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LETTERS

Facile synthesis of pyrazoles and pyrroles via thermolysis of tetrazolo[1,5-*b*]pyridazines, tetrazolo[1,5-*a*]pyrimidines and tetrazolo[1,5-*a*]pyridines

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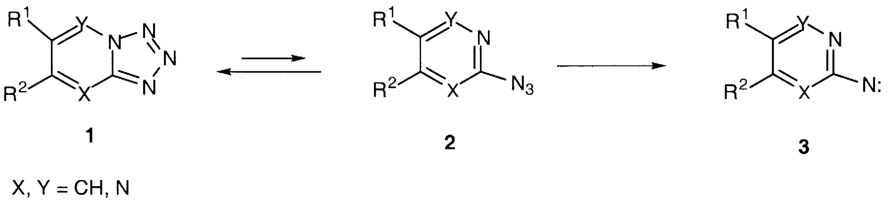
Abstract

A simple and high yielding preparation of pyrazoles and pyrroles is described. Thermolysis of tetrazolo[1,5-*b*]pyridazines, tetrazolo[1,5-*a*]pyrimidines and tetrazolo[1,5-*a*]pyridines allowed easy ring contraction thus providing a facile preparation of cyanopyrazole and cyanopyrrole heterocycles. Since the cyano group is a versatile precursor of other functionalities, the reaction appears of particular interest for the construction of a variety of pyrazoles and pyrroles. The simple preparation of the starting tetrazole derivatives, the relatively mild conditions employed, and the very short reaction times make this versatile procedure of great synthetic utility and applicable both to small and large scale preparation. © 2000 Elsevier Science Ltd. All rights reserved.

The thermal or photochemical decomposition of phenyl and heterocyclic azides **2** is a well known process which gives phenyl- and heteroarylnitrenes **3**.[1] The reaction has attracted attention as a means of constructing new heterocyclic compounds which are otherwise inaccessible by ring synthesis or by modification of existing heterocycles.[2–5] It has been also demonstrated that an azide–tetrazole tautomerism exists (Scheme 1) in tetrazoloazines and the tetrazole compounds may be the main tautomers.[6]



Scheme 1.

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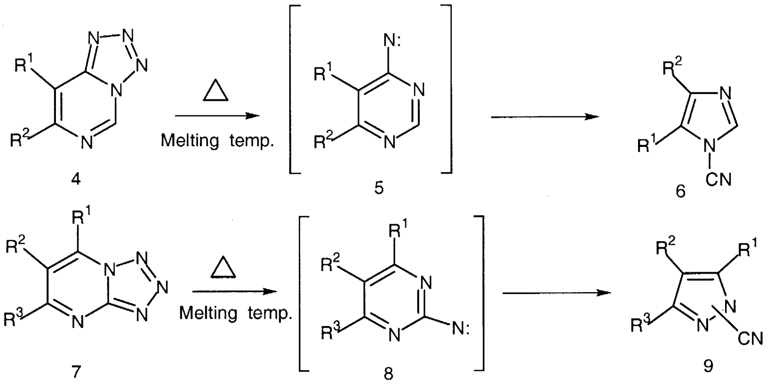
The work of Wentrup was particularly significant in this field.[5,7–11] In fact, he demonstrated that nitreno-azines and -diazines, generated by gas-phase pyrolysis of the corresponding tetrazolo-azines and -diazines, may produce the cyano derivatives of the corresponding five-membered heterocycles. However, these cyano heterocycles were obtained, as the main products, only in the case of the tetrazolo[1,5-*c*]pyrazines[7] and tetrazolo[1,5-*c*]pyrimidines.[7] In the other cases gas-phase pyrolysis produced mixtures of compounds and the cyano components were present only in small amounts.

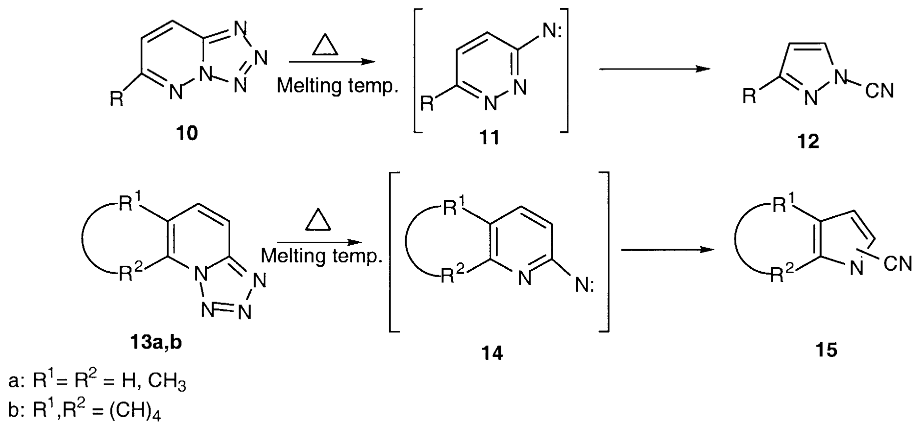
We were very surprised to ascertain that little is known about the ring contraction of heterocyclic azides when the reaction is performed at the melting temperature. In this regard, we anticipated that pyrolysis of the tetrazolo[1,5-*c*]pyrimidines **4** (Scheme 2) may be obtained by warming the starting tetrazole derivatives at about 10–20°C over the melting temperature,[12] and we described this reaction as a practical means to achieve the preparation of many 1-cyanoimidazole heterocycles. In addition, alkyl- and arylimidazoles were also obtained in high yield by pyrolysis of azidopyrazines.[13,14]



Scheme 2.

Thus, our ongoing interest in the thermolysis of azido-azines and -diazines prompted us to extend the above cited ring contraction to other heterocyclic azides. In this letter we wish to report our preliminary results concerning the thermolysis of the tetrazolo[1,5-*a*]pyrimidines **7** and tetrazolo[1,5-*b*]pyridazine **10** which allowed a facile preparation of 1-cyanopyrazoles. The reaction was also attempted with the tetrazolo[1,5-*a*]pyridines **13a** thus providing an easy preparation of 1-cyanopyrroles which is of great synthetic utility. Therefore, unlike Wentrup, our methodology affords higher yields of the corresponding cyano heterocycles by means of simpler operational conditions. Since the cyano group is a versatile precursor of other functionalities, the reaction appears to be of particular interest for the construction of a variety of pyrazoles and pyrroles.

Pyrolyses of the tetrazolo[1,5-*a*]pyrimidines **7** and tetrazolo[1,5-*b*]pyridazines **10** (Schemes 2 and 3) were performed in a standard pyrex tube (35/5 cm) joined to a condenser and plunged (about 5 cm) in an oil bath.[15] About 20 mmoles of the opportune tetrazole were put on the bottom of the tube and the system was carefully heated at about 10–20°C over the melting temperature of the sample. As soon as the compound melted evolution of nitrogen was observed. The reaction was particularly fast (few minutes), then the tube was allowed to cool to room temperature and the desired cyano heterocycles were in general collected from the walls of the tube. Both the tetrazolo[1,5-*a*]pyrimidine and tetrazolo[1,5-*b*]pyridazine heterocycles gave facile thermolysis and the ring contraction produced the pyrazole derivatives **9** and **12** as the only detectable products (Table 1: a selected list of representative results). On the contrary, when pyrolysis of the tetrazolo[1,5-*b*]pyridazines was performed at 380°C/0.02–0.03 mm, as described by Wentrup,[7] a mixture of cyanoallene, tetralonitrile, propargyl cyanide and 2-cyanocyclopropene was obtained. Surprisingly, there was no evidence of the presence of the 1-cyanopyrazole. Moreover, pyrolysis of the tetrazolo[1,5-*a*]pyrimidines, performed at 600°C/0.1 mm,[7] gave the 1-cyanopyrazoles in only 33% yield.



Scheme 3.

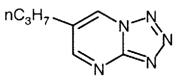
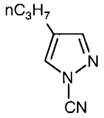
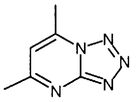
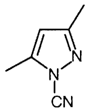
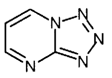
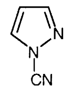
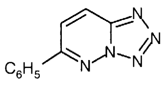
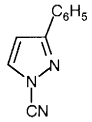
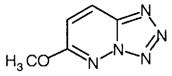
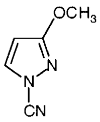
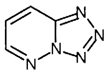
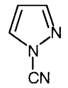
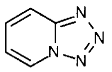
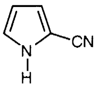
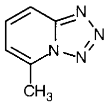
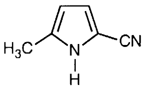
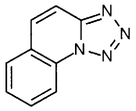
The interpretation of our results is not easy: Wentrup hypothesized that in some cases fragmentation of the starting tetrazole derivative can occur rather than ring contraction because of an inherent instability of the nitrene intermediate;[8] it is likely that in our experiments the formation of the five-membered heterocycles is due to the milder conditions of the reaction. Therefore, we may advance the hypothesis that the instability of the nitrene intermediate, firstly hypothesized by Wentrup, is simply due to the higher temperature used to generate the ring contraction.

Having demonstrated that the tetrazolo-diazines **7** and **10** can undergo facile thermolysis, we decided to investigate the same procedure applied to the tetrazolo[1,5-*a*]pyridine system. Thermolysis of derivatives **13a** gave the corresponding cyanopyrroles in 70–75% yield (see Scheme 3 and Table 1) thus offering significant advantages when compared to the preparation described in the literature.[10,11] Surprisingly, further attempts to affect the ring contraction of the tetrazole derivative **13b** failed, resulting in a very complex mixture of products in which only traces of the desired cyanoindole were identified.

Finally, the thermolysis of the above cited heterocyclic tetrazoles was also attempted in organic solvents as described by Wentrup for the tetrazolopyrazines.[9] In our experiments somewhat lower yields of the pyrazole and pyrrole derivatives were obtained but appreciable amounts of the starting materials were recovered unchanged.

In summary, as shown in Table 1, the present methodology is particularly suitable to using the tetrazolo[1,5-*a*]pyridines, tetrazolo[1,5-*b*]pyridazines and the tetrazolo[1,5-*a*]pyrimidines as substrates allowing the isolation of pyrroles and pyrazoles in good to excellent yields. In particular, when compared with results previously described in the literature,[7,10,11] our methodology appears to be very promising since the pyrazole and pyrrole heterocycles were obtained in a surprisingly high yield. The following noteworthy features of the methodology should be emphasized: (a) the reaction is of general applicability for the tetrazolo[1,5-*a*]pyridines, tetrazolo[1,5-*b*]pyridazine, and tetrazolo[1,5-*a*]pyrimidines; (b) the starting materials can be easily prepared; (c) great operational simplicity: short reaction times and no need of inert atmosphere and high vacuum conditions. We are currently investigating the feasibility of the reaction toward the preparation of natural nucleosides.

Table 1
Synthesis of pyrazoles and pyrroles via thermolysis of tetrazoloazines

Entry	Tetrazole Deriv.	Range Temp. of Thermolysis ℃	Product	Yield %
1		200-220		86
2		150-170		60
3		120-140		66
4		210-230		55
5		80-100		78
6		110-120		70
7		150-170		75
8		150-170		70
9		150-170	Traces of the cyanoindole	

Acknowledgements

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8. Wentrup, C.; Crow, W. D. *Ibid.* **1971**, *26*, 361.
9. Wentrup, C. *Helv. Chim. Acta* **1972**, *55*, 565.
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15. The starting heterocyclic tetrazoles were prepared by standard procedures starting from readily available chloro and amino heterocycles.