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Synthesis of tricyclic-2-aminoindoles by intramolecular 1,3-dipolar cycloaddition of 1-ω-azidoalkylindoles

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Abstract—Thermolysis of the 1- ω -azidoalkylindoles **4**, bearing an electron attracting substituent at C-3 (CHO, COMe, COOMe, CN) provides imidazo[1,2-*a*]indoles (**5**, *n*=1), pyrimidino[1,2-*a*]indoles (**5**, *n*=2), and 1,3-diazepino[1,2-*a*]indoles (**5**, *n*=3). © 2001 Elsevier Science Ltd. All rights reserved.

2-Aminoindoles in which the nitrogen atoms are connected by a polymethylene chain 1 are a relatively rare class of compounds, some of which have recently been patented as 5HT4-receptor antagonists.¹ The pyrimidino[1,2-*a*]indole derivatives (1, n=2) are most expeditiously synthesized by the remarkable phosphorous oxychloride induced rearrangement of 1-phenyl-2acylpyrazolidines (Golubeva synthesis).² They can also be prepared from *m*-dinitrobenzene derivatives and 1,8diazabicyclo[5.4.0] undec-5-ene (DBU),³ and by alkylation of 2-chloro-3-acylindoles with 3-chloro-N,Ndialkylaminopropane.⁴ The latter process also provides imidazo[1,2-*a*]indoles (1, n=1) where the alkylation is effected with 2-chloro-N,N-dimethylaminoethane.⁴ This communication describes a simple three-step process which provides easy access to congeners of 1 where n = 1 - 3.



N-Alkylation of the indoles **2** (Scheme 1) with the appropriate 2-bromoalkyl chloride gave the chloro compounds **3** (55-96%),⁵ which, on reaction with sodium azide in DMSO, produced the azides **4** (80–100%).⁶ These azido compounds were stable in toluene at 100°C, but heating bromobenzene solutions thereof at 180°C in a sealed metal reactor (4–12 h) did result in product formation. For these azido compounds where R is an electron attracting substituent, mixtures of the tricyclic 2-aminoindoles **5** and the indoles **2** were produced (Table 1)⁷ in which the tricyclic compounds



Scheme 1. (a) BrCH₂(CH₂)_nCl, NaH–DMF; (b) NaN₃, DMSO; (c) PhBr, 180°C.

Keywords: cycloaddition; synthesis; pyrimidinol[1,2-*a*]indoles; imidazo[1,2-*a*]indoles.

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Table 1. Thermolysis products of $1-\omega$ -azidoalkylindoles (4)

Entry	R	n	Products ¹³			
				5 Yield (%)	Mp (°C)	2 Yield (%)
1	Н	1		0		80
2	Me	1		0		75
3	CHO	1	а	80	(188–190)	20
1	CHO	2	b	53	(165–166)	25 ^a
5	CHO	3	с	60	(137–139)	20 ^a
5	COMe	1	d	50	(196–197)	20 ^a
,	COMe	2	e	65	(185–188)	25 ^a
	CO ₂ Me	2	f	50	(186–187)	30 ^a
<i>.</i>)	CN	2	g	70	(196–197)	23

^a Unreacted starting material was recovered.

predominated in all cases. In contrast, when the substituent in 4 was hydrogen or methyl, no tricyclic compounds were formed, and the indoles 2 were the only products (entries 1 and 2).

We suggest that the formation of **5** proceeds by an intramolecular 1,3-dipolar cycloaddition of the azido moiety to the indole 2,3-double bond to produce an intermediate triazoline **6**. Loss of nitrogen from **6**, perhaps via an intermediate aziridine, would lead to the observed tricyclic indoles. There is ample literature precedent for processes of this type involving the intramolecular cycloaddition of aliphatic azido functions to activated double bonds.⁹ Dipolar cycloadditions to indoles both of the intramolecular¹⁰ and intermolecular type, ^{11,12} are very rare, however, and the intramolecular azide cycloaddition described herein does not appear to have been reported previously.



We propose that the formation of the indoles 2 from the azido compound 4 is nitrene based and proceeds via the imines derived by hydrogen migration.¹⁴ For example, the four carbon derived imine 7, upon retroene fragmentation, would give rise to an *N*-vinylindole convertible into 2 on work-up.



The exclusive formation of nitrene-derived products from the azido compounds 4 (R = H, Me) implies that the activation energy for the cycloaddition process is significantly greater than that for nitrene generation. An electron attracting substituent at C-3 would be expected¹⁵ to facilitate the cycloaddition process and the results described herein suggest that in these cases the two processes have similar activation energies.

Our studies in this area are continuing.

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- 5. Typical procedure for the synthesis of 3. To a solution of indole (1.17 g, 0.1 mol) in 10 mL of DMF was added sodium hydride (0.253 g 0.11 mol 60% in mineral oil, previously washed with hexane) under a nitrogen atmosphere and the reaction mixture was stirred for 30 min at room temperature before the dihalide was added. After 2 h of stirring the reaction mixture was quenched by dropwise addition of water, extracted with EtOAc and washed with water and brine. The organic layer was dried over

 Na_2SO_4 , filtered and concentrated in vacuo and the residue purified by flash column chromatography on silica gel, using hexane–EtOAc (8:2) as eluent.

- 6. Typical procedure for the synthesis of 4. To a solution of alkylindole 3 (1 mmol) in DMSO (15 mL), sodium azide (2 mmol) was added and the mixture was stirred overnight at 60°C. The reaction mixture was quenched with water, extracted with EtOAc and washed with a sodium bicarbonate saturated solution and brine. The product was purified by flash column chromatography.
- 7. The structures of the tricyclic compounds are supported by NMR, IR and mass spectral data, and by a single crystal X-ray structure for 5 (n=2) (R=CHO), a known compound.⁸
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- Characterization of compounds 5a–e. Compound 5a: ¹H NMR (300 MHz, CDCl₃): δ 4.14 (m, 2H, CH₂-NH), 4.20 (m, 2H, CH₂-N), 6.02 (br, 1H, NH), 7.03–7.14 (m, 3H, ArH), 7.62 (d, 1H, *J*=6 Hz, ArH), 9.82 (s, 1H, CH=O); ¹³C NMR (75 MHz, CDCl₃): δ 181.7, 122.1, 121.5, 116.8, 108.9, 50.0, 42.6, 30.1; IR (film) *v*_{max} (cm⁻¹): 3246, 2921, 2889, 1607, 1138, 946; ESI-MS *m/z*: 187.1 ([MH]⁺, 100). Compound 5b: ¹H NMR (300 MHz, CDCl₃): δ 2.23 (m, 2H, CH₂), 3.54 (m, 2H, CH₂-NH), 3.97 (t, 2H, *J*=6.0 Hz, CH₂-N), 7.01–7.15 (m, 3H, ArH), 7.59 (dd, 1H, *J*=6.5 Hz, *J*=1.5 Hz), 7.83 (br, 1H, NH), 9.81 (s, 1H, CH=0); ¹³C NMR (75 MHz, CDCl₃): δ 184.6, 138.5, 124.3, 123.1, 122.3, 110, 52.3, 48.2, 44.0; IR (film) *v*_{max} (cm⁻¹): 3350,

2956, 2923, 1635, 1564, 1449, 1184, 1093; EI-MS m/z: 200 (M⁺, 85), 199 (100). 5c: ¹H NMR (300 MHz, CDCl₃): δ 2.04 (m, 4H, CH₂-CH₂), 3.44 (m, 2H, CH₂-NH), 4.04 (m, 2H, CH₂-N), 7.14 (m, 3H, ArH), 7.63 (d, 1H, J=4.5ArH), 8.46 (br, 1H, NH), 9.90 (s, 1H, CH=0). ¹³C NMR (75 MHz, CDCl₃): δ 184.4, 122.3, 121.1, 115.1, 109.2, 100.1, 52.3, 45.6, 29.8, 29.2, 23.8; IR (film) v_{max} (cm⁻¹): 3300, 2922, 2852, 1624, 1344, 1202; ESI-MS m/z: 215.2 ([MH]⁺, 100). Compound 5d: ¹H NMR (300 MHz, CDCl₃): δ 2.52 (s, 3H, CH₃CO), 4.20 (m, 4H, CH₂-CH₂), 6.12 (br, 1H, NH), 7.07 (m, 2H, ArH), 7.14 (m, 1H, ArH), 7.56 (d, 1H, J=7.0 Hz, ArH); ¹³C NMR (75 MHz, $CDCl_3$): δ 193.2, 131.5, 130.0, 121.4, 120.4, 118.9, 108.4, 49.1 29.7, 28.7, 22.6; IR (film) v_{max} (cm⁻¹): 3287, 2919, 2850, 1624, 1576; ESI-MS m/z: 201.2 ([MH]+, 100). Compound **5e**: ¹H NMR (300 MHz, CDCl₃): δ 2.22 (m, 2H, CH₂), 2.53 (s, 3H, CH₃CO), 3.54 (m, 2H, CH₂-NH) 3.97 (t, 2H, J=6.0 Hz, CH₂-N), 7.07 (m, 2H, ArH), 7.15 (m, 1H, ArH), 7.53 (d, 1H, J=8.0 Hz, ArH), 8.40 (br, 1H NH); ¹³C NMR (75 MHz, CDCl₃): δ 192.8, 132.8, 121.9, 120.1, 118.2, 107.6, 52.3, 39.3, 38.2, 29.2, 20.9; IR (film) v_{max} (cm⁻¹): 3303, 2937, 2860, 1624, 1584, 1479, 1255, 1170; ESI-MS m/z: 215.2 ([MH]⁺, 100). Compound 5f: ¹H NMR (300 MHz, CDCl₃): δ 2.22 (qt, 2H, J=6.0, CH₂), 3.53 (m, 2H, CH₂-NH), 3.87 (s, 3H, CH₃O), 3.99 $(t, 2H, J=6.0, CH_2-N)$, 7.03 (m, 2H, ArH), 7.13 (m, 2H), 7.73 (m, 1H, NH). ¹³C NMR (75 MHz, CDCl₃): δ 188.5, 136.3, 121.7, 119.6, 118.8, 107.1, 50.4, 39.5, 37.6; IR (film) v_{max} (cm⁻¹): 3369, 2973, 2950, 1648, 1599, 1480, 1266, 1169, 1051; ESI-MS m/z: 231.1 ([MH]+, 100). Compound 5g: ¹H NMR (300 MHz, CDCl₃): δ 2.23 (m, 2H, CH_2), 3.52 (m, 2H CH_2 -NH), 4.00 (t, 2H, $J = 6.0 CH_2$ -N), 5.16 (br, 1H, NH) 7.05 (m, 2H, ArH), 7.13 (m, 1H, ArH), 7.39 (d, 1H, J = 7.5, ArH); ¹³C NMR (75 MHz, CDCl₃): δ 121.9, 120.2, 117.0, 107.8, 53.2, 39.9, 39.1, 31.0, 21.3; IR (film) v_{max} : (cm⁻¹): 3298, 2983, 2958, 2189, 1600, 1470; EI-MS m/z: 197.0 (M⁺, 100).

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