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# Methylation of 4-nitro-3(5)-pyrazolecarboxylic acid

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ABSTRACT

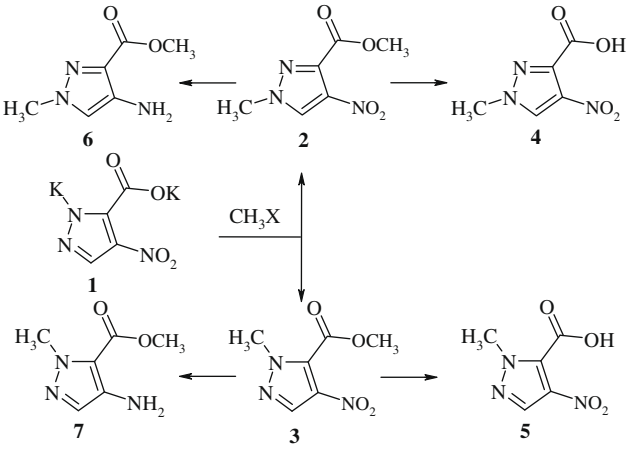
Reactions of 4-nitro-3(5)-pyrazolecarboxylic acid dipotassium salt with different methylating agents in various solvents have been investigated to improve the synthesis of isomeric 1-methyl-4-nitro-3- and -5-pyrazolecarboxylic acids.



Heterocyclic nitro acids and their derivatives are important starting materials in chemical synthesis. They are utilized as precursors to obtain various biologically active compounds especially if appropriate amino acids are not easily available. Our interest in heterocyclic amino acid derivatives was stimulated by the synthesis of 5-benzoylamine-*N*-(4-chlorophenyl)-3-methyl-4-isothiazolecarboxamide, (Denotivir ITCL, Vratizolin)[1] and the discovery of its broad spectrum of pharmacological activity. Since this compound was put into medical practice as an antiviral drug with anti-inflammatory and immunotropic activity, a number of other biologically active 5-amino-4-isothiazolecarboxylic acid derivatives have been reported.[2] Bioisoster imidazole analogues of Denotivir[3] have revealed strong anti-inflammatory and immunotropic activity which has prompted us to synthesize their pyrazole analogues. Presented herein are our preliminary studies on the synthesis of 1-methyl-4-amino-3- and -5-pyrazolecarboxylic acid derivatives as outlined in Scheme 1. Amongst various 4-nitropyrazoles particular attention should be paid to 1-methyl-4-nitro-3- and -5-pyrazolecarboxylic acids (**4** and **5**, respectively) because of their synthetic utility as well as the biological activities of their derivatives. Several synthetic applications of both isomeric *N*-methyl-4-nitropyrazolecarboxylic acids were reported recently including their use in the synthesis of potential drugs for Alzheimer's disease, cerebral apoplexy, manic-depressive illness, schizophrenia, cancer, type II diabetes and obesity,[4,5] ulcer inhibitors, secretion inhibitors, antitussive and antiemetic compounds,[6] cytokinin antagonistic compounds,[7] analgesics, anti-depressives, antiphlogistics, antipyretics,[6,8] herbicides and insecticides.[9–11]

Herein, we present various attempts towards the selective methylation of 4-nitro-3(5)-pyrazolecarboxylic acid in order to obtain the required *N*-methyl isomers with the highest possible yields and purity which is essential for further synthesis of compounds for biological testing.

N-Alkylation is an important reaction in pyrazole chemistry. It is well known that methylation of unsymmetrically substituted pyrazole derivatives usually gives mixtures of both possible alkylation products. The ratios of these products depend not only on the




**Scheme 1.**

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reaction conditions but also on the form of the alkylated pyrazole (neutral molecule or its ionic form).[12] To the best of our knowledge, no studies of solvent influence on 4-nitro-3(5)-pyrazolecarboxylic acid methylation have been conducted so far.

We found that 4-nitro-3(5)-pyrazolecarboxylic acid can form a stable dipotassium salt **1** on treatment with a methanolic KOH solution. This salt, after separation and drying, can react with methylating agents in various solvents, usually giving mixtures of the following compounds: *N*-methyl carboxylic acids **4** and **5** and their methyl esters **2** and **3**, sometimes accompanied by unreacted starting material (Scheme 1). Products of methylation were found in different molar proportions depending on the nature of the solvent and methylating agent used. The final composition of methylation products was established using $^1$H NMR spectroscopy (Table 1).

Several trials using less reactive methylating agents such as $Me_3PO_4$, $Me_3PO_3$ and $Me_2CO_3$ or other solvents (formamide, toluene, acetonitrile) were unsuccessful. If the reaction was carried out at temperatures of 70 °C, mostly unchanged dipotassium salt **1** was recovered. At elevated temperatures (80 °C or higher) the product of decarboxylation, namely *N*-methyl-4-nitropyrazole was usually obtained.

During isolation of the reaction products it proved difficult to separate and purify the isomeric *N*-methyl acids **4** and **5** in comparison to the purification of their methyl esters. For this reason, all procedures resulting in formation of esters **2** and **3** only, should be appreciated as especially valuable for preparative purposes. Although the synthesis of ester **2** was previously reported in the literature,[5] no physical data were given for this compound. Thus, both esters **2** and **3** were hydrolyzed to the corresponding acids **4** and **5** in order to identify their structures. The melting points of the resulting nitro acids were compared with literature values[13] which showed significant discrepancies. We found that isomeric acids **4** and **5** have melting points of 167–171 °C and 181–182 °C, respectively, while the melting points of 1-methyl-4-nitro-3-pyrazolecarboxylic and 1-methyl-4-nitro-5-pyrazolecarboxylic acids were reported previously[13] as 171–173 °C and 162–165 °C, respectively. Regarding the fact that there is no direct evidence in the literature for the structures of these two acids it was necessary to perform a detailed chemical analysis of our obtained compounds to unambiguously establish their structures. Elemental analyses and $^1$H/$^{13}$C NMR spectral data confirmed both hydrolysis products **4** and **5** to be *N*-methylpyrazole nitro acids. The 2D COSY $^1$H NMR spectrum of compound **4** exhibited a weak coupling between the *N*-methyl group and the pyrazole ring proton which suggested this derivative to be the 3-substituted isomer. This was confirmed by X-ray crystallography which finally allowed full assignment of the structures for both of the obtained acids (Fig. 1). Additionally, synthesis of nitro acid **5** according to the procedure described previously[5] gave the chromatographically pure (TLC with ethanol or

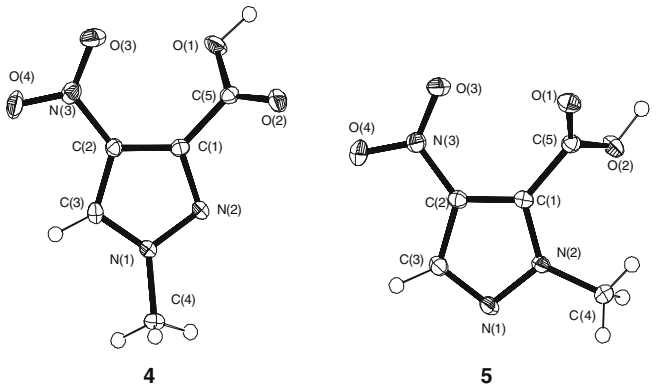


**Figure 1.** ORTEP plots of molecules **4** and **5** (50% probability level).

$CHCl_3$–methanol 3:1 as eluents) product which melted at 165–167 °C and which is very close to its reported value. The $^1$H NMR spectrum of this product indicated it to be 1-methyl-4-nitro-5-pyrazolecarboxylic acid **5** contaminated with a considerable amount of impurity, probably the isomeric 3-carboxylic acid **4**. After several recrystallizations from butanone its melting point increased to 173–175 °C, but still a trace of impurity was detectable using $^1$H NMR spectroscopy [signal near 3.90 ppm (DMSO-$d_6$)].

Initial experiments showed that methylation of dipotassium salt **1** can be accomplished with satisfactory results only if a polar solvent and moderately (MeI) or highly reactive methylating agents ($Me_2SO_4$, TosMe) are used. The composition of the methylation products depended strongly on the solvent, Table 1. Generally, in aprotic polar solvents (acetone, DMF) ester **2** was formed in the highest proportion while in polar and protic methanol, acid **5** and its ester **3** were the major products. It should be mentioned that using methanol as solvent for this reaction always resulted in a mixture of acids **4** and **5** accompanied with esters **2** and **3** even if an excess of base and methylating agent were added. This fact suggested that simultaneous reaction of the solvent with the methylating agent occurred resulting in formation of dimethyl ether as a side product. The results obtained may be explained taking into account the expected differences between the chemical behaviour of dipotassium salt **1** in protic and aprotic solvents as outlined in Figure 2.

According to our assumptions dipotassium salt **1** when dissolved in polar aprotic solvents may exist in dianionic form **A** or as intramolecular monoanion complex **B** in which the nitrogen atom nearest to the carboxylic group is shielded by the coordinated potassium cation. When methylation of **1** is carried out in aprotic solvents then, considering **B** as the predominant form, formation

**Table 1**
Results of the methylation of **1** depending on the reaction conditions expressed as the ratio of relative molar amounts of reaction products

| Conditions | Compound | | | | |
|---|---|---|---|---|---|
| | **2** | **3** | **4** | **5** | **1** |
| $Me_2SO_4$/MeOH | 2 | 3 | 0.5 | 2 | Trace |
| $Me_2SO_4$/DMF | 2 | 1 | Trace | 0.3 | 0 |
| $Me_2SO_4$/$Me_2CO$ | 4 | 1 | 0 | 0 | Trace |
| TosMe/MeOH | 2 | 5 | 1 | 2 | 0 |
| TosMe/DMF | 3 | 2 | 0 | 0 | 0 |
| TosMe/$Me_2CO$ | 4 | 2 | 3 | 1 | 0 |
| MeI/MeOH | Trace | Trace | 2 | 5 | 0 |
| MeI/DMF | 2 | 1 | 0.5 | 1 | 0 |
| MeI/$Me_2CO$ | Trace | Trace | 0 | 0 | 1 |

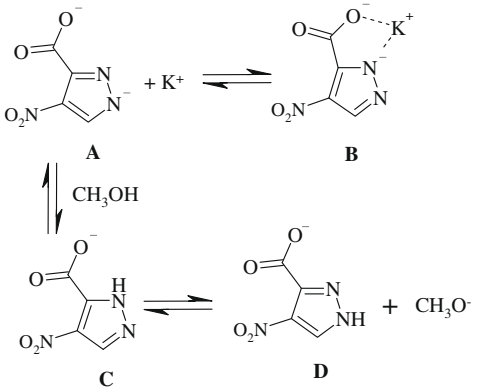


**Figure 2.**

of **2** and **4** will be preferred due to steric hindrance. In protic methanol, protonation of **1** is inevitable resulting in formation of tautomeric anions **C** and **D** from which **D** will dominate due to its higher polarity. Being more susceptible to methylation, the pyridine-type nitrogen atom of **D** is located nearer to the carboxylic moiety resulting in a higher proportion of methylation products **3** and **5**. Another mechanism can be considered involving initial O-methylation accompanied with further intramolecular N-methylation resulting in the formation of nitro acid **5**.

In conclusion, the experiments described have revealed that use of an appropriate solvent can enable partial control of the methylation of **1** resulting in a higher yield of the required isomer. Several attempts to convert both nitro acids **4** and **5** to their amino analogues were performed but none gave satisfactory results. Reduction of methyl ester **2** with $H_2$/Pd was previously described[5] and is easily reproducible. Unfortunately, this procedure failed with methyl ester **3**; also, catalytic reduction of a mixture of both esters could not be accomplished. Methyl 1-methyl-4-amino-5-pyrazolecarboxylate (**7**) was obtained in satisfactory yield using sodium dithionite as reducing agent. Both amino esters **6** and **7** are stable enough to perform elemental and spectral analyses but should not be stored for prolonged periods as they decompose in air and/or the presence of light.

CCDC 683477 for compound **4** and CCDC 683478 for compound **5** contain crystallographic details which are available at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered, free of charge, from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ; fax: (+44)1223-336-033 or deposit@ccdc.cam.ac.uk.

For correct estimation of the efficacy of the methylation process, $^1$H NMR spectra (300 MHz) of pure compounds **1**–**5** in DMSO-$d_6$ were recorded at the beginning of the experiments. Calculations of the relative molar concentrations of the methylation products were performed based on integrations of their N–$CH_3$ signals except of unchanged starting material which was identified by its single aromatic proton signal (see Table 1).

$^1$H NMR data for compounds **1**–**5** in DMSO-$d_6$ [ppm]:

**1** $\delta$ = 8.45 (s);
**2** $\delta$ = 3.87 (s, 3H, O–$CH_3$), 3.93 (s, 3H, N–$CH_3$), 8.63 (s, 1H);
**3** $\delta$ = 3.96 (s, 3H, O–$CH_3$), 3.98 (s, 3H, N–$CH_3$), 8.37 (s, 1H);
**4** $\delta$ = 3.91 (s; 3H, N–$CH_3$), 8.86 (s; 1H);
**5** $\delta$ = 4.03 (s; 3H, N–$CH_3$), 7.99 (s; 1H).

*Dipotassium salt of 4-nitro-3(5)-pyrazolecarboxylic acid* (**1**): 4-Nitro-3(5)-pyrazolecarboxylic acid (15.7 g, 0.1 mol) was suspended in 200 mL of 5.6% methanolic KOH solution (1 M). The mixture was stirred at room temperature for 2 h and refluxed for 30 min. After evaporating the solvent under reduced pressure, the solid residue was dried *in vacuo* over concd $H_2SO_4$ (24 h) and used without purification as a starting material for further reactions.

*General procedure for examination of the methylation of* **1**: Dipotassium salt **1** (0.47 g, 2 mmol) was suspended in 10 mL of appropriate water-free solvent and cooled in an ice bath to 0 °C with stirring. Then, 4 mmol of the methylating agent (except $CH_3I$ which was used in fourfold molar excess) was added to the reaction mixture in several small portions over 15 min. The reaction mixture was stirred for 2 h at room temperature, warmed to 55–60 °C (reflux) (40 °C when $CH_3I$ was used) for 1 h and left to stand overnight at 40 °C with constant stirring. Finally, the reaction mixture was carefully neutralized with 5% HCl to free the carboxylic acids from their potassium salts, then evaporated to dryness under reduced pressure and the solid residue was dried *in vacuo* over concd $H_2SO_4$ (24 h). To test the results of the methylation, 10 mg of dry homogenous sample from each crude reaction mixture was dissolved in 0.5 mL of DMSO-$d_6$ and the $^1$H NMR spectrum was recorded (see Table 1).

*Methyl 1-methyl-4-nitro-3-pyrazolecarboxylate* (**2**): Dipotassium salt **1** (2.33 g, 10 mmol) was suspended in 15 mL of dry acetone and cooled on an ice bath with stirring, then a solution of $Me_2SO_4$ (2.5 mL) in 10 mL of acetone was added dropwise over 15 min. The reaction mixture was stirred at room temperature for 1 h and then refluxed for 3 h. After this time, the solid residue was filtered off, acetone was evaporated *in vacuo* to dryness and the solid residue was extracted in a Soxhlet apparatus with $CCl_4$ (also, $CHCl_3$ or $CH_2Cl_2$ can be used) from which, after partial evaporation of the solvent to about 20 mL and cooling to −5 °C, white crystals of the final product were collected. Yield 1.25 g (68%) mp 122–123 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ [ppm] = 3.92, 3.94, 8.10; $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ [ppm] = 40.5, 53.1, 131.0, 135.0, 138.3, 160.3. Elemental anal. [%]. Calcd for $C_6H_7N_3O_4$: C, 38.93; H, 3.81; N, 22.70. Found: C, 38.71; H, 3.99; N, 22.52.

*Methyl 1-methyl-4-nitro-5-pyrazolecarboxylate* (**3**): Dipotassium salt **1** (2.33 g, 10 mmol) was suspended in 25 mL of dry methanol and cooled on an ice bath with stirring, then 2.5 mL of $Me_2SO_4$ was added dropwise over 15 min. After 1 h, the ice bath was removed and the reaction mixture was stirred at room temperature for 2 h and additionally refluxed for 1 h. Next, 0.56 g (10 mmol) of pulverized KOH was dissolved in the reaction mixture with stirring and the methanol was evaporated to dryness under reduced pressure. The resulting solid residue was dried *in vacuo* for 24 h and suspended in 20 mL of dry DMF. To the resulting mixture, 1.2 mL of $Me_2SO_4$ was added dropwise over 15 min and the reaction mixture was stirred for 2 h at room temperature. After evaporation of the solvent *in vacuo*, the resulting solid residue was extracted in a Soxhlet apparatus with $CCl_4$, from which after cooling to −5 °C, ester **2** crystallized (0.65 g, 35%) as a side product. The filtrate was evaporated and the resulting oily residue containing mostly 5-pyrazolecarboxylic methyl ester was purified by column chromatography on silica gel with chloroform as eluent, giving after recrystallization from heptane, 0.95 g (50%) of product **3**, mp 38–41 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ [ppm] = 3.93, 3.94, 7.92; $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$[ppm] = 39.3, 53.5, 130.9, 134.7, 134.9, 158.6. Elemental anal. [%]. Calcd for $C_6H_7N_3O_4$: C, 38.93; H, 3.81; N, 22.70. Found: C, 39.09; H, 4.08; N, 22.47.

*1-Methyl-4-nitro-3-pyrazolecarboxylic and -5-pyrazolecarboxylic acids* (**4** or **5**): The appropriate ester **2** or **3** (1.85 g, 0.01 mol) was dissolved in 40 mL of ethanol and 10 mL of 6% KOH solution was added. The reaction mixture was left overnight, then neutralized with 10% HCl and evaporated to dryness. The resulting solid residue was extracted in a Soxhlet apparatus with acetone giving, after evaporation of the solvent, the appropriate acid in almost quantitative yield. Both *N*-methyl acids **4** and **5** may be additionally purified by recrystallization from acetone, butanone, ethyl acetate or water.

*Methyl 1-methyl-4-amino-3-pyrazolecarboxylate* (**6**): To a solution of **2** (185 mg, 1 mmol) in 20 mL of methanol, a small amount of 10% palladium on charcoal (about 1 mg) was added and the reaction mixture was stirred vigorously under a hydrogen atmosphere under normal pressure for 5 h. Next, the catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo* to afford a brownish residue of crude methyl 4-amino-1-methyl-3-pyrazolecarboxylate (**6**) (150 mg, 97%) mp 97–102 °C. Additional purification by crystallization from cyclohexane gave an analytical sample of white crystals, mp 99–104 °C, which slowly decomposed in air with darkening. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ [ppm] = 3.80 (s, 3H), 3.86 (s, 3H), 4.15 (s, 2H, br s), 6.93 (s, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ [ppm] = 39.8, 51.4, 117.7, 129.4, 134.9, 163.8. Elemental

anal. [%]. Calcd for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.24; H, 6.11; N, 27.10.

*Methyl 1-methyl-4-amino-5-pyrazolecarboxylate* (**7**): To a stirred solution of **3** (185 mg, 1 mmol) in 35 mL of 60% aqueous methanol, 0.9 g of 80% sodium dithionite (about 4 mmol) was added in several small portions over 30 min. Next, the reaction mixture was stirred at 50 °C for 3 h and then left to stand overnight at room temperature. After this time the solvent was evaporated and the solid residue was dried and triturated several times with chloroform. After evaporation of the chloroform, 120 mg (75%) of a solid brown residue (mp 57–61 °C) was obtained. The crude product could be crystallized from cyclohexane–heptane mixture (2:1) giving light brownish coloured crystals mp 65–68 °C, which slowly decomposed in air with darkening. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ [ppm] = 3.89 (s, 3H), 4.01 (s, 3H), 4.50 (s, 2H, br s), 7.09 (s, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ [ppm] = 40.1, 51.4, 117.5, 126.9, 136.2, 160.7. Elemental anal. [%]. Calcd for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.17; H, 5.98; N, 26.83.

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