An Improved Preparation of 3-Alkoxypyrazoles

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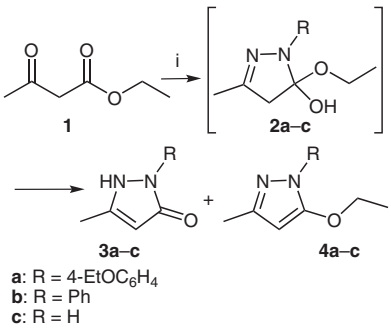
Abstract: The condensation between alkyl acetoacetates and hydrazines constitutes the very well-known Knorr synthetic method leading to pyrazol-3/5-ones. However, contemporary reports describe an alternate reaction pathway leading to low yields of 3/5-alkoxypyrazoles using hydrazine salts. No general method for the selective synthesis of 3-alkoxypyrazoles has been reported to date, hence we focused on this side reaction in an attempt to turn it into the main transformation. Depending on the starting material, various 3-alkoxypyrazoles (methoxy, ethoxy, benzyloxy, isopropoxy, allyloxy) were obtained in up to 56% yield.

Key words: condensation, cyclizations, heterocycles, pyrazoles, Knorr reaction



Scheme 1 *Reagents and conditions*: (i) $RNHNH_2$ or its salts (see text).

The well known Knorr pyrazol-3/5-ones synthesis consists of a double condensation reaction between, for example, ethyl acetoacetate (**1**), and various hydrazines.[1,2] The reaction proceeds via intermediates **2a–c** followed by an elimination reaction of the alcohol moiety to give pyrazol-5-ones **3a–c** bearing, if relevant, a substituent on N1 (Scheme 1). However, very early (1895),[3–5] the reaction was noted to partially proceed in a different fashion, leading to 5-ethoxypyrazoles **4a–c** via elimination of water instead of ethanol.

Further studies were undertaken in 1926, in the course of which intermediate **2c** was postulated and compound **4c** was isolated in 30% yield along with **3c**. This result was obtained by reacting hydrazine with **1** in the presence of two equivalents of hydrochloride acid in boiling alcohol;[6] remarkably few reports followed these early studies.[7–16] This is quite surprising as O-protected pyrazoles, such as compound **4**, could be starting materials for many syntheses aimed at selective reactions either on N1 or C4. Another possible synthesis of 3-alkoxypyrazoles is by the alkylation of the corresponding pyrazol-3-ones. However, the selectivity of the reaction is highly dependent on the alkylating agent, the reaction conditions, and the substrate used. Diazomethane was used in the past[17] as well as Mitsunobu-based alkylation[18] and we previously obtained adequate amounts of a 3-isopropoxypyrazole derivative in one case.[19] Moreover, we reported that a method using trimethyl orthocarboxylates could not be adapted to the selective O-methylation of compound **3c**.[20] On the other hand, a very recent patent[21] extended a method, which had been reported in one case,[22] to many pyrazol-3-ones. The strategy involves initial N-acetylation of the pyrazol-3-ones, followed by selective O-benzylation, and then removal of the acetyl group during the work up. This strategy provides selective access to many 3-(benzyloxy)pyrazoles[21] and may actually be an excellent alternative to the method described in the present work. Related approaches, based on a transitory N-carboxylation, have also been reported.[23,24] An even more recent report[25] describing results related to ours prompted us to describe our finding in the following. Scheme 2 provides an illustration of the selectivity problem encountered with the alkylation of pyrazol-3-ones.

We indeed undertook the study of the benzylation of 5-methyl-1,2-dihydro-3*H*-pyrazol-3-one (**3c**) under basic conditions (without the preparatory acetylation step mentioned above). This led to the O-benzyl derivative **5** as well as, at least, the fully characterized compounds **6–8**. This result not only illustrates the multiple reactive centers of pyrazol-3-ones, but also a potential for chemical diversity; although one needs to control the regioselectivity of the chemical transformations. Even if the preparation of compound **5** was reported in a 82% yield from benzyl acetoacetate and hydrazine in acetic acid,[14] in our hands, using the described method, we only observed the occurrence of benzyl acetate and compound **3c**.

Moreover, neither the partial description of **5** provided in this report[14] nor data described more recently[26] correspond with our data (see the experimental part). In any case, the potential of this ancient synthetic access to 3-alkoxypyrazoles led to the present investigation. Trials were undertaken with ethyl acetoacetate (**1**) under various conditions. The use of 1.05 equivalents of hydrazine monohydrochloride in boiling ethanol led to 3-ethoxy-5-methyl-1*H*-pyrazole (**4c**) in 55% yield. Increasing the proportion to two equivalents of hydrazine monohydro-

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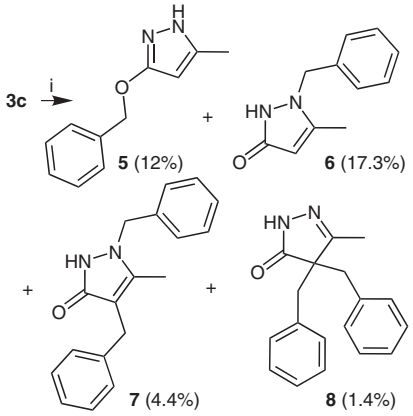
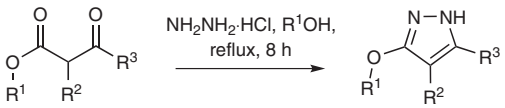


Scheme 2 *Reagents and conditions*: (i) NaH, BnBr, DMF, r.t.

chloride led to a lower yield. A trial run with 0.5 equivalents of hydrazine and 0.5 equivalents of hydrazine monohydrochloride also led to a lower yield of **4c**. Replacing the hydrazine monohydrochloride with hydrazine sulfate in refluxing ethanol gave compound **4c**, although still in lower yield, whereas hydrazine acetate only led to compound **3c**. Other salts were tried (hydrobromide, tetrafluoroboride, or monophosphate) without any improvement. The reaction could also be run with hydrazine monohydrochloride overnight at room temperature and gave a similar yield of **4c**. The absence of ethanol or the use of a different solvent (THF, toluene, DMF, H_2O) at room temperature gave lower yields of **4c**. Compounds **10b–k** were obtained by using the optimal conditions found so far, i.e. alkyl acetoacetates **9a–k** (1 equiv), hydrazine monohydrochloride (1.05 equiv), reflux, in either the corresponding alkyl alcohol or isopropyl alcohol in the case of compound **9a**, for eight hours. From the allyl acetoacetate **9m**, a transesterification was observed in boiling isopropyl alcohol and, thus, the reaction was undertaken at room temperature overnight instead.

The results reported in Table 1 show that starting from ethyl or isopropyl acetoacetates **1** or **9c** the reaction led mainly to the corresponding alkoxypyrazoles **4c** and **10c** (55% yield). On the other hand, the methyl or benzyl acetoacetates **9a**,**b** gave lower yield of alkoxypyrazoles. The acidic lability of the benzyl and the methyl group may explain the lower yield observed and the volatility and water solubility of **10b** may also provide an explanation in this case. However, concerning eventual acidic lability, trials at room temperature or with shorter reaction time provided compound **5** or **10b** in the same yield range. In the case of the *tert*-butyl acetoacetate, a mixture of compounds that could not be properly purified was obtained. The ethyl or the benzyl group of ethyl acetoacetates **9e** and **9f** do not seem to hinder this reaction, however, the phenyl of compound **9g** leads to a lower yield of **10g**. Interestingly, a fluorine atom is compatible with the reaction conditions and we obtained the 4-fluoropyrazole **10i** in 40% yield. Moreover, an ester function did not hinder the preparation of the carboxy-bearing compound **10j** in 39% yield from diethyl 2-methyl-3-oxosuccinate (**9j**). From the commercially available sodium salt of diethyl 2-oxosuccinate (**9k**) a different procedure was used, which led to the expected compound **10k** although in an unoptimized 9% yield (see experimental part). Finally, the comparison of the trials starting with the cyclic compounds **9h** and **9n**,**o** illustrates some of the structural constraints which limit this method. Thus, the six-membered cyclic acetoacetate **9h** gave the corresponding 3-ethoxytetrahydroindazole **10h** in 54% yield, but the five-membered cyclic acetoacetate **9n** led to an inseparable mixture, which probably contained the target compound. In the case of **9o**, the water elimination seems to be even more disfavored and no O-alkylated substances could be detected in ^{1}H NMR spectra of the reaction mixture. This method has the advantage of providing a very simple access to many 3-alkoxypyrazole-bearing compounds as, quite often, an extraction is the sole work-up required. By using 1.05 equivalents of hydrazine monohydrochloride, we were able to double the yields of this side reaction, when compared to previously reported cases which used the sulfate or, more often,[6] the dihydrochloride salts. As shown in Scheme 3, a similar yield in-

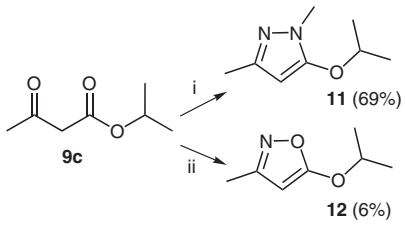
Table 1 Formation of 3-Alkoxypyrazoles



9a–o **10b–o**

Entry	Substrate	R^1	R^2	R^3	Product	Yield (%)
1	**1**	Et	H	Me	**4c**	55
2	**9a**	Bn	H	Me	**5**	22[a]
3	**9b**	Me	H	Me	**10b**	25
4	**9c**	*i*-Pr	H	Me	**10c**	55
5	**9d**	*t*-Bu	H	Me		–[b]
6	**9e**	Et	Et	Me	**10e**	56
7	**9f**	Et	Bn	Me	**10f**	55
8	**9g**	Et	H	Ph	**10g**	40
9	**9h**	Et	$(CH_2)_4$		**10h**	54
10	**9i**	Et	F	Me	**10i**	40
11	**9j**	Et	Me	CO_2Et	**10j**	39
12	**9k**	Et	H	CO_2Et	**10k**	9[c]
13	**9l**	Et	H	CF_3	**10l**	25
14	**9m**	$CH_2CH=CH_2$	H	Me	**10m**	48[d]
15	**9n**	Et	$(CH_2)_3$			–[b]
16	**9o**	$(CH_2)_2$		Me		0

[a] In *i*-PrOH.
[b] Mixture.
[c] See text and experimental part.
[d] Reaction performed in *i*-PrOH at r.t.



Scheme 3 *Reagents and conditions*: (i) $MeNHNH_2$, HCl, *i*-PrOH, reflux 8 h; (ii) $NH_2OH{\cdot}HCl$, *i*-PrOH, r.t., 48 h.

crease was also observed when reacting 1.05 equivalents of methylhydrazine monohydrochloride with isopropyl acetoacetate (**9c**) as the corresponding 5-isopropoxy-1,3-dimethyl-1*H*-pyrazole (**11**) was obtained in 69% yield instead of the previously reported 30%.[13] The regioselectivity of this reaction, which corresponds to the reported examples,[7,13] was determined by ^{13}C–^{1}H long distance correlations.

Finally, we also performed the condensation of 1.05 equivalent of hydroxylamine hydrochloride on **9c** in the absence of the usual base (Scheme 3).[27] To our surprise, when running this trial at room temperature in isopropanol (reflux was detrimental to the yield), we did isolate 6% of the volatile 5-isopropoxy-3-methylisoxazole (**12**) also resulting from an unprecedented water elimination from the intermediate oxime. An HMBC–^{15}N experiment was instrumental in the structural assignment of **12** as heteronuclear correlations were noted between the nitrogen ^{15}N signal and the methyl hydrogen's on C3 as well as with the hydrogen on C4.

In conclusion, this work allows the preparation an array of novel O-protected pyrazoles. Moreover, it paves the way to our current work on the synthesis of new chemical entities as most of the chemistry of 3-alkoxypyrazoles remains to be explored.

Melting points were measured on a Kofler bench and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, respectively; TMS was used as an internal reference. ^{15}N NMR used $MeNO_2$ (δ = 0.00) as an external reference Column chromatography were performed over Merck silica gel 60 (0.035–0.070 mm), using a solvent pump operating at pressure between 2 and 7 bar (25–50 mL/min) and an automated collecting system driven by a UV detector set to 254 nm unless otherwise stated. LR-MS data were obtained on an Agilent 1100 series LC/MSD system using an atmospheric ESI system. HRMS were obtained by the laboratoire de spectrométrie de masse, CNRS.-ICSN, 91198 Gif/Yvette, France or on a Waters Micromass Q-Tof (ESI source).

Preparation of Compounds 5–8

In a 500-mL flask mounted with a $CaCl_2$ guard, NaH (60% in oil, 1.23 g, 0.031 mol) was added to a soln of 5-methyl-1,2-dihydro-3*H*-pyrazol-3-one (**3c**, 3 g, 0.031 mol) in anhyd DMF (75 mL; dried over 4 Å molecular sieves). At the end of the gaseous evolution, the soln was cooled to 0 °C with an ice bath and BnBr (3.7 mL, 0.031 mol) was added. The ice bath was removed and the resulting suspension was stirred overnight. The DMF was removed under vacuum and the residue was dispersed in H_2O (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O (5 × 50 mL) to remove the traces of DMF, dried (Na_2SO_4), and concentrated to dryness. The resulting residue was dissolved in CH_2Cl_2 (100 mL), extracted with 1 M NaOH (3 × 50 mL), washed back to neutrality with brine (3 × 50 mL), dried (Na_2SO_4), and concentrated to dryness to give product mixture A. The basic aqueous phase was made acid with concd HCl and extracted with CH_2Cl_2 (3 × 50 mL). This organic layer was washed to neutrality with brine (3 × 30 mL), dried (Na_2SO_4), and concentrated to dryness to give product mixture B. Chromatography of mixture A (silica gel, CH_2Cl_2–EtOH, 98:2) provided a mixture containing compounds **5** and **8**, free of mineral oil. This was recrystallized in toluene to provide compound **8** (0.12 g, 1.4%). The filtrate was concentrated to dryness and purified by chromatography (silica gel, cyclohexane–EtOAc, 3:1); this provided two crude fractions. The least migrating fraction (1 g) was purified again by chromatography (silica gel, 0.020–0.045 mm, CH_2Cl_2–EtOH, 99.5:0.5) and yielded compound **5** (0.72 g, 12%). Chromatography of mixture B (silica gel, CH_2Cl_2–EtOH, 98.5:1.5) provided, in order of elution, a fraction containing **7** and **6** and a second fraction containing pure compound **6** (0.74 g, 12.7%). The mixture of compounds **7** and **6** were further purified by chromatography (silica gel, cyclohexane–EtOAc, 4:1 to 1:1), which gave compound **7** (0.37 g, 4.4%) and more compound **6** (0.27 g, 4.6%).

3-(Benzyloxy)-5-methyl-1*H*-pyrazole (5)

Oil that slowly crystallizes; mp 91 °C.

Note: the ^{1}H NMR data previously reported[26] for **5** fit much better with the data we obtained for compound **6**.

^{1}H NMR ($CDCl_3$): δ = 2.24 (s, 3 H), 5.21 (s, 2 H), 5.55 (s, 1 H), 7.33–7.47 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 12.0, 71.0, 90.4, 128.1, 128.3, 128.9, 137.6, 141.3, 164.2.

MS (EI): *m*/*z* (%) = 91 (100), 188 (4).

HRMS could not be obtained as the compound readily loses its benzyl moiety.

1-Benzyl-5-methyl-1,2-dihydro-3*H*-pyrazol-3-one (6)[28]

A fraction was recrystallized (cyclohexane) for analytical purposes; mp 171 °C (cyclohexane) (Lit.[28] 224–226 °C).

^{1}H NMR ($CDCl_3$): δ = 2.15 (s, 3 H), 5.07 (s, 2 H), 5.46 (s, 1 H), 7.13–7.16 (m, 1 H), 7.28–7.35 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 11.7, 52.3, 91.8, 127.1, 128.0, 129.1, 137.3, 140.9, 161.9.

HRMS: *m*/*z* [M + Na] calcd for $C_{11}H_{12}N_2NaO$: 211.0847; found: 211.0885.

1,4-Dibenzyl-5-methyl-1,2-dihydro-3*H*-pyrazol-3-one (7)

Note: long distance correlations between the benzyls ^{1}H signals and the ^{13}C of the pyrazole ring established the regioselectivity of the N-benzylation; mp 161 °C (cyclohexane).

^{1}H NMR ($CDCl_3$): δ = 2.02 (s, 3 H), 3.69 (s, 2 H), 5.07 (s, 1 H), 7.14–7.16 (m, 2 H), 7.25–7.33 (m, 8 H).

^{13}C NMR ($CDCl_3$): δ = 10.3, 28.4, 52.5, 102.7, 126.0, 127.3, 127.9, 128.6, 128.7, 129.1, 137.6, 138.2, 141.8, 160.6.

HRMS: *m*/*z* [M + Na] calcd for $C_{18}H_{18}N_2NaO$: 301.1317; found: 301.1327.

4,4-Dibenzyl-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (8)[29]

Mp 202 °C (toluene) (Lit.[29] 204 °C).

^{1}H NMR ($CDCl_3$): δ = 2.11 (s, 3 H), 2.98 (d, *J* = 13.6 Hz, 2 H), 3.29 (d, *J* = 13.6 Hz, 2 H), 7.15–7.28 (m, 10 H), 8.14 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 15.6, 41.4, 60.6, 127.6, 128.8, 129.6, 135.3, 161.7, 178.7.

HRMS: *m/z* [M + Na] calcd for $C_{18}H_{18}N_2NaO$: 301.1317; found: 301.1322.

3-Alkoxy-1*H*-pyrazoles 4c, 5, 10b–10l and 11–12; General Procedure

The acetoacetate (0.01 mmol) and hydrazine hydrochloride (0.0105 mmol) were refluxed in the relevant solvent [**1**, **9e–l** (EtOH, 60 mL), **9a**, **9c** (*i*-PrOH, 60 mL) or **9d** (*t*-BuOH, 60 mL)] for 8 h. In the case of the allyl acetoacetate **9m**, the reaction was run at r.t. overnight in *i*-PrOH. The solvent was removed under reduced pressure, the residue was dispersed in CH_2Cl_2 (100 mL) and excess 1 M $NaHCO_3$ soln (50 mL). The organic phase was washed with 1 M $NaHCO_3$ soln (3 × 30 mL), dried (Na_2SO_4), and concentrated to dryness. The resulting residue was either pure enough for analytical characterization (>95% pure as seen by ^{1}H NMR and LC/MS) or further purified as described below.

3-Ethoxy-5-methyl-1*H*-pyrazole (4c)[30]

Oil that solidified; mp 62 °C (Lit.[30] 67–68 °C).

^{1}H NMR ($CDCl_3$): δ = 1.39 (t, *J* = 7.2 Hz, 3 H), 2.25 (s, 3 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 5.48 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 12.0, 15.2, 65.0, 89.9, 141.2, 164.2.

3-(Benzyloxy)-5-methyl-1*H*-pyrazole (5)

This compound was further purified first using a high vacuum pump to remove most of the BnOH present and then further purified by chromatography (silica gel, CH_2Cl_2–EtOH, 98:2). The fraction obtained slowly crystallized as described above.

3-Methoxy-5-methyl-1*H*-pyrazole (10b)[8,31]

Oil that solidified; mp 46 °C (Lit.[8] 49–50 °C).

^{1}H NMR ($CDCl_3$): δ = 2.25 (s, 3 H), 3.88 (s, 3 H), 5.50 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 12.0, 56.5, 89.9, 141.3, 165.0.

3-Isopropoxy-5-methyl-1*H*-pyrazole (10c)

Oil.

^{1}H NMR ($CDCl_3$): δ = 1.34 (d, *J* = 6.5 Hz, 6 H), 2.25 (s, 3 H), 4.65 (sept, *J* = 6.5 Hz, 1 H), 5.45 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 11.9, 22.6, 72.1, 90.3, 141.2, 163.2.

MS (EI): *m/z* (%) = 98 (100), 140 (5).

HRMS could not be obtained as the compound readily loses its isopropyl moiety.

3-Ethoxy-4-ethyl-5-methyl-1*H*-pyrazole (10e)[6]

White solid; mp 85 °C (Lit.[6] 86 °C).

^{1}H NMR ($CDCl_3$): δ = 1.11 (t, *J* = 7.5 Hz, 3 H), 1.40 (t, *J* = 7.0 Hz, 3 H), 2.18 (s, 3 H), 2.33 (q, *J* = 7.5 Hz, 2 H), 4.24 (q, *J* = 7.0 Hz, 2 H), 8.5 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 10.5, 15.0, 15.4, 15.43, 64.4, 104.8, 137.4, 162.7.

HRMS: *m/z* [M + H] calcd for $C_8H_{15}N_2O$: 155.1184; found: 155.1188.

4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazole (10f)

White solid; mp 107 °C.

^{1}H NMR ($CDCl_3$): δ = 1.38 (t, *J* = 6.7 Hz, 3 H), 2.11 (s, 3 H), 3.69 (s, 2 H), 4.25 (q, *J* = 6.7 Hz, 2 H), 7.18–7.29 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 10.7, 15.4, 28.0, 64.5, 102.4, 127.1, 128.6, 138.3, 141.6, 162.7.

HRMS: *m/z* [M + H] calcd for $C_{13}H_{17}N_2O$: 217.1341; found: 217.1387.

3-Ethoxy-5-phenyl-1*H*-pyrazole (10g)[30]

This compound was further purified using chromatography (silica gel, CH_2Cl_2–EtOH, 98:2) to give a white solid. On a larger scale, this chromatography was avoided as the residue could be recrystallized (cyclohexane, 500 mL for 11 g of crude compound; long boiling time required); mp 130 °C (Lit.[30] 126–128 °C).

^{1}H NMR ($CDCl_3$): δ = 1.40 (t, *J* = 7.0 Hz, 3 H), 4.22 (q, *J* = 7.0 Hz, 2 H), 5.96 (s, 1 H), 7.36–7.44 (m, 3 H), 7.56–7.59 (m, 2 H), 9.9 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 15.2, 65.4, 88.1, 125.7, 128.0, 129.3, 130.3, 145.3, 164.3.

HRMS: *m/z* [M + H] calcd for $C_{11}H_{13}N_2O$: 189.1028; found: 189.1036.

3-Ethoxy-4,5,6,7-tetrahydro-1*H*-indazole (10h)

Mp 113 °C.

^{1}H NMR ($CDCl_3$): δ = 1.40 (t, *J* = 7.0 Hz, 3 H), 1.73–1.80 (m, 4 H), 2.37–2.40 (m, 2 H), 2.53–2.56 (m, 2 H), 4.26 (q, *J* = 7.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 15.1, 19.2, 22.1, 22.9, 23.3, 64.4, 101.3, 141.2, 161.4.

HRMS: *m/z* [M + H] calcd for $C_9H_{15}N_2O$: 167.1184; found: 167.1184.

3-Ethoxy-4-fluoro-5-methyl-1*H*-pyrazole (10i)

Recrystallization (cyclohexane) gave yellow crystals; mp 91 °C.

^{1}H NMR ($CDCl_3$): δ = 1.42 (t, *J* = 7.0 Hz, 3 H), 2.22 (s, 3 H), 4.25 (q, *J* = 7.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 8.9, 15.1, 65.4, 125.9 (d, *J* = 23.5 Hz), 134.1 (d, *J* = 237.8 Hz), 150.8 (d, *J* = 9.1 Hz).

HRMS: *m/z* [M + H] calcd for $C_6H_{10}FN_2O$: 145.0777; found: 145.0783.

Ethyl 3-Ethoxy-4-methyl-1*H*-pyrazole-5-carboxylate (10j)

Chromatography (silica gel, CH_2Cl_2) gave white crystals; mp 95 °C.

^{1}H NMR ($CDCl_3$): δ = 1.36–1.43 (m, 6 H), 2.14 (s, 3 H), 4.30 (q, *J* = 7.0 Hz, 2 H), 4.37 (q, *J* = 7.0 Hz, 2 H), 10.7 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 7.0, 14.2, 14.8, 61.0, 64.8, 105.5, 130.9, 160.3, 162.3.

HRMS: *m/z* [M + H] calcd for $C_9H_{15}N_2O_3$: 199.1083; found: 199.1116.

Ethyl 3-Ethoxy-1*H*-pyrazole-5-carboxylate (10k)

This compound was prepared from the sodium salt of diethyl 2-oxosuccinate (**9k**) as follow: diethyl 2-oxosuccinate sodium salt (27.8 g, 0.132 mol; 95% pure) was dissolved in EtOH (300 mL) and H_2O (20 mL). To this was added NH_2NH_2·2 HCl (14.3 g, 0.136 mol) and the suspension was stirred at r.t. overnight and then heated to reflux for an additional 12 h. The solvent was removed under reduced pressure; the residue was dispersed in H_2O (400 mL) and made basic with the addition of small portion of solid $NaHCO_3$. The aqueous phase was extracted with EtOAc (5 × 50 mL), the combined organic layers were dried (Na_2SO_4) and concentrated to dryness. The residue was further purified by chromatography (silica gel, CH_2Cl_2–EtOH, 97:3) to yield **10k** (2.19 g, 9%) as a low melting solid.

^{1}H NMR ($CDCl_3$): δ = 1.36–1.42 (m, 6 H), 4.26 (q, *J* = 7.0 Hz, 2 H), 4.38 (q, *J* = 7.0 Hz, 2 H), 6.22 (s, 1 H), 10.6 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 14.2, 14.7, 61.4, 65.3, 93.2, 134.3, 159.6, 163.4.

HRMS: *m/z* [M + H] calcd for $C_8H_{13}N_2O_3$: 185.0926; found: 185.0980.

3-Ethoxy-5-(trifluoromethyl)-1*H*-pyrazole (10l)[32]
Oil that slowly crystallized.

^{1}H NMR ($CDCl_3$): δ = 1.43 (t, *J* = 7.1 Hz, 3 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 5.86 (d, 1 H), 11.3 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 14.4, 67.4, 85.2, 120.0 (q, *J* = 267 Hz), 141.1 (m), 158.3.

3-(Allyloxy)-5-methyl-1*H*-pyrazole (10m)
Oil.

^{1}H NMR ($CDCl_3$): δ = 2.25 (s, 3 H), 4.65–4.67 (m, 2 H), 5.25–5.28 (m, 1 H), 5.39 (dd, *J* = 1.6, 17.2 Hz, 1 H), 6.04–6.11 (m, 1 H), 8.9 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 11.9, 70.1, 90.1, 117.8, 133.8, 141.3, 163.9.

HRMS: *m/z* [M + H] calcd for $C_7H_{11}N_2O$: 139.0871; found: 139.0900.

5-Isopropoxy-1,3-dimethyl-1*H*-pyrazole (11)
Following the general procedure using $MeNHNH_2$·HCl (1.05 equiv) and acetoacetate **9c** gave **11** as an oil.

^{1}H NMR ($CDCl_3$): δ = 1.32 (d, *J* = 6.1 Hz, 6 H), 2.16 (s, 3 H), 3.53 (s, 3 H), 4.31 (sept, *J* = 6.1 Hz, 1 H), 5.26 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 14.7, 22.3, 33.5, 75.5, 85.5, 147.1, 154.3.

Anal. Calcd for $C_8H_{14}N_2O$: C, 14.55; H, 8.55; N, 33.94. Found: C, 14.61; H, 8.51; N, 33.97.

5-Isopropoxy-3-methylisoxazole (12)
Isopropyl acetoacetate (2.7 g, 0.019 mol) was dissolved in anhyd *i*-PrOH (30 mL, dried over 4A molecular sieves). To this was added NH_2OH·HCl (1.43 g, 0.02 mol) and the suspension was stirred at r.t. for 48 h. The resulting soln was processed as described in the general procedure and gave an oil that was further purified by chromatography (silica gel, CH_2Cl_2) to give **12** (0.16 g, 6%) as an oil. Note: if compound **12** was weakly detected by the UV monitor of the chromatography apparatus set at 254 nm, on TLC, it was only visible using a spraying reagent (EtOH soln containing 2% phosphomolybdic acid); R_f = 0.31 (CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 1.41 (d, *J* = 6.2 Hz, 6 H), 2.21 (s, 3 H), 4.62 (sept, *J* = 6.2 Hz, 1 H), 5.03 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 12.8, 22.3, 76.6, 79.1, 162.5, 173.1.

^{15}N NMR ($CDCl_3$,): δ = –27.

This compound was too volatile for HRMS analysis.

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