Tetrahedron Letters,Vol.27,No.19,pp 2173-2176,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

A NEW SYNTHETIC APPROACH TO THE BENZAZOLE RING SYSTEM. SYNTHESIS AND ELECTROCYCLIC RING CLOSURE OF DIALKENYL AND ALKENYL-ARYL SUBSTITUTED PYRROLES, IMIDAZOLES AND OXAZOLES[1]

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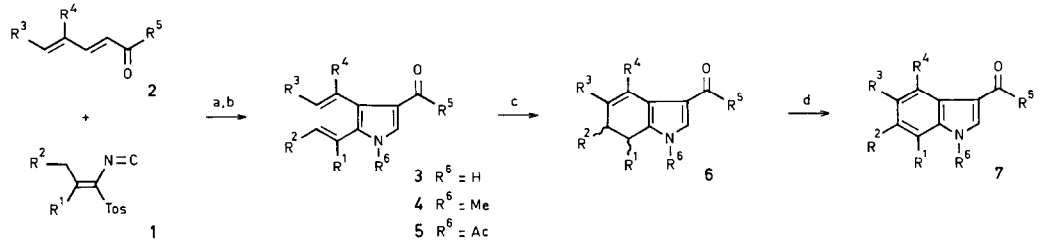
An efficient synthesis is described of the substituted azoles referred to in the title, which are precursors of an equally successful new synthetic approach to indoles, benzimidazoles and benzoxazoles.

Benzazoles are synthesized almost exclusively by formation of the azole ring on to a benzene nucleus, either from a monosubstituted or an ortho-disubstituted benzene precursor. For example, the well-known Fischer, Madelung, Reissert (and other) indole syntheses are based on such principles.[2,3] The same is true for benzimidazoles and benzoxazoles.[3] Benzazole ring systems, indoles in particular, often form the core of pharmaceutically, or otherwise, important natural products.[3]

This letter presents a promising alternative to the classical methods of preparing benzazoles. Scheme I outlines our new synthetic approach to indoles (7), Scheme II does the same for benzimidazoles (13) and benzoxazoles (14). The yields compiled in the Tables show the efficiency of the reactions involved.

SCHEME I



(a) t-BuOK, THF, -20°C, 1 h, to 3; (b) conditions a, followed by MeI, PTC (benzene, KOH, TEBACl) to 4; or conditions a, followed by t-BuOK, THF, AcCl, to 5; (c) thermally: triglyme, reflux (ca. 216°C), 1 h (includes H shifts); or photochemically: cyclohexane with 3-5% EtOH, room temp., 12 h (high pressure UV lamp, Hanau TQ 150, quartz filter); (d) DDQ, triglyme or benzene, 80°C, 1h.

TABLE I. Pyrroles 3, 4, 5, Dihydroindoles 6 and Indoles 7 Synthesized According to Scheme I

Compd[a]	R^1	R^2	R^3	R^4	R^5	R^6	Mp (°C)	Yield (%)	Prepared from
3a	$-(CH_2)_4-$	Ph	H	Ph	H	208-209	91	1 + 2	
4a	$-(CH_2)_4-$	Ph	H	Ph	Me	150-151	91	3a + MeI	
5a	$-(CH_2)_4-$	Ph	H	Ph	Ac	168-170	82	3a + AcCl	
4b	$-(CH_2)_4-$	Ph	H	MeO	Me	81-83	90	1 + 2; MeI	
4c	$-(CH_2)_3-$	Ph	H	Ph	Me	141-142	84	1 + 2; MeI	
4d	Me	H	Ph	H	Ph	Me	136-137	90	1 + 2; MeI
4e	$-(CH_2)_5-$	Ph	H	Me	Me	109-110	87	1 + 2; MeI	
4f	$-(CH_2)_{10}-$	Ph	H	Ph	Me	164-165	82	1 + 2; MeI	
4g	$-(CH_2)_3-$	$-(CH=CH)_2-$	Ph	Me	156-157	84	1 + 2; MeI		
4h	$-(CH_2)_4-$	-CH=CH-S-	2-thienyl	Me	108-110	94	1 + 2; MeI		
4i	$-(CH_2)_5-$	-CH=CH-O-	Ph	Me	n_D^{24} 1.605	93	1 + 2; MeI		
6a	$-(CH_2)_4-$	Ph	H	Ph	H	251-254	94	3a, Δ	
6b	$-(CH_2)_4-$	Ph	H	Ph	Me	168-170	96	4a, Δ	
6c	$-(CH_2)_3-$	Ph	H	Ph	Me	148-151	92	4c, Δ	
6d	Me	H	Ph	H	Ph	Me	75-79	87[b]	4d, Δ
7a	$-(CH_2)_4-$	Ph	H	Ph	Me	177-178	93	4a, Δ or hν, DDQ; or 6b, DDQ	
7b	$-(CH_2)_4$	Ph	H	Ph	H	233-234	31	5a, Δ, DDQ, hydrolysis	
7c	$-(CH_2)_4$	Ph	H	MeO	Me	156-157	86	4b, Δ, DDQ	
7d	$-(CH=CH)_2-$	Ph	H	Ph	Me	238-239	98	6b + 2.2 equiv. DDQ	
7e	$-(CH_2)_3-$	Ph	H	Ph	Me	172-173	83	4c, Δ or hν, DDQ; or 6c, DDQ	
7f	Me	H	Ph	H	Ph	Me	164-165	90	4d, Δ, DDQ; or 6d, DDQ
7g	$-(CH_2)_5-$	Ph	H	Me	Me	192-193	90	4e, Δ, DDQ	
7h	$-(CH_2)_{10}$	Ph	H	Ph	Me	186-187	89	4f, Δ, DDQ	
7i	$-(CH_2)_3-$	$-(CH=CH)_2-$	Ph	Me	148-149	76	4g, hν, DDQ		
7j	$-(CH_2)_4-$	-CH=CH-S-	2-thienyl	Me	205-206	78	4h, hν, DDQ		
7k	$-(CH_2)_5-$	-CH=CH-O-	Ph	Me	207-209	73	4i, hν, DDQ		

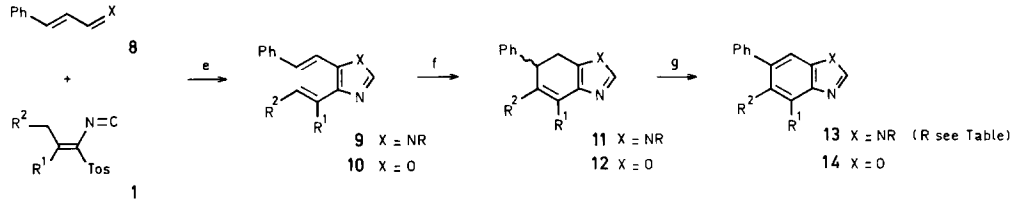
[a] See Note 10. [b] Mixture (ca. 1:1) of 6,7-dihydroindole 6d, and the 4,5-dihydroisomer.

Benzazoles 7, 13 and 14 are formed effectively by a thermal (or photochemical) electrocyclic ring closure of disubstituted azoles 3-5, 9 and 10, followed by dehydrogenation (DDQ). This benzazole synthesis involves the construction of a benzene ring on to a preformed azole, which, in a way, is a reversal of the classical approach.[4] Surprisingly, electrocyclizations as in Schemes I and II have not been realized previously,[5] plainly because a good synthesis of the requisite precursors (3-5, 9, 10) was lacking. In this letter we also offer an efficient method to synthesize these precursors.

Dialkenylpyrroles 3 were formed in one operation by a base-induced site- and regiospecific cycloaddition of 1-tosylalk-1-enyl isocyanides[6] to α,β-γ,δ-unsaturated ketones and esters 2 (Scheme I, Table I).[7,8] In most cases, pyrroles 3 were converted, without being isolated, to N-methyl derivatives (4) or N-acetyl derivatives (5), because N-protection is necessary in the final dehydrogenation step.

The dialkenyl-precursors of benzoxazoles 10 and benzimidazoles 9 were obtained by an analogous cycloaddition of 1 to α,β-unsaturated aldehydes 8 (X = O) or α,β-unsaturated imines 8 (X = N-R), respectively (Scheme II, Table II).[8] In case of imines, the nitrogen of 8 (X = NR) was substituted with an electron-withdrawing substituent (R = p-nitrophenyl, tosyl) to direct cycloaddition of 1 to the C,N double bond.[9] The N-tosyl group is spontaneously removed to give 13c (X = NH, 79%) during the process of electrocyclization and dehydrogenation of 9 (X = N-tosyl).

SCHEME II



(e) t-BuOK, THF, -78° to 20°C in 2 h, to 9; or K_2CO_3, MeOH reflux, 2 h, to 10; (f) triglyme, reflux (ca. 216°C), 1 h (includes H shifts); (g) DDQ, triglyme or toluene, 110°C, 1h.

References and Notes

1. Chemistry of Sulfonylmethyl Isocyanides 29. For part 28, see A.M. van Leusen, R. Oosterwijk, E. van Echten and D. van Leusen, Recl. Trav. Chim. Pays-Bas, 104, 50 (1985).
2. An excellent brief introduction is given by L.A. Paquette, "Modern Heterocyclic Chemistry", Benjamin, New York 1968, Ch. 5.
3. More complete coverage of syntheses and applications are: (a) (for indoles) "The Chem. of Heterocycl. Compds.", A. Weissberger and E.C. Taylor Eds., Vol. 25, Parts 1 and 4, Wiley-Interscience, New York 1972 and 1983; (b) (for benzimidazoles), ibid., Vol. 40, Parts 1 and 2, New York 1980 and 1981; (c) (for benzoxazoles) J.W. Cornforth in "Heterocycl. Compds." (R.C. Elderfield, Ed.), Vol. 5, p. 418, Wiley, New York 1957.
4. Indoles have been prepared earlier from pyrroles by formation of the benzene ring, e.g. by a Diels-Alder of 2-vinylpyrroles,[a] or by ring closure of alkadienylpyrrole derivatives:[b,c,d] (a) R. Alan Jones, T.A. Saliente and J.S. Arques, J.C.S. Perkin Trans. I, 1984, 2541, and earlier work of Jones' group; (b) B.I. Rosen and W.P. Weber, Tetrahedron Lett. 1977, 151; (c) A.P. Kozikowski, presented at the XIth Eur. Colloq. Heterocycl. Chem., Ferrara, Italy, Oct. 1985; (d) V.H. Rawal and M.P. Cava, Chem. Commun. 1984, 1526.

5. Electrocyclization of the carbocyclic analogues, i.e. o-divinylbenzenes is a known process: see E.N. Marvell, "Thermal Electrocyclic Reactions", Academic Press, New York 1980.*
6. A.M. van Leusen and J. Wildeman, Recl. Trav. Chim. Pays-Bas 101, 202 (1982); A.M. van Leusen, F.J. Schaart and D. van Leusen, ibid. 98, 258 (1979).
7. A similar reaction takes place, obviously, when in 2 the unit $R^3CH=CR^4$ forms part of an aromatic ring, in which case electrocyclization has to be effected photochemically (Table I).
8. These reactions are related to the azole syntheses of Michael acceptors and tosylmethyl isocyanide (TosMIC), see A.M. van Leusen, Lect. in Heterocycl. Chem. 5, S111 (1980); O. Possel and A.M. van Leusen, Heterocycles 7, 77 (1977), and ref. cited therein.
9. (a) With 8 (X = N-Tos) a 1:1 mixture was obtained of imidazole 9c (Table II) and a pyrrole derivative [2-(cyclohex-1-enyl)-3-phenyl-4-pyrrolecarboxaldehyde N-tosylimine, 34%] by reaction of 1 with the C,N and C,C double bonds, respectively. (b) With, for example, 8 (X = NC_6H_5) reaction occurs at the C,C double bond to form a pyrrole [2-(cyclohept-1-enyl)-3-phenyl-4-pyrrolecarboxaldehyde N-phenylimine, 70%], which, by the way, forms an interesting precursor in a new synthesis of 3-pyrrolecarboxaldehydes, R. van Stralen, unpublished results.
10. All compounds listed in Tables I and II are new; the structures are supported by NMR data and correct combustion analyses or exact mass determinations.

TABLE II. Imidazoles 9, Oxazoles 10, Dihydrobenzimidazole 11, Benzimidazoles 13 and Benzoxazole 14 Synthesized According to Scheme II

Compd[a]	R^1	R^2	X	Yield (%)	Mp (°C)	Prepared from
9a	$-(CH_2)_3-$	p-$O_2NC_6H_4N$		70	143-145	1 + 8
9b	$-(CH_2)_4-$	p-$O_2NC_6H_4N$		70	154-156	1 + 8
9c	$-(CH_2)_4-$	p-$CH_3C_6H_4SO_2N$		34[b]	162-164	1 + 8
9d	$-(CH_2)_5-$	p-$O_2NC_6H_4N$		80	114-116	1 + 8
9e[c]	$-(CH_2)_4-$	PhN		29[d]	115-116	[e]
10a	$-(CH_2)_4-$	O		90	oil	1 + 8
10b	$-(CH_2)_5-$	O		90	oil	1 + 8
11	$-(CH_2)_4-$	p-$O_2NC_6H_4N$		100[f]	159-170[f]	9b, Δ
13a	$-(CH_2)_4-$	p-$O_2NC_6H_4N$		70	202-204	9b, Δ, DDQ
13b	$-(CH_2)_5-$	p-$O_2NC_6H_4N$		67	194-196	9d, Δ, DDQ
13c	$-(CH_2)_4-$	NH[g]		79	211-212	9c, Δ, DDQ
13d	$-(CH_2)_4-$	PhN		78	ca. 159	9e, hν
14	$-(CH_2)_5-$	O		60	99-101	10b, Δ, DDQ

[a] See Note 10. [b] See Note 9(a). [c] Compd. 9e carries a PhC C- group at C-5 rather than PhCH=CH-. [d] Yield not optimized. [e] Prepared from 1 + phenylpropargylaldehyde phenylimine. [f] Contaminated with ca. 25% of dehydrogenated material (13a) according to ^{1}H NMR. [g] See text.

* A referee kindly focussed our attention to two recent papers dealing with successful as well as unsuccessful electrocyclizations of 2,3-dialkenylindoles to carbazoles: S. Kano, E. Sugino, S. Shibuya and S. Hibino, J. Org. Chem. 46, 3856 (1981); R.A. Jones, P.M. Fresneda, T.A. Saliente and J. Sepúlveda Arques, Tetrahedron 40, 4837 (1984).

(Received in UK 27 January 1986)