

SYNTHESIS AND PROPERTIES OF UNUSUALLY STABLE, HETEROCYCLIC NITRILIUM-YLIDES

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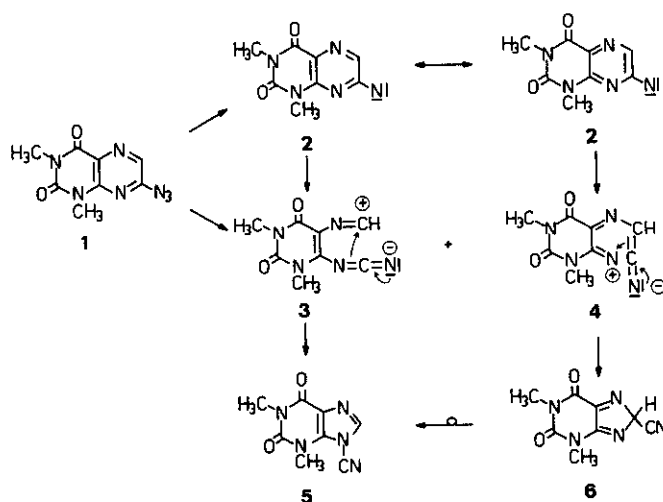
Sir Derek Barton dedicated to his 70th birthday and in admiration of his many important contributions to chemistry.

Abstract - 7-Azido-1,3-disubstituted lumazines show at elevated temperatures two new ring contractions leading to 9-cyanoxanthines and a new type of stable purin-8-yl nitrilium ylides. This high stability is due to a strong resonance stabilization of the negatively charged purinyl anion moiety, which does not even afford a bulky substituent at the nitrilium C-atom to counteract secondary reactions. The structures of the new nitrilium ylides have been proven by spectral means and comparisons with model substances.

The chemistry of nitrilium ylides¹ is under investigation for more than 25 years and revealed numerous syntheses, which generate this reactive function under a variety of conditions²⁻⁵. It is generally agreed that only in special cases a stable isolable nitrilium ylide can be expected due to the high reactivity of this functionality in 1,3-dipolar cycloaddition reactions and towards nucleophiles. Only recently the synthesis of the first stable nitrilium ylide could be achieved by the photolysis of diazotetrakis(trifluoromethyl)cyclopentadiene in presence of 1-adamantyl nitrile to form 1-adamantyl nitrilium N-tetrakis(trifluoromethyl)cyclopentadienylide⁶, which was crystallized and its structure proven unequivocally by X-ray structure determination⁷. This result is not unexpected in view of the anion stabilizing ability of the tetrakis(trifluoromethyl)cyclopentadienylide moiety as well as the steric bulk of the adamantyl residue. The first example of a thermally generated nitrilium ylide is derived from 5-tert.-butyl-3,3-bis(trifluoromethyl)-2,3-dihydro-1,4, λ^5 -oxazaphosphol by vacuum flash pyrolysis at 400°/10⁻³ Torr and matrix isolation at -196°C⁸.

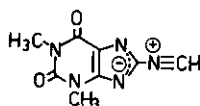
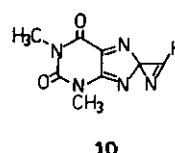
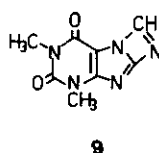
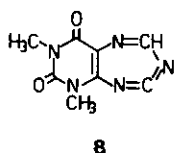
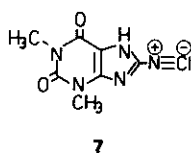
Our interest in nitrilium ylides arose more or less accidentally during studies of various relatively unstable 7-azidolumazine derivatives. We noticed that 7-azido-

1,3-dimethylumazine (1) converts on drying at 100°C in the oven in a solid state reaction without change of its habitus into a new product, which was identified as 9-cyano-1,3-dimethylxanthine (5). We assume that this new pteridine → purine ring-contraction proceeds either via the intermediary nitrene 2 or directly in a zwitterazo cleavage^{9,10} to the intermediates 3 and 4 respectively, which cyclize directly to 9-cyano-1,3-dimethylxanthine (5) or via the 8-cyano isomer 6 followed by a 1,5-sigmatropic shift of the functional group.

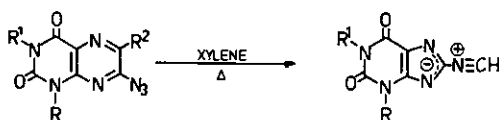


There are already some precedences in literature of analogous ring contractions of 2-azidopyrazines into N-cyanoimidazoles^{11,12}.

In a second experiment we heated 1 in xylene and obtained a relatively insoluble material isomeric with 5 according to elemental analysis and the distinct differences of their uv and ir spectra. Treatment of this product in H₂O or n-BuOH led to 8-aminotheophylline indicating that another pyrazine ring contraction has taken place on heating of 1 in an aprotic solvent. From the nmr spectrum in D₆-DMSO can be concluded that the structure of theophyllin-8-yl isocyanide (7) has to be excluded as a sensible possibility due to the presence of a singlet at 8.58 ppm, which is rather a C-H than a N-H signal from its stability in a D₂O exchange experiment. Since heterocyclic azides¹³⁻¹⁷ show a broad variety of reactions the structures of a cyclic carbodiimide (8), a condensed 1,3-diazeto[1,2-f]purine derivative (9), a spiro-compound (10) or a resonance stabilized nitrilium ylide (11) cannot a priori be eliminated.



It is obvious that the solution of the difficult structural problem will arise from spectral data and comparisons with model substances. From the ir spectrum, which exhibits a characteristic band at 2180 cm^{-1} we can conclude that the cyclic carbodiimid **8**, the tricyclic ring system **9**, and the spiro-structure **10** respectively are very much unlikely, whereas the existence of a stable nitrilium ylide (**11**) is in favour. The uv spectrum in methanol shows two strong bands at 234 and 295 nm and a shoulder at 250 nm, which resembles best with 8-ethynyltheophylline¹⁸ as the closest structural analog (Table). Very similar spectral features are also found for the reaction products derived from 7-azido-1-isopropyl-3-methylumazine (**12**) and its 1-neopentyl- (**13**) and 1-neopentyl-3-n-octyl analog (**14**) in a similar manner and leading to better soluble nitrilium ylides (**18-20**). The presence of an additional alkyl substituent in 6-position (**15**, **16**) or the removal of the N-1 substituent (**17**) does not favour the nitrilium ylide formation but leads to the 9-cyano-xanthines **21-23**.



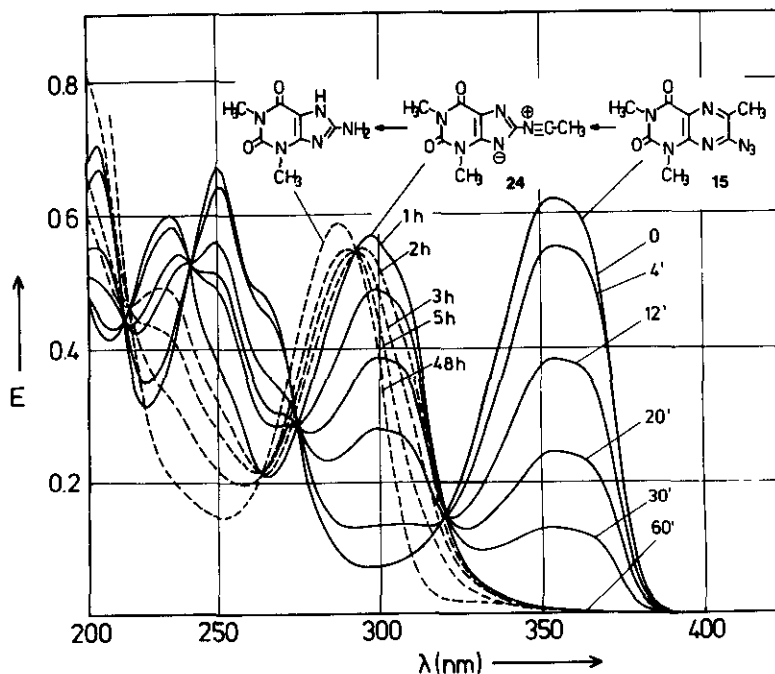
	R	R ¹	R ²
12	CH(CH ₃) ₂	CH ₃	H
13	CH ₂ C(CH ₃) ₃	CH ₃	H
14	CH ₂ C(CH ₃) ₃	C ₈ H ₁₇	H
15	CH ₃	CH ₃	CH ₃
16	CH ₃	CH ₃	CH(CH ₃) ₂
17	H	CH ₃	H

	R	R ¹
18	CH(CH ₃) ₂	CH ₃
19	CH ₂ C(CH ₃) ₃	CH ₃
20	CH ₂ C(CH ₃) ₃	C ₈ H ₁₇

	R	R ¹
21	CH ₃	CH ₃
22	CH ₃	CH(CH ₃) ₂
23	H	H

In the case of 7-azido-1,3,6-trimethylumazine (**15**) the formation of the corresponding nitrilium ylide (**24**) could only be detected on photolysis in methanol as

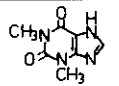
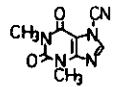
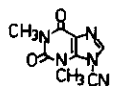
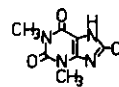
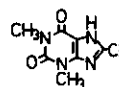
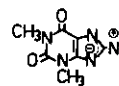
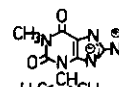
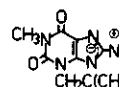
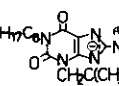
an intermediate which is further hydrolysed to give 8-aminotheophylline.



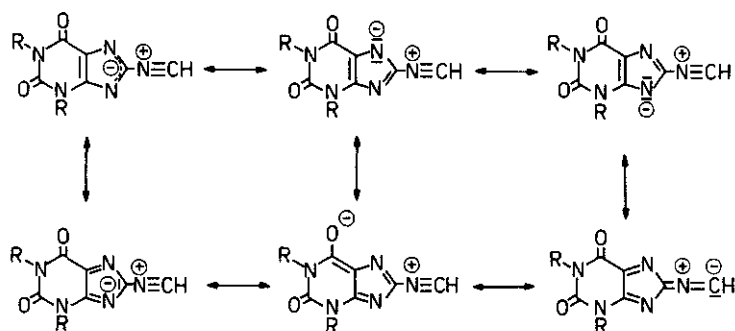
More information was finally obtained from ^{13}C -nmr spectra, which are in excellent agreement with the proposed stable nitrilium ylide structures 11, 18-20.

It was found with the well-soluble nitrilium ylide 20 in a gated decoupling experiment in CDCl_3 a ^1H - ^{13}C coupling of 246 Hz at 145.5 ppm, which is due to the nitrilium moiety of the molecule proving directly this unusual structure. There was also observed another long-range coupling of 10 Hz of the signal at 109.5 ppm, which has to be assigned logically to the C-8 atom. Comparing the ^{13}C -nmr spectra of the purinium-betaine structures with those of the other xanthine derivatives (table) it is obvious that the different electron distributions in both systems show similarities only at C-6, C-2 and C-4, whereas in the zwitter-ion molecules the chemical shifts of C-5 are moved down-field to some extent and C-8 is altered tremendously up-field indicating a relatively high electron density at this center.

Regarding the mechanism of formation of the nitrilium ylides we assume first cleavage to the intermediate 3, which shows an electrocyclization to 8 followed by a valence tautomerism to 9 and finally ring opening to 11.

	Uv Spectra IN MeOH		Ir cm ⁻¹	¹³ C-Nmr Spectra IN DMSO-d ₆					
	λ _{MAX}	lg ε		C-6	C-2	C-4	C-8	C-5	-XEG
	270	4.02		154.0	150.9	147.5	139.9	106.1	
	[230] 283	[3.85] 3.84	2258	152.7	150.7	147.3	146.0	103.0	105.8
	245 [260]	4.00 [3.94]	2260	155.7	149.9	137.2	140.0	103.0	114.6
	218 296	4.38 4.12	2220	154.0	150.6	146.5	121.1	110.3	111.4
	222 [246] 294	4.40 [3.63] 4.25	2140	153.7	150.9	147.0	131.8	107.2	84.0 73.5
	234 [250] 295	4.22 [3.95] 4.21	2180	156.9	154.0	148.5	109.4	114.4	146.5
	237 [250] 296	4.19 [3.97] 4.19	2200	156.9	154.9	147.8	109.4	114.2	146.6
	237 [250] 297	4.19 [3.98] 4.19	2190	157.6	154.1	149.1	109.5	114.3	146.8
	238 [250] 297	4.22 [3.98] 4.25	2180	157.7	152.7	148.8	110.1	114.5	145.5

The unusual high thermodynamical stability of the new type of heterocyclic nitrilium ylides is due to a strong resonance stabilization of the negatively charged anion moiety of the molecule. We have isolated with this type of compounds the first case of a stable nitrilium ylide, which does not afford a further bulky substituent at the nitrilium ylide C-atom to counteract secondary reactions.



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