Synthesis of 4,5-dihydroisoxazoles from N-nitroso-4,5-dihydropyrazoles under microwave irradiation

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4,5-Dihydroisoxazoles have been used as key intermediates in the synthesis of a bioactive molecules [1], and are found in pharmaceutical agents such as glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors [2] and human leukocyte elastase inhibitors [3]. In the present work 4,5-dihydroisoxazoles have been prepared by thermal removal of nitrogen from N-nitroso-4,5-dihydropyrazoles under microwave irradiation.

We performed thermolysis of N-nitrosodihydropyrazoles 1a-j and 3a-i using microwave irradiation in chlorbenzene – DMF (3–4:1) mixture, chlorbenzene – AcOH mixture (3:1) or SiO_2 in solvent–free conditions. All the reactions have been carried out in sealed reaction vial by the focused microwave reactor Minotavr® with measurement and control of power and temperature by thermocouple. In order to compare the efficiency of microwave irradiation to carry out thermolysis of N-nitrosodihydropyrazoles we performed these reactions by classical heating in boiling chlorobenzene [4].

From compounds 1a-j we obtained ethyl(methyl) 5-aryl-4,6-dioxo-4,5,6,6a-tetrahydro-3a*H*-pyrrolo[3,4-*d*]isoxazole-3-carboxylates 2a-j in up to 75% yield. Thermolysis of esters 3a-i under microwave irradiation gave ethyl(methyl) 7-aryl-6,8-dioxo-1-oxa-2,7-diazaspiro[4.4]non-2-ene-3-carboxylates 4a-i which were isolated in up to 56% yield. The structure of compounds **2a-j** and **4a-i** have been established by spectral methods and X-ray analysis of the compound **2a**.

We believe that the reaction occurs through the corresponding intermediate nitrosocyclopropane **6** which undergoes rearrangement in a way similar to the azacyclopropanedihydropyrazole rearrangement.

References

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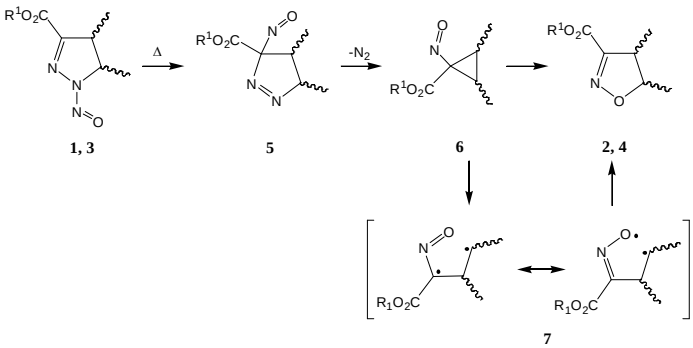
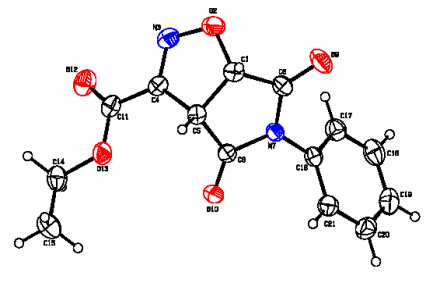
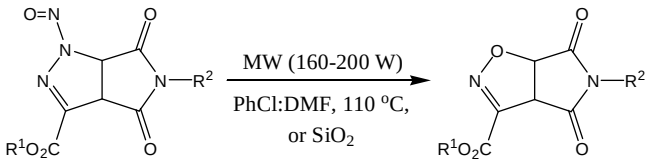


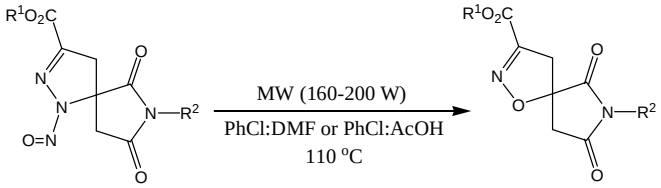


X-ray structure of compound **2a**



1a-f **2a-f** (up to 75%)

1, **2**, R1 = Et, R2 = Ph (**a**), 4-MeC6H4 (**b**), 4-ClC6H4 (**c**), 4-MeOC6H4 (**d**), 4-BrC6H4 (**e**), 4-EtC6H4 (**f**)



3a-f **4a-f** (up to 67%)

3, **4**, R1 = Et, R2 = Ph (**a**), 4-ClC6H4 (**b**); 3,4-Cl2C6H3 (**c**); R1 = Me, R2 = 4-ClC6H4 (**d**); 4-FC6H4 (**e**), 4-BrC6H4 (**f**)

Entry	Substrate	Product	Yield (%)	
			Microwave Irradiation	*Thermal Heating* [a]
1	**1a**	**2a**	59 (PhCl-DMF, 3:1, 3 min) 75 (SiO_2, 4 min)	61
2	**1b**	**2b**	44 (PhCl-DMF, 3:1, 3 min) 59 (SiO_2, 4 min)	44
3	**1c**	**2c**	61 (PhCl-DMF, 3:1, 3 min) 73 (SiO_2, 4 min)	51
4	**1d**	**2d**	67 (PhCl-DMF, 3:1, 3 min) 71 (SiO_2, 4 min)	45
5	**1e**	**2e**	63 (PhCl-DMF, 3:1, 3 min)	47
6	**1f**	**2f**	71 (PhCl-DMF, 3:1, 3 min)	67
7	**3a**	**4a**	40 (PhCl-DMF, 4:1, 4 min) 54 (PhCl-AcOH, 3:1, 4 min)	49
8	**3b**	**4b**	66 (PhCl-AcOH, 3:1, 4 min) 41 (SiO_2, 8 min)	58
9	**3c**	**4c**	61 (PhCl-AcOH, 3:1, 4 min)	55
10	**3d**	**4d**	67 (PhCl-AcOH, 3:1, 4 min)	63
11	**3e**	**4e**	66 (PhCl-AcOH, 3:1, 4 min)	58
12	**3f**	**4f**	57 (PhCl-AcOH, 3:1, 4 min)	49

[a] PhCl, 130 °C, 30 min.

Acknowledgement

We sincerely thank Lumex® Ltd for access to the Minotavr®.