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ON THE SYNTHESIS OF ISOANNULATED PYRROLES AND α-PYRIDONES[1]

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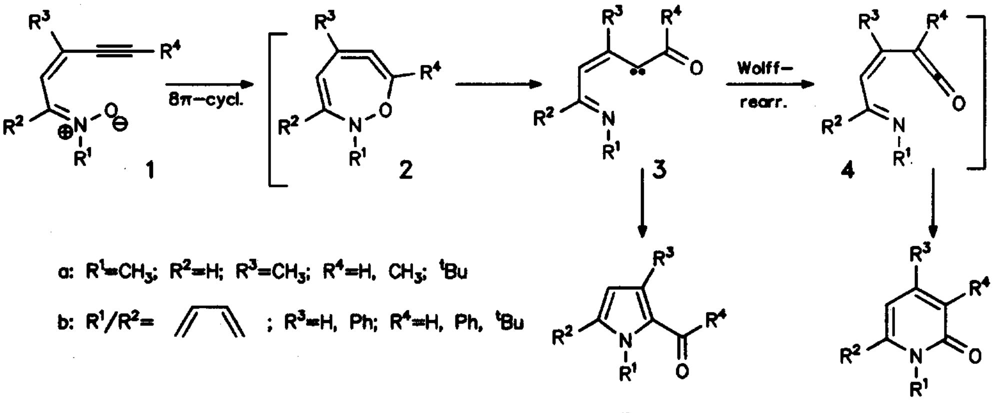
Summary: The synthesis of furo- and thieno[2,3-c]pyridones **13a,b** as well as the corresponding pyrroles **14a,b** by using the 1,7-dipolar cyclization route of conjugated nitrones **9a,b** is reported. In the presence of O_2 and light the pyridones are converted into the pyridinediones **17a,b**.

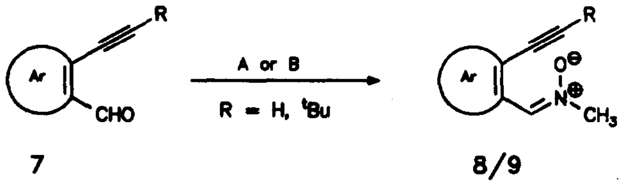
N-heterocycles incorporated in mono- and polycyclic systems are important structural features of innumerous naturally ocurring substances. Therefore any new synthetic approach complementing the existing methodologies is highly desirable. Within the broad domain of dipolar reactions in the field of heterocyclic synthesis[2] we became particularly interested in 8π-electrocyclization reactions which involve terminal alkyne groups. Recent investigations with nitrones as dipolar component revealed an efficient and versatile access to pyrroles and α-pyridones **5a/6a**[3] as well as to indolizines and quinolizines **5b/6b**[4a] involving oxazepins **2**, ketocarbenes **3** and ketenes **4** as intermediates. Analogous work with respective carbonyl ylide systems gave rise to the formation of a whole series of simple and differently annulated 2-vinyl furans.[5]



Scheme 1

Since it is now well established that aromatic and heteroaromatic rings can effectively participate in 6π- and 8π-cyclizations[2,4,5c,6] we have studied - on the basis of the above concept - the thermal behavior of nitrones like **8/9** as potential precursors of previously less known isoannulated pyrroles and pyridones.

The synthesis of the benzo, thieno and furo derivatives was accomplished by simply reacting the aldehydes **7** with hydroxylamine derivatives affording **8** and **9a,b** in excellent yields (see Table 1).

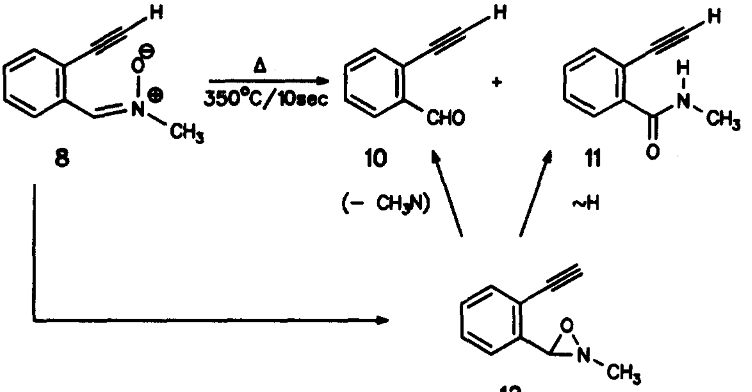


	Ar	R
8	benzo	H
9a	thieno	ᵗBu
9b	furo	ᵗBu

Table 1: ***Selected data of 8 and 9a,b***

	method	yield [%]	mp [°C]	^{1}H-NMR (δ-values) [ppm]
8	A	82	135	8.01 (N=CH); 3.93 (N–CH$_3$); 3.44 (R); 9.32, 7.57, 7.46, 7.36 (Ar–H)
9a	B	90	121	7.98 (N=CH); 3.93 (N–CH$_3$); 1.37 (R); 7.10, 7.34 (Ar–H)
9b	A	86	134	7.29 (N=CH); 3.81 (N–CH$_3$); 1.27 (R); 6.41; 7.45 (Ar–H)
A: TMS–N(CH$_3$)–OTMS; CF$_3$SO$_3$TMS; B: CH$_3$NH–OH*HCl; CH$_3$CO$_2$Na				

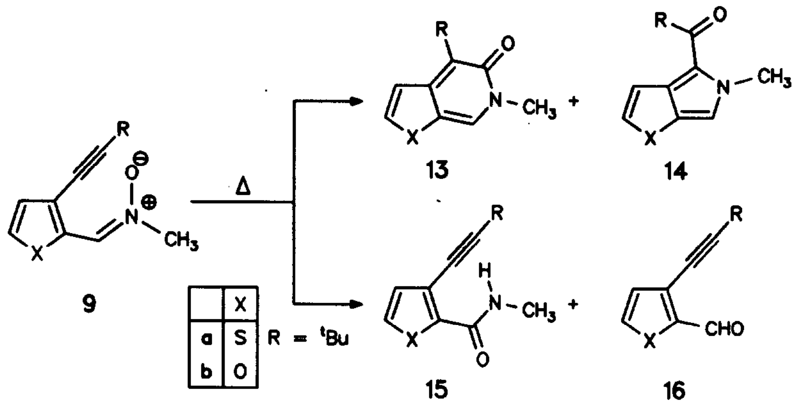
Upon thermal activation of the benzo annulated nitrone 8 by using the short time thermolysis technique[5] (350°C/10 sec) a complex mixture was formed containing starting material (30%), o-ethynyl benzaldehyde (10, ca. 30%) and the N-methylbenzamide 11 (ca. 3%) as the only monomolecular products. The formation of the two products can be explained by assuming oxaziridine 12 as an intermediate[7] which undergoes either fragmentation to 10 and methylnitrene or rearrangement to 11 involving H-migration.



Scheme 2

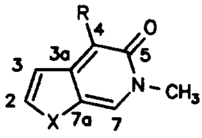
Complete conversion of the thieno derivative 9a was achieved at 420°C. In this case oxaziridine formation takes place only to a small extent as judged by the ca. 5% yield of the secondary products 15a/16a. The major components are identified as the thieno[2,3-c]pyridone 13a (25%) and the thieno[2,3-c]pyrrole 14a (11%), respectively. Whereas only one reference exists for the former heterocycle,[9] the latter system is already described for some derivatives as well as for the parent compound.[10]

Short time thermolysis of the furo-annulated nitrone 9b (350°C/10 sec) afforded a product mixture containing predominately the furopyridone 13b and the furopyrrole 14b (54% and 26%, respectively). Again the oxaziridine route, affording the aldehyde 15b and the amide 16b, is a very minor pathway (<3%). 13b and 14b are the first representatives of these isoannulated heteroaromatic systems[11] (see Table 2 for a selection of NMR data).

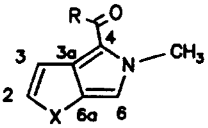


Scheme 3

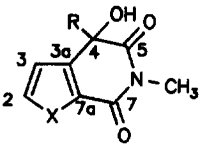
Table 2: *Selected ^{1}H- (CDCl$_3$ /250 MHz) and ^{13}C-NMR data (CDCl$_3$ /100 MHz) of* ***13a,b, 14a,b*** *and* ***17a,b***

		X	2-H	3-H	7-H	CH_3	R		$^3J_{2,3}$	$^5J_{3,7}$
	13a	S	7.63	7.44	7.84	3.68	1.62		6	1
	13b	O	7.45	6.96	7.62	3.65	1.55		2.5	1

		C-2	C-3	C-3a	C-4	C-5	C-7	C-7a	CH_3	R
R = ^{t}Bu	13a	150.3	106.7	138.2	127.2	160.3	117.4	141.0	38.9	37.4, 29.6

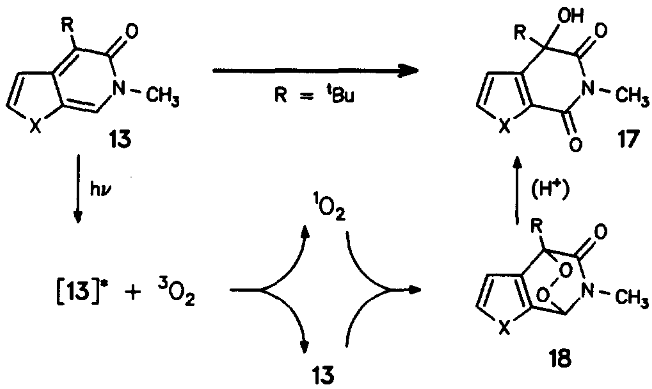
		X	2-H	3-H	6-H	CH_3	R		$^3J_{2,3}$	$^5J_{3,6}$
	14a	S	7.22	7.27	7.00	4.06	1.42		6	<0.5
	14b	O	7.46	6.60	6.73	4.05	1.40		2.2	0.7

		C-2	C-3	C-3a	C-4	C-6	C-6a	C=O	CH_3	R
R = ^{t}Bu	14a	129.1	120.0	135.7	123.4	120.8	127.5	196.3	40.3	43.0, 31.0
	14b	148.4	106.0	122.5	115.3	108.5	147.0	196.1	40.8	42.9, 27.3

		X	2-H	3-H	OH	CH_3	R		$^3J_{2,3}$
	17a	S	7.63	7.20	3.72	3.28	0.90		5.2
	17b	O	7.69	6.69	3.58	3.29	0.79		2.2

		C-2	C-3	C-3a	C-4	C-5	C-7	C-7a	CH_3	R
R = ^{t}Bu	17a	132.5	127.1	145.8	80.5	177.6	160.4	129.1	27.0	41.6, 24.9
	17b	147.7	111.5	132.1	79.5	177.3	156.2	140.6	26.6	40.7, 24.6

During the purification procedure a significant loss of both pyridone derivatives, **13a** and **13b**, has been observed with concomitant formation of a new substance in each case. According to the structural analysis (MS, ^{1}H/ ^{13}C-NMR) the compounds were identified as **17a** and **17b** , formally obtained by addition of oxygen. Control experiments showed that the transformations take place neither in the dark nor in the absence of oxygen. Therefore a mechanism is proposed which involves [4+2]-addition of singlet oxygen formed on photosenzitization by the pyridones[12] (13b: $\lambda_{max}=354$ nm; $\varepsilon=7800$); the initially produced endo-peroxides 18 undergo H^+-catalyzed ring cleavage affording the diketones17.[15,16]



Scheme 4

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11. The results with compounds 9 bearing a terminyl alkyne group (R= H) are very similar and will be reported in our forthcoming full paper.
12. This pathway is supported by results with simple α-pyridones[13] and α-pyrazinones.[14]
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15. Prelimenary studies on the general Diels-Alder reactivity of the furo-pyridone 13b showed no substantial rate enhancement compared to the behavior of simple pyridones.
16. All new compounds are characterized by spectroscopic data as well as elemental analysis and/or mass spectra.

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