An Easy Synthesis of Electron-withdrawing Substituted 2-Aza-1,3-dienes and their 1,4-Cycloaddition with Enamines

José Barluenga*, Miguel Tomás, Alfredo Ballesteros, and Vicente Gotor

Departamento de Química Organometálica, Facultad de Química, Universidad de Oviedo, 33071 Oviedo, Spain

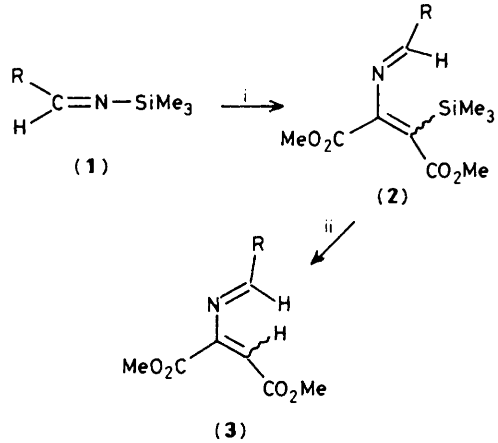
An easy procedure for the synthesis of electron-poor 2-aza-1,3-dienes from silylimines is described; the ability of these azadienes to undergo cycloaddition to electron-rich alkenes is demonstrated for the first time.

The [4 + 2] cycloadditions of aza-1,3-dienes have been much less investigated than those of the corresponding all-carbon systems.[1] It has been reported that electron-donating substituted 2-azadienes react with electron-poor dienophiles to form pyridine derivatives;[2] furthermore, we have developed an easy route to electronically neutral 2-azadienes and have demonstrated their ability to undergo normal [4 + 2] cycloaddition reactions.[3] However, the potential value of 2-azadienes with appended electron-withdrawing substituents remains unexplored, probably owing to the lack of general methods of synthesis of these heteradienes;† the dimerization[5] of the highly reactive 1-biphenylyl-3-methoxycarbonyl-2-aza-1,3-diene prepared from the Schiff's base of serine methyl ester[6] appears to be the sole example of a [4 + 2] cycloaddition of a simple system.

Taking advantage of the fact that the imino nitrogen–silicon bond is capable of adding to the carbon–carbon triple bond of activated acetylenes,[7] we have developed an easy route to the 3,4-bismethoxycarbonyl-2-aza-1,3-dienes (**2**) and (**3**) from the silylimines (**1**), and have studied their cycloaddition to electron-rich dienophiles,‡§ *e.g.* the enamines (**4**) and (**5**).

Thus, the reaction of (**1**)[10] with dimethyl acetylenedicarboxylate (toluene; 25 °C; 4 h) gave the azadienes (**2**) in 94—97% yield after distillation. Fluoride-induced desilylation occurred smoothly; when the diene (**2a**) was treated with caesium fluoride (MeOH; 25 °C; 15 h) and the resulting mixture distilled, the 2-azadiene (**3a**) was formed in nearly quantitative yield (Scheme 1; Table 1). In both processes only one stereoisomer was obtained in the crude product.¶

The reactivity of the diene (**3a**) towards electron-rich alkenes was then investigated. Treatment of (**3a**) with the pyrrolidine enamines (**4**) and (**5**) (CH_2Cl_2; 25 °C; 4 h) led to a crude product which was chromatographed (basic alumina; toluene–ether, 5 : 1) or triturated with hexane, respectively, to afford exclusively the *exo*-cycloadducts (**6**) and (**7**) in excellent yields** (Scheme 2; Table 2). The regio- and stereo-chemical assignments were deduced from ^1H n.m.r. (200 MHz) spectral data; thus the appearance of a singlet at δ *ca.* 4.5 assigned to C(1) H clearly shows the C_α-enamine carbon of the dienophile to be bonded to C(1) of the diene. Nuclear Overhauser enhancement experiments on (**7**) reveal a *cis*-fused bicyclic structure in which H(1) and H(4a) are axially oriented in a chair-like conformation.††,‡‡ Acid hydrolysis of (**6**) (2M-HCl; THF; 50 °C; 2 h) and (**7**) (2M-HCl; THF; 50 °C; 10 h) resulted in their aromatization [quantitative for (**6**) and 70% for (**7**)] to yield the dihydro-2-pyrindine (**8**) and the tetrahydroisoquinoline (**9**), respectively.§§



Scheme 1. *Reagents:* i, $MeO_2CC{\equiv}CCO_2Me$, toluene, 25 °C, 4 h; ii, (a) CsF–MeOH, 25 °C, 15 h; (b) distillation.

Table 1. Azadienes (**2**) and (**3**) from silylimines (**1**).

Compound[a]	R	Yield[b](%)	M.p. (°C) or b.p. (°C)/torr
(**2a**)	Ph	95	48—50 (108/10^{-2})
(**2b**)	p-ClC_6H_4	97	105—106[c]
(**2c**)	p-$MeOC_6H_4$	96	84—86[c]
(**2d**)	2-Thienyl	96	103/10^{-2}
(**2e**)	PhCH=CH	94	(Oil)[d]
(**3a**)	Ph	96	57—59 (105/10^{-2})

[a] All new compounds reported here gave satisfactory elemental analytical figures. [b] Yields of distilled compounds. [c] Recrystallised from hexane–chloroform. [d] Pure compound; decomposes on column chromatography or when distilled.

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† Despite two reports dealing with the synthesis of this type of azadiene, no cycloadditions have been reported.[4]

‡ Cycloaddition of electron-rich olefins with electronically neutral 2-azadienes takes place sluggishly.[8]

§ The inverse electron demand Diels–Alder reaction of electron-poor 1,2,4-triazines with enamines has been exploited for the synthesis of natural products.[9]

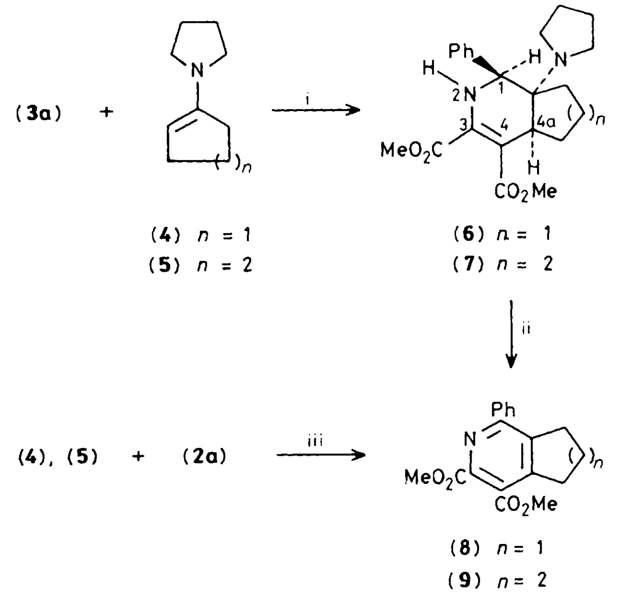
¶ Structures (**2**) and (**3**) were established by spectroscopic means (i.r., mass, ^1H and ^{13}C n.m.r.); their stereochemistry has not been yet defined. For example: (**2a**), ^{13}C n.m.r. (20 Mhz; $CDCl_3$) δ 170.20 (s), 164.30 (s), 163.89 (d), 151.42 (s), 136.46(s), 132.70 (d), 129.83 (d), 129.56 (d), 52.62 (q), 52.00 (q), and 0.41 (q); (**3a**), ^{13}C n.m.r. (20 MHz; $CDCl_3$) δ 164.65(s), 163.76 (d), 163.33 (s), 151.74 (s), 134.48 (s), 131.70 (d), 128.69 (d), 128.18 (d), 108.13 (d), 52.36 (q), and 50.87 (q).

** Compounds (**6**) and (**7**) were characterized by spectroscopic means (i.r., mass, ^1H and ^{13}C n.m.r.). For example: (**7**), ^1H n.m.r. (200 MHz; $CDCl_3$) δ 1.25—1.93 (m, 12H), 2.16—2.34 (m, 2H), 2.74—2.88 (m, 2H), 3.25 (t, J 4 Hz, 1H), 3.75 (s, 6H), 4.21 (s, 1H, NH), 4.56 (s, 1H), and 7.26—7.44 (m, 5H, Ar).

†† Selectivities towards the *exo*-isomers have been found in some 2-azadienes.[8,11]

‡‡ Despite the presence of a single stereoisomer, further studies to ascertain whether this cycloaddition is concerted are needed.

§§ Compounds (**8**) and (**9**) gave the expected spectral data. For example: (**8**), ^{13}C n.m.r. (20 MHz; $CDCl_3$) δ 166.81 (s), 166.60 (s), 155.72 (s), 154.96 (s), 140.13 (s), 138.35 (s), 128.87 (d), 128.51 (d), 128.15 (d), 52.62 (q), 52.31 (q), 32.61 (t), 32.47 (t), and 24.92 (t).



Scheme 2. *Reagents:* i, CH_2Cl_2, 25 °C, 4 h; ii, 2M-HCl, THF, 50 °C, 2—10 h; iii, (a) CH_2Cl_2, 25 °C, 4 h; (b) 2M-HCl, THF, 50 °C, 2 h.

Table 2. Cycloadducts (**6**)—(**9**) from 2-azadienes (**2a**) and (**3a**), and enamines (**4**) and (**5**).

Compound[a]	2-Azadiene	Enamine	Yield[b](%)	M.p. (°C)
(**6**)	(**3a**)	(**4**)	82(70)	122—124
(**7**)	(**3a**)	(**5**)	95(85)	156—158
(**8**)	(**2a**)	(**4**)	92(78)	89—90
(**9**)	(**2a**)	(**5**)	95(92)	103—105

[a] All new compounds reported here gave satisfactory elemental analytical figures. [b] Yields in parentheses refer to purified compounds; see text.

The trimethylsilyl-substituted azadienes (**2**) represent useful synthons for the straightforward formation of (**8**) and (**9**). Thus, treatment of the diene (**2a**) with the enamines (**4**) and (**5**) (CH_2Cl_2; 25 °C; 4 h), hydrolysis of the resulting mixture (2M-HCl; THF; 50 °C; 2 h), and purification of the resulting oily residue by recrystallisation or column chromatography (SiO_2; toluene–ether, 2:1), respectively, gave high yields of (**8**) and (**9**) (Scheme 2; Table 2).

In conclusion, we have demonstrated the inverse electron demand [4 + 2] cycloaddition of 2-azadienes bearing electron-withdrawing substituents to enamines, leading to the 2-pyrindine and isoquinoline skeletons. The ease with which this type of 2-azadiene is prepared from readily available starting materials, and the high yields obtained in all instances, are noteworthy.

Financial support of this work by Comisión Asesora de Investigación Científica y Técnica (CAICYT) is gratefully acknowledged.

Received 26th March 1987; Com. 382

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