A General Synthetic Method for Preparation of Pyrazolopyridazine Systems

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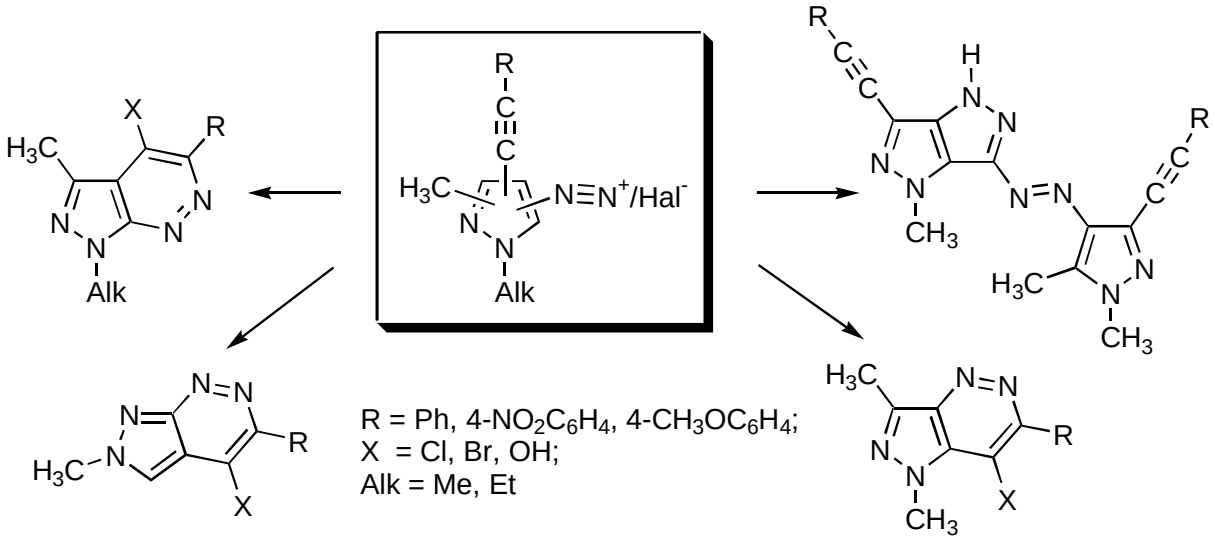
In a years to come in order to increase receptor subtype selectivity and *in vivo* stability a search for bioisosters of the parent indole ring system, including condensed pyrazoloazines, has been intense [1]. Various 3,4-disubstituted pyrazolopyridazine nucleus are of interest for pharmaceutical use. However, the straightforward synthesis of the pyrazolopyridazine derivatives having this substitution pattern from readily available starting materials is not so easy.

We have currently developed the synthesis of fused ring systems based on an intramolecular cyclization of functionally substituted *vic*-functionalized arylacetylenes. In our study of this approach to polycyclic compounds we devised a general procedure for preparation of pyrazolopyridazine systems.

Our previous communication [2] has demonstrated that the so-called Richter reaction can be applied to the synthesis of not only 4-hydroxy -, but also 4-bromo- and 4-chlorocinnolines, as opposed to the known data. Attempting to widen the applicability of the reaction, we have found that the behaviour of alkynylpyrazolyldiazonium chlorides differs from that of their benzene analogies. Thus, the cyclization of 1,3-dimethyl-5-phenylethynylpyrazolyl-4-diazonium salts has revealed no 4-hydroxydiazine. Therefore, in the present work we report on a study of hetrocyclization of diazotised alkynylamino-1-alkylpyrazoles.



Using the cyclization of *vic*-alkynylpyrazolyldiazonium salts, we have synthesized a number of funtionalized chloro-, bromo- and hydroxyderivatives of 1*H*-pyrazolo[3,4-*c*]pyridazines, 2*H*-pyrazolo[3,4-*c*]pyridazines and 1*H*-pyrazolo[4,3-*c*]pyridazines. Unexpectedly, the cyclization of 3-alkynylpyrazolyl-4-diazonium halogenides affords 7-chloro-1*H*-pyrazolo[4,3-*c*]pyridazines. Thus, the cyclization of 3-alkynyl-pyrazolyl-4-diazonium salts is accompanied by methyl group migration towards the neghbouring nitrogen atom. Besides, the cyclization of pyrazolyl-4-diazonium salts containing methyl groups in position 5 of the cycle gives both azopolypyrazoles and pyrazolo[4,3-*c*]pyrazoles.

References

[1] J.B. Hansen et al, *Bioorg. Med. Chem. Lett.*. **1994**, *4*, 695.

[2] S.F. Vasilevsky, E.V. Tretyakov, *Liebigs Ann. Chem*. **1995**, 775.