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1-ACYL-3-HYDROXY-1*H*-PYRAZOLES AND RELATED DERIVATIVES AS USEFUL ACYLATING AGENTS[#]

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ABSTRACT

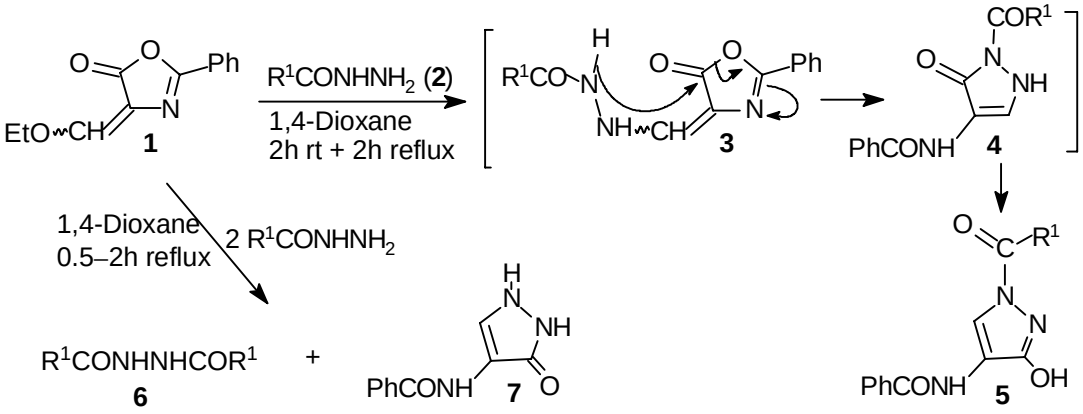
A general application of 1-acyl-3-hydroxy-1*H*-pyrazoles **5** as useful acylating agents for alcohols or phenols, amines and hydrazines is described. The use of a hydrazide for a direct acylation of an alcohol in the presence of 4-ethoxymethylene-2-phenyl-5(4*H*)-oxazolone (**1**) is also discussed.

Acylation is one of the fundamental reactions in organic chemistry and can be carried out by wide variety of reagents [1]. Acyl groups play an important role in the chemistry of biomolecules [2], they are fragments of important natural products, such as peptides [2–3] or modified peptide bond isosteres [4], they serve as protecting groups [5], etc. Pyrazole derivatives are important synthons and reagents in organic synthesis and have found applications as pharmaceuticals, agrochemicals, dyestuffs, etc. [6]. They can be obtained by various methods from different starting materials [6–9]. In a previous communication pyrazoles were described as relatively inert acylating agents, although their alcoholysis was dramatically accelerated under the influence of a strong acid or base [10]. On the other hand, 1-acyl-3-hydroxy-1*H*-pyrazoles and related compounds

[#] Dedicated to the memory of Professor Anton Šebenik.

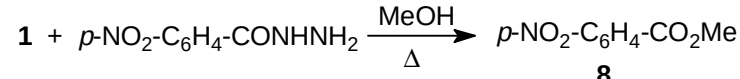
have not been so often investigated, although several acetyl derivatives have been prepared and further studied [11–13]. Their potential as acylating *N*-acyl agents has not been described, but it was found that 3-acetoxy group in 3-acetoxy-1-acetyl-5-methylpyrazole has higher acetylating potential than its 1-acetyl group.

Recently, we have described a synthesis of 1-acyl-3-hydroxy-1*H*-pyrazoles **5** and related derivatives from ethoxymethyleneoxazolone derivative **1** and hydrazides or related derivatives **2** (Scheme 1) [6]. The method includes a migration of an acyl group in the intermediary-formed pyrazolone derivative **4** to yield the rearranged 1-acyl-3-hydroxy-1*H*-pyrazoles **5** in high yields. In contrast, in the reaction of the oxazolone derivative **1** with two equivalents of an appropriate hydrazine derivative the corresponding symmetrically *N*,*N*′-disubstituted hydrazines **6** were obtained together with the oxazolone derivative **7**.

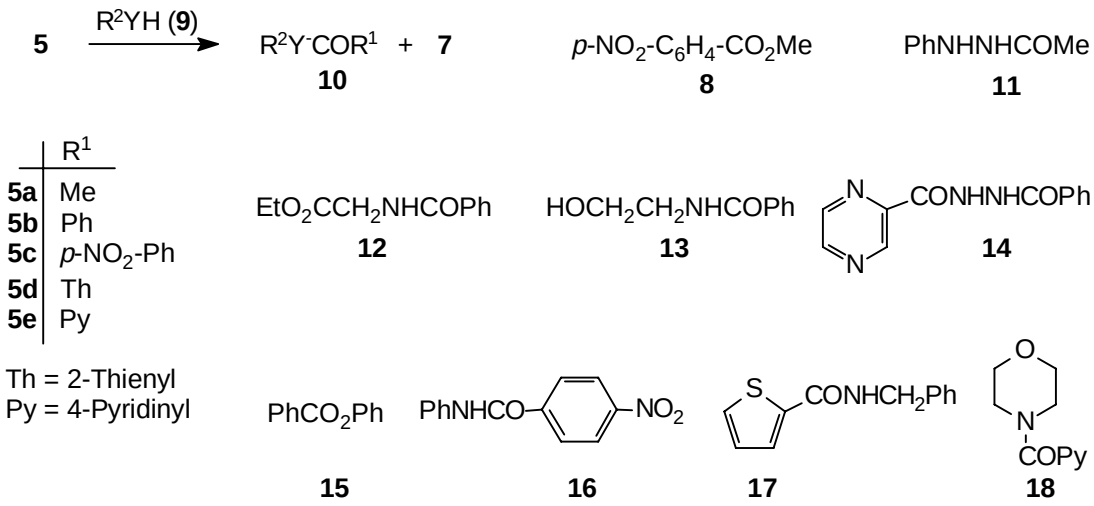


Scheme 1

Here, we report a possibility of using pyrazole derivatives **5a**–**e** as acylating agents. In contrast to the previous investigation of pyrazoles for such purposes [10], we wanted to explore the influence of an electron-rich hydroxy group on the acylating potential of pyrazole derivatives. When a mixture of equimolar amounts of the oxazolone derivative **1** and *p*-nitrophenylcarbohydrazide was heated for 30 h in a methanolic solution, we isolated the corresponding methyl *p*-nitrobenzoate (**8**) in 74% yield.



From the described reaction it is not clearly evident if pyrazole derivative is an acylating agent, since the acyl group might also be transferred onto methanol in the intermediary step. For this reason, the reaction of the pyrazole **5c** in methanol was carried out. It required a long heating period, but in the presence of an equimolar amount of sodium methoxide the reaction was over in 10 min at room temperature and we isolated methyl *p*-nitrobenzoate (**8**) in 72% yield (Scheme 2). Then we performed several reactions starting from equimolar amounts of the pyrazoles **5a**–**e** and various derivatives of type **9** (Y = O, NH) in boiling 1,4-dioxane and the corresponding products of type **10** were obtained in 55–87% yield (Table 1). By this method the acyl groups were transferred from pyrazoles **5a**–**e** to various amines, hydrazines, amino acid derivative and phenol yielding the corresponding amides, hydrazides or esters (**11–18**).



Scheme 2

For the synthesis of products **12** and **15** triethylamine was used as a catalyst. All other products were obtained after a short heating period of time in reasonable yields. With ethanolamine as a substrate, a selective *N*-acylation occurred to yield product **13**.

The separation of the products of type **10** from the pyrazolone derivative **7** was achieved by an alkaline water solution of the crude material from which the products separated or were extracted with a mixture of chloroform and 1,4-dioxane and finally purified by column chromatography.

Table 1. Reaction Conditions and Yields of Compounds 11-18

Entry	Pyrazole **5** (2 mmol)	Substrate **9** (2 mmol)	Conditions (dioxane, Δ)	Acylated Product	Yield (%)
1	**5a**	$PhNHNH_2$	2 h	**11**	67
2	**5b**	$EtO_2CCH_2NH_2$	2 h[a]	**12**	59
3	**5b**	$HOCH_2CH_2NH_2$	1 h	**13**	74[c]
4	**5b**	Pyrazinyl-$CONHNH_2$	2 h	**14**	84[d]
5	**5b**	PhOH	4 h[a]	**15**	55
6	**5c**	$PhNH_2$	2 h[b]	**16**	77
7	**5d**	$PhCH_2NH_2$	2 h	**17**	87
8	**5e**	Morpholine	1 h	**18**	72

[a]Et_3N was added as a catalyst. [b]Due to solubility problems DMF was used as a solvent. [c]Yield after isolation by column chromatography. [d]Isolation by work-up with 1 M NaOH, followed by filtration.

In conclusion, we have demonstrated the use 1-acyl-3-hydroxy-1*H*-pyrazoles as a convenient source of an acyl unit. The whole method starting from hydrazides represents a possible way of an activation of hydrazides, which are known as poor donors of acyl units due to their high resonance stability. The main advantages of this method are easily available and cheap chemicals, relatively mild reaction conditions and a simple work-up.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and are uncorrected. Thin-layer chromatography was carried out on Fluka silica gel TLC-cards. Column chromatography was carried out on Fluka silica gel 60 (220–440 mesh). 4-

Ethoxymethylene-2-phenyl-5(4*H*)-oxazolone (**1**) [14], 2-pyrazinecarbohydrazide [15] and 2-(benzoylamino)acetohydrazide [16] were prepared as described in the literature. 1,4-Dioxane was purified as described [17]. All other compounds and reagents were used as received from commercial suppliers (Fluka, Aldrich).

Preparation of Methyl 4-Nitrobenzoate (8).

Method A. A mixture of oxazolone **1** (0.436 g, 2 mmol) and 4-nitrobenzohydrazide (0.363 g, 2 mmol) was refluxed in methanol (10 mL) for 30 hours. The product was isolated by column chromatography on silica gel (ethyl acetate–petroleum benzine, 1:1). Yield 0.268 g (74%) of a white solid, which was identical with commercially available ester; mp 94–96 °C (lit [18] mp 94–95 °C).

Method B. Pyrazole **5c** (0.704 g, 2 mmol) was dissolved in a freshly prepared 1 M solution of NaOMe in methanol (2 mL). The reaction was completed in 10 min (TLC evidence), methanol was removed under reduced pressure and methyl 4-nitrobenzoate was isolated by column chromatography (ethyl acetate–petroleum benzine, 1:1). Yield 0.261 g (72%) of a white solid.

General Procedure for Reactions of Pyrazoles 5 with Nucleophilic Reagents 9.

A pyrazole **5** (2 mmol) was added to a solution of a nucleophile **9** (2 mmol) in dioxane (4 mL) and the reaction mixture was refluxed for 1–4 hours. The mixture was cooled, then chloroform (8 mL) and water (2 mL) were added. The pH value of the water layer was adjusted to 13 with 1 M NaOH in order to dissolve pyrazolone **7** in water. The layers were separated and the water layer was extracted with a mixture of chloroform (8 mL) and dioxane (4 mL). Organic layers were collected, washed with water (5 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The products (with the exception of **14**) were purified by column chromatography and were obtained as TLC-pure compounds. Reaction conditions and yields of products **11**–**18** are given in Table 1.

The following products were obtained by the General Procedure:

***N*-(2,3-Dihydro-3-oxo-1*H*-pyrazol-4-yl)benzamide (7).**

This compound can be isolated from the water layer by acidification to pH 5 with acetic acid and filtration of the resulting solid; mp 205–206 °C (lit [14] mp 204–205 °C).

***N'*-Phenylacetohydrazide (11).**

This compound was prepared by refluxing pyrazole **5a** and phenylhydrazine for 2 h. Yield 0.201 g (67%) of a white solid; mp 125–127 °C (lit [19] mp 129 °C).

Ethyl 2-(benzoylamino)acetate (12).

This compound was prepared by refluxing pyrazole **5b** and glycine ethyl ester hydrochloride in the presence of triethylamine (0.6 mL, 4.3 mmol) for 2 h. Yield 0.245 g (59%) of a white solid; mp 59–60 °C (lit [20] mp 60.5 °C).

***N*-(2-Hydroxyethyl)benzamide (13).**

This compound was prepared by refluxing pyrazole **5b** and 2-aminoethanol for 1 h. It was isolated by column chromatography on silica gel (chloroform–methanol, 5:1). Yield 0.244 g (74%) of a beige solid; mp 56–59 °C (lit [21] mp 58 °C).

***N'*-(2-Pyrazinylcarbonyl)benzohydrazide (14).**

This compound was prepared by refluxing pyrazole **5b** and 2-pyrazinecarbohydrazide for 2 h. The reaction mixture was cooled, water (5 mL) was added and the pH value was adjusted to 10 with 1 M NaOH. The resulting solid was filtered off and washed with 1,4-dioxane. Yield 0.407 g (84%) of a white solid; mp 217–219 °C (lit [22] mp 217 °C).

Phenyl benzoate (15).

This compound was prepared by refluxing pyrazole **5b**, phenol and triethylamine (0.3 mL, 2.1 mmol) for 4 h. Yield 0.218 g (55%) of a white solid; mp 67–69 °C (lit [23] mp 70 °C).

***N*-Phenyl-4-nitrobenzamide (16).**

This compound was prepared by refluxing pyrazole **5c** and aniline in DMF for 2 h. DMF was evaporated under reduced pressure, 1,4-dioxane (4 mL) was added and the product was isolated as described in the General Procedure. Yield 0.360 g (77%) of a yellowish solid; mp 219–220 °C (lit [24] mp 218 °C).

***N*-Benzyl-2-thiophenecarboxamide (17).**

This compound was prepared by refluxing pyrazole **5d** and benzylamine in 1,4-dioxane for 2 h. Yield 0.378 g (87%) of white crystals; mp 117–120 °C (lit [25] mp 119.5–120.5 °C).

4-(4-Pyridinylcarbonyl)morpholine (18).

This compound was prepared by refluxing pyrazole **5e** and morpholine for 1 h. Yield 0.276 g (72%) of a white solid; mp 73–74 °C (lit [26] mp 75–76 °C).

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POVZETEK

Opisana je splošna metoda za uporaba 1-acil-3-hidroksi-1*H*-pirazolov **5** kot primernih acilirnih sredstev za alkohole ali fenole, amine in hidrazine. Opisan je tudi primer uporabe hidrazida ob prisotnosti 4-etoksimetilen-2-fenil-5(4*H*)-oxazolona (**1**) za neposredno aciliranje alkohola.