of the doublet corresponding to the *E* precursor (δ_H=5.70 ppm, $^{4}J_{PH}$=3.2 Hz). Configuration of vinylic double bonds was also determined on the basis of heteronuclear HOESY ^{19}F–^{1}H experiments. Similar isomerizations have been observed previously by us[19] and by others.[20]

2.2. Aza-Wittig reaction of fluoroalkyl substituted *N*-vinylic phosphazenes 4 with carbonyl compounds 5

We then turned our attention to the preparation of

Table 1. *N*-Vinylic phosphazenes **4** obtained

Entry	Compound	R	R^1	R^2	R_F	Time (h)	Solvent	Yield (%)	Mp (°C)	*E*/*Z* (%)
1	**4a**	Ph	Ph	Ph	CF_3	12	Et_2O	90[a]	134–135	100:0[b,c]
2	**4b**	Ph	Ph	Ph	C_2F_5	24	Et_2O	81[a]	105–106	100:0[b,c]
3	**4c**	Ph	Ph	Ph	C_7F_{15}	12	Toluene	83[a]	120–121	100:0[c]
4	**4d**	Ph	Ph	CO_2Me	CF_3	12	Et_2O	65[a]	101–102	0:100
5	**4e**	Ph	Ph	CO_2Me	C_2F_5	24	Et_2O	99[a]	93–94	0:100
6	**4f**	Ph	Me	CO_2Me	C_7F_{15}	48	Toluene	—[d]	—	0:100
7	**4g**	Me	Me	CO_2Me	CF_3	12	Et_2O	—[d]	—	0:100
8	**4h**	Me	Me	CO_2Me	C_7F_{15}	12	Et_2O	—[d]	—	0:100
9	**4i**	Ph	Ph	CN	CF_3	24	Et_2O	—[d]	—	60:40[c]
10	**4j**	Ph	Ph	CN	C_7F_{15}	48	Toluene	—[d]	—	100:0
11	**4k**	Ph	Me	CN	C_7F_{15}	48	Toluene	—[d]	—	100:0
12	**4l**	Me	Me	CN	CF_3	12	THF	86[a]	—	80:20[c]
13	**4m**	Me	Me	CN	C_2F_5	12	THF	66[a]	—	75:25[c]
14	**4n**	Me	Me	CN	C_7F_{15}	12	THF	40[a]	98–99	100:0[c]

[a] Yield of isolated compounds.
[b] Isomerization towards *Z* isomer was observed when purification by column chromatography was performed (see Section 4).
[c] Isomerization of *E* isomer towards *Z* isomer was observed when a solution of *E* isomer or the *E*/*Z* mixture was heated at 110 °C in toluene (see Section 4).
[d] Not isolated, used in situ.