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Preparation of Pyrazole and Pyrazoline Derivatives by Intramolecular Reaction of Hydrazones

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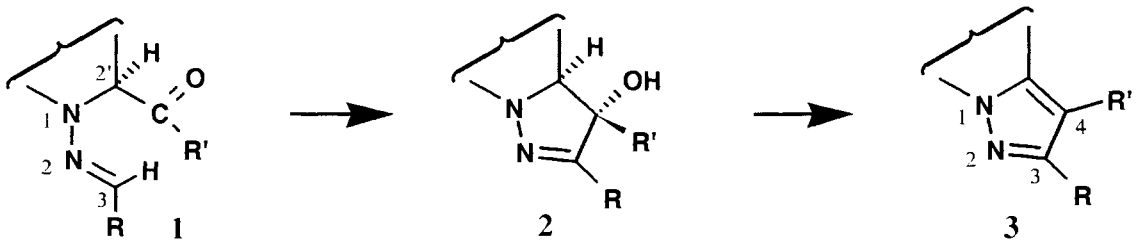
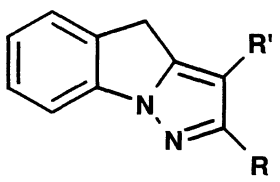
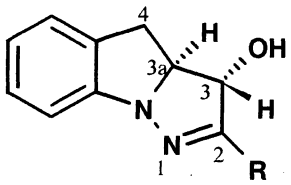
Pyrazole and pyrazoline derivatives are prepared by the intramolecular cyclization reaction of a hydrazonyl group with formyl or keto groups in the presence of a Lewis acid.

Currently we are working with pyrazolo[1,5-a]indoles[1] and are in need to have a versatile method to construct this skeleton. Inspired by the report of Roskamp and Pedersen,[2] we have investigated the intramolecular reaction of hydrazonyl group with formyl group to find a general method for the preparation of pyrazole and pyrazoline derivatives as shown below. Two reaction conditions (R.C.) were used to effect this scheme - A: Refluxing an equimolar mixture of aldehyde-hydrazone **1** and $NbCl_3$·DME complex in THF for 1 h under dry argon; B: Treating **1** with an equivalent BF_3·Et_2O in CH_2Cl_2 at 0-5 °C for a few hours. Reaction condition A gives pyrazoles **3** and B gives either pyrazolines **2** or pyrazoles **3**. The products and the yields are summarized in Table 1. For the preparation of **5**, only reaction condition B was effective. The hydrazone derived from a methyl ketone did not react in these conditions. An attempt of intermolecular reaction failed. Hydrazones **1** were prepared in good yields by the oxidation of the corresponding alcohols. Swern procedure was used when the *para* substituent X is electron-donating and the Parikh-Doering procedure was employed for the substrate bearing an electron-attracting group.[3] When R is alkyl or electron-rich aryl group (X = NMe_2), the hydrazones **1** can not survive in oxidative conditions. Pyrazoline **6a** was isolated along with **4a** when reaction condition A was conducted at room temperature. Pyrazoline **6a** readily underwent dehydration into **4a** by treating with either one of the above two reagents in refluxing THF. The *trans* stereochemistry between H-3 and H-3a in **6a** was deduced from the coupling constant (J = 2.4 Hz) of H-3 (δ 5.34, d) as well as the NOE spectrum (βH-4/H-3) and further confirmed by X-ray analysis of its $LiAlH_4$ reduction and N-methylation product. Thus, $NbCl_3$·DME



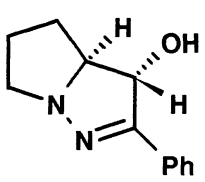


4 R = C_6H_4-X-*p*, R' = H
5 R = Ph, R' = Me



6 R = C_6H_4-X-*p*
7 R = CH=CH-Ph

a X = H
b X = Me
c X = OMe
d X=Cl
e X=CN
f X=NO_2



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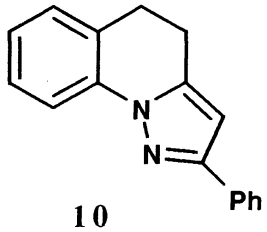

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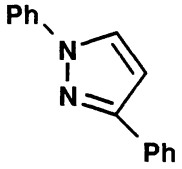

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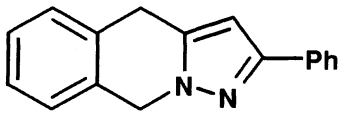

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Table 1. Yields of Pyrazoles and Pyrazolines

Products	R.C.	Yield/%	Products	R.C.	Yield/%	Products	R.C.	Yield/%
4a	A	64	**4f**	A	63	**7**	B	63
4b	A	69	**5**	B	81	**8**	B	44
4c	A	73	**6a**	B	96	**9**	B	86
4d	A	63	**6c**	B	81	**10**	B	90
4e	A	64	**6f**	B	79	**11**	B	81

complex did not work as a reductive coupling agent but did as a Lewis acid to coordinate on the carbonyl oxygen of **1**. Then the hydrazone carbon added to the carbonyl group[4] to lead to the *trans* 3,3a-configuration. The adducts **2** were then dehydrated into pyrazoles **3**. Pyrazolines **2** are available only when the dehydration is slow. The above method is novel[5,6] and pyrazolines **2** can be the potential precursors for the syntheses of biologically active 4-hydroxypyrazole derivatives.[6]

References

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