REACTIONS OF AZAPYRYLIUM IONS WITH NUCLEOPHILES: FROM CRAZY PRODUCTS TO A NOVEL PYRIDINE SYNTHESIS[1]

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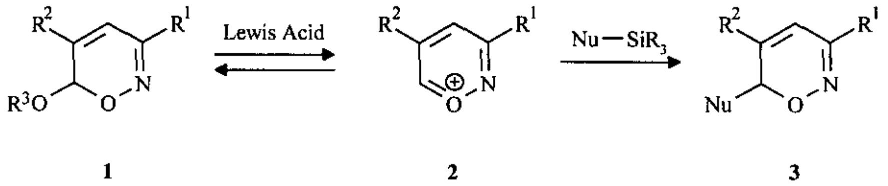
Abstract - Reaction of an azapyrylium ion as generated from a 6*H*-1,2-oxazine provided a β-azidoaldehyde by subsequent substitution, [3,3] sigmatropic rearrangement, and retro-Diels-Alder reaction. With moderately electron-rich alkynes azapyrylium ions react in a Diels-Alder reaction with inverse electron demand, and after fragmentation of a formyl cation pyridine derivatives are formed. Mechanism, scope and limitations of this novel pyridine synthesis are discussed.

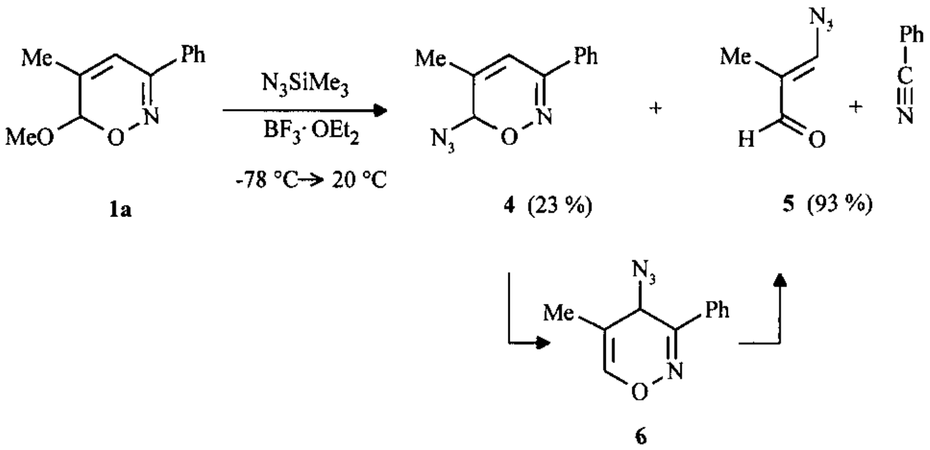
We recently described that easily prepared[2] 6*H*-1,2-oxazines (**1**) react with nucleophiles in the presence of Lewis acids, furnishing 6-substituted heterocycles of general formula (**3**).[3] This transformation smoothly proceeds with silylated nucleophiles and electron-rich aromatic compounds. The azapyrylium ion (**2**) is a logical intermediate in these substitution reactions.

Dedicated to Professor Rolf Huisgen, on the occasion of his 75th birthday.

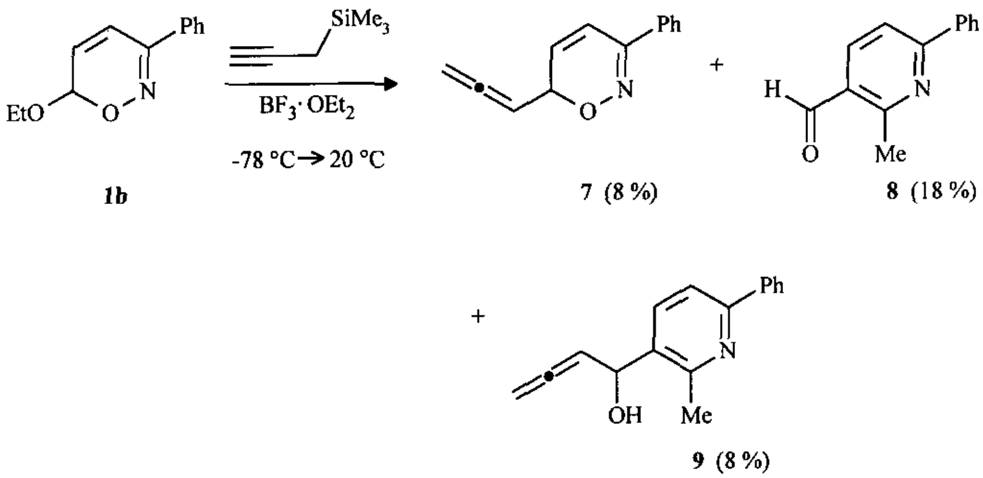


Employing trimethylsilyl cyanide or triethylphosphite as nucleophiles we obtained unusual γ-lactams as products showing that path **1**→**2**→**3** is not the exclusive manner for Lewis acid induced reactions of 6*H*-1,2-oxazines (**1**).[4] In this report we describe further unexpected transformations of **1** involving azapyrylium ions (**2**) as intermediates.

Treatment of **1a** with trimethylsilyl azide and $BF_3 \cdot OEt_2$ gave the expected adduct (**4**) in low yield, but the crude product contained already traces of aldehyde (**5**) and benzonitrile; attempts to purify **4** by distillation led to complete conversion into β-azidoaldehyde (**5**) and benzonitrile. Formation of these components can be explained by the sequence [3,3] sigmatropic rearrangement **4**→**6**, which apparently proceeds even at room temperature,[5] and retro-Diels-Alder reaction **6**→**5**. 4*H*-1,2-oxazines seem to have a very high tendency to undergo thisfragmentation process.[6]



More puzzling was the reaction of **1b** with propargyltrimethylsilane. In the presence of $BF_3 OEt_2$ at least three compounds were formed; after column chromatography the expected product (**7**) was isolated in 8 % yield only, but two other components **8** (isomeric to **7**, vide infra) and **9** were also found.[7]



1b

7 (8 %)

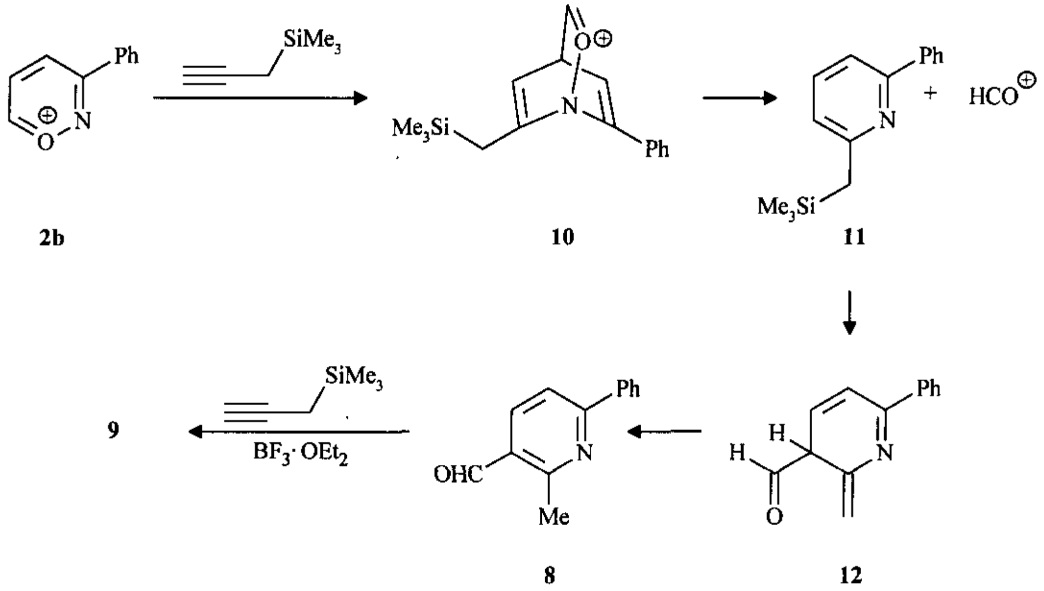
8 (18 %)

9 (8 %)

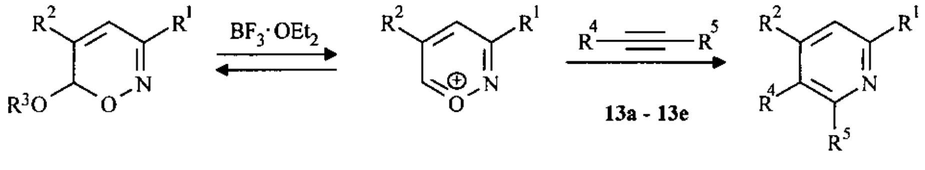
An X-ray analysis[8] of crystals of **8** revealed that a pyridine-3-carbaldehyde was formed, and the spectroscopic data of **9** are consistent with an allenyl adduct of this aldehyde. Control experiments proved that "primary adduct" (**7**) is not converted into major product (**8**) under the reaction conditions or even more forced conditions. Similar results were obtained by the $BF_3 OEt_2$ induced reaction of **1a** with propargyltrimethylsilane: 2,4-Dimethyl-6-phenylpyridine-3-carbaldehyde was the major product (28 % yield).

At first glance formation of **8** was surprising, but a mechanism can be envisaged as illustrated in Scheme I. The azapyrylium ion (**2b**) as formed by ionization of **1b** reacts with the alkyne in a [4+2] fashion[9] to provide intermediate (**10**) which rearomatizes in a retro-Diels-Alder reaction to furnish pyridine derivative (**11**) and a formyl cation. Pyridine (**11**) incorporates an allylsilane moiety, and therefore it is able to re-add the formyl cation affording intermediate (**12**). A proton shift delivers the isolated pyridine-3-carbaldehyde (**8**) which, however, can react again with propargyltrimethylsilane in the usual Lewis acid catalyzed manner to provide allenyl alcohol (**9**).

Scheme 1



It is admitted that the mechanism in Scheme I is speculative. Only very few examples[10] exist for [4+2] cycloadditions which involve components with two directly bonded heteroatoms giving products with one of the heteroatoms found at a bridgehead position. On the other hand, this mechanism suggests that azapyrylium ions (**2**) should also react with other alkynes (or alkenes) to afford pyridine derivatives. This new pyridine synthesis was put into practice by reacting 6*H*-1,2-oxazines (**1**) with several alkynes (**13**) in the presence of Lewis acids.[11]



1a, b **2a, b** **14**

Table 1: Synthesis of Pyridine Derivatives (**14**) from 6*H*-1,2-Oxazines (**1**) with Alkynes (**13**) According to the Typical Procedure[11]

1	R^1	R^2	R^3	**13**	R^4	R^5	**14**	yield (%)	mp (°C)	ref.
b	Ph	H	Et	**a**	H	Ph	**a**	67	80.5-81	12
b	Ph	H	Et	**b**	Ph	Ph	**b**	48	110.5-112	13
b	Ph	H	Et	**c**	$SiMe_3$	Ph	**c**	67	66.5-68.5	--
b	Ph	H	Et	**d**	H	n-Bu	**d**	40	180[a]	14
b	Ph	H	Et	**e**	Et	Et	**e**	33	150-160[a]	--
a	Ph	Me	Me	**a**	H	Ph	**f**	39	72.5-73.5	15
c	CO_2Et	H	Et	**a**	H	Ph	--	--	--	--
d	CF_3	H	Et	**a**	H	Ph	--	--	--	--

[a] bp at 0.01 Torr (Kugelrohr distillation)

As shown by the results collected in Table 1 the reaction of azapyrylium ions with alkynes is fairly general giving pyridine derivatives (**14**) in moderate to good yields. Since the products do not contain an activating trimethylsilylmethyl group the formyl cation is not trapped and the reaction stops at the stage of **14**. According to our mechanistic scheme the reaction of **2** with alkynes can be regarded as a Diels-Alder reaction with inverse electron demand. Therefore it is not unexpected that only moderately electron-rich alkynes add to **2**. Methyl propargyl ether is not an apt dienophile, while ethoxy acetylene is apparently destroyed in the presence of $BF_3 \cdot OEt_2$. No adducts were isolated in these cases. Further restrictions were found with respect to the oxazine substituent R^1. For R^1 = CO_2Et or CF_3 no pyridines (**14**) were formed.

Thus the scope of this novel pyridine synthesis is apparently limited with respect to the substitution pattern. Nevertheless, it may be of interest for the preparation of aryl-substituted pyridine derivatives which are of considerable importance as building blocks in supramolecular chemistry.

ACKNOWLEDGEMENT

Financial support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is most gratefully appreciated.

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11. *Typical experimental procedure:* Under an atmosphere of nitrogen 6*H*-1,2-oxazine (**1b**) (1.00 mmol) was dissolved in dry CH_2Cl_2 (20 ml) and at - 78 °C alkyne (**13a**) (3.00 mmol) was added. Then the mixture was treated with $BF_3 OEt_2$ (2.00 mmol) and allowed to warm up to room temperature within 24 h . After addition of water (20 ml) the resulting mixture was extracted with CH_2Cl_2 (3 x 20 ml), the combined organic phases were dried (Na_2SO_4), the solvent was evaporated, the residue was dissolved in *tert*-BuOMe and then filtered through a short pad of Al_2O_3. Chromatography and recrystallization provided pyridine (**14a**) (67 %) as colourless crystals (mp 80.5 - 81 °C; ref.[12] 81.5 - 82 °C).
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Received, 17th June, 1994