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THERMAL BEHAVIOR OF DIPOLAROPHILE-CONTAINING 2-AZIDOCARBONYLPYRROLES AND -INDOLES

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Abstract – The thermal reaction of *N*-allyl- or *N*-propargyl-2-azidocarbonyl-pyrroles (**2**) or -indoles (**9**) involves competition between intramolecular azide cycloaddition and Curtius rearrangement.

INTRODUCTION

Azide cycloadditons were the object of recent investigations as the ideal representative of the "click" chemistry concept.[1] As a consequence, an intense research was developed upon the azide cycloadditions from both the synthetic[2,3] and the theoretical[4] point of view. The thermal behavior of acyl azides associated with the Curtius reaction have been investigated being traditionally well-known.[5] Among the rare examples available, the intramolecular version of acylazide 1,3-dipolar cycloadditions has been applied to the synthesis of some thieno[1,2,3]triazolo[5,1-*c*][1,4]diazepines[6] and as the key step in the enantioselective synthesis of (+)-biotine.[7] Here it is presented a study onto *N*-propargyl- or *N*-allyl-2-azidocarbonylpyrroles (**2**) or -indoles (**6**) in order to establish the degree of competition between intramolecular cycloaddition and Curtius rearrangement. The resulting pyrrolo[1,2-*d*][1,2,3]triazolo-[5,1-*a*]pyrazine skeleton is an aza-analogue of potent hypotensive drugs[8] as well as inhibitor of the serotonine contractile factor,[9] thus representing a valuable target in medicinal chemistry.

RESULTS AND DISCUSSION

1-Substituted 2-azidocarbonylpyrroles or -indoles (**2**) and (**9**) were readily synthesised from the corresponding carboxylic acids (**1**) or (**5**), respectively (see Scheme). Subsequent heat treatment of (**2**) or (**6**) was carried out in boiling toluene. Reaction times, products and product yields are summarised in Table 1. Structural assignements are unequivocal and rely upon analytical and spectral data (see EXPERIMENTAL). In particular, the ^{1}H NMR spectra of cycloadducts (**4**) are perfectly consistent with literature data concerning 5-substituted 1*H*-1,2,3-triazoles.[10]

Scheme

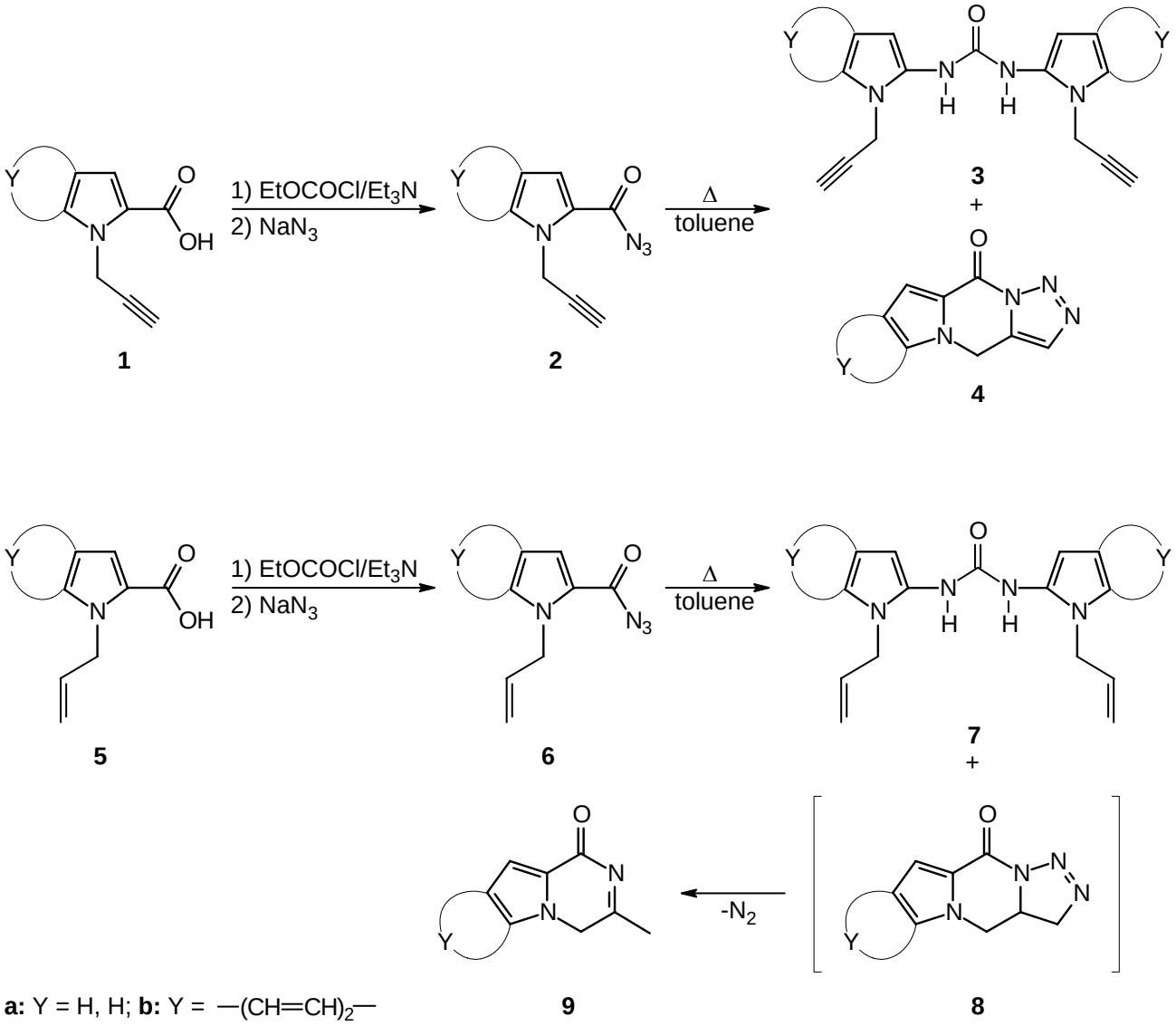

Table 1. Thermal behavior of acylazides (**2**) and (**6**).

Compd	Time[a] (h)	Products and Yields (%)[b]	
		3 or **7**	**4** or **9**
2a	8	31	49
2b	7	40	48
6a	12	53	16
6b	13	59	19

[a]In refluxing toluene. [b]Isolated yields.

As it may be argued from the Scheme, *sym*-ureas (**3**) and (**7**) were isolated as a consequence of the Curtius rearrangement of starting acylazieds (**2**) and (**6**), respectively. On the other hand, the intramolecular cycloaddition products (**4**) were obtained only from substrates (**2**) bearing an acetylenic dipolarophile. In fact, in the case of ethylenic acylazides (**6**) further evolution of the first-formed cycloadducts (**8**) was operative with the extrusion of molecular nitrogen, reflecting a well-known behaviour pattern of 1,2,3-triazolines.[11]

The results listed in Table 1 show that the intramolecular cycloaddition pattern is more effective in the case of acetylenic acylazides (**2**). This behaviour matches with the reduced degree of rotational freedom of the latter substrates (**2**) with respect to the ethylenic acylazides (**6**), thus facilitating the approach of the reactive π systems as required for concerted cycloadditions.[12] On the other hand, the Curtius rearrangement can overwhelm the intramolecular azide cycloaddition pathway due to the powerful driving force exerted by the loss of molecular nitrogen from both acylazides (**2**) and (**6**).

EXPERIMENTAL

Melting points were determined with a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded with a Perkin-Elmer 1725 X spectrophotometer. MS spectra were determined with a VG-70EQ apparatus. ^{1}H NMR (300 MHz) spectra were taken with a Bruker AMX 300 instrument (in $CDCl_3$ solutions at room temperature). Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in Hz.

Compounds (**1a**),[13] (**1b**),[15] (**6a**),[14] and (**6b**)[16] are known in the literature.

Synthesis of acylazides (2) and (6). A solution of the appropriate *N*-substituted 2-carboxy-pyrrole or -indole (**1**) or (**5**) (6.0 mmol) in dry acetone (20 mL) was cooled to 0°C. Triethylamine (0.61 g, 6.0 mmol) and ethyl chloroformate (0.65 g, 6.0 mmol) were added and the mixture was stirred at 0°C for 45 min. Sodium azide (0.63 g, 9.7 mmol) was added portionwise under cooling and vigorous stirring. After 2 h the mixture was evaporated, taken up with water (10 mL) and extracted with dichloromethane (2 x 30 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure affording crude (**2**) or (**6**). The oily residue was chromatographed on a silica gel column with ethyl acetate-hexane (3:1) giving analytically pure acylazides (**2**) or (**6**).

1-Propargyl-2-azidocarbonylpyrrole (**2a**) (0.81 g, 77%) as undistillable yellow oil; IR (nujol): 2130, 1670 (cm^{-1}); ^{1}H-NMR: 2.48 (1H, t, *J*=2.5 Hz), 5.20 (2H, d, *J*=2.5 Hz), 6.24 (1H, dd, *J*=2.7, 1.4 Hz), 6.91 (1H, dd, *J*=3.7, 1.4 Hz), 7.13 (1H, dd, *J*=3.7, 2.7 Hz); MS: 174 *m/z* (M^+). *Anal*. Calcd for $C_8H_6N_4O$: C, 55.17; H, 3.47; N, 32.17. Found: C, 55.23; H, 3.53; N, 32.10.

1-Propargyl-2-azidocarbonylindole (**2b**) (1.13 g, 84%) as undistillable pale yellow oil; IR (nujol): 2140, 1670 (cm^{-1}); ^{1}H-NMR: 2.27 (1H, t, *J*=2.5 Hz), 5.48 (2H, d, *J*=2.5 Hz), 6.95 (1H, s), 7.18-7.60 (4H, m); MS: 224 *m/z* (M^+). *Anal*. Calcd for $C_{12}H_8N_4O$: C, 64.28; H, 3.60; N, 24.99. Found: C, 64.33; H, 3.64; N, 25.07.

1-Allyl-2-azidocarbonylpyrrole (**6a**) (0.71 g, 67%) as undistillable yellow oil; IR (nujol): 2130, 1680 (cm^{-1}); ^{1}H-NMR: 4.94-5.05 (2H, m), 5.07 (1H, dd, *J*=10.9, 1.8 Hz), 5.18 (1H, dd, *J*=7.9, 1.8 Hz), 5.90-6.10 (1H, m), 6.20 (1H, dd, *J*=3.0, 1.5 Hz), 6.98 (1H, dd, *J*=3.8, 1.5 Hz), 7.06 (1H, dd, *J*=3.8, 3.0 Hz); MS: 176 *m/z* (M^+). *Anal*. Calcd for $C_{14}H_{13}N_3O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.60; H, 5.03; N, 31.86.

1-Allyl-2-azidocarbonylindole (**6b**) (1.08 g, 80%) as undistillable pale yellow oil; IR (nujol): 2120, 1680 (cm^{-1}); ^{1}H-NMR: 5.08 (2H, m), 5.26 (1H, dd, *J*=10.8, 1.8 Hz), 5.31 (1H, dd, *J*=7.7, 1.8 Hz), 6.05 (1H, m), 6.91 (1H, s), 7.15-7.57 (4H, m); MS: 226 *m/z* (M^+). *Anal*. Calcd for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.76. Found: C, 63.66; H, 4.50; N, 24.82.

Thermal behavior of acylazides (2) and (6). A solution of the appropriate acylazide (**2**) or (**6**) (4.5 mmol) in dry toluene (225 mL) was refluxed for the time indicated in Table 1. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with ethyl acetate-hexane (6:1). Cycloadducts (**4**) was eluted first, followed by pyrrolo- or indolo[1,2-*a*]pyrazine (**9**). Further elution gave urea derivatives (**3**) or (**7**).

N,*N*'-*bis*-(1-Propargyl-2-pyrrolyl)urea (**3a**) (0.19 g, 31%) as white amorphous powder having mp 194°C (from acetone-chloroform); IR (nujol): 1670 (cm^{-1}); ^{1}H-NMR: 2.53 (2H, t, *J*=2.7 Hz), 5.35 (4H, d, *J*=2.7 Hz), 6.15-6.95 (6H, m), 8.78 (2H, br s); MS: 266 *m/z* (M^+). *Anal*. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.70; H, 5.33; N, 20.08.

N,*N*'-*bis*-(1-Propargyl-2-indolyl)urea (**3b**) (0.33 g, 40%) as white amorphous powder having mp 185°C (from acetone-chloroform); IR (nujol): 3280, 1720 (cm^{-1}); ^{1}H-NMR: 2.54 (2H, t, *J*=2.4 Hz), 5.02 (4H, d, *J*=2.4 Hz), 6.52 (2H, s), 7.05-7.82 (8H, m), 8.92 (2H, br s); MS: 366 *m/z* (M^+). *Anal*. Calcd for $C_{23}H_{18}N_4O$: C, 75.39; H, 4.95; N, 15.29. Found: C, 75.44; H, 4.99; N, 15.36.

8-Oxo-pyrrolo[1,2-*d*][1,2,3]triazolo[5,1-*a*]pyrazine (**4a**) (0.31 g, 39%) as white amorphous powder having mp 166°C (from methanol); IR (nujol): 1680 (cm^{-1}); ^{1}H-NMR: 5.35 (2H, s), 6.20 (1H, dd, *J*=2.8, 1.5 Hz), 6.96 (1H, dd, *J*=3.7, 1.5 Hz), 7.05 (1H, dd, *J*=3.7, 2.8 Hz), 7.66 (1H, s); MS: 174 *m/z* (M^+). *Anal*. Calcd for $C_8H_6N_4O$: C, 55.17; H, 3.47; N, 32.17. Found: C, 55.24; H, 3.51; N, 32.24.

10-Oxo-indolo[1,2-*d*][1,2,3]triazolo[5,1-*a*]pyrazine (**4b**) (0.43 g, 43%) as pale yellow amorphous powder having mp 98°C (from diisopropyl ether); IR (nujol): 1650 (cm^{-1}); ^{1}H-NMR: 5.02 (2H, s), 6.82 (1H, s), 7.05-7.40 (4H, m), 7.81 (1H, s); MS: 224 *m/z* (M^+). *Anal*. Calcd for $C_{12}H_8N_4O$: C, 64.28; H, 3.60; N, 24.99. Found: C, 64.33; H, 3.63; N, 25.07.

N,*N*'-*bis*-(1-Allyl-2-pyrrolyl)urea (**7a**) (0.32 g, 53%) as white amorphous powder having mp 172°C (from acetone-chloroform); IR (nujol): 3285, 1640 (cm^{-1}); ^{1}H-NMR: 4.90-4.97 (4H, m), 5.18 (4H, dd, *J*=11.0, 1.7 Hz), 6.06 (2H, ddd, *J*=11.0, 7.4, 5.2 Hz), 6.20-6.90 (6H, m), 8.85 (2H, br s); MS: 270 *m/z* (M^+). *Anal*. Calcd for $C_{15}H_{18}N_4O$: C, 66.64; H, 6.71; N, 20.73. Found: C, 66.60; H, 6.67; N, 20.80.

N,*N*'-*bis*-(1-Propargyl-2-indolyl)urea (**7b**) (0.49 g, 59%) as white amorphous powder having mp 179°C (from acetone-chloroform); IR (nujol): 3280, 1685 (cm^{-1}); ^{1}H-NMR: 5.02-5.12 (4H, m), 5.20 (2H, dd, *J*=10.9, 1.8 Hz), 5.28 (2H, dd, *J*=7.8, 1.8 Hz), 6.2-6.12 (2H, m), 6.84 (2H, s), 7.0-7.4 (8H, m), 8.85 (2H, br s); MS: 370 *m/z* (M^+). *Anal*. Calcd for $C_{23}H_{22}N_4O$: C, 74.57; H, 5.99; N, 15.12. Found: C, 74.62; H, 6.03; N, 15.20.

2-Methyl-7-oxo-pyrrolo[1,2-*a*]pyrazine (**9a**) (0.11 g, 16%) as pale yellow undistillable oil; IR (nujol): 1670 (cm^{-1}); ^{1}H-NMR: 2.89 (3H, s), 5.06 (2H, s), 6.18 (1H, dd, *J*=2.8, 1.5 Hz), 6.89 (1H, dd, *J*=3.7, 1.5 Hz), 6.97 (1H, dd, *J*=3.7, 2.8 Hz); MS: 148 *m/z* (M^+). *Anal*. Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.89; H, 5.40; N, 18.97.

2-Methyl-10-oxo-indolo[1,2-*a*]pyrazine (**9b**) (0.17 g, 19%) as pale yellow undistillable oil; IR (nujol): 1680 (cm^{-1}); ^{1}H-NMR: 2.90 (3H, s), 5.11 (2H, s), 6.82 (1H, s), 6.9-7.4 (4H, m); MS: 198 *m/z* (M^+). *Anal*. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.75; H, 5.12; N, 14.20.

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