Enamines; Part 46[1]. Synthesis of 5-Dialkylamino-1-aryl-1,2,3-triazoles Functionalized at C-4

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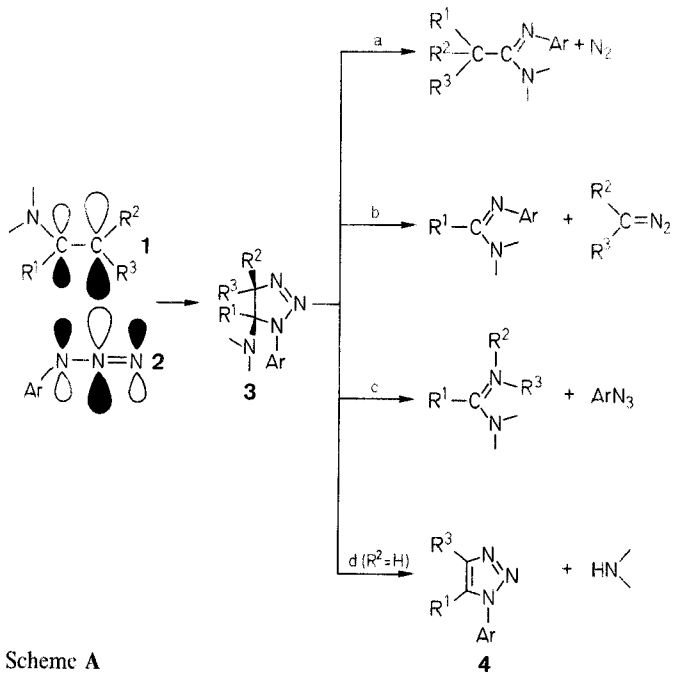
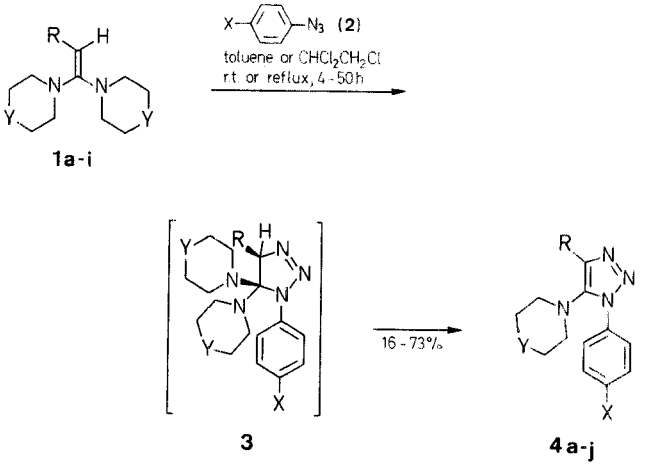
Aryl azides undergo a [3+2]-cycloaddition with 1,1-diaminoethenes having an electron-withdrawing group at C-2 to give unstable 5,5-diamino-4,5-dihydro-1,2,3-triazoles from which one amino group is eliminated to afford 5-amino-1-aryl-1,2,3-triazoles functionalized at C-4.

Azidoarenes **(2)** react with enamines **(1)** to give 4,5-dihydro-1,2,3-triazoles **(3)**; in general, these [3+2]-cycloaddition products are unstable and rearrange rapidly or undergo cycloreversion according to various pathways[2] (Scheme **A**). In some cases, especially with $R^2 = H$ and R^3 = electron-withdrawing group, the cycloaddition products **3** undergo deamination to afford stable 1-aryl-1,2,3-triazoles **(4)**[3-6] (Scheme **A**, Pathway d).

4,5-Dihydro-1,2,3-triazoles having two (geminal) amino groups at C-5 have hitherto been little investigated. The only report on the isolation of such a compound refers to 5,5-dimorpholino-1-(4-nitrophenyl)-4,5-dihydro-1,2,3-triazole[7] which is quite stable in the solid state but which decomposes to unidentified products in solution[8]. We investigated if the presence of an electron-withdrawing group at C-4 of the 5,5-diamino-1-aryl-4,5-dihydro-1,2,3-triazole would direct the decomposition process toward amine elimination, thus giving rise to the formation of 5-dialkylamino-1-aryl-1,2,3-triazoles **(4)** having reactive groups at C-4 (NO_2, CO – R, COOR, SO_2 – R).



Scheme A

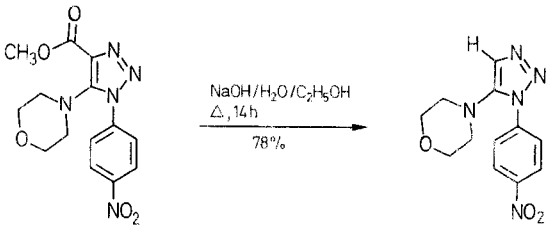


Scheme B

The enediamines **1** (R = acyl, Y = O) were prepared by acylation of 1,1-dimorpholinoethene[9,10], the sulfonyl derivative **1f** (R = tosyl, Y = O) was prepared from 1,1-dimorpholinoethene and tosyl chloride, and the 1,1-dimorpholino-, 1,1-dipiperidino-, and 1,1-dipyrrolidino-2-nitroethenes were prepared from nitroketene *S,S*-dimethyl acetal and the respective secondary cyclic amines[11].

The reactions of enediamines **1** with 4-azido-1-nitrobenzene or 4-azido-1-chlorobenzene were performed in toluene or 1,1,2-trichloroethane at temperatures varying from 25 °C to the boiling point of the solvent. From the reaction mixtures, compounds **4a–j** were isolated as the main products. In no case could a 4,5-dihydrotriazole **3** be isolated or detected; the deamination process proceeds so rapidly that NMR monitoring of the reaction mixture did not allow detection of signals unequivocally associated with the structure **3**.

In each case, only one regioisomer was formed, in agreement with the molecular-orbital approach[12] and with the previously reported results of the reaction between aryl azides and ketene acetals[13]. In fact, because of the presence of two geminal amino groups the difference between the C-α and C-β values of HOMO of the enediamine **1** (a ketene aminal) in the dominant interaction with LUMO of the azide **2** is enhanced in favour of C-β. Further, the regioselectivity of the cycloaddition between **1** and **2** is proven by the fact that 4-methoxycarbonyl-5-morpholino-1-(4-nitrophenyl)-1,2,3-triazole (**4c**) upon hydrolysis and decarboxylation affords 5-morpholino-1-(4-nitrophenyl)-1,2,3-triazole (**5**) (Scheme C) the structure of which was confirmed by m.p. and NMR comparison to be identical with that of the product obtained from α-morpholinoacrylonitrile and 4-azido-1-nitrobenzene[14].



Scheme C

1,1-Diaminoethenes (Ketene Aminals, 1a–i):

Compounds **1a, b, e**[9,10] and **1g, h, i**[11] are known compounds. Compounds **1c, d, f** are new and were prepared according to the procedure of Lit.[10].

Methyl 3,3-Dimorpholinoacrylate (**1c**); yield: 60%; m.p. 114–117 °C.

$C_{12}H_{20}N_2O_4$	calc.	C 56.23	H 7.86	N 10.93
(256.3)	found	56.40	7.79	10.78

Ethyl 3,3-Dimorpholinoacrylate (**1d**); yield: 73%; m.p. 140–144 °C.

$C_{13}H_{22}N_2O_4$	calc.	C 57.75	H 8.20	N 10.36
(270.3)	found	57.71	8.21	10.18

4-Methylphenyl 2,2-Dimorpholinovinyl Sulfone (**1f**); yield: 43%; m.p. 174–178 °C.

$C_{17}H_{24}N_2O_4S$	calc.	C 57.93	H 6.86	N 7.95	S 9.08
(352.4)	found	58.04	6.79	8.03	9.00

4-Substituted 5-Dialkylamino-1-aryl-1,2,3-triazoles (4a–j); General Procedure:

A mixture of the 1,1-diaminoethene **1** (0.01 mol), the azidoarene **2** (0.011 mol), and toluene or 1,1,2-trichloroethane (30 ml) is stirred until no more 1,1-diaminoethene is detectable by TLC on silica plates (Merck F 254) (for solvent, times, and temperatures, see Table). The solvent is then removed under reduced pressure and the crude product purified by crystallization or by column chromatography on silica gel using the eluent given in the Table.

5-Morpholino-1-(4-nitrophenyl)-1,2,3-triazole (5):

To a stirred solution of 4-methoxycarbonyl-5-morpholino-1-(4-nitrophenyl)-1,2,3-triazole (**4c**; 0.5 g, 15 mmol) in ethanol (5 ml), a solution of sodium hydroxide (0.066 g, 1.65 mmol) in water (5 ml) is added and the mixture is heated to reflux for 14 h, then concentrated to a volume of 5 ml under reduced pressure. This residue is cooled, and neutralized with 10% hydrochloric acid. The phases are separated and the aqueous phase is extracted with ethyl acetate (2 × 10 ml). The combined organic phases are dried with sodium

Table. 4-Substituted 5-Amino-1-aryl-1,2,3-triazoles (**4**) Prepared

4	Reaction solvent	Time [h] (Temperature)	Eluent for chromatography	Yield[a] [%]	m.p.[b] [°C] (solvent)	Molecular Formula[c]	^{1}H-NMR ($CDCl_3$)[d] δ from TMS [ppm]
a	toluene	4 (reflux)	–	45	170–173 (ethyl acetate/ diisopropyl ether)	$C_{14}H_{15}N_5O_4$ (317.30)	2.73 (s, 3H, CH_3); 3.13 [m, 4H, $(CH_2)_2N$]; 3.70 [m, 4H, $(CH_2)_2O$]; 7.87 (d, $2H_{arom}$); 8.43 (d, $2H_{arom}$)
b	toluene	5 (reflux)	–	49	170 (ethyl acetate/ diisopropyl ether)	$C_{19}H_{17}N_5O_4$ (379.4)	3.13 [m, 4H, $(CH_2)_2N$]; 3.70 [m, 4H, $(CH_2)_2O$]; 7.40–7.74 (m, $3H_{arom}$); 7.86–9.66 (m, $6H_{arom}$)
c	toluene	50 (r.t.)	–	72	167–169 (ethyl acetate)	$C_{14}H_{15}N_5O_3$ (333.3)	3.23 [m, 4H, $(CH_2)_2N$]; 3.76 [m, 4H, $(CH_2)_2O$]; 4.04 (s, 3H, CH_3); 7.95 (d, $2H_{arom}$); 8.48 (d, $2H_{arom}$)
d	toluene	4 (reflux)	ethyl acetate/ benzene 10/90	50	161–163 (ethyl acetate)	$C_{15}H_{17}N_5O_5$ (347.3)	1.53 (t, 3H, CH_3); 3.20 [m, 4H, $(CH_2)_2N$]; 3.70 [m, 4H, $(CH_2)_2O$]; 4.46 (d, 2H, CH_2); 7.90 (d, $2H_{arom}$); 8.48 (d, $2H_{arom}$)
e	toluene	4 (reflux)	–	73	194–197 (ethyl acetate)	$C_{20}H_{19}N_5O_5$ (409.4)	3.13 [m, 4H, $(CH_2)_2N$]; 3.60 [m, 4H, $(CH_2)_2O$]; 5.40 (s, 2H, CH_2); 7.26–7.63 (m, $5H_{arom}$); 7.90 (d, $2H_{arom}$); 8.45 (d, $2H_{arom}$)[e]
f	1,1,2-trichloroethane	8 (reflux)	ether/ benzene 50/50	25	200–202 (ethyl acetate)	$C_{19}H_{19}N_5O_5S$ (429.45)	2.53 (s, 3H, CH_3); 3.33 [m, 4H, $(CH_2)_2N$]; 3.78 [m, 4h, $(CH_2)_2O$]; 7.45 (d, $2H_{arom}$); 7.75–8.23 (m, $4H_{arom}$); 8.52 (d, $2H_{arom}$)
g	toluene	4 (reflux)	–	47	186–187 (ethyl acetate)	$C_{12}H_{12}N_6O_5$ (320.3)	3.23 [m, 4H, $(CH_2)_2N$]; 3.65 [m, 4H, $(CH_2)_2O$]; 8.02 (d, $2H_{arom}$); 8.53 (d, $2H_{arom}$)[f]
h	toluene	4 (reflux)	ethyl acetate/ benzene 50/50	30	160 (ethyl acetate/ diisopropyl ether)	$C_{13}H_{14}N_6O_4$ (318.3)	1.67 (m, 6H, CH_2); 3.13 [m, 4H, $(CH_2)_2N$]; 7.80 (d, $2H_{arom}$); 8.50 (d, $2H_{arom}$)
i	toluene	4 (r.t.)	ethyl acetate/ benzene 80/20	30	174–176 (ethyl acetate/ diisopropyl ether)	$C_{12}H_{12}N_6O_4$ (304.3)	1.98 (m, 4H, CH_2); 3.35 [m, 4H, $(CH_2)_2N$]; 7.80 (d, $2H_{arom}$); 8.50 (d, $2H_{arom}$)
j	toluene	48 (reflux)	ethyl acetate/ benzene 50/50	16	146–148 (ethyl acetate)	$C_{12}H_{12}ClN_5O_3$ (309.7)	3.20 [m, 4H, $(CH_2)_2N$]; 3.75 [m, 4H, $(CH_2)_2O$]; 7.60 (s, $4H_{arom}$)

[a] Isolated analytically pure product.
[b] Uncorrected.
[c] The microanalyses were in good agreement with the calculated values: C ±0.25, H ±0.20, N ±0.15.
[d] Recorded at 60 MHz on a Varian A360 Spectrometer.
[e] Recorded in $CDCl_3$/DMSO-d_6 95/5.
[f] Recorded in DMSO-d_6.

sulfate, and evaporated under reduced pressure. The remaining crude product is purified by crystallization from ethyl acetate/ethanol (80:20); yield: 0.32 g (78%); m.p. 168°C (Lit.[14], m.p. 167°C).

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[1] For part 45, See: Rossi, E., Sassano, S., Stradi, R. *Synthesis*, **1986**, 765.
[2] Pocar, D., Trimarco, P. *J. Chem. Soc. Perkin Trans. 1*, **1976**, 622.
[3] Bianchetti, G., Pocar, D., Dalla Croce, P., Stradi, R. *Gazz. Chim. Ital.* **1967**, *97*, 304.
[4] Fusco, R., Bianchetti, G., Pocar, D., Ugo, R. *Gazz. Chim. Ital.* **1962**, *92*, 1040.
[5] Maiorana, S., Pocar, D., Dalla Croce, P. *Tetrahedron Lett.* **1966**, 6043.
[6] Pocar, D., Maiorana, S., Dalla, Croce, P. *Gazz. Chim. Ital.* **1968**, *98*, 949.
[7] Stradi, R., Pocar, D., Bianchetti, G. *Org. Magn. Reson.* **1972**, *4*, 247.
[8] Vivaldi, F. *Dissertation*, Università di Cagliari, 1970.
[9] Opitz, G., Zimmermann, F. *Chem. Ber.* **1964**, *97*, 1266.
[10] Armati, A., De Ruggieri, P., Rossi, E., Stradi, R. *Synthesis*, in press.
[11] Gompper, R., Schaefer, H. *Chem. Ber.* **1967**, *100*, 591. Rajappa, S., Advani, B.G., Sreenivasan, R. *Synthesis* **1974**, 656.
[12] Bourgois, J., Bourgois, M., Texier, F. *Bull. Soc. Chim. Fr. II* **1978**, 485.
[13] Graziano, M.L., Scarpati, R. *J. Heterocycl. Chem.* **1976**, *13*, 205. Scarpati, R., Graziano, M.L., Nicolaus, R.A. *Gazz. Chim. Ital* **1968**, *98*, 681.
[14] Texier, F., Derdour, A., Benhaoua, H., Benabdellah, T., Yebdri O. *Tetrahedron Lett.* **1982**, *23*, 1893.