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Synthesis and oxidation of all isomeric 2-(pyrazolyl)ethanols

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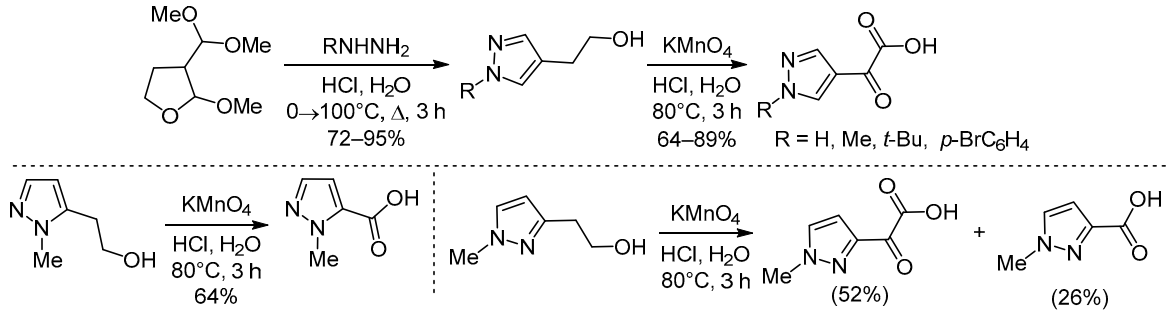


An efficient approach to the preparation of *N*-substituted 2-(pyrazol-4-yl)ethanols based on recyclization reaction of 3-(dimethoxymethyl)-2-methoxytetrahydrofuran with hydrazines is described. Oxidation by $KMnO_4$ led to 2-(pyrazol-4-yl)-2-oxoacetic acids. In contrast, 2-(pyrazol-5-yl)ethanol under similar conditions gave only pyrazole-5-carboxylic acid, which formed as a result of oxidation followed by decarbonylation. 2-(Pyrazol-3-yl)ethanol in this oxidation reaction gave a mixture of 2-oxo-2-(pyrazol-3-yl)acetic acid and pyrazole-3-carboxylic acid.

Keywords: keto acids, pyrazoles, building blocks, oxidation, recyclization.

Pyrazoles are class of heterocycles which provides important scaffolds for development of compounds for medicine,[1] agriculture,[2] supramolecular chemistry,[3] as well as for materials science.[4] Among the diverse pyrazole derivatives with various beneficial features, compounds bearing the pyrazole moiety linked with another functional group or heterocyclic fragment by a linker of two carbon atoms are of special interest. For example, such compounds include anxiolytic drug enpiprazole (**1**),[5] 5-hydroxytryptamine 1F receptor agonist **2**,[6] dopamine D3 receptor antagonist **3**[7] (Fig. 1). Also such pyrazole derivatives were actively used for the structure–activity relationship studies as potential γ-secretase modulators[8] or PDE8B inhibitors.[9] Therefore, compounds of general formula **4** and **5**, which can be used for easy synthesis of the above-mentioned biologically active compounds, are important building blocks for medicinal chemistry. The pyrazolylethyl and pyrazolylacetyl moieties represented by compounds **4** and **5**, respectively, are small alkyl substituents which comply with the "rule of two" (Ro2),[10] therefore, compounds **4** and **5** were selected as the targets of our the investigation.

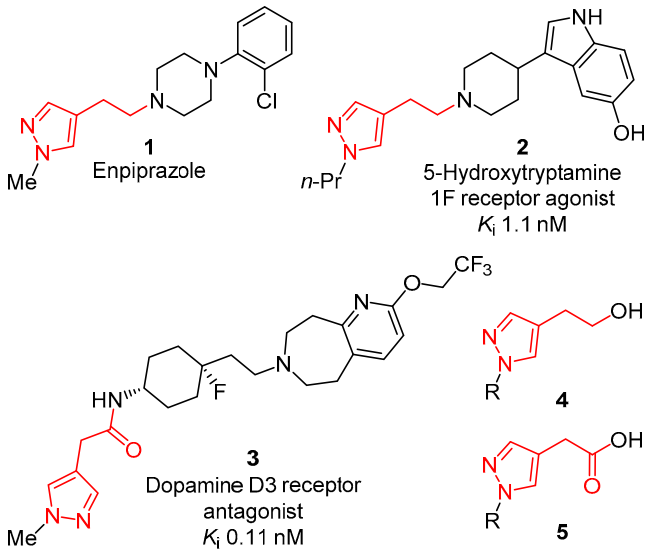
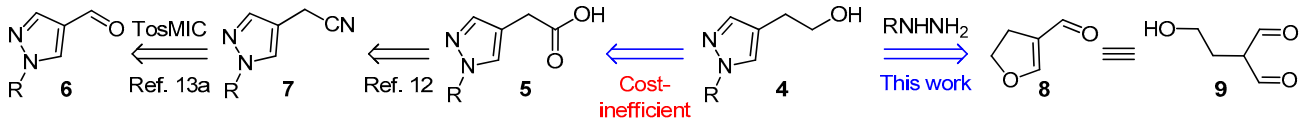
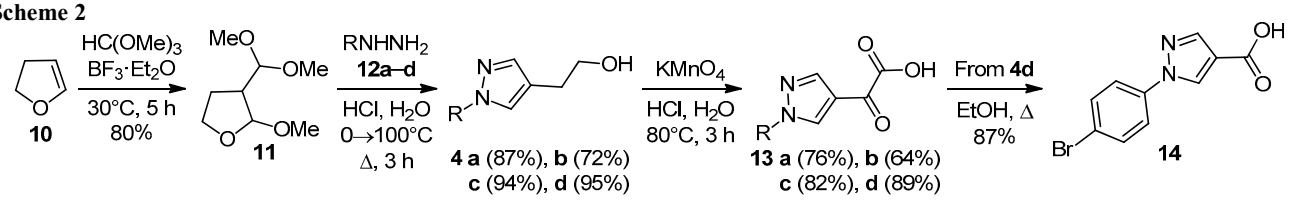


Figure 1. Examples **1**–**3** of biologically active compounds containing a pyrazole ring linked to another pharmacophore through two carbon atoms and building blocks **4**, **5** for their synthesis.

Scheme 1



Scheme 2



a R = H, **b** R = Me, **c** R = *t*-Bu, **d** R = *p*-BrC_6H_4

Surprisingly, the synthesis of such simple compounds has not been described properly, ready-to-use synthesis protocols as well as characterization data of the compounds obtained are absent, although these building blocks are commercially available and mentioned as starting materials in patents.[11] The synthesis of compound **5** (R = Me) was recently published by us.[12] Meanwhile the synthesis and characteristics of compound **4** with R = Me have not been described yet. Therefore, continuing our in-house program directed toward design and synthesis of azolyl-containing building blocks relevant to medicinal chemistry,[13] we decided to expand their spectrum by compounds **4** and **5**.

In an earlier project,[12,13a] we developed the synthesis of 2-(pyrazol-4-yl)acetic acids **5** starting from commercially available aldehydes **6** through nitriles **7**. In the case of R = Me the sequence gave 65% yield on TosMIC-mediated formation of nitrile **7** and 65% on the alkaline hydrolysis step using about 10 g of the starting compound **6**. The scale-up of the sequence appeared to be problematic, and the synthesis of 2-(pyrazol-4-yl)ethanol **4** from aldehydes **6** through synthesis and reduction of acid **5** by $LiAlH_4$ proved to be cost-inefficient (Scheme 1). Alternatively, we decided to investigate the way to compounds **4** *via* recyclization reaction of hydrazines with 3-formylated dihydrofuran **8** which is a synthetic equivalent of malondialdehyde **9** bearing CH_2CH_2OH function in position 2. Earlier we used similar approach for the cyclization leading to fused pyrimidines decorated by CH_2CH_2OH substituent.[14]

Among synthetic equivalents of aldehydes **8**, we chose 3-(dimethoxymethyl)-2-methoxytetrahydrofuran (**11**), easily accessible from 2,3-dihydrofuran (**10**) by treatment with trimethyl orthoformate in the presence of $BF_3·Et_2O$ (Scheme 2).[15] Moreover the ethyl analog of reagent **11** was previously tested in similar recyclization reaction with the parent hydrazine hydrate affording *N*-unsubstituted pyrazole **4a**.[16] The reaction of compound **11** with substituted hydrazine (alkyl-, sterically hindered alkyl-, and aryl-substituted) in acidic medium also proceeded smoothly giving the desired pyrazoles **4b**–**d**. The products were obtained in 72–95% preparative yields.

The oxidation of pyrazolylethanols **4a**–**d** was further studied for the development of preparative approach to 2-(pyrazol-4-yl)acetic acids. Unexpectedly all our attempts to oxidize the alcohol function to carboxylic acids of type **5** using various oxidants failed (Table 1). Under some standard oxidation conditions (entries 3–6), the complex reaction mixture formed. In turn, the use of $KMnO_4$ as the oxidant produced one main product (entries 1, 2). When 2.7 equiv of $KMnO_4$ in slightly alkaline H_2O at 90°C were used oxo acids **13a**–**d** formed in 64–89% preparative yields (entry 2, see also Scheme 2).

Table 1. Oxidation step optimization for the preparation of oxo acid **13b**

Entry	Conditions	Yield*, %
1	1.2 equiv $KMnO_4$, H_2O, K_2CO_3, 90°C	17**
2	2.7 equiv $KMnO_4$, H_2O, K_2CO_3, 90°C	64
3	$NaClO_2$/TEMPO, MeCN***	–*[4]
4	1.2 equiv CrO_3, 2.4 equiv H_2SO_4, H_2O 70°C	18
5	2.5 equiv CrO_3, 5 equiv H_2SO_4, H_2O 70°C	27
6	7 equiv 30% aq H_2O_2, 60°C	–*[4]

* Isolated yield.
** The 76% of starting material was recovered.
*** The procedure for 2-(4-methoxyphenyl)ethanol oxidation was used.[17]
*[4] No reaction was observed.

The structure of products **13a**–**d** was proved by ^1H, ^{13}C NMR spectroscopy as well as APCI HPLC MS spectrometry. It should be noted that in positive mode the $[M+H]^+$ ions of compounds **13a**–**d** were not registered, meanwhile the $[M–H]^-$ ions in negative mode were successfully detected, which agrees with the structure containing a carboxylic group. Finally the structure of compound **13b** was unambiguously determined by single X-ray diffraction study (Fig. 2). Keto acids **13a**–**c** (with unsaturated pyrazole

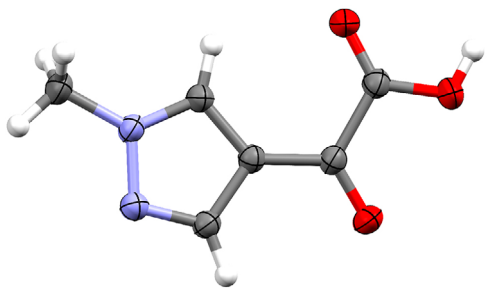


Figure 2. Molecular structure of compound **13b** with atoms represented as thermal vibration ellipsoids of 50% probability.

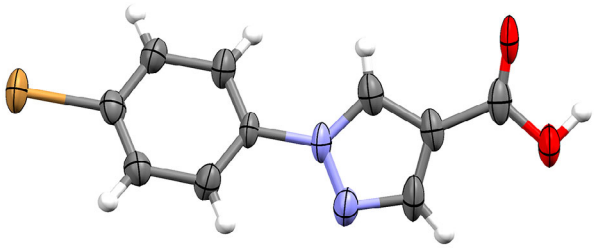
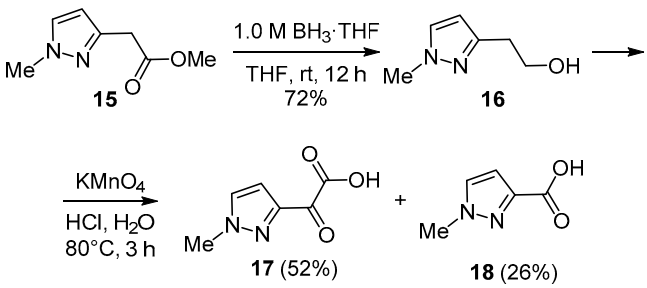


Figure 3. Molecular structure of compound **14** with atoms represented as thermal vibration ellipsoids of 50% probability.

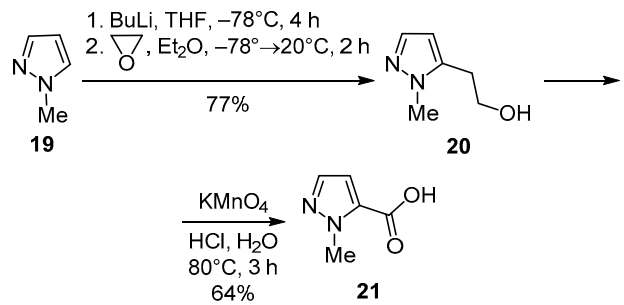
nitrogen and alkyl substituent at N-1) appeared to be stable to recrystallization and could be kept at room temperature during more than 6 months without decomposition. Meanwhile compound **13d** bearing an aryl substituent at nitrogen atom slowly decomposed at room temperature and quantitatively underwent decarbonylation upon recrystallization from EtOH giving acid **14**. The structure of compound **14** also was proved by spectral characterization and single crystal X-ray diffraction study (Fig. 3).

Such unusual behavior of 2-(pyrazol-4-yl)ethanols **4a**–**d** upon oxidation prompted us to check another isomeric 2-(pyrazolyl)ethanols in the reaction. The model *N*-methyl-2-(1*H*-pyrazol-3-yl)ethanol (**16**) was prepared by a BH_3·THF reduction of ester **15** previously synthesized by us.[12] Oxidation of alcohol **16** using the conditions described above led to formation of a mixture of keto acid **17** and the product of its decarbonylation **18** (Scheme 3). Both compounds were separated by column chromatography on SiO_2, purified, and characterized. In the case of substitution at position 5, the model compound 2-(*N*-methylpyrazol-5-yl)ethanol (**20**) was synthesized from *N*-methylpyrazole (**19**) by lithiation with subsequent oxirane treatment. Oxidation of alcohol **16** under the conditions described above led to formation of decarbonylated acid **21** as the sole reaction product (Scheme 4).

Scheme 3



Scheme 4



To sum up, an efficient approach to the preparation of *N*-substituted 2-(pyrazol-4-yl)ethanols, relevant to medicinal chemistry, was elaborated and optimized, using the approach based on recyclization of 3-(dimethoxymethyl)-2-methoxytetrahydrofuran with hydrazines. The oxidation of 2-(pyrazol-4-yl)ethanols and isomeric 2-(pyrazol-3-yl)- and 2-(pyrazol-5-yl)ethanols were studied. The oxidation unexpectedly lead to the corresponding 2-oxo-2-pyrazolylacetic acids, their decarbonylation products, or mixtures thereof. Such oxidative behavior of different isomeric 2-(pyrazolyl)ethanols is unclear and needs more profound investigation.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (500 and 126 MHz, respectively). NMR chemical shifts are referenced using NMR solvent peaks at 7.26 and 77.2 ppm for ^{1}H nuclei and ^{13}C nuclei, respectively, in $CDCl_3$, 2.50 and 39.5 ppm for ^{1}H nuclei and ^{13}C nuclei, respectively, in DMSO-d_6. ^{13}C signals were assigned with the help of APT experiment. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (atmospheric pressure chemical ionization (APCI)) or an Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). Elemental analyses were performed at the Analytical Laboratory of the Institute of Organic Chemistry of NAS Ukraine. Melting points were determined on an MPA100 OptiMelt automated melting point system. The preparative HPLC was performed on an Agilent 1260 HPLC-MSD instrument. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using silica gel (230–400 mesh) as the stationary phase.

The starting compounds and purified solvents were obtained from Enamine Ltd.

3-(Dimethoxymethyl)-2-methoxytetrahydrofuran (11).[15b] Compound **10** (freshly distilled, 17.5 g, 0.25 mol) was added dropwise to a stirred mixture of $HC(OMe)_3$ (133.0 g, 1.25 mol) and BF_3·Et_2O (1 ml) at 30°C during 1 h. The mixture was maintained at 30°C for 5 h. Then K_2CO_3 (5 g) was added to the mixture, and after 1 h, the precipitate was filtered off. The excess of $HC(OMe)_3$ was distilled from the filtrate at 130°C. The residue was distilled under reduced pressure, and the fraction 87–90°C / 20 mmHg was collected affording 35 g (80%) of compound **11** as colorless liquid. ^{1}H NMR spectrum ($CDCl_3$, the compound exist as a mixture of two diastereomers), δ, ppm (*J*, Hz): 1.66–2.17 (2H, m, 4-CH_2); 2.38–2.59 (1H, m, 3-CH); 3.28–3.56 (9H, m, 3OCH_3); 3.76–4.09 (2H, m, 5-CH_2); 4.22 (0.63H, d, *J* = 8.0) and 4.49 (0.27H, d, *J* = 9.0, C<u>H</u>$(OMe)_2$); 4.86 (0.27H, d, *J* = 4.0) and 4.90 (0.63H, d, *J* = 1.0, 2-CH). ^{13}C NMR spectrum ($CDCl_3$, major diastereomer), δ, ppm: 26.1 (C-4); 48.4 (C-3); 52.3 (OCH_3); 53.5 (OCH_3); 54.7 (OCH_3); 66.5 (C-5); 104.4 (<u>C</u>H$(OMe)_2$), 106.8 (C-2). Mass spectrum (EI, 70 eV, major diastereomer), *m*/*z* (I_{rel}, %): 85 [M^+–$2CH_2O$–MeO] (58), 75 (100).

Synthesis of 2-(1*H*-pyrazol-4-yl)ethanols 4a–d (General method). Concd aq HCl (50 ml) was added dropwise to a mixture of compound **11** (90 g, 0.51 mol), the appropriate

hydrazine **12a**–**d** (0.51 mol), and H_2O (20 ml) at 0°C during 2 h. The temperature of the reaction mixture was slowly raised to 100°C within 1 h, and then the mixture was refluxed for 3 h, afterwards was cooled to room temperature, and solution of NaOH (20 g) in H_2O (20 ml) was added. The product was extracted by *n*-BuOH (2×100 ml). The *n*-BuOH was evaporated under reduced pressure, and the residue was purified by distillation *in vacuo* (for compounds **4a**–**c**) or by flash chromatography on SiO_2 using *n*-hexane–EtOAc, 1:1, as eluent (for compound **4d**).

2-(1*H*-Pyrazol-4-yl)ethanol (4a).[16] Yield 49.7 g (87%). Viscous oil. Bp 185–187°C / 20 mm Hg. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.57 (2H, t, *J* = 7.0, C$\underline{H}_2$CH$_2$OH); 3.51 (2H, t, *J* = 7.0, CH$_2$C$\underline{H}_2$OH); 4.66 (1H, s, OH); 7.42 (2H, s, H-3,5); 12.53 (1H, s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 28.1 (C$\underline{H}_2$CH$_2$OH); 62.5 (CH$_2$C$\underline{H}_2$OH); 117.2 (C-4); 127.1 (br. s, C-3(5)); 138.7 (br. s, C-5(3)). Mass spectrum (APCI), *m*/*z*: 113 $[M+H]^+$. Found, %: C 53.72; H 7.16; N 25.04. $C_5H_8N_2O$. Calculated, %: C 53.56; H 7.19; N 24.98.

2-(1-Methyl-1*H*-pyrazol-4-yl)ethanol (4b). Yield 46.3 g (72%). Viscous oil. Bp 129–130°C / 20 mm Hg. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.53 (2H, t, *J* = 7.0, C$\underline{H}_2$CH$_2$OH); 3.50 (2H, t, *J* = 7.0, CH$_2$C$\underline{H}_2$OH); 3.77 (3H, s, NCH$_3$); 4.68 (1H, s, OH); 7.29 (1H, s, H-5); 7.49 (1H, s, H-3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 28.1 (C$\underline{H}_2$CH$_2$OH); 38.7 (NCH$_3$); 62.3 (CH$_2$C$\underline{H}_2$OH); 118.4 (C-4); 129.9 (C-3); 138.4 (C-5). Mass spectrum (APCI), *m*/*z*: 127 $[M+H]^+$. Found, %: C 57.42; H 7.96; N 22.04. $C_6H_{10}N_2O$. Calculated, %: C 57.12; H 7.99; N 22.20.

2-(1-*tert*-Butyl-1*H*-pyrazol-4-yl)ethanol (4c). Yield 80.5 g (94%). Viscous oil. Bp 150–152°C / 20 mm Hg. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.41 (9H, s, 3CH$_3$); 2.57 (2H, t, *J* = 7.0, CH$_2$C$\underline{H}_2$OH); 3.62 (2H, t, *J* = 7.0, CH$_2$C$\underline{H}_2$OH); 4.01 (1H, br. s, OH); 7.22 (1H, s, H-5); 7.27 (1H, s, H-3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 27.4 (C($\underline{C}$H$_3$)$_3$); 29.3 ($\underline{C}$H$_2$CH$_2$OH); 57.6 ($\underline{C}$(CH$_3$)$_3$); 62.3 ($\underline{C}$H$_2$CH$_2$OH); 116.6 (C-4); 124.4 (C-3); 138.6 (C-5). Mass spectrum (APCI), *m*/*z*: 169 $[M+H]^+$. Found, %: C 64.42; H 9.56; N 16.84. $C_9H_{16}N_2O$. Calculated, %: C 64.25; H 9.59; N 16.65.

2-[1-(4-Bromophenyl)-1*H*-pyrazol-4-yl]ethanol (4d). Yield 129.4 g (95%). Oil. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.57 (2H, t, *J* = 7.0, CH$_2$C$\underline{H}_2$OH); 3.55 (2H, t, *J* = 7.0, CH$_2$C$\underline{H}_2$OH); 4.66 (1H, br. s, OH); 7.54 (2H, d, *J* = 7.2, H Ar); 7.55 (1H, s, H-5); 7.66 (2H, d, *J* = 7.2, H Ar); 8.19 (1H, s, H-3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 28.1 (CH$_2$C$\underline{H}_2$OH); 61.9 (CH$_2$C$\underline{H}_2$OH); 118.4 (C-4); 120.3 (C Ar); 121.5 (C Ar); 126.5 (C-3); 132.7 (C Ar); 139.2 (C-5); 142.1 (C Ar). Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 269 $[M+H]^+$ (99), 267 $[M+H]^+$ (100). Found, %: C 49.35; H 4.16; N 10.55. $C_{11}H_{11}BrN_2O$. Calculated, %: C 49.46; H 4.15; N 10.49.

Synthesis of keto acids 13a–d (General method). $KMnO_4$ (42.7 g, 0.27 mol) was added in small portions to a solution (in case of compounds **4a**–**c**) or suspension (in case of compound **4d**) of alcohol **4** (0.1 mol) and K_2CO_3 (5 g) in H_2O (200 ml) at 70°C during 1 h. The mixture was heated with stirring at 80°C for 3 h, cooled to room temperature, and the precipitate that formed was filtered off. The mother liquid was acidified by 0.1 M aq HCl to pH 5. The precipitated product was filtered and dried at room temperature *in vacuo*.

2-Oxo-2-(1*H*-pyrazol-4-yl)acetic acid (13a). Yield 10.6 g (76%). Colorless solid. Mp >280°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.02 (1H, s, H-5); 8.17 (1H, s, H-3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 119.8 (C-4); 136.5 (C-3); 137.6 (C-5); 164.3 (CO); 185.8 (COOH). Mass spectrum (APCI), *m*/*z*: 139 $[M–H]^-$. Found, %: C 42.72; H 2.82; N 20.14. $C_5H_4N_2O_3$. Calculated, %: C 42.87; H 2.88; N 20.00.

2-(1-Methyl-1*H*-pyrazol-4-yl)-2-oxoacetic acid (13b). Yield 9.9 g (64%). Colorless solid. Mp 125–127°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.91 (3H, s, NCH$_3$); 8.03 (1H, s, H-5); 8.55 (1H, s, H-3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 40.0 (NCH$_3$); 119.4 (C-4); 137.0 (C-3); 141.8 (C-5); 164.5 (CO); 179.9 (COOH). Mass spectrum (APCI), *m*/*z*: 153 $[M–H]^-$. Found, %: C 46.72; H 3.82; N 18.11. $C_6H_6N_2O_3$. Calculated, %: C 46.76; H 3.92; N 18.18.

2-[1-(*tert*-Butyl)-1*H*-pyrazol-4-yl]-2-oxoacetic acid (13c). Yield 16.1 g (82%). Colorless solid. Mp 148–150°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.55 (9H, s, 3CH$_3$); 8.08 (1H, s, H-5); 8.51 (1H, s, H-3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 29.5 ((C$\underline{H}_3$)$_3$C); 60.1 ((CH$_3$)$_3$$\underline{C}$); 119.0 (C-4); 132.7 (C-3); 141.5 (C-5); 164.6 (CO); 180.1 (COOH). Mass spectrum (APCI), *m*/*z*: 195 $[M–H]^-$. Found, %: C 55.22; H 6.02; N 14.11. $C_9H_{12}N_2O_3$. Calculated, %: C 55.09; H 6.16; N 14.28.

2-[1-(4-Bromophenyl)-1*H*-pyrazol-4-yl]-2-oxoacetic acid (13d). Yield 26.3 g (89%). Colorless solid. Mp 148–150°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.73 (2H, d, *J* = 9.0, H Ar); 7.92 (2H, d, *J* = 9.0, H Ar); 8.36 (1H, s, H-5); 9.26 (1H, s, H-3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 120.1 (C-4); 120.9 (C Ar); 121.2 (C Ar); 132.2 (C Ar); 132.8 (C Ar); 137.6 (C-3); 142.8 (C-5); 163.3 (CO); 179.4 (COOH). Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 295 $[M–H]^-$ (100), 293 $[M–H]^-$ (99). Found, %: C 44.56; H 2.46; N 9.56. $C_{11}H_7BrN_2O_3$. Calculated, %: C 44.77; H 2.39; N 9.49.

1-(4-Bromophenyl)-1*H*-pyrazole-4-carboxylic acid (14). Compound **13d** (100 mg) was recrystallized from boiling EtOH. Yield 85 mg (87%). Colorless solid. Mp 202–203°C (mp 202–203°C[18]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.71 (2H, d, *J* = 9.0, H Ar); 7.89 (2H, d, *J* = 9.0, H Ar); 8.09 (1H, s, H-5); 9.04 (1H, s, H-3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 117.9 (C-4); 120.1 (C Ar); 121.5 (C Ar); 131.8 (C Ar); 132.9 (C Ar); 138.7 (C-3); 142.8 (C-5); 163.9 (COOH). Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 267 $[M–H]^-$ (100), 265 $[M–H]^-$ (100). Found, %: C 45.05; H 2.46; N 10.55. $C_{10}H_7BrN_2O_2$. Calculated, %: C 44.97; H 2.64; N 10.49.

2-(1-Methyl-1*H*-pyrazol-3-yl)ethanol (16). 1.0 M solution of BH_3·THF complex in THF (1.3 l) was added to a solution of compound **15**[12] (78 g, 0.5 mol) in THF (1 l). The mixture was stirred at room temperature for 12 h. MeOH (1 l) and H_2O (1 l) were added, and the resulting mixture was extracted with EtOAc (3×2 l). The organic

layers were combined and washed with brine (2 l). The organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by distillation *in vacuo*. Yield 46.3 g (72%). Viscous oil. Bp 129–130°C / 20 mmHg. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.80 (2H, t, *J* = 7.0, C<u>H</u>$_2$CH$_2$OH); 3.50 (1H, s, OH); 3.76 (3H, s, NCH_3); 3.81 (2H, t, *J* = 7.0, CH$_2$C<u>H</u>$_2$OH); 7.29 (1H, s, H-5); 7.49 (1H, s, H-3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 32.2 (<u>C</u>H$_2$CH$_2$OH); 38.6 (NCH_3); 61.4 (CH$_2$<u>C</u>H$_2$OH); 104.6 (C-4); 131.3 (C-3); 149.5 (C-5). Mass spectrum (APCI), *m*/*z*: 127 $[M+H]^+$. Found, %: C 57.42; H 7.96; N 22.04. $C_6H_{10}N_2O$. Calculated, %: C 57.12; H 7.99; N 22.20.

Oxidation of alcohol 16. Alcohol **16** (10.0 g, 0.079 mol) was subjected to oxidation by $KMnO_4$ following the general method for oxidation of alcohols **4**. After the workup, about 8 g of crude mixture was obtained containing acids **17** and **18** in 2:1 ratio according to ^{1}H NMR. A portion of this crude product (200 mg) was subjected to preparative HPLC. The Waters SunFire C18 19 × 100 mm, 5 μm column was used. Gradients: from 5 to 30% of MeCN in H_2O or from 15 to 40% of MeCN in <u>H</u>$_2$O in 6.5 min, flow rate 34 ml/min. After lyophilization of two main fractions, compound **17** and compound **18** were obtained.

2-(1-Methyl-1*H*-pyrazol-3-yl)-2-oxoacetic acid (17). Yield 0.103 g (52%). White solid. Mp 137–140°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.97 (3H, s, NCH_3); 6.90 (1H, d, *J* = 2.0, H-4); 7.92 (1H, d, *J* = 2.0, H-5). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 40.0 (NCH_3); 108.4 (C-4); 134.1 (C-5); 146.7 (C-3); 166.7 (CO); 183.6 (COOH). Mass spectrum (APCI), *m*/*z*: 153 $[M–H]^-$. Found, %: C 46.79; H 3.87; N 18.21. $C_6H_6N_2O_3$. Calculated, %: C 46.76; H 3.92; N 18.18.

1-Methyl-1*H*-pyrazole-3-carboxylic acid (18) . Yield 49 mg (26%). White solid. Mp 154–156°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.97 (3H, s, NCH_3); 6.90 (1H, d, *J* = 2.0, H-4); 7.92 (1H, d, *J* = 2.0, H-5); 12.6 (1H, br. s, COO<u>H</u>) ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 39.6 (NCH_3); 108.7 (C-4); 132.8 (C-5); 143.6 (C-3); 163.6 (COOH). Mass spectrum (APCI), *m*/*z*: 127 $[M+H]^+$. Found, %: C 47.79; H 4.87; N 21.38. $C_5H_6N_2O_2$. Calculated, %: C 47.62; H 4.80; N 22.21.

2-(1-Methyl-1*H*-pyrazol-5-yl)ethanol (20).[19] 1.6 M solution of *n*-BuLi in hexane (63 ml) was added dropwise with stirring to a solution of pyrazole **19** (8.2 g, 0.1 mol) in THF (100 ml) at –78°C during 1 h, and the reaction mixture was left stirring at that temperature for 4 h. Then the solution of oxirane (0.1 mol) in Et_2O (50 ml) was added dropwise to the mixture formed. The temperature of the mixture was allowed slowly warm to 20°C for 2 h. Saturated aq NH_4Cl (20 ml) was added to the mixture formed. The ether layer was separated, and the solvent was evaporated *in vacuo*. The residue was purified by distillation *in vacuo.* Yield 9.7 g (77%). Viscous oil. Bp 145–147°C / 20 mm Hg. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.83 (2H, t, *J* = 7.0, C<u>H</u>$_2$CH$_2$OH); 3.75 (3H, s, NCH_3); 3.82 (2H, t, *J* = 7.0, CH$_2$C<u>H</u>$_2$OH); 6.05 (1H, d, *J* = 2.0, H-4); 7.31 (1H, d, *J* = 2.0, H-3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 28.8 (<u>C</u>H$_2$CH$_2$OH); 36.0 (NCH_3); 60.6 (CH$_2$<u>C</u>H$_2$OH); 104.3 (C-4); 137.6 (C-3); 139.6 (C-5). Mass spectrum (APCI), *m*/*z*: 127 $[M+H]^+$. Found, %: C 57.25; H 7.89; N 22.07. $C_6H_{10}N_2O$. Calculated, %: C 57.12; H 7.99; N 22.20.

1-Methyl-1*H*-pyrazole-5-carboxylic acid (21) was synthesized from alcohol **20** (9.7 g) in accordance with procedure described above for alcohols **4**. After reaction mixture treatment. Yield 6.2 g (64%). Colorless solid. Mp 222–224°C (mp 221–222°C[20]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 4.06 (3H, s, NCH_3); 6.80 (1H, s, H-4); 7.49 (1H, s, H-3); 13.30 (1H, s, COOH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 39.6 (NCH_3); 111.4 (C-4); 133.4 (C-5); 137.9 (C-3); 161.1 (COOH). Mass spectrum (APCI), *m*/*z*: 127 $[M+H]^+$. Found, %: C 47.82; H 4.88; N 21.92. $C_5H_6N_2O_2$. Calculated, %: C 47.62; H 4.80; N 22.21.

X-ray structural study of compounds 13b and 14. Crystal data for compound **13b**: $C_6H_6N_2O_3$, *M* 154.13, monoclinic, space group $P2_1/c$; *a* 8.3083(3), *b* 12.2717(4), *c* 7.1688(3) Å; β 112.252(3)°; *V* 676.48(4) Å^3; *Z* 4; d_{calc} 1.513, μ 0.124 мм$^{-1}$, *F*(000) 320, crystal size ca. 0.05 × 0.26 × 0.41 mm. All crystallographic measurements were performed at 173 K on a Bruker Smart Apex II diffractometer operating in the ω-scan mode. The intensity data were collected within the $\theta_{max} \le 26.37°$ using MoKα radiation (λ 0.71078 Å). The intensities of 6424 reflections were collected (1384 unique reflections, R_{merg} 0.0365). The structure was solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using the Bruker SHELXTL program package.[21] All carbon-bound hydrogen atoms were placed at calculated positions and refined using the riding model, and the hydrogen atom of the OH group was located from difference Fourier synthesis and refined isotropically. Convergence for molecule **13b** was obtained at R_1 0.0493 and wR_2 0.1328 for 1047 observed reflections with $I \ge 2\sigma(I)$; R_1 0.0673 and wR_2 0.1469, *GOF* 1.03 for 1384 independent reflections, 104 parameters; the largest and minimal peaks in the final difference map were 0.28 and –0.31 e/Å^3, respectively.

Crystal data for compound **14**: $C_{10}H_7BrN_2O_2$, *M* 267.09, triclinic, space group *P*1; *a* 4.800(3), *b* 5.721(3), *c* 18.122(10) Å; α 92.054(15), β 94.049(14), γ 99.636(16)°; *V* 488.8(5) Å^3; *Z* 2; d_{calc} 1.815; μ 4.183 мм$^{-1}$; *F*(000) 264, crystal size ca. 0.11 × 0.17 × 0.37 mm. All crystallographic measurements were performed at ambient temperature on a Bruker Smart Apex II diffractometer operating in the ω-scan mode. The intensity data were collected within the $\theta_{max} \le 26.62°$ using MoKα radiation (λ 0.71078 Å). The intensities of 5269 reflections were collected (2021 unique reflections, R_{merg} 0.0885). The structure was solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using the Bruker SHELXTL program package.[21] All carbon-bound hydrogen atoms were placed at calculated positions and refined using the riding model. Convergence for molecule **14** was obtained at R_1 0.0864 and wR_2 0.1823 for 1256 observed reflections with $I \ge 2\sigma(I)$; R_1 0.1410 and wR_2 0.2033, *GOF* 1.074 for 2021 independent reflections, 140 parameters, the largest and minimal peaks in the final difference map were 1.08 and –1.17 e/Å^3, respectively.

Crystallographic data for the structures in this paper have been deposited at the Cambridge Crystallographic Data Center (deposits CCDC1976447 (compound **13b**) and CCDC1976448 (compound **14**)).

Supplementary information file containing ^{1}H, ^{13}C NMR and mass spectra of the synthesized compounds is available at the journal website at http://link.springer.com/journal/10593.

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