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1,4-CYCLOADDITION OF 1,3-DIAZABUTADIENES WITH ENAMINES: AN EFFICIENT ROUTE TO THE PYRIMIDINE RING

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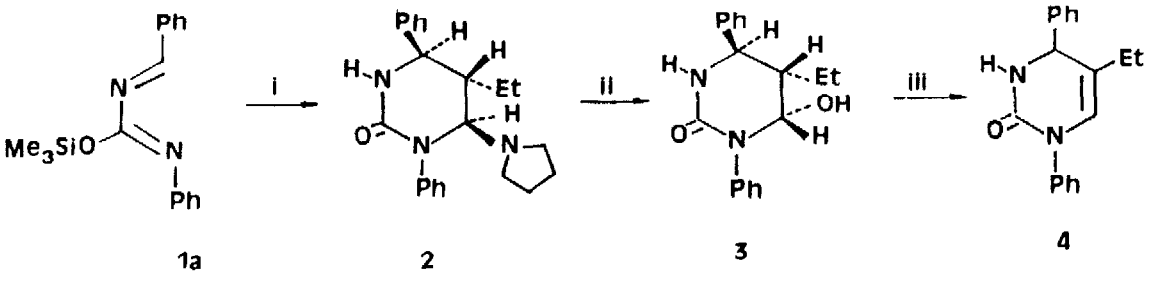
Summary: [4+2] Cycloaddition reactions of 2-trimethylsilyloxy- and 2-trimethylsilylthio-1,3-diazabutadienes with enamines leading to pyrimidone derivatives are described.

The [4+2] cycloaddition reaction of azadienes has proved to be of great potential for synthesis of six-membered nitrogen containing heterocycles[1,2] . However, reports concerning [4+2] cycloadditions of 1,3-diaza-1,3-butadienes are rare[3,4,5] ; thus, unactivated 1,3-diazadienes have been shown to cycloadd to heterocumulenes (isocyanates[3a] and ketenes[3b]) and 4-amino-1,3-diazabutadienes react in the same way with ketenes[3b,3c] and sulfene[3d] . On the other hand, I. Matsuda *et al.* published some years ago the preparation of 4,4-diphenyl-2-trimethylsilyloxy-1,3-diazabutadienes and demonstrated their ability to undergo [4+2] cycloadditions with isocyanates and dimethyl acetylenedicarboxylate[6] ; furthermore, by taking advantage of the availability of simple trimethylsilyl imines[7] , we synthesized 2-trimethylsilyloxy- and 2-trimethylsilylthio-4-aryl-1,3-diazadienes (**1**) and used them to prepare triazinedione derivatives[8].

We report here that 1,3-diazadienes (**1**) are able to undergo [4+2] cycloadditions with electron-rich dienophiles, e.g. enamines derived from butyraldehyde and cyclohexanone[9].

Thus, compound (**1a**) (5 mmol), formed *in situ* from N-(trimethylsilyl)-phenylmethanimine and phenylisocyanate[8] , was stirred at room temperature in methylene chloride (30 ml) with 1-pyrrolidino-1-butene (5.5 mmol) overnight. Then, methanol (10 ml) was added and stirring continued for 1 h; removing the solvents *in vacuo* led to solid, pure tetrahydropyrimidinone (**2**) (yield 80%; m.p. 138-139°C from hexane-chloroform) as a single diastereoisomer (^{1}H n.m.r., 300 MHz) (Scheme 1)[10]. The regio- and stereochemistry shown, the latter arising from an *endo*-transition state, were assigned on the basis of the ^{1}H n.m.r. (300 MHz) spectral data; nuclear Overhauser enhancement experiments clearly reveal a *cis* relationship for H-4, H-6, and the ethyl group and the ^{13}C n.m.r. shifts of the ring carbon atoms, C-4 (57.50), C-5 (44.78), C-6 (79.50), must rule out

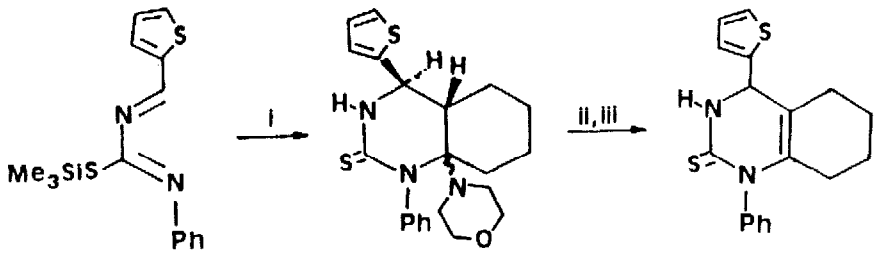
the 5-pyrrolidino regioisomer. Acid hydrolysis of (2) resulted in the exclusive formation of the hydroxypyrimidinone (3) (84% yield; m.p. 133-135°C from hexane-tetrahydrofuran)[10]; the stereochemistry of the isomer isolated, in which the hydroxy group is axially oriented in the corresponding chair-like conformation, was based on the ^{1}H n.m.r. data ($^3J_{H4\text{-}H5}$ = 11.3 Hz, $^3J_{H5\text{-}H6}$ = 2.5 Hz, and NOE experiments) and clearly reflects the contribution of the anomeric effect[11]. This compound (3) was, in turn, dehydrated to yield the 3,4-dihydropyrimidin-2(1H)-one (4) (96% yield; m.p. 112-114°C from hexane-chloroform) (Scheme 1)[10]; the appearance of H-4 (δ 5.0 ppm) and H-6 (δ 6.1 ppm) as singlets in the ^{1}H n.m.r. spectrum undoubtedly confirms the regiochemistry given for its precursor (2).



1a 2 3 4

Scheme 1.- Reagents: i, (a) *E*-1-pyrrolidino-1-butene, CH_2Cl_2, 25°C, 12h; (b) CH_3OH, 25°C, 1h; ii, 1M H_2SO_4, THF, 25°C, 2h; iii, C_6H_6, *p*-TsOH, reflux, 12h.

The scope of this process was then tested for sulfur-containing dienes and cyclic enamines (Scheme 2). Thus, treatment of diazadiene (**1b**), prepared *in situ* from the corresponding silyl imine and phenylisothiocyanate[8], with 1-morpholino-1-cyclohexene furnished the quinazolinethione (**5**)(^{13}C n.m.r. $\delta_{C=S}$ = 180.06 ppm).



1b 5 6

Scheme 2.- Reagents: i, (a) 1-morpholino-1-cyclohexene, CH_2Cl_2, 25°C, 12h; (b) CH_3OH, 25°C, 1h; ii, (a) 1M H_2SO_4, THF, 25°C, 2h; (b), C_6H_6, *p*-TsOH, reflux, 12h.

as a single stereoisomer (N-C*H* : doublet at 5.25 ppm, ^3J = 11.95 Hz) in 82% yield after washing with diethyl ether; and analytical sample (m.p. 138-140°C) was obtained by recrystallization from hexane-chloroform. The relative stereochemistry of the aminal carbon could not be unambiguously defined because of signals overlaping in the ^1H n.m.r. spectrum. Compound (**5**) was then hydrolyzed and dehydrated as above to yield crude 3,4,5,6,7,8-hexahydroquinazoline-2(1H)-thione (**6**), which was washed with diethyl ether (84% yield) and recrystallized from hexane-chloroform (m.p. 108-110°C)[10] (Scheme 2).

In conclusion, we have demonstrated the inverse electron demand [4+2] cycloaddition of 1,3-diazadienes to enamines leading to pyrimidine and quinazoline skeletons; it should be pointed out that this approach to the pyrimidine ring involves formation of N1-C6 and C4-C5 bonds (synthesis from 4+2 atom fragments), which is uncommon in the literature[12]. Moreover, the easy with which this type of 1,3-diazadiene is made from readily available starting materials, and the high yields obtained are noteworthy[13].

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References and notes.

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4.- For less representative examples, see: (a) G. Morel, E. Marchand and A. Foucaud, *J. Org. Chem.*, **1989**, *54*, 1185; (b) Ibid, *J. Org. Chem.*, **1985**, *50*, 771; (c) K. Burger and S. Penninger, *Synthesis*, **1978**, 524.

5.- For papers on [4+1] cycloaddition reactions of 1,3-diazadienes see, for instance, Ref. 4a.

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9.- Enamines have been shown to cycloadd to imidoyl isothiocyanates to give mixtures of cyclic and open-chain adducts. See, H. M. Blatter and H. Lukaszewski, *J. Org. Chem.*, **1966**, *31*, 722.

10.- Selected spectroscopic data:

Compound (2) δ_H 0.85(3H, t, J=7.5Hz), 1.3-1.5(6H, m), 2.2(1H, m), 2.35(4H, m), 4.35(1H, d, J=7.1Hz), 4.55(1H, d, J=6.5Hz), 4.9(1H, s broad), 7.1-7.4(10H, m) ppm; δ_C 10.87(q), 22.93(t), 24.00(t), 44.78(d), 48.21(t), 57.50(d), 79.50(d), 126.17(d), 127.03(d), 127.60(d), 128.18(d), 128.30(d), 128.50(d), 141.55(s), 142.35(s), 156.46(s) ppm.

Compound (3) δ_H 0.85(3H, t, J=7.5Hz), 1.1(1H, m), 1.35(1H, m), 1.95(1H, m), 4.4(1H, d, J=11.3Hz), 4.95(1H, s broad), 5.1(1H, d, J=2.5), 7.15-7.5(11H, m) ppm.

Compound (4) δ_C 11.40(q), 23.13(t), 59.99(d), 116.54(s), 123.32(d), 126.12(d), 126.45(d), 126.96(d), 128.23(d), 128.84(d), 128.89(d), 140.90(s), 142.44(s), 152.12(s) ppm.

Compound (5) δ_H 1.3-1.9(8H, m), 2.1(1H, td, J=14.4 and 3.4Hz), 2.6-2.85(4H, m), 3.35-3.6(4H, m), 5.25(1H, d, J=11.95), 6.65(1H, s broad), 7.0-7.6(8H, m) ppm.

Compound (6) δ_C 21.25(t), 22.42(t), 26.05(t), 26.81(t), 53.86(d), 112.29(s), 125.06(d), 125.64(d), 126.81(d), 128.02(d), 128.13(d), 130.68(s), 140.57(s), 145.91(s), 176.42(s) ppm.

All spectra were run in $CDCl_3$ at 300MHz (^1H) and 75MHz (^{13}C).

11.- In terms of the anomeric effect, the axial conformation for the hydroxy group is strongly favoured since, besides that the C-O bond is a good acceptor, nitrogen is a stronger donor than oxygen. See, H. Booth and K. A. Khedhair, *J. Chem. Soc., Chem. Commun.*, **1985**, 467; J. Barluenga, F. Aznar, R. Liz, M. P. Cabal, F. H. Cano and C. Foces-Foces, *Chem. Ber.*, **1986**, *119*, 887.

12.- D. J. Brown in *Comprehensive Heterocyclic Chemistry*, A. R. Katritzky and C. W. Rees, Ed.; Pergamon Press, Oxford, 1984, Vol. 3, p. 57.

13.- All new compounds gave satisfactory spectroscopic (i.r., ^1H and ^{13}C n.m.r., and mass) and analytical data.

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