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Synthesis of *N*-aminopyrazoles by Fe(II)-catalyzed rearrangement of 4-hydrazonomethyl-substituted isoxazoles

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ABSTRACT

A novel effective method is reported for the preparation of 1-amino-1*H*-pyrazole-4-carboxylic acid derivatives by Fe(II)-catalyzed rearrangement of isoxazoles having (2,4-dinitrophenylhydrazono)methyl substituent at C4. The reaction proceeds smoothly for both *E* and *Z* isomers of 4-(hydrazonomethyl) isoxazoles, and this means it is not necessary to separate mixtures of *E*/*Z*-isomers of the hydrazones prepared by reaction of 5-methoxy/pirrolidino-4-carbonylisoxazoles and 2,4-dinitrophenylhydrazine. The rearrangement proceeds via the formation of an aziridine intermediate which can be isolated in certain cases. The 2-nitro group in the synthesized 1-[(2,4-dinitrophenyl)amino]-1*H*-pyrazole-4-carboxylic esters can be selectively reduced in two steps via acylation of the amino group followed by hydrogenation-deacylation using H_2-Pd/C.

1. Introduction

Many medicines, including the best-selling drugs, are derivatives of heterocycles from the list of privileged structures of medical chemistry [1]. Pyrazole is one such privileged structure [2]. *N*-aminopyrazole derivatives in particular exhibit antiprotozoal activity [3,4] and are patented as agents for the treatment of depression [5,6] and heart failure [6]. *N*-Aminopyrazoles are also used as intermediates in the production of a variety of nitrogen-containing heterocycles [7]. The main method for the preparation of *N*-aminopyrazoles is the electrophilic amination of a pyrazole nitrogen. Recyclizations of hydrazinyl-substituted isoxazoles, heterocyclization with the participation of azides and reduction of nitro derivatives are less often used [7]. The thermal rearrangement of isoxazol-5-ylhydrazines gives 1-aminopyrazolin-5-ones [8]. Photochemical rearrangement of isoxazolopyridines [9] and isoxazolopyridazines [10], containing a hydrazinyl substituent in the azine ring, yields *N*-aminopyrazole derivatives fused to the corresponding azine ring in low yields. Catalytic transformation of isoxazoles into to *N*-aminopyrazole derivatives is to the best of our knowledge unknown [7,11].

Earlier we found that isoxazoles containing a C=C unsaturated moiety in the C4 position rearrange to the corresponding 1*H*-pyrrole derivatives under Fe(II)-catalysis [12]. Thus 4-vinylisoxazoles are precursors of substituted pyrroles [12a], whereas 4-arylisoxazoles give substituted indoles [12b] (Scheme 1). We hypothesized that a replacement of the C=C moiety, which participates in the 1,5-cyclization of transient species during rearrangement of 4-vinylisoxazoles, by another unsaturated fragment such as RNHN = C would lead to the corresponding *N*-aminopyrazoles as products of the cyclization (Scheme 1).

2. Results and discussion

To check this hypothesis we tried to synthesize some hydrazones of 4-carbonyl-5-methoxyisoxazoles **1**, which were prepared according to modified published procedures by acylation of the corresponding 3-substituted isoxazol-5(4*H*)-ones **2**, followed by methylation of the resulting 4-acyl-5-hydroxyisoxazoles **3** with diazomethane (Scheme 2).

Unexpectedly, it was found that the corresponding hydrazones were not formed by the reactions of 4-carbonylisoxazoles **1** with hydrazine, phenylhydrazine and tosylhydrazine. Only the reaction of 2,4-dinitrophenylhydrazine (DNPH) with isoxazoles **1** gave hydrazones **4**, either as the *E*-isomer or as a mixture of *E*/*Z*-isomers, usually in good yields (Table 1). The *E*/*Z*-isomers were separated by

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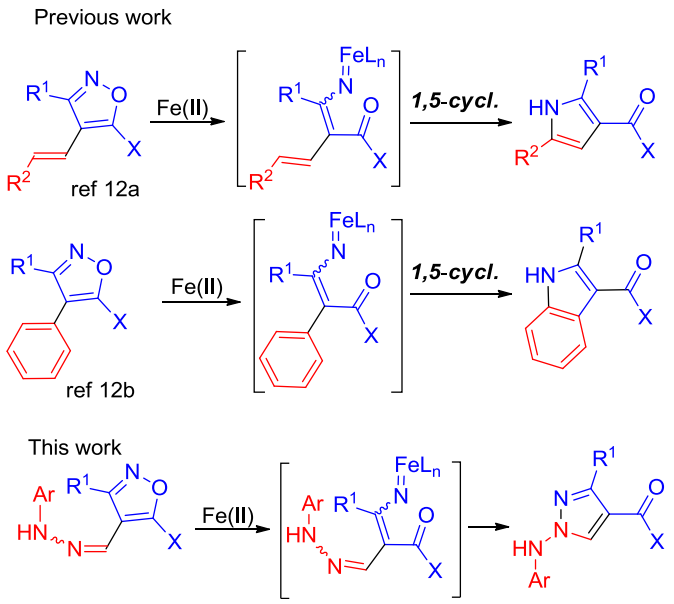
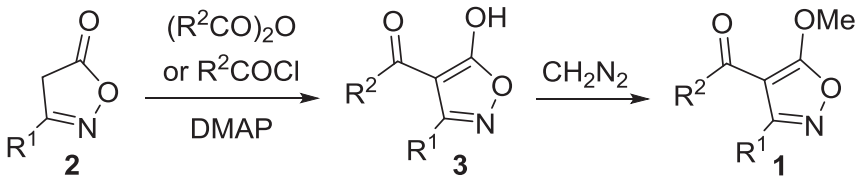


Scheme 1. The routes of Fe(II)-catalyzed transformations of izoxazoles with unsaturated substituent in the C4 position.

chromatography and their structures were established by standard spectroscopic methods. The stereochemistry of the isomers of hydrazones **4a-e,g,h** were elucidated by 2D-NOESY ^{1}H NMR spectroscopy, whereas XRD-analysis was used for hydrazone Z-**4f** (Fig. 1).

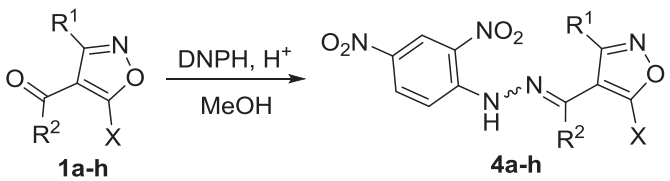
Special experiments have shown that the interconversion of the *E* and *Z* isomers of hydrazones **4** does not occur by boiling their solutions in acetonitrile or methanol. This would mean that a barrier for the isomerization is too high for it to occur under these conditions. Quantum-chemical calculations at the B3LYP/6-31G+(d,p) level of the *E* and *Z* isomers of hydrazones **4a-e** and of the transition states of their *Z*/*E*-isomerization were performed to evaluate the corresponding energy barriers. The barriers for the transformation of the *Z*-hydrazones **4a-e** to the corresponding *E*-isomers are in the region of 35–37 kcal mol^{-1} and for the back transformation are in the region of 34–37 kcal mol^{-1}. The calculated barriers are high enough to prevent isomerization at the temperatures used in this study. It is noteworthy that in the case when only the *E* isomer (**4a**, **b**, **d**) was formed in the reaction of DNPH with 4-carbonylisoxazoles **1a**, **b**, **d** the corresponding *Z* isomer according to the calculation is thermodynamically more stable. The ratio of isomers is, therefore, defined by the reaction kinetics.

Next, we studied the reactivity of hydrazones **4a-h** towards $FeCl_2$, including the effect of stereochemistry. The rearrangement of the hydrazone of isoxazolecarbaldehyde *E*-**4a** proceeds easily already at rt to give pyrazole **5a** in 94% yield after 2 d (Table 2, entry 1). Changing the R^2 substituent from H to Et has no influence on the time of rearrangement (Table 2, entry 2), whereas introduction of a nitro group into the phenyl moiety (R^1) makes the reaction a little slower, *E*- and *Z*-isomers react identically (Table 2, entry 3–5). Isomer *Z*-**4e** rearranges much faster than isomer *E*-**4e** at rt, but at 70 °C both the individual isomers as well as a mixture of isomers gives **5e** in 77%–92% yield only after 1 d (Table 2, entry 7–9). Steric congestion in compound **4f** with two Ph-substituents makes the rearrangement at rt slower. The reaction of isomer *Z*-**4f** was also accompanied by formation of some unidentified products. The isomer *E*-**4f** under these conditions afforded azirine **6**, which



Scheme 2. Synthesis of starting 4-carbonyl-5-methoxyisoxazoles **1**.

Table 1
Hydrazones of 4-carbonylisoxazoles.



entry	R^1	R^2	X	Yield of 4,[a] %	Z/E ratio,[b] %	Z, $TS^{Z/E}$, E; MeOH[c]	Z, $TS^{Z/E}$, E; MeCN[c]
1	Ph	H	MeO	**a**, 91	0/100	0.0, 35.4, 1.7	0.0, 35.4, 1.8
2	Ph	Et	MeO	**b**, 84	0/100	0.0, 36.7, 1.0	0.0, 36.7, 1.1
3	4-$NO_2C_6H_4$	Et	MeO	**c**, 83	26/74	0.0, 37.0, 0.4	0.0, 37.0, 0.3
4	thien-2-yl	Et	MeO	**d**, 59	0/100	0.0, 36.8, 1.5	0.0, 36.8, 1.5
5	Me	Ph	MeO	**e**, 66	46/54	0.0, 35.7, 0.0	0.0, 35.8, 0.3
6	Ph	Ph	MeO	**f**, 85	65/35		
7	4-MeC_6H_4	3-ClC_6H_4	MeO	**g**, 67	57/43		
8	Ph	H	$(CH_2)_4N$	**h**, 85	0/100		

[a] Isolated yield.
[b] According to ^{1}H NMR analysis.
[c] Relative Gibbs free energies of *Z*, *E* isomers **4** and transition states of their *Z*/*E*-isomerization computed at the DFT B3LYP/6-31 + G(d,p) level (kcal mol^{-1}, 298 K, PCM model for MeOH and MeCN).

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