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Synthesis of 3-substituted and 3,4-disubstituted pyrazolin-5-ones

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Abstract—The synthesis of 3-substituted and 3,4-disubstituted pyrazolin-5-ones from acylated ethyl acetoacetates and diethyl malonates is described. The reaction of acylated ethyl acetoacetates and diethyl acetylmalonate with hydrazine (98%) gave 3-substituted pyrazolin-5-ones and malonyldihydrazide, respectively, following a deacetylation–condensation sequence. The reaction of ethyl 2-acetyl-3-hydroxy-2-butenoate and diethyl 2-(1-hydroxyethylidene)malonate with hydrazine monohydrochloride yielded ethyl 3,5-dimethyl-1*H*-pyrazole-4-carboxylate and 4-ethoxycarbonyl-3-methylpyrazolin-5-one, respectively, following a dehydration–cyclocondensation sequence, in high yields.

1. Introduction

Pyrazolinones are an important class of compounds, which possess widespread pharmacological properties[1] such as analgesic, antipyretic, antiphlogistic, antirheumatic, anti-arthritic, uricosuric, and antiinflammatory activities. They are also useful intermediates for many industrial products such as herbicides,[2] color photography,[3] liquid crystals,[4] and dyestuffs.[5] Chemically, they are known to undergo oxidation with $PhI(OAc)_2$,[6] $Tl(NO_3)_3$[7] and $Pb(OAc)_4$[8] to give general 2-alkynoates, 2,3-alkadienoates and the unstable pyrazol-3-ones, which are azo dienophiles and, as such, may be trapped as cycloadducts[9] in the presence of 1,3-dienes. Pyrazolin-5-ones are customarily made by treating the corresponding β-keto esters[10a–e] with aqueous hydrazine or substituted hydrazine; however, they have also been synthesized using β-amino esters and diesters,[11a–c] β-keto diesters,[12a,b] α-cyano esters,[13a,b] or α,β-unsaturated esters and diesters.[14a–c] Several pyrazolin-5-one derivatives have been made from 3-alkyl-5-benzylidene-2,4-dioxo-1,3-thiazolidines,[15] substituted uracils,[16] β-acylhydrazino esters,[17] coumarins,[18] β-lactams,[19] or pyrans.[20] Methods for the preparation of pyrazolin-5-ones on solid support have also been developed, utilizing either resin-bound β-keto esters[21] or resin-bound hydrazide.[22] Our research required large quantities of substituted pyrazolin-5-ones to serve as potential scaffolds for combinatorial synthesis. We therefore became interested in studying the scope of these cyclization reactions. In a preliminary communication, we have reported[23] the efficient two-step synthesis of 4-ethoxycarbonylpyrazolin-5-ones, involving carbon-acylation in the presence of base, followed by ring cyclization with hydrazine (pH 7)[24] or hydrazine mono-hydrochloride. In a continuation of these studies, we report on the synthetic usefulness of this method for preparing 3-substituted and 3,4-disubstituted pyrazolin-5-ones.

2. Results and discussion

We reasoned that good precursors to the 3-substituted and 3,4-disubstituted pyrazolin-5-ones would be α-acylated ethyl acetoacetates or α-acylated diethyl malonates, respectively. The required α-acylated esters **2a**–**t** could be synthesized, in high yields, by treatment of ethyl acetoacetate (**1a**) or diethyl malonate (**1b**) with the appropriate acyl chloride in the presence of magnesium/ethanol in anhydrous toluene (Table 1). The acylation reactions were also performed in the presence of several Lewis acids such as LiCl, montmorillonite, and tin (IV) chloride, but these reagents, for the most part, resulted in low yields (5–29%) of the product, while starting materials were quantitatively recovered. In previous studies,[23] we have found that, of several bases tested, $Mg(OEt)_2$ gave consistently higher yields in the acylation of diethyl malonate. This result was attributed to a magnesium (II)-chelation effect.[25] The scope of the acylation reactions proved to be quite general. The esters (**1**) were successfully acylated with both aliphatic and aryl acid chlorides, including hindered and unhindered acid chlorides (Table 1). In each case, the desired α-acylated esters were obtained in high yields.

With the ethyl acyl acetoacetates and diethyl acyl malonates in hand, we turned our attention to formation of the desired

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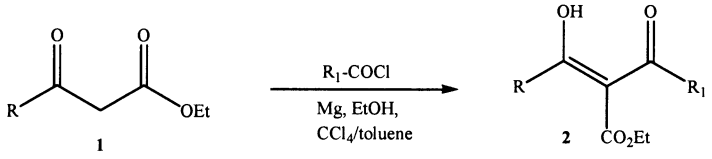
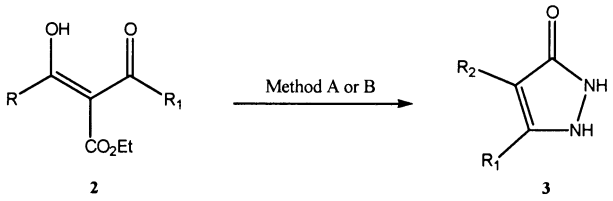
Table 1. Acylation of ethyl acetoacetate and diethyl malonate



Entry	1	R	R_1	Product (2)	Yield of 2 (%)[a]
1	**a**	Me	Me	**a**	91
2	**a**	Me	*i*-Pr	**b**	94
3	**a**	Me	*c*-C_3H_5	**c**	96
4	**a**	Me	*t*-Butyl	**d**	80
5	**a**	Me	*c*-C_5H_9	**e**	87
6	**a**	Me	2-Furyl	**f**	95
7	**a**	Me	2-Thienyl	**g**	90
8	**a**	Me	Ph	**h**	92
9	**a**	Me	4-$MeOC_6H_4$	**i**	95
10	**a**	Me	2,6-Dimethoxy nicotinyl	**j**	81[b]
11	**b**	OEt	Me	**k**	82
12	**b**	OEt	*i*-Pr	**l**	90
13	**b**	OEt	*c*-C_3H_5	**m**	91
14	**b**	OEt	*t*-Butyl	**n**	88
15	**b**	OEt	*c*-C_5H_9	**o**	87
16	**b**	OEt	2-Furyl	**p**	92
17	**b**	OEt	2-Thienyl	**q**	90
18	**b**	OEt	Ph	**r**	89
19	**b**	OEt	Bz	**s**	90
20	**b**	OEt	2,6-Dimethoxy nicotinyl	**t**	83[b]

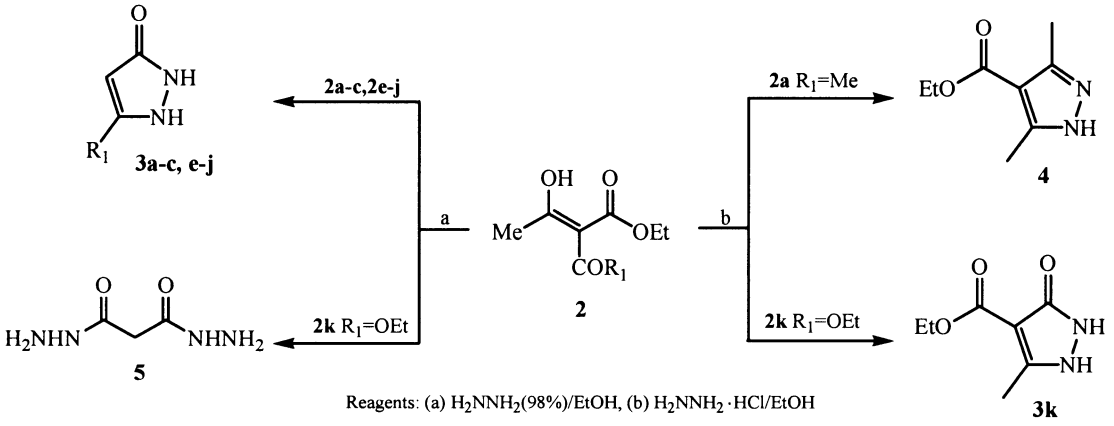
[a] Isolated yields.
[b] Two-step yield (in situ generation of acyl chloride using thionyl chloride, urea/toluene from the corresponding acid).[26a,b]

Table 2. Results of cyclocondensation reactions



Entry	2	R	R_1	R_2	Method[a]	Product	Yield of 3 (%)[b]
1	**a**	Me	Me	H	A	**3a**	85
2	**b**	Me	*i*-Pr	H	A	**3b**	79
3	**c**	Me	*c*-C_3H_5	H	A	**3c**	81
4	**d**	Me	*t*-Butyl	H	A	**3d**	–[c]
5	**e**	Me	*c*-C_5H_9	H	A	**3e**	71
6	**f**	Me	2-Furyl	H	A	**3f**	80
7	**g**	Me	2-Thienyl	H	A	**3 g**	76
8	**h**	Me	Ph	H	A	**3 h**	70
9	**i**	Me	4-$MeOC_6H_4$	H	A	**3i**	72
10	**j**	Me	2,6-Dimethoxy nicotinyl	H	A	**3j**	75
11	**k**	OEt	Me	CO_2Et	B	**3k**	86
12	**l**	OEt	*i*-Pr	CO_2Et	B	**3 l**	70
13	**m**	OEt	*c*-C_3H_5	CO_2Et	B	**3m**	73
14	**n**	OEt	*t*-Butyl	CO_2Et	B	**3n**	–[d]
15	**o**	OEt	*c*-C_5H_9	CO_2Et	B	**3o**	–[c]
16	**p**	OEt	2-Furyl	CO_2Et	B	**3p**	–[d]
17	**q**	OEt	2-Thienyl	CO_2Et	B	**3q**	–[d]
18	**r**	OEt	Ph	CO_2Et	B	**3r**	–[d]
19	**s**	OEt	Bz	CO_2Et	B	**3s**	81
20	**t**	OEt	2,6-Dimethoxy nicotinyl	CO_2Et	B	**3t**	–[d]

[a] Method A: hydrazine (98%)/ethanol; Method B: hydrazine monohydrochloride/ethanol.
[b] Isolated yields.
[c] Complex mixture.
[d] No ring cyclization.



Scheme 1. Various products available from ethyl acyl acetoacetates or diethyl acyl malonates (**2**).

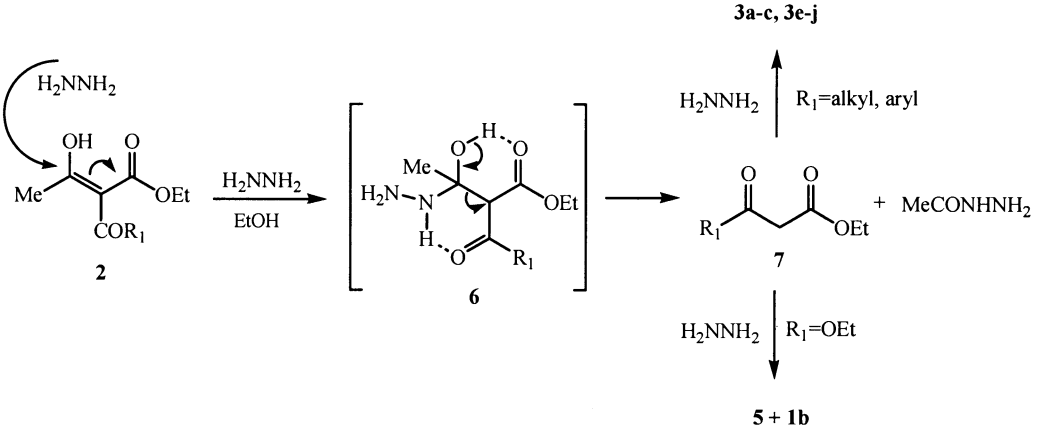
pyrazolin-5-ones (**3**). The acylated ethyl acetoacetates **2a–c**, **2e–j** were easily and cleanly converted to 3-substituted pyrazolinones **3a–c**, **3e–j** by treatment with hydrazine (98%) in ethanol at room temperature, while acylated diethyl malonates **2k–m**, **2s** were cleanly transformed into 4-ethoxycarbonyl-3-substituted pyrazolinones[27] **3k–m**, **3s** by treatment with hydrazine monohydrochloride in ethanol. The results of the ring cyclizations are shown in Table 2. The α-acylated acetoacetates cyclized uneventfully. Unfortunately, many of the α-acylated diethyl malonates failed to give the desired cyclic products **2n–r**, **2t**. A possible explanation for this observation will be explored in the discussion.

Interestingly, when ethyl 2-acetyl-3-hydroxy-2-butenoate (**2a**) was treated with hydrazine (98%) in ethanol (Scheme 1, path a), pyrazolinone **3a** was isolated as the only product; however, when **2a** was treated with hydrazine monohydrochloride in ethanol (Scheme 1, path b), ethyl 3,5-dimethyl-1*H*-pyrazole-4-carboxylate (**4**) was isolated in 91% yield. Furthermore, when diethyl 2-(1-hydroxyethylidene)malonate (**2k**) was treated with hydrazine monohydrochloride in ethanol (Scheme 1, path b), 4-ethoxycarbonyl-3-methylpyrazolin-5-one (**3k**) was isolated in 86% yield. However, upon treatment of **2k** with hydrazine (98%) in ethanol (Scheme 1, path a), a mixture of diethyl malonate (**1b**) and malonyldihydrazide (**5**), due to β-carbon cleavage, was isolated in 24% and 45% yields, respectively.

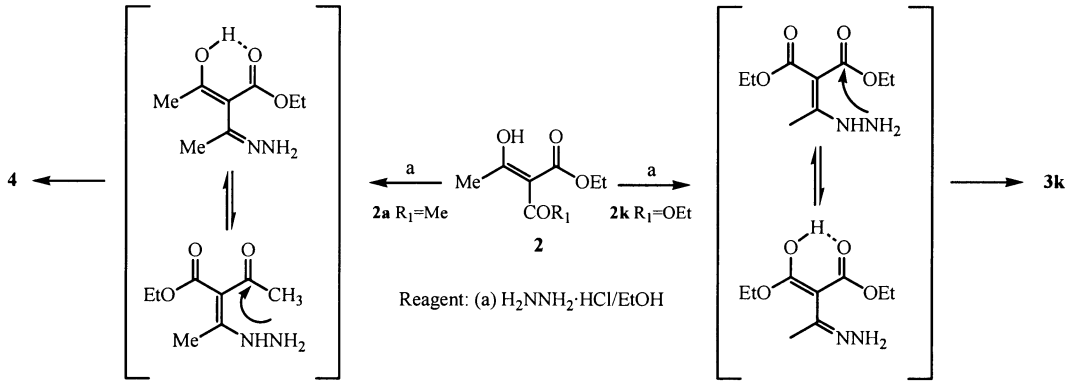
Schemes 2 and 3 suggest possible explanations for the observations mentioned in Scheme 1. When α-acylated diethyl malonates (**2**, R_1=OEt) are treated with hydrazine (98%) in ethanol, they undergo a Michael-type addition[28] to give intermediate **6**. Under these basic conditions, **6** undergoes a retro-aldol-type reaction, which leads to the formation of acetic hydrazide and a malonate derivative **7** (R_1=OEt),[29] which can undergo further reaction with hydrazine to give malonyldihydrazide (**5**).

Likewise, when the α-acylated ethyl acetoacetates **2a–c**, **2e–j** undergo reaction with hydrazine (98%) in ethanol, they also undergo β-carbon cleavage, with the elimination of acetic hydrazide to give a β-ketoester **7** (R_1=alkyl, aryl), which condenses with hydrazine in ethanol at room temperature to form 3-substituted pyrazolinones **3a–c**, **3e–j**. In the instances where R_1 is aliphatic (i.e. **2d**), **2** exists as a mixture of enols, which gives a complex array of products upon cyclization (Table 2, entry 4).

Scheme 3 shows a possible mechanism for the formation of **3k** and **4**. Under acidic conditions, the initial step in the mechanism involves formation of a hydrazone through condensation of hydrazine with the ketone of either



Scheme 2. Possible mechanism for the formation of **3a–c**, **3e–j** and **5** under basic conditions.



Scheme 3. Possible mechanism for the synthesis of **3k** and **4** under acidic conditions.

α-acylated ethyl acetoacetate or α-acylated diethyl malonate **2**. The next step involves, not a retro-aldol as under basic conditions, but simply condensation to give the desired products. In the case of **2k** (R_1=OEt), ring cyclization takes place on the ester to give 3,4-disubstituted pyrazolinone **3k**, while ethyl 2-acetyl-3-hydroxy-2-butenoate (**2a**, R_1=Me) undergoes cyclocondensation on the ketone to give ethyl 3,5-dimethyl-1*H*-pyrazole-4-carboxylate (**4**). The cyclization of α-acyl diethyl malonates has been shown to occur with a wide variety of substituents, making the method quite synthetically useful. Unfortunately, attempts to generalize the pyrazole synthesis proved to be unfruitful because of alkyl group scrambling, leading to a complex mixture of inseparable products. Furthermore, since the initial step in the reaction of hydrazine with **2** is a Michael-type addition, acylated diethyl malonates that exist primarily in the keto form (R_1=aromatic), as determined by integration of the ^{1}H NMR, fail to undergo ring cyclization but rather undergo β-carbon cleavage (Table 2, entries 14–18, 20).

In conclusion, we report on the scope of a simple and efficient method for preparing 3-substituted pyrazolin-5-ones under basic conditions [hydrazine (98%), in ethanol] and 3,4-disubstituted pyrazolin-5-ones under acidic conditions (hydrazine monohydrochloride in ethanol). These methods have shown to be quite useful synthetically, allowing for the large-scale production of various pyrazolin-5-ones in high yields.

3. Experimental

3.1. General

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Thin layer chromatography (TLC) was performed on precoated silica gel G and GP Uniplates from Analtech. The plates were visualized with a 254 nm UV light. Flash chromatography was carried out on silica gel 60 (Scientific Adsorbents Incorporated (SAI), particle size 32–63 μm, pore size 60 Å). Melting points were measured on a MEL-TEMP II apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 300 at 300 and 76 MHz, respectively. The chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane, and *J*-values are in Hz. IR spectra were obtained on an ATI Mattson FT/IR spectrometer. Low-resolution mass spectra were recorded with a Waters Micromass ZQ LC-Mass system, while high-resolution mass spectra (HRMS) were recorded with a Bruker BioApex FTMS system by direct injection using an electrospray interface (ESI). Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ. When necessary, chemicals were purified according to the reported procedures.[30]

3.2. General procedure for the preparation of α-acylated ethyl acetoacetates (2a–j) and diethyl malonates (2k–t)

A mixture of ethyl acetoacetate (**1a**, 12.0 mmol) or diethyl malonate (**1b**, 12.0 mmol), magnesium (12.1 mmol), ethanol (40.0 mmol), CCl_4 (0.3 mL) and anhydrous toluene (30 mL) was stirred under argon at room temperature for 30 min. The mixture was refluxed for 1 h, and then cooled to 0–5°C. The acylating agent (12.1 mmol) was added dropwise to the solution at 0–5°C over 30 min, and the reaction mixture was stirred at room temperature for 1 h. The resulting mixture was re-cooled to 0–5°C and washed with cold 5% aq. HCl solution (25 mL), satd $NaHCO_3$ solution (25 mL) and brine (25 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give pale yellow liquids.

3.2.1. Ethyl 2-acetyl-3-hydroxy-2-butenoate (2a). R_f=0.4 (10% ethyl acetate in hexanes); IR (neat, NaCl) 2984, 1713, 1416, 1084 cm^{-1}; ^{1}H NMR[31a] ($CDCl_3$) δ 15.86 (s, 1H), 4.20 (q, *J*=7.19 Hz, 2H), 2.30 (s, 6H), 1.27 (q, *J*=7.19 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 196.9, 167.4, 109.0, 61.0, 26.2, 14.5; MS (ESI) (*m*/*z*) 173 $[M+H]^+$, 127, 85 (base peak); 195 $[M+Na]^+$.

3.2.2. Ethyl 3-hydroxy-2-isobutyryl-2-butenoate (2b). R_f=0.7 (10% ethyl acetate in hexanes); IR (neat, NaCl) 2979, 1714, 1563, 1097 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 15.02 (s, 1H), 4.26 (q, *J*=7.10 Hz, 2H), 3.13 (q, *J*=6.23 Hz, 1H), 2.28 (s, 3H), 1.31 (q, *J*=7.10 Hz, 3H), 1.14 (s, 3H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 202.5, 195.6, 167.9, 108.5, 61.3, 35.1, 25.6, 19.8, 14.5; HRMS (ESI) (*m*/*z*) calcd for $C_{10}H_{16}O_4Na$: 223.0941 $[M+Na]^+$, found 223.0928.

3.2.3. Ethyl 2-cyclopropanecarbonyl-3-hydroxy-2-butenoate (2c). R_f=0.5 (10% ethyl acetate in hexanes); IR

(neat, NaCl) 2986, 1714, 1556, 1445, 1104 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.05 (s, 1H), 4.27 (q, J=6.78 Hz, 2H), 2.43–2.41 (m, 1H), 2.28 (s, 3H), 1.31 (q, J=6.78 Hz, 3H), 1.18–0.96 (m, 4H); ^{13}C NMR ($CDCl_3$), δ 200.0, 168.1, 162.7, 109.3, 61.1, 25.2, 16.9, 14.6, 12.4; HRMS (ESI) (*m/z*) calcd for $C_{10}H_{14}O_4Na$: 221.0784 $[M+Na]^+$, found 221.0767.

3.2.4. Ethyl 2-(2,2-dimethylpropionyl)-3-hydroxy-2-butenoate (2d). R_f=0.5 (15% ethyl acetate in hexanes); IR (neat, NaCl) 2974, 1746, 1722, 1478, 1242 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.92 (br s, 1H), 4.06 (q, J=7.12 Hz, 2H), 2.11 (s, 3H), 1.11 (s, J=7.12 Hz, 3H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 205.2, 198.5, 165.5, 67.5, 62.3, 46.1, 27.6, 29.1, 14.2; MS (ESI) (*m/z*) 215 $[M+H]^+$, 173, 127, 85, 57 (base peak); 237 $[M+Na]^+$, HRMS calcd for $C_{11}H_{18}O_4$: 215.1278 $[M+H]^+$, found 215.1270.

3.2.5. Ethyl 2-cyclopentanecarbonyl-3-hydroxy-2-butenoate (2e). R_f=0.6 (10% ethyl acetate in hexanes); IR (neat, NaCl) 2958, 1714, 1565, 1079 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.25 (q, J=7.14 Hz, 2H), 3.27 (t, J=7.84 Hz, 1H), 2.28 (s, 3H), 1.84–1.57 (m, 8H), 1.32 (q, J=7.14 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 200.9, 193.9, 167.2, 108.3, 60.3, 45.2, 30.4, 29.5, 25.9, 25.3, 24.6, 13.7; HRMS (ESI) (*m/z*) calcd for $C_{12}H_{18}O_4$: 227.1278 $[M+H]^+$, found 227.1271.

3.2.6. Ethyl 2-(furan-2-carbonyl)-3-hydroxy-2-butenoate (2f). R_f=0.3 (10% ethyl acetate in hexanes); IR (neat, NaCl) 3136, 2983, 1746, 1720, 1471, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.17, 5.19 (br s, br s, total 1H), 7.55 (d, J=3.60 Hz, 1H), 7.19 (d, J=3.50 Hz, 1H), 6.61–6.52 (m, 1H), 4.24 (q, J=7.11 Hz, 2H), 2.27 (s, 3H), 1.23 (s, J=7.11 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 192.3, 179.5, 175.4, 150.2, 146.7, 118.7, 113.5, 107.7, 61.8, 20.3, 14.4; HRMS (ESI) (*m/z*) calcd for $C_{11}H_{12}O_5Na$: 247.0577 $[M+Na]^+$, found 247.0573.

3.2.7. Ethyl 3-hydroxy-2-(thiophene-2-carbonyl)-2-butenoate (2g). R_f=0.3 (10% ethyl acetate in hexanes); IR (neat, NaCl) 3095, 2983, 1741, 1660, 1243 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.03, 3.90 (br s, br s, total 1H), 7.74–7.64 (m, 2H), 7.14–7.04 (m, 1H), 4.20 (q, J=7.09 Hz, 2H), 2.24 (s, 3H), 1.23 (s, J=7.09 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 185.8, 177.9, 167.4, 145.9, 136.4, 135.3, 128.2, 105.7, 61.5, 20.4, 14.3; HRMS (ESI) (*m/z*) calcd for $C_{11}H_{12}O_4SNa$: 263.0348 $[M+Na]^+$, found 263.0345.

3.2.8. Ethyl 2-benzoyl-3-hydroxy-2-butenoate (2h). R_f=0.5 (20% ethyl acetate in hexanes); IR (neat, NaCl) 3372, 2983, 1715, 1244, 1071 cm^{-1}; ^1H NMR[31a] ($CDCl_3$) δ 13.24, 5.37 (br s, br s, total 1H), 7.54–7.34 (m, 5H), 4.09–3.90 (m, 2H), 2.38, 2.04 (s, s, total 3H), 0.96–0.82 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 199.0, 194.0, 168.3, 137.8, 131.9, 129.3, 129.0, 128.7, 127.7, 109.1, 61.3, 24.6, 14.0; MS (ESI) (*m/z*) 235 $[M+H]^+$, 171, 104 (base peak); 257 $[M+Na]^+$.

3.2.9. Ethyl 3-hydroxy-2-(4-methoxybenzoyl)-2-butenoate (2i). R_f=0.5 (20% ethyl acetate in hexanes); IR (neat, NaCl) 3335, 2981, 1744, 1715, 1258 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.06, 5.31 (br s, br s, total 1H), 7.83, 7.51 (ddd, J=8.79, 8.82, 8.70 Hz, 2H), 6.88 (dd, J=7.56, 6.72 Hz, 2H), 4.25–3.97 (m, 2H), 3.84, 3.81 (s, s, total 3H), 2.35, 1.97 (s, s, total 3H), 1.24–0.95 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 193.7, 190.3, 177.9, 131.5, 131.3, 114.6, 114.0, 105.4, 61.3, 55.9, 20.3, 14.3; MS (ESI) (*m/z*) 265 $[M+H]^+$, 135 (base peak); 287 $[M+Na]^+$, HRMS calcd for $C_{14}H_{16}O_5$: 265.1071 $[M+H]^+$, found 265.1059.

3.2.10. Ethyl 2-(2,6-dimethoxypyridine-3-carbonyl)-3-hydroxy-2-butenoate (2j). R_f=0.5 (10% ethyl acetate in hexanes); IR (neat, NaCl) 3631, 2985, 1716, 1594, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.20, 5.32 (br s, br s, total 1H), 7.76 (d, J=8.30 Hz, 1H), 6.35 (d, J=8.30 Hz, 1H), 4.17 (q, J=7.12 Hz, 2H), 3.95 (s, 3H), 3.81 (s, 3H), 2.40 (s, 3H), 1.24 (q, J=7.12 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 194.1, 189.1, 167.3, 166.1, 162.3, 141.5, 113.0, 103.8, 101.8, 60.1, 53.6, 50.0, 24.6, 13.6; HRMS (ESI) (*m/z*) calcd for $C_{14}H_{17}O_6$: 296.11128 $[M+H]^+$, found 296.1135.

3.2.11. Diethyl 2-(1-hydroxyethylidene)malonate (2k). R_f=0.5 (20% ethyl acetate in hexanes); IR (neat, NaCl) 2984, 1729, 1650, 1469, 1090 cm^{-1}; ^1H NMR[31b] ($CDCl_3$) δ 13.45, 4.38 (br s, br s, total 1H), 4.23–4.13 (m, 4H), 2.27, 2.13 (s, s, total 3H), 1.27–1.19 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 197.0, 171.6, 166.4, 100.2, 62.2, 61.4, 21.0, 14.4, 14.3; MS (ESI) (*m/z*) 203 $[M+H]^+$, 179, 157 (base peak); 225 $[M+Na]^+$.

3.2.12. Diethyl 2-(1-hydroxy-2,2-methylpropylidene)-malonate (2l). R_f=0.6 (10% ethyl acetate in hexanes); IR (neat, NaCl) 2986, 1733, 1609, 1242 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.28, 4.62 (br s, br s, total 1H), 4.24–4.18 (m, 4H), 2.81 (q, J=6.95 Hz, 1H), 1.28–1.10 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 203.1, 186.3, 165.0, 98.9, 62.6, 61.6, 41.3, 19.9, 18.5, 14.4, 14.3; HRMS (ESI) (*m/z*) calcd for $C_{11}H_{18}O_5Na$: 253.1046 $[M+Na]^+$, found 253.1028.

3.2.13. Diethyl 2-(cyclopropylhydroxymethylene)malonate (2m). R_f=0.5 (10% ethyl acetate in hexanes); IR (neat, NaCl) 2992, 1733, 1714, 1281 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.67, 4.55 (br s, br s, total 1H), 4.30–4.17 (m, 4H), 2.14–2.05 (m, 1H), 1.29–0.90 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 199.6, 184.2, 165.0, 99.0, 62.6, 61.5, 20.9, 13.9, 12.9, 10.0, 9.4; HRMS (ESI) (*m/z*) calcd for $C_{11}H_{16}O_5Na$: 251.0890 $[M+Na]^+$, found 251.0865.

3.2.14. Diethyl 2-(1-hydroxy-2,2-dimethylpropylidene)-malonate (2n). R_f=0.5 (10% ethyl acetate in hexanes); IR (neat, NaCl) 3654, 2978, 1736, 1478, 1038 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.83 (br s, 1H), 4.15 (q, J=7.12 Hz, 4H), 1.19 (q, J=7.12 Hz, 6H), 1.10 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 203.9, 165.0, 62.5, 60.1, 45.8, 26.1, 14.2; MS (*m/z*) 245 $[M+H]^+$, 161, 84 (base peak); 267 $[M+Na]^+$, HRMS calcd for $C_{12}H_{20}O_5$: 245.1384 $[M+H]^+$, found 245.1366.

3.2.15. Diethyl 2-(cyclopentylhydroxymethylene)malonate (2o). R_f=0.6 (15% ethyl acetate in hexanes); IR (neat, NaCl) 3583, 2963, 1730, 1601, 1241, 1035 cm^{-1}; ^1H NMR[31c] ($CDCl_3$) δ 13.28, 4.52 (br s, br s, total 1H), 4.22–4.23 (m, 4H), 3.05–2.90 (m, 1H), 1.78–1.52 (m, 8H), 1.27–1.18 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 202.1, 171.4, 165.0, 99.5, 62.5, 61.5, 43.1, 31.3, 29.9, 26.7, 26.3, 14.6, 14.3; MS (ESI) (*m/z*) 257 $[M+H]^+$, 202, 115, 96, 55 (base peak); 279 $[M+Na]^+$.

3.2.16. Diethyl 2-(furan-2-yl-hydroxymethylene)malonate (2p). R_f=0.3 (10% ethyl acetate in hexanes); IR (neat, NaCl) 3143, 2986, 1740, 1681, 1471, 1038 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.84, 5.09 (br s, br s, total 1H), 7.57 (d, J=3.08 Hz, 1H), 7.28 (d, J=3.08 Hz, 1H), 6.56 (d, J=1.72 Hz, 1H), 4.27–4.20 (m, 4H), 1.28–1.20 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 177.9, 164.7, 162.7, 151.7, 147.6, 119.1, 113.4, 62.7, 62.0, 14.3; HRMS calcd for $C_{12}H_{14}O_6$: 255.0863 $[M+H]^+$, found 255.0846.

3.2.17. Diethyl 2-(hydroxythiophene-2-yl-methylene)-malonate (2q). R_f=0.3 (10% ethyl acetate in hexanes); IR (neat, NaCl) 3110, 2986, 1746, 1674, 1412, 1032 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.26, 5.14 (br s, br s, total 1H), 7.71 (d, J=4.90 Hz, 1H), 7.68 (d, J=3.40 Hz, 1H), 7.13 (dd, J=4.21, 4.51 Hz, 1H), 4.25 (q, J=7.13 Hz, 4H), 1.24 (q, J=7.13 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 181.7, 164.8, 142.8, 135.9, 133.7, 128.8, 62.9, 14.3; HRMS (ESI) (*m/z*) calcd for $C_{12}H_{14}O_5SNa$: 293.0454 $[M+Na]^+$, found 293.0465.

3.2.18. Diethyl 2-(hydroxyphenylmethylene)malonate (2r). R_f=0.5 (20% ethyl acetate in hexanes); IR (neat, NaCl) 3463, 3063, 1734, 1692, 1294, 1037 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.41, 5.28 (br s, br s, total 1H), 7.89–7.42 (m, 5H), 4.23 (q, J=7.13 Hz, 4H), 1.23 (t, J=7.13 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 189.4, 165.3, 135.8, 134.4, 129.1, 128.7, 62.8, 61.9, 14.4, 14.0; MS (ESI) (*m/z*) 265 $[M+H]^+$, 219, 104 (base peak); 287 $[M+Na]^+$, HRMS calcd for $C_{14}H_{16}O_5$: 265.1071 $[M+H]^+$, found 265.1065.

3.2.19. Diethyl 2-(hydroxyphenylethylidene)malonate (2s). R_f=0.5 (20% ethyl acetate in hexanes); IR (neat, NaCl) 3584, 3031, 1731, 1650, 1243, 1037 cm^{-1}; ^1H NMR[31c] ($CDCl_3$) δ 13.40, 4.58 (br s, br s, total 1H), 7.34–7.19 (m, 5H), 4.29–4.21 (m, 4H), 3.94, 3.80 (s, s, total 2H), 1.34–1.25 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 197.1, 171.5, 164.9, 135.9, 130.2, 129.5, 129.1, 128.6, 127.4, 100.8, 63.8, 61.7, 40.0, 14.5, 14.4; MS (ESI) (*m/z*) 279 $[M+H]^+$, 202, 161 (base peak), 104, 90; 301 $[M+Na]^+$.

3.2.20. Diethyl 2-[(2,6-dimethoxypyridin-3-yl)-hydroxy methylene]malonate (2t). R_f=0.5 (15% ethyl acetate in hexanes); IR (neat, NaCl) 3637, 2985, 1735, 1668, 1008 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.17 (d, J=8.32 Hz, 1H), 6.34 (d, J=8.32 Hz, 1H), 5.18 (br s, 1H), 4.19 (q, J=7.17 Hz, 4H), 3.93 (s, 3H), 3.90 (s, 3H), 1.21 (t, J=7.17 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 186.8, 166.8, 166.0, 162.6, 143.7, 112.0, 104.1, 66.1, 62.1, 54.5, 54.0, 14.4; HRMS calcd for $C_{15}H_{19}NO_7$: 326.1235 $[M+H]^+$, found 326.1226.

3.3. General procedure for the preparation of 3-substituted pyrazolin-5-one derivatives (3a–c, 3e–j)

To a stirred solution of the α-acylated ethyl acetoacetate (**2a–c**, **2e–j**, 5.0 mmol) in ethanol (10 mL), hydrazine (7.5 mmol, 98%) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 16 h. The mixture was concentrated under reduced pressure, and the residue was treated with diethyl ether (10 mL). The resulting solid was filtered and washed with diethyl ether and recrystallized from 10% ethanol in diethyl ether to give white crystals.

3.3.1. 3-Methyl-3-pyrazolin-5-one (3a). R_f=0.2 (10% methanol in dichloromethane); mp 223–224°C (lit.[32] mp 223°C); IR (Nujol, NaCl) 2923, 1615, 1456, 1192 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.30 (br s, 2H), 5.20 (s, 1H), 2.06 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 161.9, 140.4, 89.8, 12.0; MS (ESI) (*m/z*) 99 $[M+H]^+$ (base peak), 82, 56; 121 $[M+Na]^+$.

3.3.2. 3-Isopropyl-3-pyrazolin-5-one (3b). R_f=0.3 (10% methanol in dichloromethane); mp 188–189°C; IR (Nujol, NaCl) 2967, 1625, 1556, 1076 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.38 (br s, 2H), 5.20 (s, 1H), 2.75 (q, J=6.74 Hz, 1H), 1.14 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 161.6, 151.3, 87.1, 26.5, 23.0; HRMS calcd for $C_6H_{10}N_2O$: 127.0866 $[M+H]^+$, found 127.0856.

3.3.3. 3-Cyclopropyl-3-pyrazolin-5-one (3c). R_f=0.3 (10% methanol in dichloromethane); mp 215–216°C; IR (Nujol, NaCl) 2940, 1615, 1563, 1097 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.41 (br s, 2H), 5.10 (s, 1H), 1.76–1.67 (m, 1H), 0.84–0.76 (m, 2H), 0.60–0.55 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 161.7, 147.7, 86.6, 8.4, 8.1; HRMS calcd for $C_6H_8N_2O$: 125.0710 $[M+H]^+$, found 125.0702.

3.3.4. 3-Cyclopentyl-3-pyrazolin-5-one (3e). R_f=0.3 (10% methanol in dichloromethane); mp 243°C; IR (Nujol, NaCl) 3585, 2925, 1621, 1008 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.36 (br s, 2H), 5.21 (s, 1H), 2.85 (t, J=7.71 Hz, 1H), 1.90–1.85 (m, 2H), 1.64–1.45 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 161.7, 149.3, 87.5, 37.6, 33.4, 25.5; HRMS calcd for $C_8H_{12}N_2O$: 153.1023 $[M+H]^+$, found 153.1014.

3.3.5. 3-Furan-2-yl-3-pyrazolin-5-one (3f). R_f=0.4 (10% methanol in dichloromethane); mp 213–214°C; IR (Nujol, NaCl) 3583, 2914, 1648, 1360, 1084 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.79 (br s, 2H), 7.65 (br s, 1H), 6.68 (br s, 1H), 6.51 (br s, 1H), 5.68 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 161.1, 147.0, 143.2, 112.4, 106.7, 86.8; HRMS calcd for $C_7H_6N_2O_2$: 151.0502 $[M+H]^+$, found 151.0499.

3.3.6. 3-Thiophene-2-yl-3-pyrazolin-5-one (3g). R_f=0.4 (10% methanol in dichloromethane); mp 203–204°C; IR (Nujol, NaCl) 3583, 2921, 1616, 1169 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.93 (br s, 2H), 7.42 (d, J=3.67 Hz, 1H), 7.30 (br s, 1H), 7.04 (d, J=3.00 Hz, 1H), 5.68 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 162.2, 143.8, 131.9, 128.5, 125.8, 124.5, 86.3; HRMS calcd for $C_7H_6N_2OS$: 167.0274 $[M+H]^+$, found 167.0273.

3.3.7. 3-Phenyl-3-pyrazolin-5-one (3h). R_f=0.2 (5% methanol in dichloromethane); mp 235–236°C (lit.[10b] mp 236°C); IR (Nujol, NaCl) 2923, 1615, 1456, 1192 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.79 (br s, 2H), 7.64–7.26 (m, 5H), 5.88 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 161.9, 144.2, 131.4, 129.6, 128.6, 125.6, 87.7; MS (ESI) (*m/z*) 161 $[M+H]^+$ (base peak), 118, 99, 56; 183 $[M+Na]^+$, HRMS calcd for 161.0710 $[M+H]^+$, found 161.0712. Anal. calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.01; H, 4.99; N, 17.37.

3.3.8. 3-(4-Methoxyphenyl)-3-pyrazolin-5-one (3i). R_f=0.2 (5% methanol in dichloromethane); mp 220–221°C; IR (Nujol, NaCl) 2923, 1615, 1456, 1192 cm^{-1};

^{1}H NMR (DMSO-d_6) δ 10.33 (br s, 2H), 7.57 (d, J=8.73 Hz, 2H), 6.94 (d, J=8.73 Hz, 2H), 5.77 (s, 1H), 3.73 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 162.0, 159.8, 144.1, 127.0, 124.0, 115.0, 87.1, 56.0; MS (ESI) (*m/z*) 191 $[M+H]^+$ (base peak), 148, 121; 213 $[M+Na]^+$. HRMS calcd for 191.0815 $[M+H]^+$, found 191.0815. Anal. calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.58; H, 5.16; N, 14.47.

3.3.9. 3-(2,6-Dimethoxypyridin-3-yl)-3-pyrazolin-5-one (3j). R_f=0.4 (10% methanol in dichloromethane); mp 221–222°C; IR (Nujol, NaCl) 3471, 2925, 1616, 1587, 1012 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.67 (br s, 2H), 7.94 (d, J=8.17 Hz, 1H), 6.43 (d, J=8.15 Hz, 1H), 5.86 (s, 1H), 3.95 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 162.4, 161.8, 158.8, 139.5, 139.0, 105.9, 102.2, 89.6, 54.2; HRMS calcd for $C_{10}H_{11}N_3O_3$: 222.0873 $[M+H]^+$, found 222.0867.

3.4. General procedure for the preparation of 4-ethoxycarbonyl-3-substituted pyrazolin-5-one derivatives (3k–m, 3s)

3.4.1. Method A. To a stirred solution of α-acylated diethyl malonate (**2k–m**, **2s**, 2.0 g, 10.0 mmol) in ethanol, hydrazine monohydrochloride (0.8 g, 12.0 mmol) was added portionwise at room temperature. The reaction mixture was heated at reflux for 3 h, and filtered hot. After cooling, the solvent was evaporated, and the residue was treated with diethyl ether (15 mL). The resulting solid was filtered and washed with diethyl ether and then recrystallized from 10% ethanol in diethyl ether to give white crystals.

3.4.2. Method B. To a stirred solution of diethyl malonate (**1b**, 6.1 g, 38.1 mmol) and acetonitrile (1.6 g, 38.1 mmol) in 1,2-dichloroethane, tin (IV) chloride (19.8 g, 14 mL, 76.2 mmol) was added dropwise under argon at room temperature. The reaction mixture was heated at reflux for 16 h. After cooling, the solvent was evaporated under reduced pressure, and the residue was treated with acetone (120 mL), and satd Na_2CO_3 (100 mL) was added until a pH of 7 was reached. The resulting white solid was removed by filtration and washed with dichloromethane (4×60 mL). The combined filtrates were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a pale yellow liquid. The product was purified by flash column chromatography (50% ethyl acetate in hexanes) to give ethyl 3-amino-2-ethoxycarbonyl-2-butenoate[13] as a colorless oil (2.0 g, 26%; recovered starting material, 67%). IR (neat, NaCl) 3422, 2983, 1695, 1666, 1257 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.79 (br s, 1H), 5.88 (br s, 1H), 4.11–4.00 (m, 4H), 2.02 (s, 3H), 1.19–1.12 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 169.0, 168.9, 164.3, 92.8, 60.6, 59.8, 21.9, 14.6, 14.5. This compound (ethyl 3-amino-2-ethoxycarbonyl-2-butenoate) was ring cyclized with hydrazine monohydrochloride to give 4-ethoxycarbonyl-3-methylpyrazolin-5-one (**3k**) in 86% yield as white crystals.

3.4.3. 4-Ethoxycarbonyl-3-methylpyrazolin-5-one (3k). R_f=0.1 (5% methanol in dichloromethane); mp 202°C (lit.[12b] mp 206–207°C); IR (Nujol, NaCl) 3256, 2923, 1682, 1538, 1456, 1131 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.03 (br s, 2H), 4.12 (q, J=7.05 Hz, 2H), 2.28 (s, 3H), 1.21 (t, J=7.05 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 164.4, 161.9, 144.9, 95.7, 59.6, 15.2, 13.0; MS (ESI) (*m/z*) 171 $[M+H]^+$ (base peak), 157, 143, 125.

3.4.4. 4-Ethoxycarbonyl-3-isopropylpyrazolin-5-one (3l). R_f=0.2 (5% methanol in dichloromethane); mp 170–171°C; IR (Nujol, NaCl) 2986, 1733, 1609, 1242 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.90 (br s, 2H), 4.13 (q, J=7.05 Hz, 2H), 3.45 (q, J=6.96 Hz, 1H), 1.21–1.16 (m, 9H); ^{13}C NMR (DMSO-d_6) δ 163.1, 162.3, 159.8, 94.6, 59.7, 26.1, 21.3, 14.6; HRMS calcd for $C_9H_{14}N_2O_3$: 199.1077 $[M+H]^+$, found 199.1074.

3.4.5. 4-Ethoxycarbonyl-3-cyclopropylpyrazolin-5-one (3m). R_f=0.2 (5% methanol in dichloromethane); mp 144–145°C; IR (Nujol, NaCl) 2992, 1733, 1714, 1281 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.42 (br s, 2H), 4.15 (q, J=7.09 Hz, 2H), 2.38 (m, 1H), 1.22 (t, J=7.09 Hz, 3H), 0.94–0.86 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 164.3, 162.7, 160.9, 151.4, 96.4, 59.9, 15.2, 9.1, 8.3; HRMS calcd for $C_9H_{12}N_2O_3$: 197.0921 $[M+H]^+$, found 197.0907.

3.4.6. 4-Ethoxycarbonyl-3-benzylpyrazolin-5-one (3s). R_f=0.2 (10% methanol in dichloromethane); mp 146°C; IR (Nujol, NaCl) 3203, 3062, 1725, 1685, 1461, 1107 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.87 (br s, 2H), 7.20–7.15 (m, 5H), 4.09 (q, J=7.10 Hz, 2H), 4.06 (s, 2H), 1.14 (t, J=7.10 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 163.8, 161.0, 147.9, 139.0, 129.2, 127.2, 95.4, 59.9, 32.2, 15.1; MS (ESI) (*m/z*) 247 $[M+H]^+$, 201, 133 (base peak), 89; 269 $[M+Na]^+$.

3.4.7. Ethyl 3,5-dimethyl-1*H*-pyrazole-4-carboxylate (4). To a stirred solution of ethyl 2-acetyl-3-hydroxy-2-butenoate (**2a**, 1.72 g, 10.0 mmol) in ethanol, hydrazine monohydrochloride (0.84 g, 12.0 mmol) was added portionwise at room temperature. The reaction mixture was stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure, and the residue was treated with diethyl ether (15 mL). The resulting solid was filtered and washed with diethyl ether and then recrystallized from 10% ethanol in diethyl ether to give white crystals (1.53 g, 91%). R_f=0.1 (10% methanol in dichloromethane); mp 97–98°C (lit.[33] mp 98°C); IR (Nujol, NaCl) 3244, 2923, 1683, 1462, 1130 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.33 (br s, 1H), 4.15 (q, J=7.09 Hz, 2H), 2.34 (s, 3H), 2.33 (s, 3H), 1.23 (t, J=7.09 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 164.1, 147.9, 109.2, 60.3, 15.0, 13.1; MS (ESI) (*m/z*) 169 $[M+H]^+$, 141 (base peak), 97; 191 $[M+Na]^+$.

3.4.8. Malonyldihydrazide (5). To a stirred solution of diethyl 2-(1-hydroxyethylidene)malonate (**2k**, 5.0 g, 24.7 mmol) in ethanol, hydrazine (98%, 1.2 g, 36.7 mmol) was added dropwise at room temperature. The reaction mixture was heated at reflux for 3 h. After cooling, the solvent was evaporated under reduced pressure, and the residue was treated with diethyl ether (36 mL). The resulting solid was filtered and washed with diethyl ether and recrystallized from 10% ethanol in diethyl ether to give **5** as white crystals (1.5 g, 45%). R_f=0.3 (10% methanol in dichloromethane); mp 153°C (lit.[34,35] mp 154°C); IR (Nujol, NaCl) 3305, 2923, 1681, 1461, 1052 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.04 (br s, 2H), 4.22 (br s, 4H), 2.88 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 166.9, 39.7; MS (ESI) (*m/z*)

133 $[M+H]^+$, 100 (base peak); 155 $[M+Na]^+$, also isolated was diethyl malonate (**1b**, 0.95 g, 24%).

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