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FUSED TRIAZOLES AND TRIAZOLIUM SALTS WITH BRIDGEHEAD NITROGEN ATOM. NOVEL SYNTHESES AND SELECTIVE TRANSFORMATIONS

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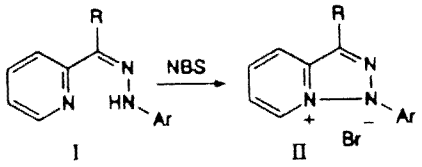
INTRODUCTION

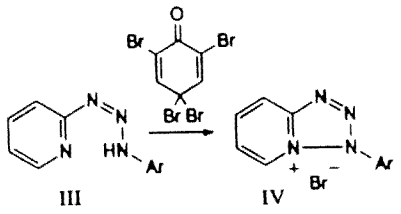
Study on fused triazoles with bridgehead nitrogen atom has a long history in our research group. First, two old literature data [1, 2], both concerning a powerful and general ring closure methodology, should be mentioned in this respect.

More than forty years ago, Kuhn et al. [1] described a very efficient ring closure to [1,2,3]triazolo [1,5-*a*]pyridinium salts: they found that 2-pyridyl ketone hydrazones (I) can easily be oxidized by N-bromosuccinimide (NBS) to the ring-closed triazolium salt II in good yield.



I II

A decade later, Messmer et al. [2] investigated this methodology in more detail and found that 2,4,6,6-tetrabromocyclohexa-2,5-diene-1-one (generally abbreviated as TBB) can be used for this ring closure more effectively, and even those related compounds (e.g., the triazene III) that react fairly slowly with NBS undergo a rapid analogous ring closure (e.g., triazene III gave the tetrazolopyridinium salt IV in good yield).



III IV

Detailed investigations revealed that compounds of general pattern V react with NBS or TBB to give the fused azolium salt VI.

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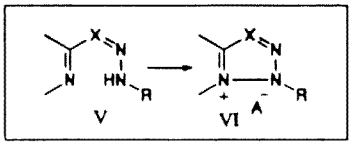
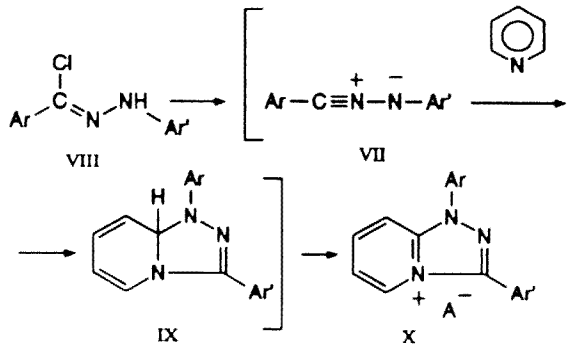


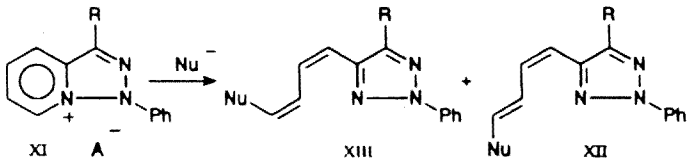
Another interesting ring closure reaction has been published in the 1970s. Messmer et al. [3] described that pyridine undergoes 1,3-dipolar cyclization in the presence of nitrilimines VII (generated from chlorohydrazones VIII) and the cyclization product IX undergoes spontaneous oxidation to give 1,3-disubstituted [1,2,4]triazolo[4,3-*a*]pyridinium salts (X).



Both methodologies (i.e., oxidative ring closure and 1,3-dipolarcycloaddition) served as bases in our recent investigations, and their extension allowed the synthesis of various new fused triazole systems with bridgehead nitrogen atom and also observation of a number of synthetically useful new conversions. In the following sections, these results will be presented.

A. RING OPENING OF TRIAZOLOPYRIDINIUM SALTS TO TRIAZOLYLDIENES

The fact that azolopyridinium salts easily react with nucleophilic reagents in such a manner that the pyridine moiety undergoes ring opening has been well known for a long time [4]. In these reactions, azolyldienes are formed as shown below.

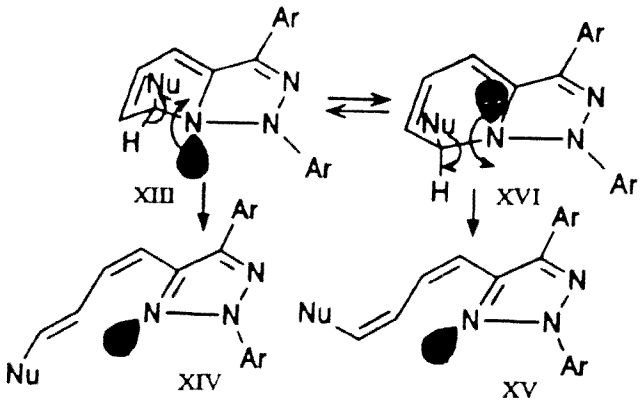


R	Nu	Product ratios	
Ph	morpholide	-	100 %
Me	MeO^-	40 %	60 %
Ph	CN^-	92 %	8 %

In the course of our detailed study on such reactions, we found that the geometry of the diene product can sensitively be influenced by varying the nucleophilic reagents. Thus, when the v-triazolopyridinium salt XI is reacted with sodium morpholide (generated from morpholine by sodium hydride) the 1-*cis*-3-*trans*-diene XII is formed. With sodium methoxide, on the other hand, a mixture of the 1-*cis*-3-*trans* XII and 1-*cis*-3-*cis* XIII products (in a ratio of 3:2, respectively) is formed,

whereas in the reaction of the same starting compound XI with sodium cyanide, the fully *cis* compound XIII was found as the main product, and the 1-*cis*-3-*trans* isomer XII was present only as an impurity.

Comparison of these findings with our earlier results with fused tetrazolium salts [5] revealed that this dramatic change of the geometry of the diene product can be rationalized by consideration of two major effects: a) steric conditions; b) the electron-withdrawing property of the substituent introduced by the nucleophilic reagent. This can be well visualized by Scheme 1.



Scheme 1. Consequences of the nitrogen inversion in the course of formation of triazolyldienes

In the first step, the addition of the nucleophilic reagent to the heteroaromatic cation takes place and intermediate XIII is formed, in which the group Nu is antiperiplanar with the lone pair of the nitrogen atom. As the ring opening to the diene product is obviously a disrotatory process, two senses of electron movements should be considered, of which, however, only one – that shown by the arrows – is possible, as the lone pair in the product is necessarily situated outside of the azole ring. Thus, opening this intermediate XIII should result in formation of the 1-*cis*-3-*trans* product XIV.

Formation of the 1-*cis*-3-*cis* product XV, on the other hand, can only be rationalized by supposing a nitrogen inversion in the intermediate XIII leading to isomer XVI. The lone pair of the azole nitrogen atom in XVI – for the above reasons – should move left down and, therefore, the group Nu and the lone pair are turning to each other. As this motion is sterically hindered, formation of such a product cannot be expected with large nucleophilic groups (e.g., with morpholide anion). If, however, the introduced Nu has a strong electron withdrawing property, a considerable σ^*—n interaction can develop, which increases the order of the bond to be opened. Thus, in these cases – provided that no serious steric hindrance occurs and the equilibrium between XIII and XVI exists – the opening of species XVI is more probable, which leads to the fully *cis* product XV.

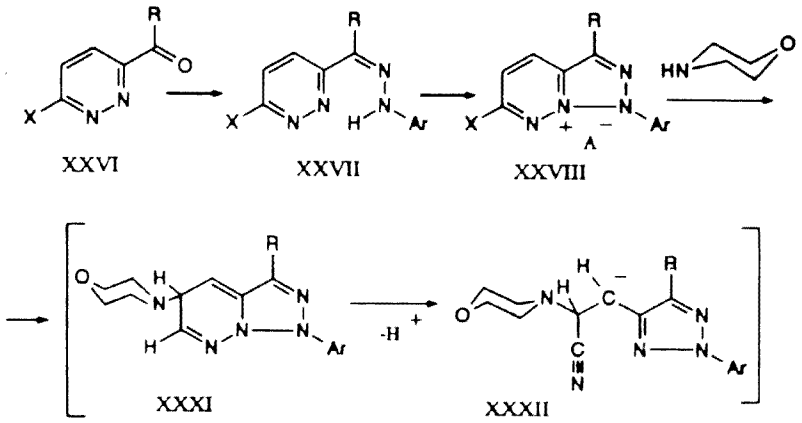
These data obtained with the fused triazole systems, as well as our earlier published findings [5] with related other systems, seem to be in good agreement with these arguments.

B. SYNTHESIS OF TRIAZOLODIAZINIUM SALTS AND THEIR TRANSFORMATIONS

1. v-Triazolopyrimidinium Salts

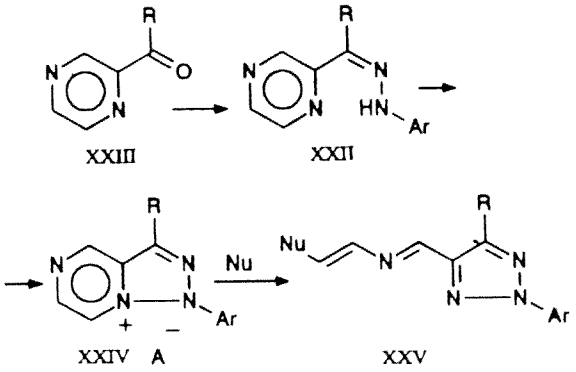
Hydrazones of both 2-pyrimidinyl XVII and 4-pyrimidinyl ketones XVIII proved to be suitable starting compounds for the synthesis of triazolopyrimidines. Thus, the 2-pyrimidinylhydrazone XVII when reacted with TBB gave v-triazolo[1,5-*a*]pyrimidinium salt XIX, whereas the 4-pyrimidinyl isomer XVI afforded the isomeric v-triazolo[1,5-*c*]pyrimidinium system XX [6]. The new triazolopyrimidinium salts easily reacted with nucleophiles, and a similar ring opening as observed with the

triazolopyridinium compounds (see below) was observed. Thus, reaction of XIX with secondary amine gave the 1-azabutadiene XXI.



2. v-Triazolopyrazinium Salts

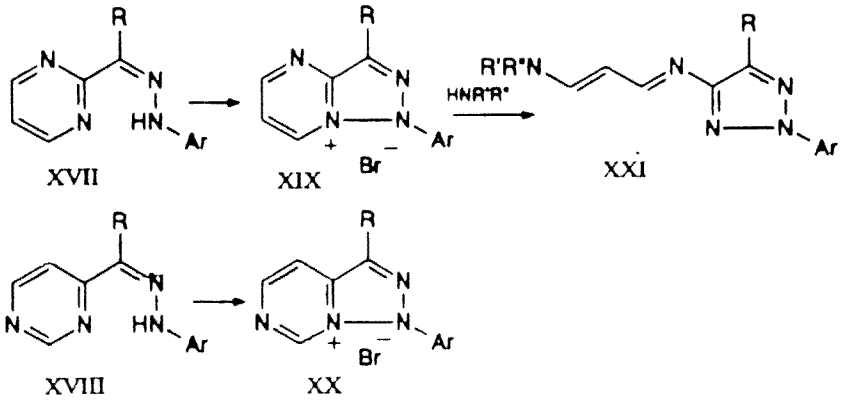
The ring closure methodology to v-triazolium salts proved to be extendable for fused pyrazinium salts, too. Thus, pyrazine ketone hydrazones XXII obtained from pyrazine ketone XXIII by routine procedures were treated with NBS to give the expected bicyclic compound XXIV. This new triazolium salt showed a similar reactivity towards nucleophiles as in the previous case: its reaction with morpholine resulted in ring opening of the pyrazine moiety, and the 2-azadiene compound XXV (Nu = morpholinyl group) was obtained in good yield.

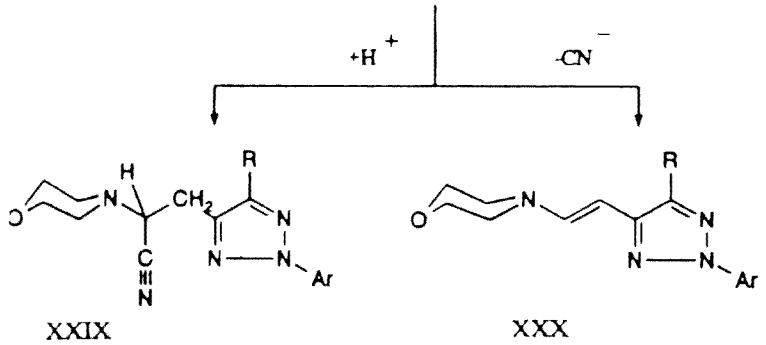


3. v-Triazolopyridazinium Salts

This ring system was also synthesized by our general methodology [6]: 2-pyridazyl ketone XXVI was transformed to the hydrazone XXVII, which was closed ring by NBS to the triazolium salt XXVIII.

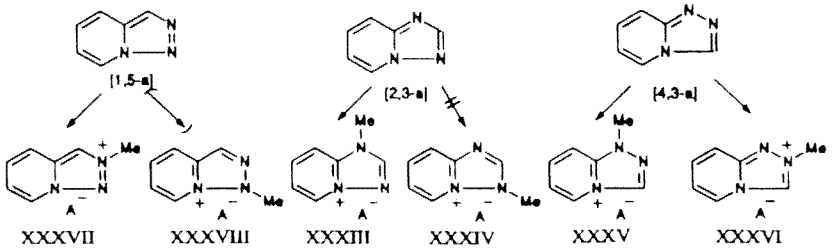
The new bicyclic system XXVIII, however, had a structural peculiarity in contrast to the previous triazolodiazinium salts XIX, XX, XXIV: because of the location of the pyridazine nitrogen atom in position 5, no nucleophile attack can be expected at this site. This is nicely shown by the reaction of XXVIII with morpholine: two products were isolated from this reaction: the cyano group containing XXIX and the morpholinoethenyltriazole XXX. The simultaneous formation of these compounds can be rationalized by supposing formation of the adduct XXXI first, which upon deprotonation undergoes ring opening to give the intermediate XXXII. The two products XXIX and XXX are results of either uptake of proton or elimination of the cyanide anion, respectively [7].





C. SYNTHESIS OF *s*-TRIAZOLOPYRIDINIUM SALTS BY DIRECT ALKYLATION

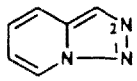
Recently we studied alkylation of fused heteroaromatic systems containing several nitrogen atoms in detail [8]. Supposing an in-the-plane attack of the alkylating agent, we suggested that the selectivities of these alkylations can be successfully correlated with the electronic densities of the lone pairs of the ring-nitrogen atoms (called c^2n-HOMO). The result of alkylation experiments with the possible three triazolopyridines containing bridgehead nitrogen atom is shown above.



Alkylation of the [4,3-*a*] system was investigated in the literature long ago [9], whereas such reactions with the [1,5-*a*] and [2,3-*a*] fused systems have been carried out by us recently [8]. The results can be summarized as follows: the [2,3-*a*] system gives exclusively the only product XXXIII, while isomeric product XXXIV was not formed at all; the [4,3-*a*] isomer simultaneously gave two products: XXXV and XXXVI; and alkylation experiments with the v-triazolo [1,5-*a*]pyridine system revealed that the salt XXXVII was mostly formed, whereas compounds with bulky substituents in position 3 also afforded a small amount of an isomer XXXVIII.

Quantum chemical calculations of the electronic densities of the lone pairs shown by Scheme 2 reveal our earlier observation: the c^2 value for N-2 is significantly higher than that for N-1. It is interesting to note that the corresponding density values of the real HOMO show the opposite trend and do not correlate with the observed phenomenon.

c^2 Coefficients (GAUSSIAN 86 (STO-3G) basis SET)



	π -HOMO	n-HOMO
N-1	0.160	0.37
N-2	0.013	0.53

Scheme 2. Comparison of the electronic densities of N-1 and N-2 of [1,2,3]triazolo[1,5-*a*]pyridine

A general strategy for estimation of the site of alkylation reactions of planar N-heteroaromatic compounds is as follows:

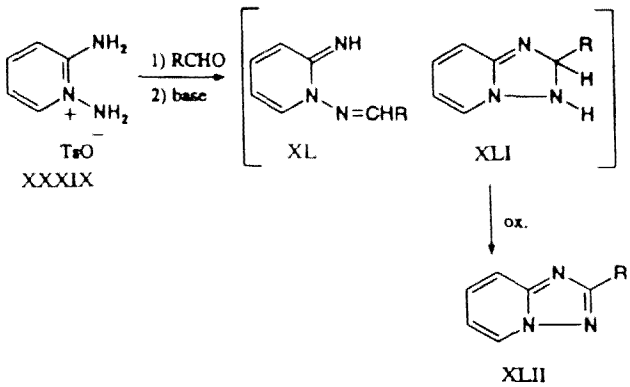
n-HOMO control works with planar or quasi-planar unsaturated or aromatic heterocycles (*in-the-planar attack*). Using the strategy, one should keep in mind several points:

1. Do MO analysis, (e.g., AM 1);
2. Look for the n-HOMO;
3. Calculate electronic densities;
4. Be sure that no re-alkylation takes place.

D. NEW AND EFFICIENT SYNTHESIS OF s-TRIAZOLO[1,5-*a*]PYRIDINES

Although various procedures [10] are known for the synthesis of *s*-triazolopyridines, they are each limited to certain kinds of substituted compounds. Recently we elaborated a very simple and effective method for the synthesis of these derivatives [11].

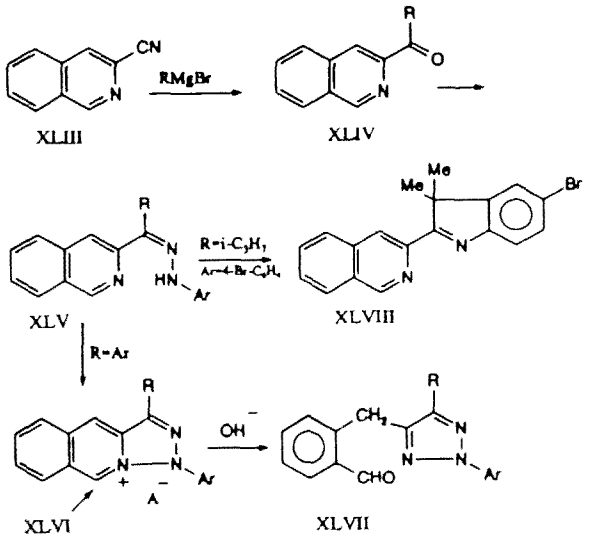
We found that 1,2-diaminopyridinium salts XXXIX, when treated with aldehyde and subsequently with base, undergo condensation reaction to give the Schiff base XL, which easily undergoes ring-chain tautomerism to a bicyclic dihydro intermediate XLI, and the spontaneous oxidation of this intermediate leads to the target system XLII. The reaction can be widely extended to various derivatives.



E. SYNTHESIS AND REACTIONS OF THE LINEARLY ANNELATED v-TRIAZOLO[1,5-*b*]ISOQUINOLINIUM SALTS

The ring closure methodology applied successfully for several bicyclic cases as shown above in Sec. B was found to be suitable also for the synthesis of the linearly fused title system. The synthetic path starts from 3-cyanoisoquinoline (XLIII). This compound was reacted with Grignard reagent to give the 3-ketones XLIV which were routinely transformed to the hydra-

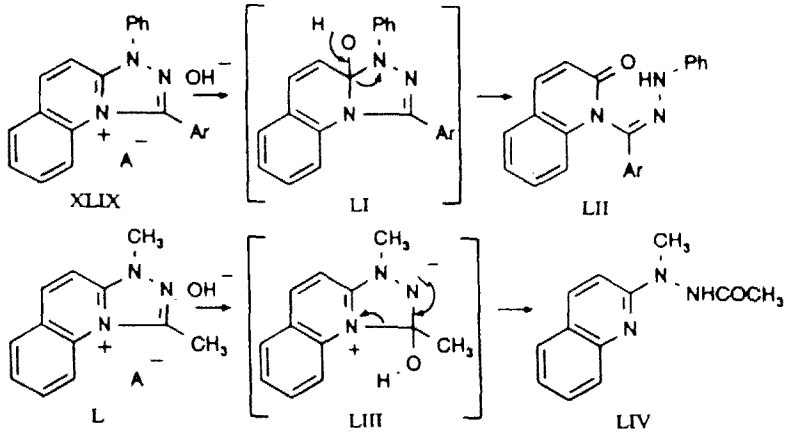
zones XLV. In the last step, reaction of XLV with TBB was carried out and the ring closure led to the linearly fused tricyclic compound XLVI. This new heteroaromatic salt proved to be fairly sensitive towards nucleophiles: thus, in the presence of aqueous base, the pyridine moiety opened up and the aldehyde compound XLVII was formed in acceptable yield.



An unexpected side reaction was observed in the case when the R group was an isopropyl chain. When we tried to transform the ketone XLIV (R = *i*-Pr) to the appropriate hydrazone under acidic conditions, the indole derivative XLVIII was obtained instead of the expected XLV. Formation of XLVIII is actually a manifestation of the well-known Fischer-type indole synthesis [12].

F. SYNTHESIS AND RING OPENING OF SOME 5-TRIAZOLOQUINOLINIUM SALTS

The 1,3-disubstituted s-triazolo [4,3-*a*]quinolinium salts XLIX and L were synthesized according to the procedure cited in the introductory section [3]. Both the diaryl XLIX and dimethyl L compounds reacted with hydroxide ion but resulted in different products. Compound XLIX was attacked at the bridgehead carbon atom adjacent to the bridgehead nitrogen atom to yield intermediate LI, which underwent ring opening, as shown by the arrows, to yield the amidrazone compound LII. The dimethyl substituted starting salt L, in turn, was found to react at the triazole carbon atom in position 1 to yield first the zwitterionic intermediate LIII, which was stabilized by ring opening to substituted 2-quinolylhydrazine LIV.



ACKNOWLEDGMENTS

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