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Straightforward transformation of isoxazoles into pyrazoles: renewed and improved

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Abstract—Isoxazoles bearing alkyl or carbamoyl groups were transformed into the corresponding pyrazoles in high yields by the treatment with hydrazine in methanol in the presence of a hydrogenation catalyst, e.g., Raney nickel, at ambient temperature. For the synthesis of *N*-substituted pyrazoles, hydrogenolysis of isoxazole followed by the treatment with substituted hydrazine was required. 3(5)-Aryl- or acylamido-substituted isoxazoles are less suitable for such transformations.

1. Introduction

The straightforward preparation of pyrazoles from the corresponding isoxazoles with retention of the substitution pattern by treating them with hydrazines is a rare and nearly forgotten reaction. Approximately ten publications[1–3] mostly from the 1940 to 1950s were briefly reviewed in more recent years,[4] whereas this reaction is not mentioned at all in the modern comprehensive multi-volume editions.[5,6] Apparently, this transformation has received little use because of modest or even unreported yields and a strong substrate dependence, which was difficult to systematize. Isoxazoles bearing electron-withdrawing nitro or carbonyl groups in position 4 could give pyrazoles upon heating with hydrazines in the absence of catalysts.[1] The effect of copper catalysis in the case of isoxazole-3-carboxylic acids was stated.[2] A two-step protocol involving catalytic hydrogenolysis of the isoxazole ring followed by hydrazine-assisted heterocyclization of the acyclic intermediate was proposed based on extensive investigations.[3]

With the aim of performing transformation of a complex nitrobenzene derivative bearing a remote isoxazole fragment into the corresponding aniline, we used standard hydrazine reduction in boiling methanol in the presence of Raney nickel. To our surprise, reduction of the nitro group was accompanied by complete transformation of the isoxazole residue into the pyrazole. Taking into account the available data,[1–3] our finding stimulated us to investigate the possibilities of isoxazole–pyrazole conversion and examine its scope and limitations. In the present publication we report a simple and efficient procedure for the preparation of pyrazoles from certain isoxazoles by simply stirring them in methanol in the presence of hydrazine and Raney nickel. Although both isoxazoles and pyrazoles are generally obtained from the same precursors, it should be noted that in some cases isoxazole diversity can be greater, which is important for combinatorial chemistry. For example, sufficient CH-acidity of the alkyl group in position 5 of isoxazoles allows the preparation of coupling products of the corresponding (isoxazol-5-yl)carbinyl anions with a variety of electrophiles.

2. Results and discussion

3,5-Dimethylisoxazole (**1a**) was chosen as a model compound to search for conditions for its conversion into the corresponding 3,5-dimethylpyrazole (**2a**) (Scheme 1, Table 1). Simple storage of **1a** in the presence of hydrazine in methanol in the absence of a catalyst gave only traces of product **2a** (entry 1), whereas stirring of this mixture in the presence of Raney nickel ultimately leads to its complete conversion into pyrazole **2a** (entries 2–4). The use of elevated temperature (entry 5) allows acceleration of the process. Raney nickel may be recycled (entry 6); however, once the reaction is complete the catalyst should not be kept in contact with the reaction components otherwise it loses its activity (entry 7). Active palladium on carbon (10%) showed satisfactory results (entries 8 and 9), whereas less active 0.8% Pd/C (entry 10) and Lindlar catalyst (entry 11) proved to be essentially inactive. The catalysts Ni/SiO_2 and Cu/Cr_2O_3 designed

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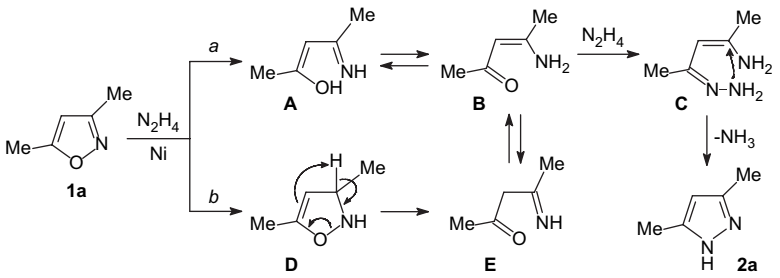


Scheme 1.

Table 1. Influence of the nature of the catalyst on hydrazinolysis of 3,5-dimethylisoxazole

Entry	Catalyst[a]	Time, h	GLC composition, %	
			1a	**2a**
1	None	24	~100	Traces
2	Ni (Ra)	1	37	63
3	Ni (Ra)	4	10	90
4	Ni (Ra)	24	0	100
5	Ni (Ra)	4[b]	0	100
6	Ni (Ra) recycled[c]	24	0	100
7	Ni (Ra) recycled[d]	24	87	13
8	10% Pd/C	5	27	73
9	10% Pd/C	24	15	85
10	0.8% Pd/C	24	94	4
11	Lindlar catalyst	24	95	5
12	Ni/SiO_2	24	98	2
13	Cu/Cr_2O_3	24	94	6
14	$Ni(acac)_2$	24	100	—

[a] Reaction conditions: 1 mmol 3,5-dimethylisoxazole, 2 mL MeOH, 0.2 mL $N_2H_4 \cdot H_2O$, 50 mg catalyst, ~20 °C.
[b] Under reflux (~64 °C).
[c] The first cycle continued for 24 h.
[d] The first cycle continued for 10 days, when the reaction mixture turned dark brown.

for high-pressure and high-temperature hydrogenation did not assist conversion of isoxazole **1a** (entries 12 and 13). Finally, $Ni(acac)_2$ also did not catalyze the process (entry 14).

Apparently, the N_2H_4–Ni (Ra) system being the substitute for H_2–Ni causes hydrogenolysis of the N–O bond in isoxazole **1a** (Scheme 1, pathway *a*). This gives acyclic intermediate **A**, whose amino enone tautomer **B** belongs to a well-known class of organic compounds. The reaction of amino enone **B** with excess hydrazine produces hydrazone **C**, whose heterocyclization affords ultimately pyrazole **2a**. It should be noted that d'Alcontres[3] suggested the addition of a hydrogen molecule at the heterocyclic C=N bond resulting in isoxazoline derivative **D** (pathway *b*), which would undergo ring opening to give imino ketone **E**. The latter is the tautomer of amino enone **B**.

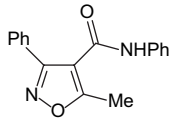
The above-described method was applied to a variety of functionalized isoxazoles **1b–f** (Table 2, entries 1–5). In most cases the corresponding pyrazoles **2b–e** were obtained in high yields. The procedure was in fact very simple: stirring of isoxazole **1** with hydrazine hydrate in MeOH in the presence of Raney nickel at ambient temperature for ca. 1 day gave essentially individual pyrazoles **2**. Their isolation presented no difficulties and was determined mainly by their solubility in methanol. Pyrazoles **2b–e** are characterized by prototropic tautomerism, which is manifested in their ^{13}C NMR spectra: signals of 3- and 5-positioned carbon atoms are usually unobservable, whereas carbons of substituents at these positions resonate as broad weak signals.

Isomeric *N*-benzoylamido-substituted isoxazoles **1f** and **1g** did not give smoothly the expected pyrazoles **2f** and **2g** (it should be noted that **2f** and **2g** are the tautomers of the same compound). The complete conversion of **1f** and **1g** afforded complex multi-component mixtures. In the case of isomer **1f** the corresponding pyrazole was obtained as an inseparable mixture with benzamide (Table 2, entry 6), whereas in case of isomer **1g** the target pyrazole was generated only in trace amounts. This phenomenon may be rationalized by considering the structures of probable primary hydrogenolysis products of these isoxazoles (Scheme 2), which are imides and are prone to easily undergo fragmentation in the presence of nucleophiles.

The unsubstituted amines corresponding to benzamides **1f** and **1g**, namely, 3-amino-5-methyl- and 5-amino-3-methylisoxazoles, remained unchanged on contact with hydrazine in the presence of Raney nickel.

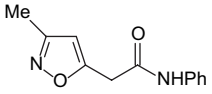
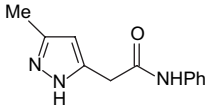
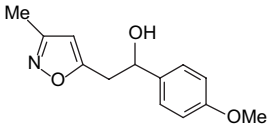
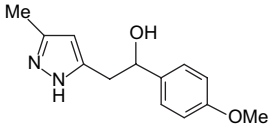
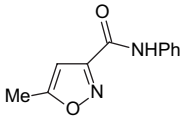
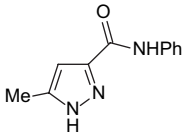
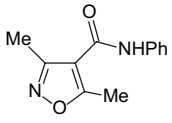
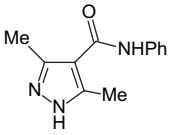
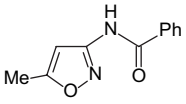
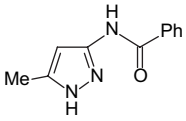
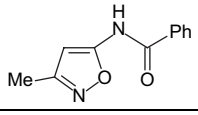
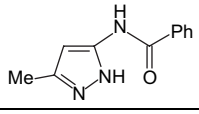
Under the same conditions, 3,5-diphenylisoxazole (**1h**) did not give the target pyrazole **2h** and the reaction stalled at the known 3-amino-1,3-diphenylprop-2-en-1-one (**3**) (Scheme 3), which confirms the general pathway of the process in question via amino enone intermediates (cf. Scheme 1). Amino enone **3** did not further react with hydrazine even on prolonged reflux in methanol. Evidently, the two phenyl groups in compound **3** are involved in conjugation with the amino enone fragment, resulting in a decrease in its electrophilicity. However, we succeeded in preparing pyrazole **2h** from compound **3** in 80% yield by replacing methanol with acetonitrile, which is more favorable for nucleophilic addition.

In contrast to isoxazole **1h**, 5-methyl-3-phenyl-4-(*N*-phenylcarbamoyl)isoxazole (**1i**), when subjected to the above two-step protocol, gave a complex mixture, in which the target 5-methyl-3-phenyl-4-(*N*-phenylcarbamoyl)pyrazole was detected by HPLC–MS in only minor quantities. However, we failed to isolate this product in the pure form because of its low yield. It is worth noting that isoxazole **1i** differs from its analog **1e** (see Table 2, entry 4) only by the presence of the 3-positioned phenyl group instead of methyl.



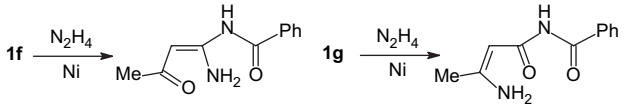
1i

Table 2. Yields of pyrazole derivatives derived from the corresponding isoxazoles[a]

Entry	Starting isoxazole		Product		Yield,[b] %
1		**1b**		**2b**	92
2		**1c**		**2c**	86
3		**1d**		**2d**	75
4		**1e**		**2e**	82
5		**1f**		**2f**=**2g**	22
			$PhC(O)NH_2$		65
6		**1g**		**2g**=**2f**	Traces

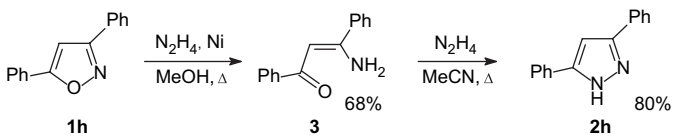
[a] Reaction conditions: $N_2H_4 \cdot H_2O$, Ni(Ra), MeOH, 20 °C, 24 h.
[b] Yield of isolated products.

The use of methyl- or phenylhydrazine in a one-step procedure did not give *N*-substituted pyrazoles, because these hydrazines do not form hydrogen in the presence of Raney nickel. The slow addition of hydrazine hydrate to a methanolic solution of isoxazole **1a** and excess methylhydrazine in the presence of Raney nickel afforded a mixture of NH- and NMe-pyrazoles. Hence for the preparation of *N*-substituted pyrazoles it seemed reasonable to apply the d'Alcontres two-step protocol.[3] In fact, hydrogenation of isoxazoles (1 atm H_2, MeOH, Raney Ni, 2–3 h)[7] followed by the treatment of the substance obtained with $RNHNH_2$ gave the target products (Scheme 4). Sufficiently nucleophilic methylhydrazine did react with intermediate amino enones in methanol at ambient temperature (synthesis of **4** and **4′**) or on heating (synthesis of **5**). In the case of the less nucleophilic phenylhydrazine heterocyclization did not take place in methanol, so it appeared to be necessary to use acetic acid as the solvent in this step (synthesis of **6**).

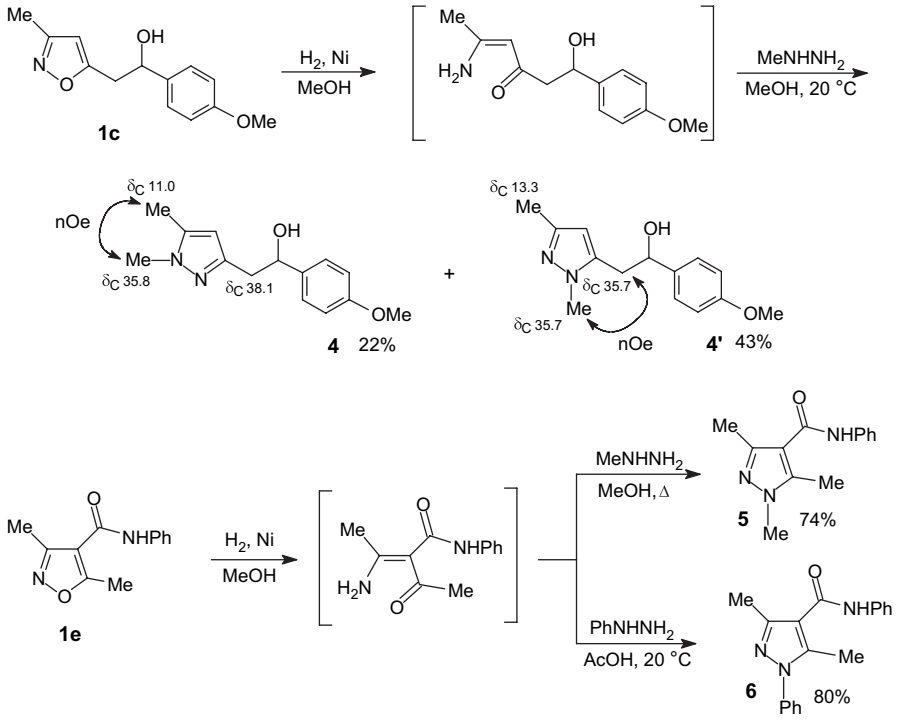


Scheme 2.

When the starting isoxazole, e.g., **1e**, bore identical substituents at positions 3 and 5, this two-step protocol gave pyrazoles differing only in substituents at nitrogen, e.g., **5** or **6** (Scheme 4). In the case of a substrate (**1c**) with different



Scheme 3.



Scheme 4.

substituents, a ~1:2 mixture of isomers **4** and **4′** was obtained. The isomers were separated by column chromatography. This may be attributed to the fact that methylhydrazine can add to both electrophilic sites of intermediate amino enone, viz. the C=O and H_2NC= carbon atoms. The structures of isomers **4** and **4′** were unambiguously derived from NOESY experiments. In addition, chemical shifts of the exocyclic 3- and 5-positioned carbon atoms in ^{13}C NMR spectra were in pairs diagnostic: the negative γ-effect of the vicinal N-*Me* substituent caused a noticeable (2.2–2.4 ppm) upfield shift of the corresponding carbon atom (see Scheme 4).

3. Conclusion

In the conclusion, we have developed a simple and efficient method for the conversion of isoxazoles into the corresponding pyrazoles by treating them with hydrazine in methanol in the presence of Raney nickel. Although this straightforward method is restricted to certain types of substituents in the heterocyclic ring, the target product can be prepared in special cases with the use of a modified procedure. We believe that our findings will promote wider use of pyrazoles in various fields of organic and combinatorial chemistry.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at 400.13 MHz (^1H) or 100.62 MHz (^{13}C) on a DRX 400 Avance (Bruker) instrument. The chemical shifts were referenced to residual protons (δ_H 7.27 ppm in $CDCl_3$ or 2.50 ppm in DMSO-d_6 for ^1H NMR) or to signals of deuterated solvent (δ_C 77.0 ppm in $CDCl_3$ or 39.6 ppm in DMSO-d_6 for ^{13}C NMR). IR spectra were recorded on Infralum FT-801 (Russia) instrument. Elemental analyses were performed at the Analytical Laboratory of the Nesmeyanov Institute of Organoelement Compounds, Moscow. To monitor the transformation of **1a→2a** GC analysis was carried out on a 25 m capillary column with SE-30 at 130 °C. TLC analyses were performed on Kieselgel 60 F_{254} aluminum sheets (Merck, 1.05554.0001). All starting materials used for the synthesis of isoxazole derivatives **1b–i** were commercially available and used as purchased. All solvents used in reactions and as eluents for column chromatography were freshly distilled.

4.2. Preparation of isoxazole derivatives

4.2.1. *N*-Phenyl-2-(3-methylisoxazol-5-yl)acetamide (1b). To a stirred suspension of 3-methylisoxazole-5-acetic acid (353 mg, 2.5 mmol) in CH_2Cl_2 (5 mL), containing 1 drop of DMF, oxalyl chloride (0.218 mL, 2.5 mmol) was added dropwise at 20 °C. After 1 h, gas evolution ceased and the solid dissolved. The solution of acid chloride thus prepared was added dropwise at 0–5 °C to a stirred solution of aniline (0.228 mL, 2.5 mmol) and triethylamine (0.7 mL, ~5 mmol) in CH_2Cl_2 (5 mL), and stirring was continued for additional 2 h. The reaction mixture was treated with 5% aqueous HCl (10 mL), the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined extracts were washed with brine (20 mL), dried with $CaCl_2$, and concentrated in vacuo. The residue was triturated with tetrachloromethane (2 mL), the solid was filtered off, recrystallized from benzene (2 mL), and washed with hexane (10 mL). Final drying in air gave 389 mg (72%) of the title compound as a white solid, mp 122–123 °C [Found:

C, 66.69; H, 5.60; N, 12.99. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.59; N, 12.95%.]; ν_{max} (Nujol) 3254, 3195, 3137, 1663, 1619, 1600, 1545, 1503 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 2.21 (3H, s, *Me*), 3.89 (2H, s, CH_2), 6.26 (1H, s, =C*H*), 7.06 (1H, t, *J* 7.8 Hz, =C*H*), 7.32 (2H, t, *J* 7.8 Hz, =C*H*), 7.58 (2H, d, *J* 7.8 Hz, =C*H*), 10.25 (1H, br s, N*H*); δ_C (100 MHz, DMSO-d_6) 11.0 (Me), 34.7 (CH_2), 104.0 (CH), 119.2 (CH), 123.6 (CH), 128.8 (CH), 138.9 (C), 159.6 (C), 165.3 (C), 166.7 (C).

4.2.2. 1-(4-Methoxyphenyl)-2-(3-methylisoxazol-5-yl)-ethan-1-ol (1c). To a stirred solution of diisopropylamine (1.7 mL, ~12 mmol) in THF (20 mL) at −78 °C under argon *n*-butyllithium (7.84 mL of 1.4 M solution in hexanes, 11 mmol) was added. After 10 min, 3,5-dimethylisoxazole (1.07 g, 11 mmol) dissolved in THF (3 mL) was added, and the mixture was stirred for an additional 30 min. 4-Methoxybenzaldehyde (1.36 g, 10 mmol) dissolved in THF (2 mL) was then added, and the mixture was allowed to reach ambient temperature. After the usual work up and column chromatography (gradient 25→100% CH_2Cl_2 in light petroleum) 1.87 g (80%) of the title compound was obtained, pale yellow solid, mp 53–54 °C. R_f (20% AcOEt/hexane) 0.26; δ_H (400 MHz, $CDCl_3$) 2.19 (3H, s, *Me*), 2.86 (1H, d, *J* 3.7 Hz, O*H*), 3.03 (1H, *A* part of *ABX* system, *J* 15.0, 5.1 Hz, CH_2), 3.14 (1H, *B* part of *ABX* system, *J* 15.0, 8.1 Hz, CH_2), 3.77 (3H, s, O*Me*), 4.96 (1H, m, OC*H*), 5.81 (1H, s, =C*H*), 6.85 (2H, d, *J* 8.8 Hz, =C*H*), 7.24 (2H, d, *J* 8.8 Hz, =C*H*). Spectral characteristics were in a good agreement with the earlier reported.[8]

4.2.3. 5-Methyl-3-(*N*-phenylcarbamoyl)isoxazole (1d). Compound **1d** was prepared analogously to amide **1b** in a yield of 75%. White solid, mp 133–135 °C (lit.[9] mp 134 °C); δ_H (400 MHz, DMSO-d_6) 2.51 (3H, s, *Me*), 6.65 (1H, s, =C*H*), 7.14 (1H, t, *J* 7.4 Hz, =C*H*), 7.36 (2H, t, *J* 7.4 Hz, =C*H*), 7.78 (2H, d, *J* 8.1 Hz, =C*H*), 10.51 (1H, br s, N*H*).

4.2.4. 3,5-Dimethyl-4-(*N*-phenylcarbamoyl)isoxazole (1e). Compound **1e** was prepared analogously to amide **1b**, yield 60%, white solid, mp 153–154 °C [Found: C, 66.63; H, 5.71; N, 12.80. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.59; N, 12.95%.]; ν_{max} (Nujol) 3289, 3248, 3192, 3128, 1650, 1594, 1530, 1504 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 2.33 (3H, s, *Me*), 2.55 (3H, s, *Me*), 7.11 (1H, t, *J* 7.6 Hz, =C*H*), 7.35 (2H, t, *J* 7.6 Hz, =C*H*), 7.66 (2H, d, *J* 7.6 Hz, =C*H*), 10.00 (1H, br s, N*H*); δ_C (100 MHz, DMSO-d_6) 10.5 (Me), 12.2 (Me), 113.7 (C), 120.0 (CH), 123.9 (CH), 128.7 (CH), 138.8 (C), 158.4 (C), 160.2 (C), 169.7 (C).

4.2.5. 3-Benzoylamido-5-methylisoxazole (1f). To a solution of 3-amino-5-methylisoxazole (587 mg, 6 mmol) in pyridine (10 mL) benzoyl chloride (0.696 mL, 6 mmol) and it was added dropwise over 2 h (TLC control). The reaction mixture was carefully treated with excess cold 5% HCl (pH=1) and extracted with CH_2Cl_2 (2×20 mL). The combined extracts were washed successively with 5% HCl, NaCl, and $NaHCO_3$ solutions (20 mL each), dried with $CaCl_2$ and concentrated. The residue was triturated with benzene (2 mL), the solid was filtered off, washed with benzene (5 mL), and dried in air to give 825 mg (68%) of the title compound as the white solid, mp 164–166 °C (lit.[10] mp 164 °C). δ_H (400 MHz, DMSO-d_6) 2.42 (3H, s, *Me*), 6.75 (1H, s, =C*H*), 7.52 (2H, t, *J* 7.6 Hz, =C*H*), 7.61 (1H, t, *J* 7.1 Hz, =C*H*), 8.01 (2H, d, *J* 7.6 Hz, =C*H*), 11.27 (1H, br s, N*H*); δ_C (100 MHz, DMSO-d_6) 12.2 (Me), 97.0 (CH), 128.1 (CH), 128.5 (CH), 132.3 (CH), 133.2 (C), 158.7 (C), 165.3 (C), 169.4 (C).

4.2.6. 5-Benzoylamido-3-methylisoxazole (1g). Compound **1g** was prepared analogously to amide **1f** from 5-amino-3-methylisoxazole in a yield of 54%, mp 144–146 °C (lit.[11] mp 147 °C). δ_H (400 MHz, DMSO-d_6) 2.22 (3H, s, *Me*), 6.33 (1H, s, =C*H*), 7.54 (2H, t, *J* 7.4 Hz, =C*H*), 7.64 (1H, t, *J* 7.4 Hz, =C*H*), 8.01 (2H, d, *J* 8.1 Hz, =C*H*), 11.90 (1H, br s, N*H*).

4.2.7. 5-Methyl-3-phenyl-4-(*N*-phenylcarbamoyl)isoxazole (1i). Compound **1i** was prepared analogously to amide **1b**, yield 45%, white solid, mp 198–200 °C (lit.[12] mp 193–195.5 °C) [Found: C, 73.11; H, 5.11; N, 10.03. $C_{17}H_{14}N_2O_2$ requires C, 73.37; H, 5.07; N, 10.07%.]; ν_{max} (Nujol) 3275, 3248, 3192, 3128, 1650, 1594, 1530, 1504 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 2.59 (3H, s, *Me*), 7.12 (1H, t, *J* 7.6 Hz, =C*H*), 7.35 (2H, t, *J* 7.6 Hz, =C*H*), 7.50 (3H, m, =C*H*), 7.63 (2H, d, *J* 7.6 Hz, =C*H*), 7.71 (2H, m, =C*H*), 10.42 (1H, br s, N*H*); δ_C (100 MHz, DMSO-d_6) 11.9 (Me), 113.4 (C), 119.8 (CH), 124.1 (CH), 127.8 (CH), 128.1 (C), 128.9 (CH), 130.1 (CH), 138.6 (C), 160.0 (C), 160.2 (C), 169.9 (C).

4.3. Straightforward conversion of isoxazoles into pyrazoles (general procedure)

To a stirred solution/suspension of an isoxazole derivative (1 mmol) in MeOH (2–4 mL depending on solubility) and hydrazine hydrate (0.4–0.8 mL) Raney nickel (50–80 mg of wet substance) was added, which resulted in evolution of hydrogen bubbles. The mixture was stirred at ambient temperature for ca. 1 day. Usually in several hours the starting compound was completely consumed, when TLC analysis showed the presence of several components (two of which being the major products were characterized by higher polarity than the starting isoxazole). Further aging of the mixture finally led to the formation of mostly one product. The nickel was removed by filtration and rinsed on a filter with MeOH (*caution*: to avoid inflammation of waste nickel it should be immediately covered with water and carefully quenched with dilute HCl or H_2SO_4). The filtrate was concentrated, and the product was isolated by crystallization. If the product precipitated during the reaction (e.g., compound **2e**), 1–2 mL of silica gel and 5 mL of toluene were added to the mixture, and the volatiles were removed in vacuo. The pre-adsorbed material was loaded on the top of a chromatography column packed with silica gel, and the product was eluted with an appropriate system of solvents (usually a gradient of MeOH in CH_2Cl_2).

4.3.1. 3,5-Dimethylpyrazole (2a). Compound **2a** was obtained from 3,5-dimethylisoxazole (see Table 1) using either Raney nickel or other catalysts. The product and the authentic sample of **2a** showed the same retention time during GC analysis and characteristic chemical shifts in ^1H NMR

spectrum; δ_H (400 MHz, DMSO-d_6) 2.13 (s, 3H), 5.74 (s, 1H), 12.01 (br s, 1H).

4.3.2. *N*-Phenyl-2-(3-methylpyrazol-5-yl)acetamide (2b). White solid, mp 164–166 °C [Found: C, 66.71; H, 6.30; N, 19.43. $C_{12}H_{13}N_3O$ requires C, 66.96; H, 6.09; N, 19.52%.]; ν_{max} (Nujol) 3293, 3267, 3184, 3124, 1676, 1614, 1598, 1540, 1503 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 2.17 (3H, s, *Me*), 3.57 (2H, s, CH_2), 5.92 (1H, s, =C*H*), 7.03 (1H, t, *J* 7.8 Hz, =C*H*), 7.29 (2H, t, *J* 7.8 Hz, =C*H*), 7.59 (2H, d, *J* 7.8 Hz, =C*H*), 10.05 (1H, br s, N*H*), 12.21 (1H, br s, N*H*); δ_C (100 MHz, DMSO-d_6) 10.6 (broad weak signal, Me), 36.7 (broad weak signal, CH_2), 103.5 (CH), 119.1 (CH), 123.2 (CH), 128.7 (CH), 139.3 (C), 168.4 (broad weak signal, C), the signals of the rest of the carbon atoms are missing.

4.3.3. 1-(4-Methoxyphenyl)-2-(3-methylpyrazol-5-yl)-ethan-1-ol (2c). White solid, mp 107–109 °C [Found: C, 67.38; H, 7.08; N, 12.00. $C_{13}H_{16}N_2O_2$ requires C, 67.22; H, 6.94; N, 12.06%.]; ν_{max} (Nujol) 3217, 3150, 3120, 1611, 1585, 1511 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 2.11 (3H, s, *Me*), 2.82 (2H, m, CH_2), 3.72 (3H, s, O*Me*), 4.72 (1H, m, OC*H*), 5.16 (1H, br s, O*H*), 5.71 (1H, s, =C*H*), 6.85 (2H, d, *J* 8.8 Hz, =C*H*), 7.23 (2H, d, *J* 8.8 Hz, =C*H*), 11.98 (1H, br s, N*H*); δ_C (100 MHz, DMSO-d_6) 9.0–14.3 (broad weak signal, Me), 34.3–38.4 (broad weak signal, CH_2), 55.0 (Me), 71.9 (CH), 103.4 (CH), 113.3 (CH), 127.2 (CH), 137.7 (C), 158.2 (C), the signals of the rest of the carbon atoms are missing.

4.3.4. 5-Methyl-3-(*N*-phenylcabamoyl)pyrazole (2d). White solid, mp 167–168 °C [Found: C, 65.71; H, 5.43; N, 20.68. $C_{11}H_{11}N_3O$ requires C, 65.66; H, 5.51; N, 20.88%.]; ν_{max} (Nujol) 3377, 3373, 3189, 3124, 1674, 1657, 1597, 1579, 1542 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 2.29 (3H, s, *Me*), 6.50 (1H, s, =C*H*), 7.06 (1H, t, *J* 7.3 Hz, =C*H*), 7.31 (2H, t, *J* 7.3 Hz, =C*H*), 7.80 (2H, d, *J* 7.3 Hz, =C*H*), 9.88 (1H, br s, N*H*), 13.05 (1H, br s, N*H*); δ_C (100 MHz, DMSO-d_6) 10.4 (Me), 104.6 (CH), 120.1 (CH), 123.3 (CH), 128.6 (CH), 138.9 (C), 140.2 (C), 147.1 (C), 160.6 (C).

4.3.5. 3,5-Dimethyl-4-(*N*-phenylcabamoyl)pyrazole (2e). White solid, mp 246–247 °C (lit.[13] mp 244–245 °C) [Found: C, 66.73; H, 6.01; N, 19.61. $C_{12}H_{13}N_3O$ requires C, 66.96; H, 6.09; N, 19.52%.]; ν_{max} (Nujol) 3329, 3152, 3095, 1643, 1597, 1525 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 2.33 (6H, s, *Me*), 7.04 (1H, t, *J* 7.8 Hz, =C*H*), 7.30 (2H, t, *J* 7.8 Hz, =C*H*), 7.66 (2H, d, *J* 7.8 Hz, =C*H*), 9.43 (1H, br s, N*H*), 12.23 (1H, br s, N*H*); δ_C (100 MHz, DMSO-d_6) 12.6 (broad low signal, Me), 114.0 (C), 119.6 (CH), 123.1 (CH), 128.6 (CH), 139.6 (C), 163.3 (C), the signals of the rest of the carbon atoms are missing.

4.3.6. 3-Benzoylamido-5-methylpyrazole (2f). Compound **2f** was obtained from 3-benzoylamido-5-methylisoxazole (**1f**) (202 mg, 1 mmol) as an inseparable by column chromatography mixture with benzamide (123 mg, 1:3 M ratio from ^1H NMR), yields were calculated as 22 and 65%, respectively; R_f (5% MeOH/CH_2Cl_2) 0.43. *3-Benzoylamido-5-methylpyrazole* (**2f**): δ_H (400 MHz, DMSO-d_6) 2.23 (3H, s, *Me*), 6.41 (1H, s, =C*H*), 7.49 (3H, m, =C*H*), 7.99 (2H, d, *J* 7.3 Hz, =C*H*), 10.6 (1H, br s, N*H*), 12.1 (1H, br s, N*H*) was in good agreement with that reported earlier;[14] δ_C (100 MHz, DMSO-d_6) 10.8 (broad low signal, Me), 96.6 (broad low signal, CH), 127.7 (CH), 128.3 (CH), 131.7 (CH), 138.2 (broad low signal, C), 164.4 (C), the rest of the signals are missing; HPLC–MS (CI): MH^+ 202. *Benzamide*: δ_H (400 MHz, DMSO-d_6) 7.43 (1H, br s, NH_2), 7.49 (3H, m, =C*H*), 7.88 (2H, d, *J* 7.3 Hz, =C*H*), 7.95 (1H, br s, NH_2); δ_C (100 MHz, DMSO-d_6) 127.5 (CH), 128.2 (CH), 131.5 (CH), 134.3 (C), 168.0 (C); HPLC–MS (CI): MH^+ 122; these spectral data were similar to those of the authentic sample.

4.4. Two-step conversion of isoxazoles into pyrazoles (representative examples)

4.4.1. 3,5-Diphenylpyrazole (2h). 3,5-Diphenylisoxazole (**1h**) (22 mg, 0.1 mmol) and hydrazine hydrate (0.08 mL) were stirred in MeOH (0.5 mL) in the presence of Raney nickel (~20 mg). The reaction was slow, so the mixture was heated to 60 °C for 1 h, which led to complete conversion of the starting material (TLC). The mixture was then kept at ambient temperature for 3 days, which did not lead to changes in its composition. Column chromatography (CH_2Cl_2 as an eluent) gave 15 mg (68%) of 3-amino-1,3-diphenylprop-2-en-1-one (**3**) as a yellow oil. R_f (3% MeOH/CH_2Cl_2) 0.66; δ_H (400 MHz, $CDCl_3$) 5.51 (1H, br s, NH_2), 6.16 (1H, s, =C*H*), 7.48 (6H, m, =C*H*), 7.65 (2H, d, *J* 7.4 Hz, =C*H*), 7.96 (2H, d, *J* 7.4 Hz, =C*H*), 10.44 (1H, br s, NH_2); δ_C (100 MHz, $CDCl_3$) 91.9 (CH), 126.3 (CH), 127.2 (CH), 128.3 (CH), 129.0 (CH), 130.7 (CH), 131.0 (CH), 137.6 (C), 140.3 (C), 162.9 (C), 190.2 (C); these spectral data were in good agreement with that reported earlier.[15] The amino enone (**3**) was dissolved in MeCN (0.5 mL), hydrazine hydrate (0.1 mL) was added, and the mixture was refluxed for 4 h. The mixture was concentrated and subjected to ^1H NMR analysis, which showed the presence of 20% intermediate amino enone (**3**) and 80% 3,5-diphenylpyrazole (**2h**), identical to the authentic sample.[16] δ_H (400 MHz, $CDCl_3$) 6.84 (1H, s, =C*H*), 7.31–7.42 (6H, m, =C*H*), 7.73 (4H, br d, *J* 7.4 Hz, =C*H*), 11.6 (1H, br s, N*H*).

4.4.2. 1-(4-Methoxyphenyl)-2-(dimethylpyrazolyl)ethan-1-ols 4 and 4′. A mixture of 1-(4-methoxyphenyl)-2-(3-methylisoxazol-5-yl)ethan-1-ol (**1c**) (466 mg, 2 mmol), methanol (5 mL), and Raney nickel (0.1 g) was stirred under hydrogen (1 atm) for 3 h. The mixture was filtered, methylhydrazine (1 mL) was added, and the mixture was kept under argon overnight. The volatiles were removed in vacuo and the remainder was subjected to column chromatography (gradient 0→2% MeOH in CH_2Cl_2 as an eluent) to give 107 mg (23%) of unreacted isoxazole derivative, 108 mg (22%) of isomer **4** as the viscous oil, and 212 mg (43%) of isomer **4′** as the viscous oil, which solidified on standing. *1-(4-Methoxyphenyl)-2-(1,5-dimethylpyrazol-3-yl)ethan-1-ol* (**4**) [Found: C, 68.00; H, 7.28; N, 11.14. $C_{14}H_{18}N_2O_2$ requires C, 68.27; H, 7.37; N, 11.37%.]; R_f (5% MeOH/CH_2Cl_2) 0.54; ν_{max} (Nujol) 3323, 3242, 1613, 1586, 1548 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.23 (3H, s, *Me*), 2.50 (1H, br s, O*H*), 2.90 (2H, m, CH_2), 3.73 (3H, s, N*Me*), 3.80 (3H, s, O*Me*), 4.90 (1H, m, OC*H*), 5.81 (1H, s, =C*H*), 6.88 (2H, d, *J* 8.8 Hz, =C*H*), 7.34 (2H, d, *J* 8.8 Hz, =C*H*); δ_C (100 MHz, $CDCl_3$) 11.0 (Me), 35.8

(Me), 38.1 (CH_2), 55.2 (Me), 72.9 (CH), 104.8 (CH), 113.6 (CH), 127.0 (CH), 136.3 (C), 139.1 (C), 148.7 (C), 158.8 (C). *1-(4-Methoxyphenyl)-2-(1,3-dimethylpyrazol-5-yl)ethan-1-ol* (**4′**) [Found: C, 68.29; H, 7.44; N, 11.21. $C_{14}H_{18}N_2O_2$ requires C, 68.27; H, 7.37; N, 11.37%.]; R_f (5% MeOH/CH_2Cl_2) 0.47; ν_{max} (Nujol) 3252, 1613, 1586, 1548 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.19 (3H, s, *Me*), 2.59 (1H, br s, O*H*), 2.91 (1H, *A* part of *ABX* system, *J* 14.7, 5.9 Hz, CH_2), 2.99 (1H, *B* part of *ABX* system, *J* 14.7, 7.4 Hz, CH_2), 3.53 (3H, s, N*Me*), 3.80 (3H, s, O*Me*), 4.84 (1H, *X* part of *ABX* system, *J* 7.4, 5.9 Hz, OC*H*), 5.84 (1H, s, =C*H*), 6.86 (2H, d, *J* 8.8 Hz, =C*H*), 7.22 (2H, d, *J* 8.8 Hz, =C*H*); δ_C (100 MHz, $CDCl_3$) 13.3 (Me), 35.7 (two signals, Me and CH_2), 55.2 (Me), 73.0 (CH), 105.1 (CH), 113.8 (CH), 126.8 (CH), 135.6 (C), 139.9 (C), 147.1 (C), 159.2 (C).

4.4.3. 1,3,5-Trimethyl-4-(*N*-phenylcabamoyl)pyrazole (5). A solution of *N*-phenyl-3,5-dimethylisoxazole-4-carboxamide (**1e**) (108 mg, 0.5 mmol) in MeOH (3 mL) was hydrogenated (1 atm H_2) in the presence of Raney nickel (~80 mg) for 3 h (TLC showed the complete conversion of the starting compound **1e**). The catalyst was filtered off, methylhydrazine (0.2 mL) was added to the filtrate, and the mixture was refluxed for 12 h (at ambient temperature reaction did not occur). Silica gel (1.5 mL) and toluene (5 mL) were added and the volatiles were removed in vacuo to leave a pre-adsorbed material, which was loaded on the top of chromatography column packed with silica gel. Eluting with gradient 0→1.5% MeOH in CH_2Cl_2 afforded 85 mg (74%) of the title compound as a white solid, mp 161–162 °C (lit.[12] mp 161–163 °C) [Found: C, 67.97; H, 6.59; N, 18.31. $C_{13}H_{15}N_3O$ requires C, 68.10; H, 6.59; N, 18.33%.]; R_f (5% MeOH/CH_2Cl_2) 0.35; ν_{max} (Nujol) 3300, 3271, 3234, 1641, 1594, 1544, 1525 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 2.27 (3H, s, *Me*), 2.36 (3H, s, *Me*), 3.69 (3H, s, N*Me*), 7.05 (1H, t, *J* 7.3 Hz, =C*H*), 7.31 (2H, t, *J* 8.3 Hz, =C*H*), 7.67 (2H, d, *J* 8.3 Hz, =C*H*), 9.58 (1H, br s, N*H*); δ_C (100 MHz, DMSO-d_6) 12.6 (Me), 12.9 (Me), 35.8 (Me), 115.1 (C), 119.7 (CH), 123.2 (CH), 128.7 (CH), 139.6 (C), 140.1 (C), 145.4 (C), 163.2 (C).

4.4.4. 3,5-Dimethyl-1-phenyl-4-(*N*-phenylcabamoyl)pyrazole (6). A solution of *N*-phenyl-3,5-dimethylisoxazole-4-carboxamide (**1e**) (108 mg, 0.5 mmol) in MeOH (3 mL) was hydrogenated (1 atm H_2) in the presence of Raney nickel (~80 mg) for 3 h (TLC showed complete conversion of the starting compound **1e**). The catalyst was filtered off and the filtrate was concentrated. Glacial AcOH (2 mL) was added to the residue followed by the addition of phenylhydrazine (108 mg, 1.0 mmol), and the mixture was stirred at ambient temperature for 3 h (TLC control). The mixture was concentrated and the rest of AcOH was removed by co-evaporating with xylene. The residue was dissolved in a toluene/CH_2Cl_2 mixture, silica gel (~1.5 mL) was added, and the volatiles were removed in vacuo to leave a pre-adsorbed material, which was loaded on the top of chromatography column packed with silica gel. Eluting with a gradient 0→1% MeOH in CH_2Cl_2 afforded 117 mg (80%) of the yellow solid. Rinsing with toluene afforded white crystals, mp 181–182 °C (lit.[12] mp 182–183 °C) [Found: C, 74.26; H, 5.84; N, 14.45. $C_{18}H_{17}N_3O$ requires C, 74.21; H, 5.88; N, 14.42%.]; R_f (5% MeOH/CH_2Cl_2) 0.43; ν_{max} (Nujol) 3300, 1646, 1632, 1595, 1556, 1553 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 2.37 (3H, s, *Me*), 2.41 (3H, s, *Me*), 7.07 (1H, t, *J* 7.8 Hz, =C*H*), 7.34 (2H, t, *J* 7.8 Hz, =C*H*), 7.41–7.62 (5H, m, *Ph*), 7.70 (2H, d, *J* 7.8 Hz, =C*H*), 9.85 (1H, br s, N*H*); δ_C (100 MHz, DMSO-d_6) 11.8 (Me), 13.0 (Me), 117.0 (C), 119.7 (CH), 123.4 (CH), 125.0 (CH), 128.1 (CH), 128.8 (CH), 129.4 (CH), 138.9 (C), 139.4 (C), 140.1 (C), 147.4 (C), 162.8 (C).

References and notes

1. (a) Musante, C. *Gazz. Chim. Ital.* **1942**, *72*, 537; (b) Musante, C. *Gazz. Chim. Ital.* **1943**, *73*, 355; (c) Musante, C.; Stener, A. *Gazz. Chim. Ital.* **1959**, *89*, 1579; (d) Fusco, R.; Zumin, S. *Gazz. Chim. Ital.* **1946**, *76*, 223; (e) Gardner, T. S.; Smith, F. A.; Wenis, E.; Lee, J. *J. Org. Chem.* **1956**, *21*, 530; (f) Lemke, T. L.; Sawhney, K. N.; Lemke, B. K. *J. Heterocycl. Chem.* **1982**, *19*, 363.
2. (a) Cusmano, C. *Gazz. Chim. Ital.* **1940**, *70*, 227; (b) Cusmano, C. *Gazz. Chim. Ital.* **1940**, *70*, 237; (c) Cusmano, C. *Gazz. Chim. Ital.* **1940**, *70*, 240.
3. d'Alcontres, G. S. *Gazz. Chim. Ital.* **1950**, *80*, 441.
4. Quilico, A. *Five- and Six-membered Compounds with Nitrogen and Oxygen*; Wiley, R. H., Ed.; The chemistry of heterocyclic compounds; Interscience: NewYork, NY, London, 1962; Vol. 17, pp 48–49.
5. (a) Elguero, J. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, New York, NY, 1984; Vol. 5, pp 167–303; (b) Lang, S. A.; Lin, Y.-i. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, New York, NY, 1984; Vol. 6, pp 1–130.
6. (a) Elguero, J. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, New York, NY, 1996; Vol. 3, pp 1–75; (b) Sutharchanadevi, M.; Murugan, R. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, New York, NY, 1996; Vol. 3, pp 221–260.
7. Reductive $Mo(CO)_6$-assisted ring opening of isoxazoles leading to amino enones, which were further transformed into pyridine-4-ones and pyran-4-ones, was also reported: (a) Nitta, M.; Higuchi, T. *Heterocycles* **1994**, *38*, 853; (b) Li, C.-S.; Lacasse, E. *Tetrahedron Lett.* **2002**, *43*, 3565.
8. Fuentes, J. A.; Maestro, A.; Testera, A. M.; Báñez, J. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2565.
9. Lepage, F.; Tombret, F.; Cuvier, G.; Marivain, A.; Gillardin, J. M. *Eur. J. Med. Chem. Chim. Ther.* **1992**, *27*, 581.
10. Buscemi, S.; Frenna, V.; Vivona, N. *Heterocycles* **1991**, *32*, 1765.
11. Yamamoto, Y.; Azuma, Y. *Heterocycles* **1978**, *9*, 185.
12. (a) Quilico, A.; Panizzi, L. *Gazz. Chim. Ital.* **1938**, *68*, 411; (b) Quilico, A.; Fusco, R. *Gazz. Chim. Ital.* **1937**, *67*, 589.
13. Huppatz, J.L. Patent DE 2701091, 1977; *Chem. Abstr.* **1977**, *87*, 147056.
14. Butler, D. E.; DeWald, H. A. *J. Org. Chem.* **1975**, *40*, 1353.
15. Seko, S.; Tani, N. *Tetrahedron Lett.* **1998**, *39*, 8117.
16. Kitajima, N.; Fujisawa, K.; Fujimoto, C.; Morooka, Y.; Hashimoto, S.; Kitagawa, T.; Toriumi, K.; Tatsumi, K.; Nakamura, A. *J. Am. Chem. Soc.* **1992**, *114*, 1277.