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In the course of our recent synthetic activity in the area of ring closure reactions we have found that relatively little had been published on azolopyridazines and related compounds, and this circumstance prompted us to explore novel pathways to such ring systems. In the present short review three such approaches from our laboratory leading to various fused azoles are discussed.

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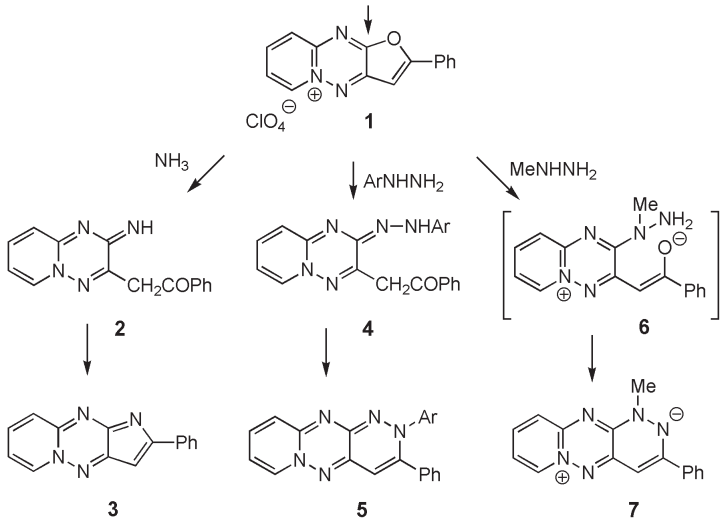
Ring transformation to [1,2,3]triazolo[4,5-*d*]pyridazinones.

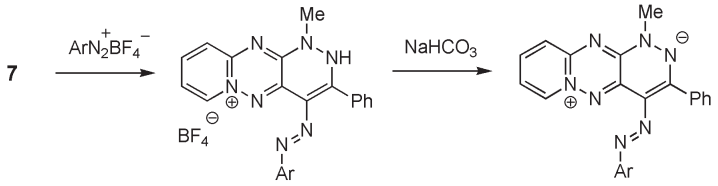
Scheme 1



In the frame of a long term cooperation with University of Graz, Austria [1,2,3], we had elaborated an easy pathway to the bridgehead-nitrogen containing tricyclic furo[2,3-*e*]pyrido[1,2-*b*][1,2,4]triazin-5-ium salt (**1**) which proved to be fairly reactive towards nucleophilic reagents and, henceforward, served as an excellent starting compound for transformations of various kinds. Thus, reaction of **1** with ammonia resulted in a ring opening to **2** which, upon treatment with an acid underwent cyclization to a pyrrole-fused tricycle **3** [4]. Also, similar ring transformations occurred in reaction of **1** with hydrazines: in the case of arylhydrazine, intermediate **4** was obtained which was cyclized to a blue colored fused tricyclic pyridazine **5**, whereas – more interestingly – reaction of **1** with methylhydrazine yielded a zwitterionic tricyclic pyridazine **7** obviously *via* formation of a non-isolated intermediate (**6**).

Because of the dipolar character of **7**, reactivity of this compound seemed of special interest. We have found that dipolar cyclizations, Michael additions and some other interesting transformations due to the zwitterionic character can be realized [5,6]. As a continuation of these studies we have investigated the reactivity of **7** toward aryldiazonium salts [7]. The rapid appearance of a deep red color of the reaction mixture indicated that most possibly an azo coupling took place, and structure analysis of the red crystals (**8**) isolated from the reaction mixture provided satisfactory support for this assumption. When the azo-substituted salt was treated with sodium hydrogen carbonate, the zwitterionic azo compound **9** was obtained in solid form which, upon storage on air, gradually lost its red color. This color change was even more apparent with the solution of **9**: it became colorless in a couple of hours indicating that a further spontaneous reaction took place.

Scheme 2

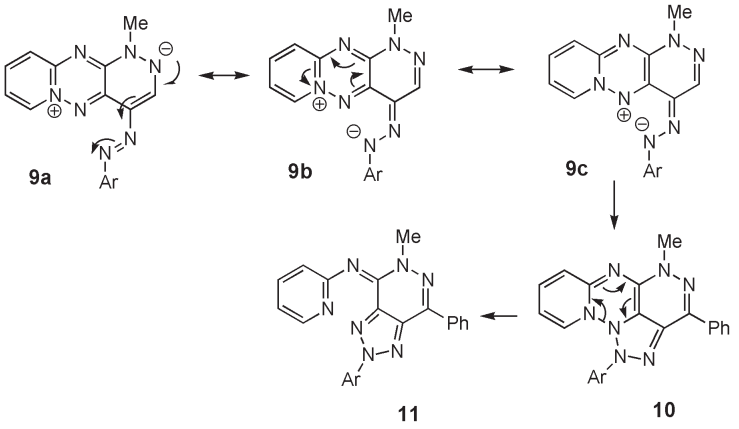


Ar = 4-Cl-C_6H_4-, 4-NO_2-C_6H_4-, 4-MeO-C_6H_4-

A reactivity resulting in the transformation of the arylazo moiety can be assumed upon inspection of the most probable valence bond structures of **9** *(i.e.* from **9a**, **9b**, **9c**). The arrows in these structures represent the possible shifts of the electron pairs leading to the replacement of the two charges: *e.g.* in structure **9c** the positive and negative charges can be localized on two nitrogen atoms that are in proximity and are able to form a sigma bond. As a result of such a ring closure, formation of a tetracyclic *ortho*- and *peri*-fused ring system (**10**) can be expected.

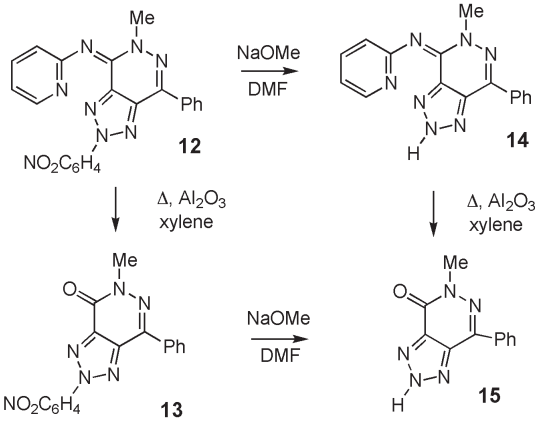
Further transformations of **11** were found in accordance with this structure. In the case of the *p*-nitrophenyl derivative **12** two important reactions could be carried out: a) the pyridine group could be removed by hydrolysis with alumina to **13**, and b) reaction with sodium methoxide resulted in a dearylation to give the unsubstituted triazole ring (**14**). This compound (**14**) was also hydrolyzed to the fused pyridazinone **15**.

Scheme 3



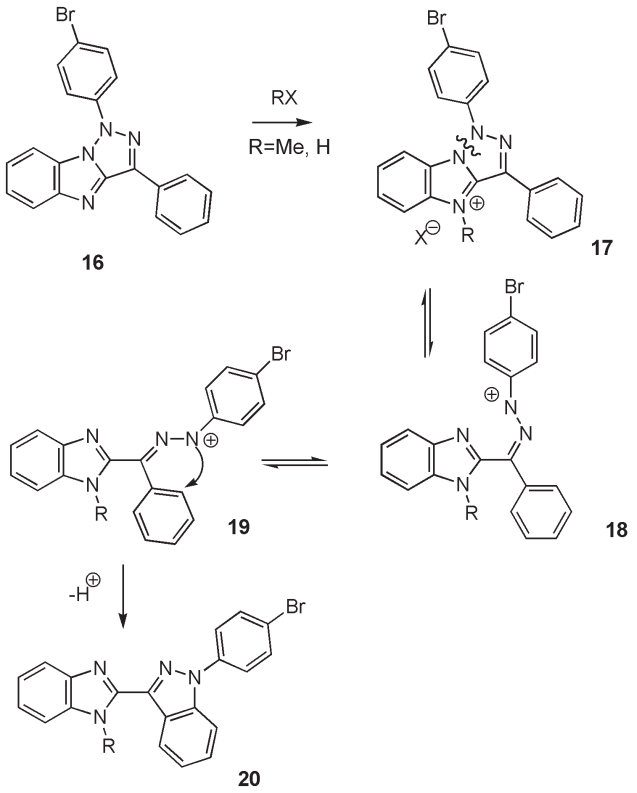
Compound **10** can, moreover, undergo a further transformation indicated by the three arrows in the structural formula: such a pericyclic ring opening can lead to a [1,2,3]triazolo[4,5-*d*]pyridazine derivative **11**. Decision between structures **10** and **11** is not easy by routine spectroscopy because of the lack of hydrogen atoms sensitive to the possible structural change. A final evidence was provided by X-ray diffraction which unambiguously supported the formation of the ring-opened species **11**. Also, a ^{15}N-^{1}H-HMBC NMR experiment has been carried out which led to the conclusion that the pyridine-nitrogen atom does not form any sigma bond with another nitrogen atom and, thereby, a further strong support for structure **11** has been provided.

Scheme 4



Formation of pyrazoloazines via valence bond isomerisation.

Scheme 5



In the course of one of our recent findings a new type of cyclization to fused pyrazoles has been experienced [8,9]. Key observation in this respect was that treatment of 1*H*-[1,2,3]triazolo[1,5-*a*]benzimidazole **16** with dimethyl sulfate at elevated temperature resulted in a substantial transformation and, instead of a simple methylation reaction to **17** (which can be isolated at low temperature when the alkylation is carried out with Meerwein salt) a ring opening reaction takes place, and *via* formation of an intermediate reactive nitrenium cation (*i.e.* rotamers **18** and **19**), an indazole (**20**) is formed.

We have shown that the thermal valence bond isomerisation of such fused [1,2,3]triazolium salts is a general phenomenon as shown in Figure 1. Thus, upon heating of the starting salt, an N-N cleavage takes place resulting in a diazaallenium cation (**b**) which can be also present in a nitrenium cation (**a**) or a carbenium cation (**c**) form.

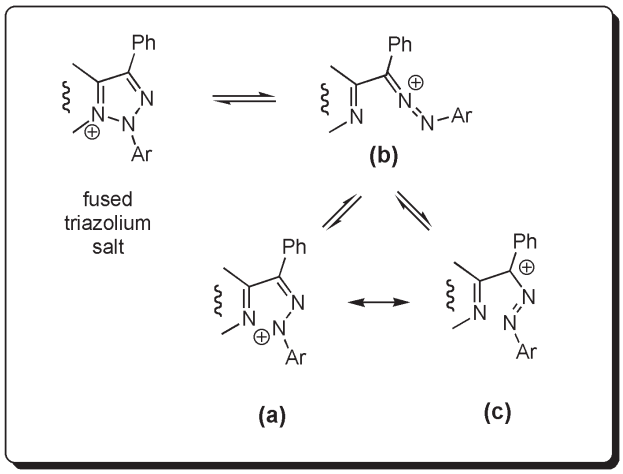
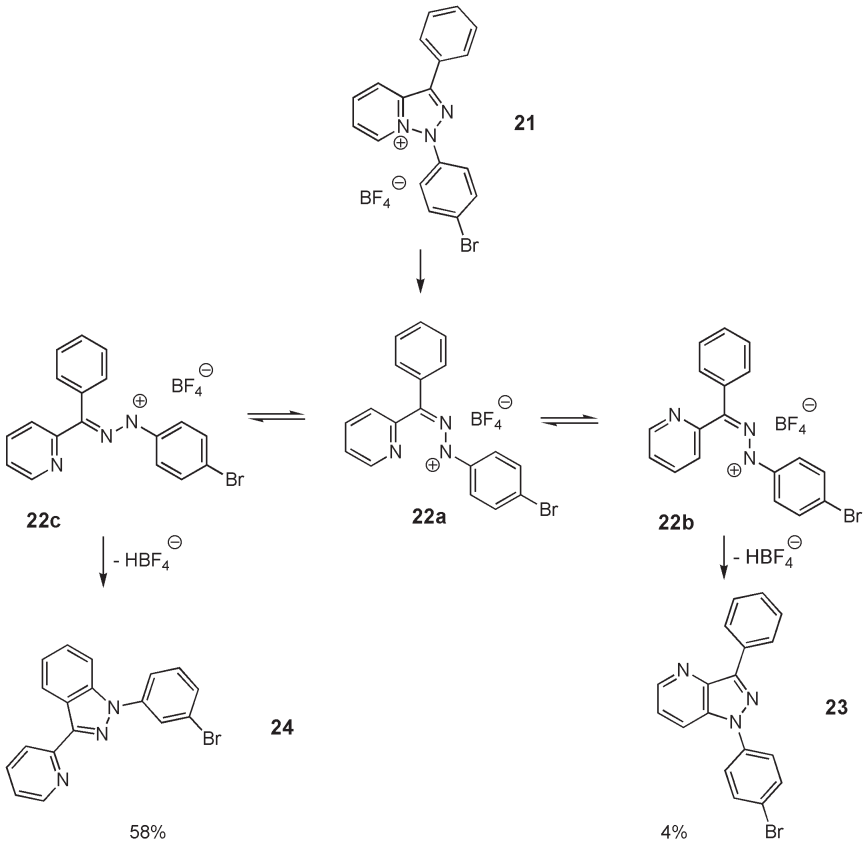


Figure 1. General pattern of the thermal valence bond isomerization of fused triazolium salts. The ring opened species as an active intermediate can be represented by a nitrenium cation (**a**), diazaallenium cation (**b**) and carbenium cation (**c**) form.

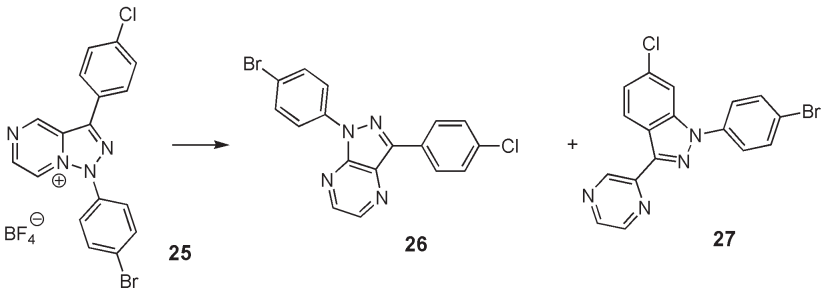
If the starting triazoloazinium salt also contains a carbon atom at the azine part which is able to be attacked by the nitrenium cation, a ring closure at this site of the molecule is also possible. Such a case has been observed with the 1*H*-[1,2,3]triazolo[1,5-*a*]pyridine-8-ium ring system (**21**) [9]. The ring opening by cleavage of the N-N bond results first in the formation of the reactive intermediate, which can be represented by rotamers **22a**, **22b**, and **22c**. Rotamer **22b** easily undergoes intramolecular cyclization to the indazole product **24**: a similar process as shown in the previous example (*i.e*. with formation of **20**). In the present case, however, attack of the positively charged nitrogen atom at the pyridine site can also occur. Thus, rotamer **22c** cyclizes – although in very poor yield - to pyrazolopyridine derivative **23**.

The preference to formation of a diazoloazine rather than an indazole is, interestingly, even more predominant in the case of 1*H*-[1,2,3]triazolo[1,5-*a*]pyrazin-8-ium salt (**25**). Treatment of this compound at higher temperature yields the two ring transformation products **26** and **27** in comparable amounts.

Scheme 6



Scheme 7



This finding that ring closure of the positively charged intermediate to the azine moiety rather than that to the phenyl ring is essentially more favoured in the case of pyrazine compared to pyridine raises the question of the reaction mechanism of this ring closure. If the investigated ring transformation involves purely an electrophilic attack of the nitrenium cation, the attachment of this nitrenium cation to the pyrazine ring can not be rationalized. Considerations on this subject led to the conclusion that – besides the electrophilic attack – also a pseudopericyclic mechanism [16] can operate.

Synthesis of azolopyridazinones via Suzuki cross-coupling.

In the course of our extensive research on the application of Suzuki coupling in heterocyclic ring closure reactions [10-12] we have elaborated a protocol generally applicable for a series of analogous ring closure reactions. The pathway is summarized in Figure 2.

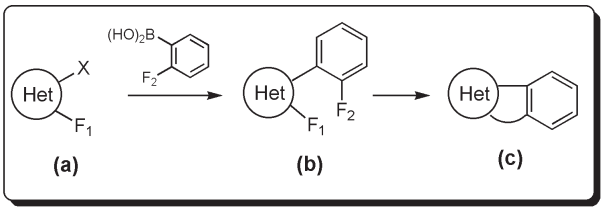


Figure 2. Scheme of the synthetic protocol to new fused heterocycles by application of Suzuki-coupling. X: appropriate leaving group for the cross-coupling reaction; F_1 and F_2: functional groups for a cyclization reaction as the last step of the pathway.

The first step is a Suzuki cross-coupling reaction starting from heterocyclic derivative (**a**) containing an appropriate leaving group (a halogen atom or triflate group in most cases) and a functional moiety (F_1) which serves as a center for the final ring closure step in the pathway. This compound is treated with an arylboronic acid containing also a functional group in *ortho* position (F_2, *e.g.* a protected amine, an aldehyde, etc.) to give a biaryl compound **b**. In this intermediate the two functional groups F_1 and F_2 can react with each other to form a new cycle, *i.e.* to yield the polycyclic product **c**.

sites of the pyridazine ring to form one or two C-N bond(s) in selective or non selective manner. Luckily, the only reaction experienced was the ring closure to the carbon atom in the vicinity of the oxo group and, thus, the tricyclic compound **32** was obtained in good yield.

Continuation of these studies and extension of the ring closure reactions to novel fused azoloazines are in progress.

Acknowledgment.

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§ Presented as an invited lecture at the 9th International Symposium on the Chemistry and Pharmacology of Pyridazines, Antwerp, June 30th – July 3rd, 2004.

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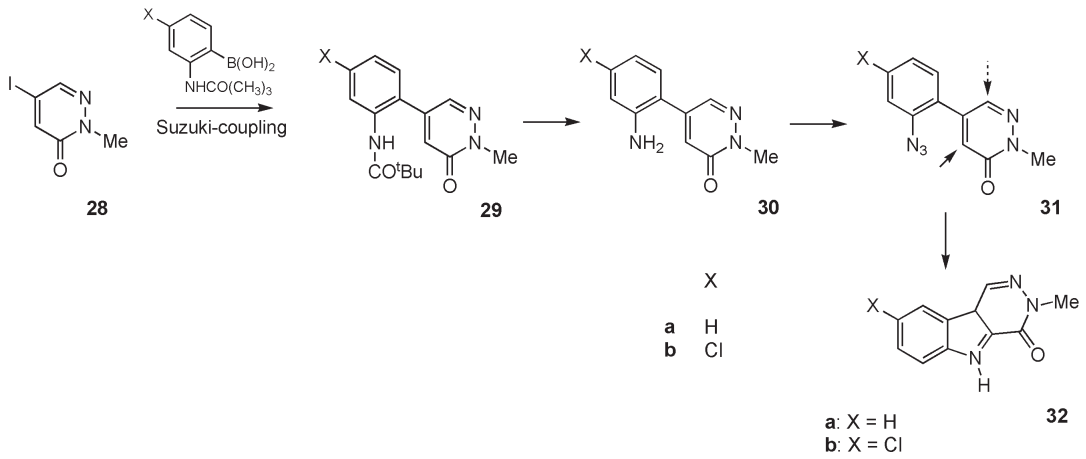
Scheme 8



This synthetic procedure has now been successfully applied for pyridazines to result in ring closure to pyrazolopyridazine [13, 14]. As a starting compound, the easily accessible 5-iodo-2-methylpyridazin-3(2*H*)-one (**28**) [15] was used. Suzuki coupling of this compound with the required arylboronic acid gave the biaryl product **29** which was deprotected to the amine **30**. Transformation of **30** to the arylazide **31** was carried out by a standard procedure as described by us earlier [10, 13]. The two arrows on structure **31** indicate that if this compound is transformed to a nitrene, the reactive nitrene can carry out attack at two

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