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Preparation and Reactivity of Electron-poor 2-Azadienes. Diels-Alder Reaction with *Trans*-Cyclooctene.

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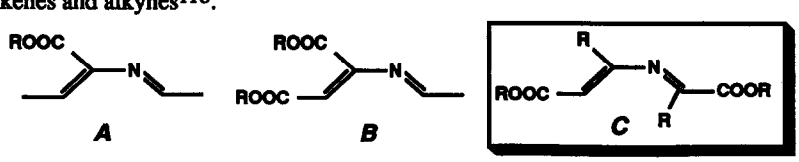
Abstract : Di-, tri- and tetra- substituted 2-azadienes **3** with electron withdrawing groups have been obtained by Aza-Wittig reaction of *N*-vinylic phosphazenes with carbonyl compounds. The Diels-Alder reaction of **3** with *trans*-cyclooctene has also been explored.

2-Aza-butadienes have become valuable buildings blocks for the construction of nitrogen six-membered rings through [4+2] cycloaddition processes[1]. The normal demand Diels-Alder reaction of 2-azabutadienes is the more commonly employed method using very electrophilic dienophiles and electronically neutral azabutadienes[1b] as well as heterodienes with electron donating substituents[2]. Six-membered heteroaromatic azadienes participate in characteristic $LUMO_{diene}$ controlled Diels-Alder reaction[1a,c]. However, the slow developement of the chemistry of 2-azabutadienes - specially in the case of the Diels-Alder reaction - could be caused by the electrophilic character of the azabutadienes[1]; the large activation energy required for its reaction with ethylene in accordance with "*ab initio*" calculations recently reported[3]; and the difficulty in preparing these reagents[1]. Therefore, it was considered worth exploring the inverse demand Diels-Alder reactions[1,4] of this class of compounds, which are accelerated by the presence of electron-withdrawing substituents in the azadiene.

Some synthetic methods for the preparation of electronically neutral 2-azadienes[1b,5], activated 2-azadienes bearing electron-releasing substituents[2,6], as well as mixed 2-azadienes with both donor and electron-withdrawing groups[7] have been reported. However, electron-poor heterodienes, in spite of being the most adequate 2-azadienes[3] for inverse demand Diels-Alder reaction[4] have received much less attention, probably owing to the lack of general methods for the synthesis of these compounds[1].

Azabutadienes of this type were limited, to the best of our knowledge, to 3-substituted electron- poor heterodienes[8,9] ***A*** as well as 4,4-[10] and 3,4-electron-withdrawing substituted[11] 2-azadienes ***B***. The use of this kind of electron-poor 2-azadienes in the construction of heterocyclic systems is restricted to the intermolecular reaction of compounds ***B*** with enamines[11a] and the intramolecular cycloadition reaction with simple alkenes and alkynes[11b].



Elsewhere, we have described the utility of phosphazenes in the preparation of acyclic[9,12] and heterocyclic compounds[13]. Our interest in the chemistry of phosphazenes[14] and β-aminoacid derivatives[15] **C** prompted us to report here the first synthesis of di-, tri- and tetra- substituted 2-azadienes **C** with electron-withdrawing substituents from *N*-functionalized phosphazenes **2** derived from α,β-dehydroaminoacid esters and the first example of intermolecular Diels-Alder reaction of electron poor heterodienes with strained cycloalkenes.

The preparation of the required *N*-vinylic-phosphazene **2**[18] was accomplished very easily through the classical Staudinger reaction[14] of azides **1** and phosphines. Aza-Wittig reaction of phosphazenes **2** with carbonyl compounds in H_2CCl_2 at room temperature gave very high yields of di-, tri- and tetra-substituted 2-azadienes **3**[19] as viscous oils isolated by means of short column chromatography.

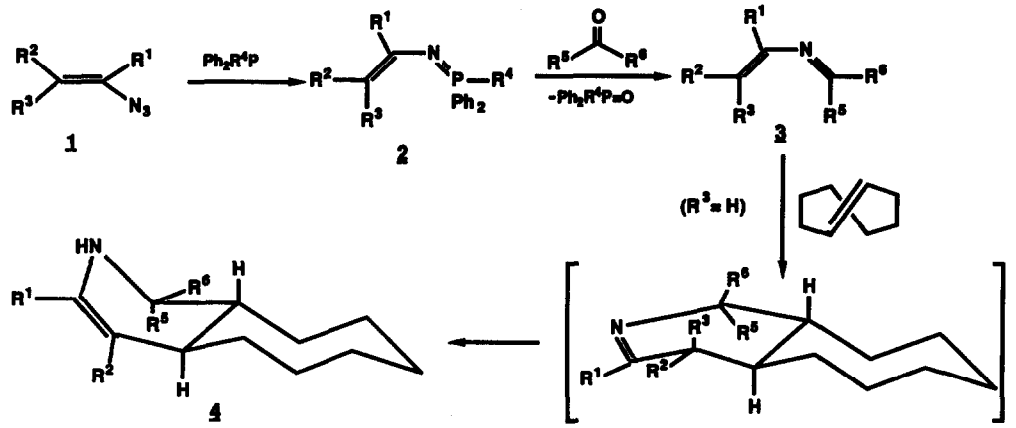


Table. Compounds **2** - **4** obtained

Compound	R^1	R^2	R^3	R^4	R^5	R^6	Yield.(%)[a]	m.p.(°C)
2a	H	COOEt	H	CH_3			93	117-118
2b	COOMe	H	COOMe	Ph			95	131-132
2c	CH_3	COOMe	H	CH_3			91	154-155
2d	CH_3	COOMe	H	Ph			95	141-142
3a	H	COOEt	H		COOEt	COOEt	92	oil[b]
3b	H	COOEt	H		H	COOEt	90	oil[b]
3c	COOMe	H	COOMe		COOEt	COOEt	89	oil[b]
3d	H	COOEt	H		CH_3	C≡N	91	oil[b]
3e	CH_3	COOMe	H		CH_3	C≡N	90	oil[b]
4a	H	COOEt			COOEt	COOEt	88	oil[b]
4b	H	COOEt			H	COOEt	87	oil[b]
4c	CH_3	COOMe			CH_3	C≡N	86	oil[b]

[a] Yield of isolated products.

[b] Purified by flash chromatography.

The reactivity of polisubstitued 2-azadienes **3** as heterodienes in Diels-Alder reaction was explored, since the presence of strong electron-withdrawing substituents could serve to enhance the rate of cycloadditions. *Trans*-cyclooctene was used as dienophile. This reagent gave excellent yield as dipolarophile in 1,3-dipolar cycloaddition reactions with low-lying π MO's 1,3-dipoles such as azoxy compounds[20]. Likewise, several *trans*-cyclooctene derivatives had been used in [4+2] cycloaddition processes with 1,3-butadiene and cyclopentadiene[21].

Thus, the reaction of **3a** with *trans*-cyclooctene (dry $HCCl_3$, 60°C, 72h.)[22] gave the cycloadduct **4a**[23] when the solvents were removed (Table). Spectral data are in agreement with enamine structure and the *trans*-ring juncture of the fused bicyclic compounds **4**.

In conclusion, we report here a convenient and stereoselective procedure for the construction of *trans*-cyclooctane-tetrahidropiridine derivatives as well as the first example of an intermolecular [4+2] cycloaddition reaction of new electron-poor 2-azadienes **3** with *trans*-cyclooctene and one easy way to obtain 2-azadienes derived from β-aminoacids. These systems could be key intermediates in the synthesis of new aminoacids and peptide derivatives[16,17], as well as alkaloids containing six membered nitrogen heterocycles[24] and biologically active compounds[25]. Further studies of compounds **3** are now in progress in our laboratories.

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18.- All new compounds reported here gave satisfactory elemental analysis. Spectral data for **2a**, $C_{18}H_{20}NO_2P$; ^{1}H-RMN ($CDCl_3$, 300 MHz) δ: 7.84 (dd, 1H $^3J_{PH}$= 30 Hz, $^3J_{HH}$= 12 Hz, HC=), 7.6-7.5 (m, 10H, Ar.), 5.26 (d, 1H, $^3J_{HH}$ =12 Hz, HC=), 4.06 (q, 2H, OCH_2); 2.11(d, 3H, $^2J_{PH}$ =13 Hz, CH_3); 1.20 (t, 3H, CH_3) ppm; ^{13}C-RMN ($CDCl_3$, 75 MHz) δ: 170.0 (d, $^4J_{PC}$=3.5 Hz), 156.8 (HC=), 132.8-127.0 (C arom.), 99.4 (d, $^3J_{PC}$=28 Hz, HC=), 58.8 (OCH_2), 14 8 (CH_3), 13.7 (d, $^1J_{PC}$= 74 Hz, CH_3) ppm; ^{31}P-RMN ($CDCl_3$, 120 MHz) δ: 8.46 ppm; MS *m/e*: 313.1 (M^+).

19.- Spectral data for **3a**, $C_{12}H_{17}NO_6$, ^{1}H-RMN ($CDCl_3$, 300 MHz) δ: 7.76 (d, 1H, $^3J_{HH}$= 13 Hz, HC=), 6.02 (d, 1H, $^3J_{HH}$= 13 Hz, HC=), 4.18 (q, 4H, OCH_2), 4.01 (q, 2H, OCH_2), 1.15 (t, 6H, CH_3), 1.07 (t, 3H, CH_3) ppm; ^{13}C-RMN ($CDCl_3$, 75 MHz) δ: 165.2 (COO), 160.7 (COO), 154.4 (C=N), 146.8 (HC=), 123.1 (HC=), 62.7 (OCH_2), 60.7 (OCH_2), 13.9 (CH_3); 13.8 (CH_3) ppm; MS *m/e* 271 (M^+).

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22.- Similar reaction conditions was used for compound **3c**, while when azadiene **3b** was used, the reaction mixture was stirred at 25°C 8 h..

23.- Spectral data for **4a**, $C_{20}H_{31}NO_6$: ^{1}H-RMN ($CDCl_3$, 300 MHz) δ: 7.38 (d, 1H, $^3J_{HH}$= 6 Hz, HC=), 5.23 (d, 1H,$^3J_{HH}$= 6Hz, HN), 4.3-4.0 (m, 6H, OCH_2), 2.7 (m, 1H, HC), 2.50 (m, 1H, HC); 2.2-1.1 (m, 21H, CH_2 and CH_3) ppm; ^{13}C-RMN ($CDCl_3$, 75 MHz) δ: 168.9 (COO), 168.2 (COO), 167.9 (COO), 140.5 (HC=), 102.6 (C=), 68.1 (N-C), 61.9 (OCH_2), 61.8 (OCH_2), 58.7 (OCH_2), 37.4 (CH), 32.0 (CH), 29.6 (CH_2), 28.2 (CH_2), 27.7 (CH_2), 27.6 (CH_2), 26.8 (CH_2), 25.8 (CH_2), 14.2 (CH_3), 13.7 (2 CH_3) ppm.

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