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SYNTHESIS AND CYCLIZATION REACTION OF PYRAZOLIN-5-ONE DERIVATIVES

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Abstract–A versatile synthetic method for preparing 3-pyrazolin-5-ones and 5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazines from simple *β*–keto esters is demonstrated. The synthetic strategies involve the acylation of *β*–keto esters, cyclocondensation with hydrazine followed by trapping with a diene under oxidative conditions.

INTRODUCTION

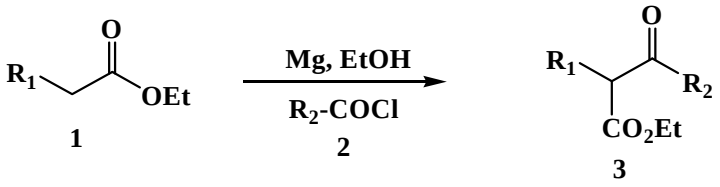
Pyrazolinones are an interesting group of compounds, many of which possess widespread pharmacological properties[1] such as analgesic, antipyretic, antiphlogistic, antiarthritic, uricosuric, antirheumatic, and antiinflammatory activities. Furthermore, they are potentially useful intermediates for many industrial products and agrochemical applications such as color photography,[2] dyestuffs,[3] liquid crystals,[4] and herbicides.[5] Chemically, pyrazolinones are known to undergo oxidation with $PhI(OAc)_2$,[6] $Tl(NO_3)_3$,[7] and $Pb(OAc)_4$[8] to give, respectively, general 2-alkynoates, 2,3-alkadienoates and the unstable pyrazol-3-ones, which are azo dienophiles and, as such, may be trapped as cycloadducts in the presence of 1,3-dienes.[9]

Our continuing interest in the chemistry of pyrazolin-5-ones relates in part to their potential use as scaffolds in combinatorial chemistry. A variety of routes for the synthesis of substituted pyrazolin-5-ones have been reported in the literature.[10] Most of these methods are based on 1,3-diketo ring-cyclizations with hydrazine or substituted hydrazines. Yields vary from substrate to substrate and from method to method. Our previous work has examined the scope and efficiency of pyrazolin-5-one synthesis.[11] This paper focuses on the chemistry of these compounds, namely on their abilities to act as azadienophiles in Diels-Alder cycloaddition reactions.

RESULTS AND DISCUSSION

The necessary α–acylated esters (**3a-n**) could easily be obtained, in high yields, by treatment of ethyl acetoacetate (**1a**), ethyl cyanoacetate (**1b**) or diethyl malonate (**1c**) with the appropriate acyl chlorides (**2**) in the presence of magnesium/ethanol in anhydrous toluene (Table 1).

Table 1. Acylation of ethyl acetoacetate (**1a**), ethyl cyanoacetate (**1b**) and diethyl malonate (**1c**).



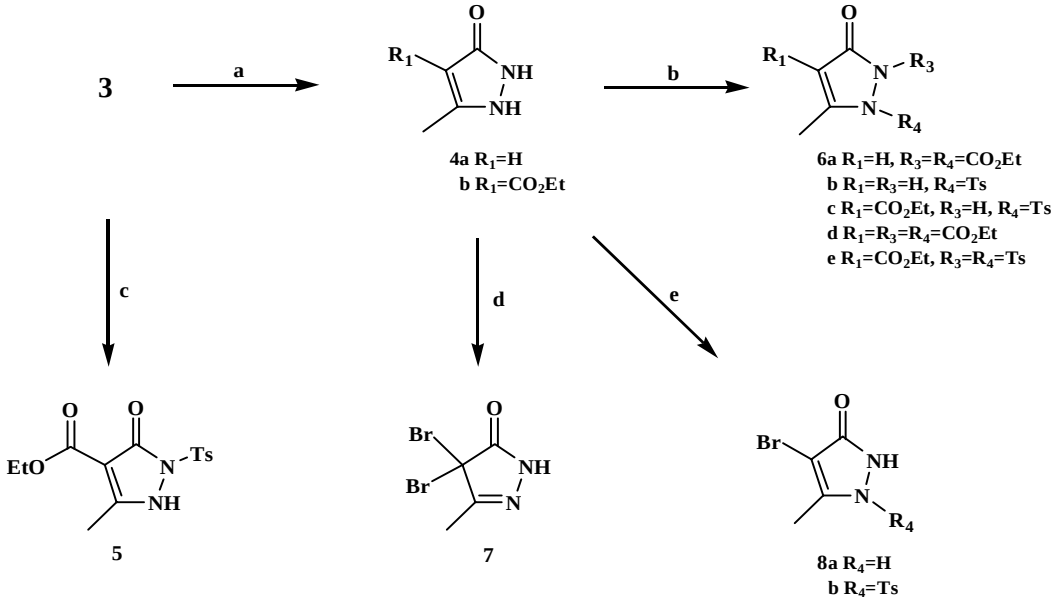
1 2 3

Entry	Compound	R_1	R_2	Yield (%)[a]	Products (K/E)[b]
1	**1a**	COMe	Me	91	**3a**[12a] (nd)[c]
2		COMe	$(CH_2)_4CH_3$	98	**3b**[12b] (nd)
3		COMe	Bz	94	**3c**[12c] (nd)
4	**1b**	CN	Me	90	**3d**[12d] (0/100)
5		CN	*c*-C_3H_5	84	**3e** (nd)
6		CN	*c*-C_5H_9	81	**3f** (nd)
7		CN	2-Thienyl	86	**3g**[12e] (0/100)
8		CN	Ph	88	**3h**[12d] (0/100)
9		CN	4-$MeOC_6H_4$	85	**3i**[12f] (0/100)
10	**1c**	CO_2Et	Me	82	**3j**[12g] (29/71)
11		CO_2Et	Et	88	**3k**[h] (50/50)
12		CO_2Et	$(CH_2)_4CH_3$	87	**3l**[12i] (39/61)
13		CO_2Et	$(CH_2)_8CH_3$	89	**3m**[12j] (37/63)
14		CO_2Et	CH_2-Bz	84	**3n**[12k] (42/58)

[a]Isolated yields: in the case of ethyl cyanoacetate (Entries 4–9), the yields were calculated based on recovered starting material. [b]Keto–enol ratios based on integration of ^{1}H–NMR. [c]nd=not determined.

The α–acylated ethyl acetoacetates were ring cyclized by treatment with hydrazine (80%) in ethanol; while the α–acylated diethyl malonates were treated with hydrazine (pH 7),[13] hydrazine (55%) in acetic acid or hydrazine monohydrochloride to give the desired pyrazolin-5-ones in good yields. We have shown previously that, in general, under these conditions ring cyclization proceeds smoothly for those α–acylated esters or diesters that exist primarily in the enol form. Compounds with aromatic substituents that exist predominately in the keto form rapidly undergo β–cleavage (retro aldol) to give either low yield or no yield of the desired pyrazolin-5-one. On the other hand, ethyl cyanoacetate (**1b**) underwent acylation with several acyl chlorides to afford α–acylated products, which exist completely in the enol form (Table 1, Entries 4 and 7–9).[14]

Diethyl acetylmalonate (**3j**) could also be cyclized with *p*-toluenesulfonyl hydrazide in ethanol to give ethyl 5-methyl-2-[4-methylphenylsulfonyl]-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxylate (**5**), regioselectively. The corresponding regioisomer (**6c**) was obtained by treating **4b** with tosyl chloride. Furthermore, the bis-tosylated derivative (**6e**) was easily formed in the presence of triethyl amine using 2 eq. of tosyl chloride. Ring bromination was carried out by treatment of **4a** or **6b** with NBS to give the corresponding products in good yield (Scheme 1).



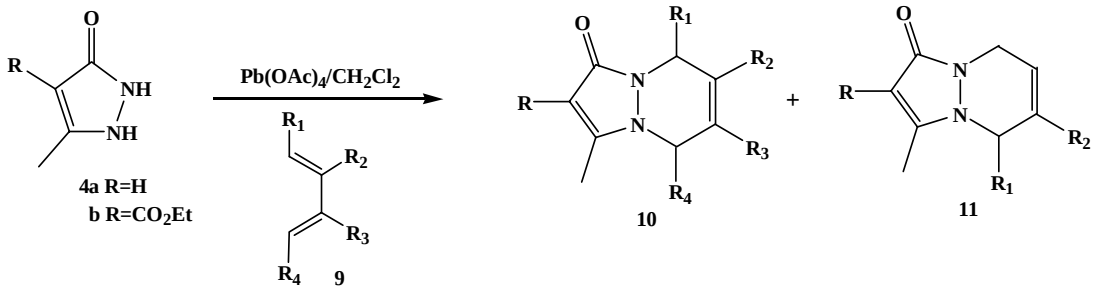
Scheme 1. Reagents and conditions: (a) Method A: H_2NNH_2 (80%)/EtOH; Method B: H_2NNH_2 (pH=7), EtOH/H_2O; Method C: H_2NNH_2 (55%)/HOAc; Method D: H_2NNH_2·HCl/EtOH; (b) Method A: $ClCO_2Et$, TEA/CH_2Cl_2; Method B: TsCl, TEA/$CHCl_3$; (c) H_2NNH-Ts/HOAc; (d) NBS, pyridine/CH_2Cl_2; (e) NBS, NaH (60%)/THF.

Having completed the synthesis of the necessary pyrazolin-5-ones, we turned our attention to their role as azadienophiles in the Diels-Alder cycloaddition reaction. It has been shown that pyrazolin-5-one could be induced to undergo Diels-Alder reactions at nitrogen upon treatment with $Pb(OAc)_4$. The reaction proceeds through the highly unstable pyrazol-3-one,[15] which is trapped by treatment with the appropriate diene.

We tried unsuccessfully to generate and isolate the unstable pyrazol-3-one using numerous oxidative conditions including Ag_2O/dichloromethane,[16a] $SiO_2/NaNO_2$/oxalic acid dihydrate,[16b-c] $K_3Fe(CN)_6$ EtOH,[16d] $PhCO_2I(OAc)_2$,[6] NBS/NaH(60%),[16a] $KClO_3/FeSO_4$/acetone,[16e] $FeCl_3·6H_2O$/2N-H_2SO_4/acetone,[16f] DDQ/dichloromethane,[16a] NaOCl/acetone,[16a] 10% Pd-C/EtOH, $In(OAc)_3$/dichloromethane, $Mn(OAc)_3$/dichloromethane and $KMnO_4$/acetone,[16a] but these reactions were all unsatisfactory, and for the most part, starting material was recovered. Given, *et al*. reported the lifetime for 2,3-diaza-2,4-cyclopentadienone, a related compound, to be 63.5 ± 0.5 sec.[10j] Based on this report, it seemed unlikely

that the pyrazol-3-ones investigated here would be isolable. Therefore, in the present study we treated two pyrazolin-5-ones with lead (IV)acetate in dichloromethane at room temperature followed by numerous dienes (Scheme 2) and isolated the reaction products (Table 2).

Pyrazolin-5-ones (**4a)** and (**4b**) were treated with $Pb(OAc)_4$ in dichloromethane in the presence of symmetrical or unsymmetrical dienes at –10 °C to give the hetero-Diels-Alder products shown in Scheme 2. The results of cyclization with isoprene, 1-methoxy-1,3-butadiene, 1-acetoxy-1,3- butadiene, 2,3-dimethyl-1,3-butadiene, 2,5-dimethyl-2,4-hexadiene, 1,4-diphenyl- 1,3-butadiene, and 2,3-dibenzyl-1,3-butadiene are shown in Table 2. Unsymmetrical dienes each gave a mixture of two products. Based on NMR spectroscopy, compounds (**10a**:**11a**) were formed in a 45:55 ratio and **10g**:**11g** were formed in a 42:58 ratio, while **10b**:**11b** were formed in a 20:80 ratio. We were unable to determine the product ratios



Scheme 2

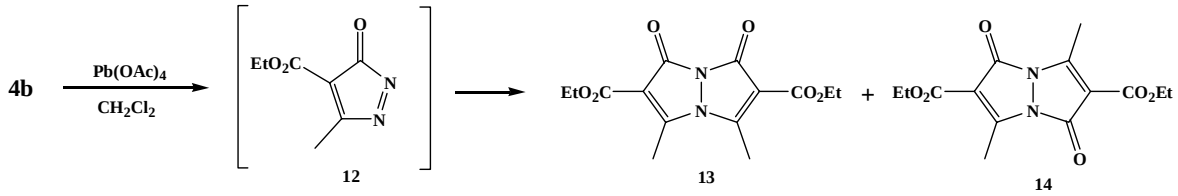
Table 2. Diels-Alder reactions of **4a** and **4b**

Entry	R	R_1	R_2	R_3	R_4	Time (h)	Product	Yield (%)[a]
1	H	H	Me	H	H	3	**10a**, **11a**	73
2	H	OMe	H	H	H	3	**10b**, **11b**	31
3	H	H	Me	Me	H	1	**10c**	85
4	H	$(Me)_2$	H	H	$(Me)_2$	1	**10d**	81
5	H	Ph	H	H	Ph	1	**10e**	74
6	H	H	Bz	Bz	H	1	**10f**	78
7	CO_2Et	H	Me	H	H	3	**10g**, **11g**	82
8	CO_2Et	OAc	H	H	H	3	**10h**, **11h**	36
9	CO_2Et	H	Me	Me	H	1	**10i**	92
10	CO_2Et	$(Me)_2$	H	H	$(Me)_2$	1	**10j**	89
11	CO_2Et	Ph	H	H	Ph	1	**10k**	75
12	CO_2Et	H	Bz	Bz	H	1	**10l**	80

[a] Isolated yields.

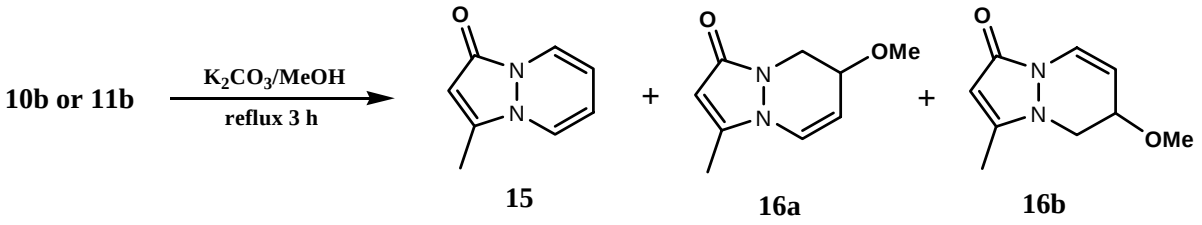
of **10h**:**11h**. The low yields associated with Entries 2 and 8 (Table 2) result from the unstable nature of the dienes under the given reaction conditions. Diels-Alder cyclization with silyloxydienes gave no yield due to their inherent acid sensitivity.

Interestingly, when **4b** was treated with $Pb(OAc)_4$ in CH_2Cl_2 in the absence of a diene at –5°C and warmed to room temperature, the isolated products were regioisomeric biamines, pyrazolo[1,2-*a*]-pyrazole-2,6-dicarboxylates (**13** and **14**), (Scheme 3). Compound (**13**) is strongly fluorescent, while compound (**14**) is strongly phosphorescent.[17]



Scheme 3

On the other hand, when compound (**10b**) or (**11b**) was treated with potassium carbonate in methanol a mixture of 3-methyl-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (**15**)[18] and 7-methoxy-3-methyl- 7,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (**16a**) / 6-methoxy-3-methyl-5,6-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (**16b**) were isolated in 16% and 42% yields, respectively (Scheme 4). The ratio of **16a** to **16b** was determined to be 78:22 by the integration of the methoxy group signals in the ^{1}H–NMR spectrum.



Scheme 4

In an effort to improve the yield of pyridazine (**15**), several additional acid or base reaction conditions were attempted, including DBU/dichloromethane, pyridine/dichloromethane, K_2CO_3/dichloromethane, and $BF_3 \cdot Et_2O$/dichloromethane. Unfortunately, these reactions failed to afford **15**, giving starting material and/or decomposed products.

In conclusion, we report a versatile synthetic method for preparing 3-pyrazolin-5-one and 5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine compounds from simple *β*–keto esters. The synthetic strategies involve

acylation, cyclocondensation, and oxidation-cycloaddition. The key intermediates were 3-pyrazolin-5-ones (**4a**) and (**4b**), which could be transformed to 5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazines (**10a-l**), (**11a-b**), (**11g-h**) and pyrazolo[1,2-*a*]pyrazole- 2,6-dicarboxylates (**13**) and (**14**) through the trapping of a highly reactive, but unstable intermediate (**12**).

EXPERIMENTAL

Reactions requiring anhydrous conditions were performed with the usual precautions for rigorous exclusion of air and moisture. Tetrahydrofuran was distilled from sodium benzophenone ketyl prior to use. Thin layer chromatography (TLC) was performed on precoated silica gel G and GP uniplates from Analtech and 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 uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 300 at 300 MHz and 76 MHz, respectively. The chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane, and *J*-values were in Hz. IR spectra were obtained on an ATI Mattson FT/IR spectrometer. MS spectrum were recorded with a Waters Micromass ZQ LC-Mass system and high resolution mass spectra (HRMS) were measured with a Bruker BioApex FTMS system by direct injection using an electrospray interface (ESI). When necessary, chemicals were purified according to the reported procedures.[19]

General Procedure for the Preparation of α–Acylated Ethyl Acetoacetates (3a–c), Ethyl Cyanoacetate (3d–i), and Diethyl Malonates (3j–3n)

A mixture of ethyl acetoacetate (1.56 g, 12.0 mmol), ethyl cyanoacetate (1.36 g, 12.0 mmol), or diethyl malonate (1.92 g, 12.0 mmol), magnesium (0.29 g, 12.1 mmol), ethanol (1.84 g, 40.0 mmol), carbon tetrachloride (0.3 mL) and anhydrous toluene (30 mL) was stirred under argon at rt for 30 min. The reaction was vigorously exothermic. The mixture was refluxed for 1 h and then cooled to 0–5°C. The acylating reagent (12.1 mmol) was added dropwise to the solution at 0–5°C for 30 min, and the reaction mixture was stirred at rt for 1 h. The resulting mixture was re-cooled to 0–5°C and washed with cold 5% *aq*. hydrochloric acid solution (24 mL), sat'd sodium bicarbonate solution (24 mL) and brine (24 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give pale yellow liquids. The compounds were purified using silica gel and ethyl acetate/hexanes as indicated.

Ethyl 2-acetyl-3-oxobutanoate (3a)

R_f=0.4 (10% ethyl acetate in hexanes); pale yellow oil; IR (neat, NaCl) 2984, 1713, 1416, 1084 cm^{-1}; ^1H NMR ($CDCl_3$) δ 15.86 (s, 1H), 4.20 (q, *J*=7.2 Hz, 2H), 2.30 (s, 6H), 1.27 (q, *J*=7.2 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 $[M+Na]^+$.

Ethyl 2-acetyl-3-oxooctanoate (3b)

R_f=0.5 (10% ethyl acetate in hexanes); pale yellow oil; IR (neat, NaCl) 2934, 1714, 1416, 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.21 (q, *J*=7.1 Hz, 2H), 2.63–2.58 (m, 2H), 2.29 (s, 3H), 1.67–1.49 (m, 2H), 1.32–1.27 (m, 7H), 0.84 (t, *J*=3.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 199.8, 196.0, 167.6, 109.0, 61.0, 38.1, 31.9, 25.9, 22.7, 14.5, 14.2; MS (ESI) (m/z) 229 $[M+H]^+$, 183 (base peak), 135, 85; 251 $[M+Na]^+$.

Ethyl 2-acetyl-3-oxo-4-phenylbutanoate (3c)

R_f=0.5 (20% ethyl acetate in hexanes); pale yellow oil; IR (neat, NaCl) 3405, 3031, 1714, 1414, 1239, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–7.27 (m, 5H), 4.31–4.23 (m, 2H), 4.04 (s, 2H), 2.34 (s, 3H), 1.35–1.27 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 196.7, 196.2, 167.3, 135.4, 129.8, 128.9, 127.3, 109.1, 61.2, 44.2, 25.9, 14.5; MS (ESI) (m/z) 249 $[M+H]^+$, 207, 131, 91 (base peak); 271 $[M+Na]^+$.

Ethyl 2-cyano-3-oxobutanoate (3d)

R_f=0.3 (ethyl acetate:hexane:methanol; 40:50:10, *v/v*); beige oil; IR (neat, NaCl) 2987, 2226, 1660, 1278, 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.50 (s, 1H), 4.27 (q, *J*=7.2 Hz, 2H), 2.29 (s, 3H), 1.30 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 189.6, 170.3, 115.1, 81.5, 60.9, 21.1, 13.7; HRMS Calcd for $C_7H_9NO_3Na$: 178.0480 $[M+Na]^+$, Found: 178.0304.

Ethyl 2-cyano-3-cyclopropyl-3-oxopropanoate (3e)

R_f=0.3 (ethyl acetate:hexane:methanol; 40:50:10, *v/v*); mp 68°C (Et_2O:hexane, 1:10, *v/v*); IR (neat, NaCl) 2946, 2222, 1683, 1577, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.30 (q, *J*=7.2 Hz, 2H), 2.21–2.13 (m, 1H), 1.36 (t, *J*=7.2 Hz, 3H), 1.30–1.26 (m, 2H), 1.18–1.15 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 191.4, 170.5, 115.6, 79.2, 62.3, 15.3, 14.1, 11.2; HRMS Calcd for $C_9H_{11}NO_3Na$: 204.0637 $[M+Na]^+$, Found: 204.0294. Anal. Calcd for C, 59.66; H, 6.12; N, 7.73. Found: C, 59.51; H, 5.95; N, 7.72.

Ethyl 2-cyano-3-cyclopentyl-3-oxopropanoate (3f)

R_f=0.3 (ethyl acetate:hexane:methanol; 40:50:10, *v/v*); pale yellow oil; IR (neat, NaCl) 2962, 2225, 1654,

1591, 1277, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.30 (q, *J*=7.2 Hz, 2H), 2.72–2.64 (m, 1H), 1.89–1.61 (m, 8H), 1.34 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 194.7, 170.5, 115.1, 79.8, 62.4, 44.1, 30.9, 30.0, 26.4, 25.8, 14.2.

Ethyl 2-cyano-3-oxo-3-(2-thienyl)propanoate (3g)

R_f=0.5 (ethyl acetate:hexane:methanol; 40:50:10, *v/v*); pale yellow oil; IR (neat, NaCl) 2984, 2359, 1653, 1575, 1278, 1063 cm^{-1}; ^1H NMR ($CDCl_3$) δ 14.28 (s, 1H), 7.85–7.75 (m, 2H), 7.25–7.18 (m, 1H), 4.38 (q, *J*=7.2 Hz, 2H), 1.38 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.8, 162.9, 137.7, 134.6, 134.4, 128.7, 116.2, 75.6, 63.0, 14.1.

Ethyl 2-cyano-3-oxo-3-phenylpropanote (3h)

R_f=0.4 (ethyl acetate:hexane:methanol; 40:50:10, *v/v*); mp 32°C (Et_2O:hexane, 1:10, *v/v*); IR (neat, NaCl) 2986, 2229, 1678, 1580, 1247, 1058 cm^{-1}; ^1H NMR ($CDCl_3$) δ 14.30 (s, 1H), 8.01 (d, *J*=7.6 Hz, 2H), 7.59 (t, *J*=7.6 Hz, 1H), 7.50 (t, *J*=7.2 Hz, 2H), 4.41 (q, *J*=7.2 Hz, 2H), 1.41 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 185.4, 170.8, 133.8, 131.5, 128.9, 115.5, 79.3, 61.5, 13.8; HRMS Calcd for $C_{12}H_{12}NO_3$: 218.0817 $[M+H]^+$, Found: 218.0809.

Ethyl 2-cyano-3-oxo-3-(4-methoxyphenyl)propanote (3i)

R_f=0.5 (ethyl acetate:hexane:methanol; 40:50:10, *v/v*); pale yellow oil; IR (neat, NaCl) 3395, 2983, 2219, 1683, 1559, 1261, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 14.26 (s, 1H), 7.03–7.90 (m, 4H), 4.30 (q, *J*=7.2 Hz, 2H), 3.46 (s, 3H), 1.31 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 182.1, 171.7, 163.7, 132.3, 131.6, 130.9, 116.6, 114.0, 113.6, 63.0, 60.4, 55.5, 14.1.

Diethyl 2-acetylmalonate (3j)

R_f=0.5 (20% ethyl acetate in hexanes); pale yellow oil; IR (neat, NaCl) 2984, 1729, 1650, 1469, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) 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 $[M+Na]^+$.

Diethyl 2-propionylmalonate (3k)

R_f=0.6 (20% ethyl acetate in hexanes); pale yellow oil; IR (neat, NaCl) 3443, 2984, 1734, 1604, 1034 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.31, 4.37 (br s, br s, total 1H), 4.17–4.07 (m, 4H), 2.53 (q, *J*=7.1 Hz, 1H), 2.35 (q, *J*=7.1 Hz, 1H), 1.21–1.15 (m, 6H), 1.08 (t, *J*=7.1 Hz, 1.5H), 0.98 (t, *J*=7.1 Hz, 1.5H); ^{13}C NMR

($CDCl_3$) δ 199.8, 171.5, 165.0, 99.5, 62.5, 61.3, 27.6, 14.3, 14.2, 7.8; MS (ESI) (m/z) 217 $[M+H]^+$, 161, 133, 104 (base peak); 239 $[M+Na]^+$.

Diethyl 2-hexanoylmalonate (3l)

R_f=0.5 (10% ethyl acetate in hexanes); pale yellow oil; IR (neat, NaCl) 3584, 2959, 1734, 1602, 1243, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.36, 4.43 (br s, br s, total 1H), 4.26–4.19 (m, 4H), 2.58 (t, *J*=7.3 Hz, 1H), 2.40 (t, *J*=7.3 Hz, 1H), 1.64–1.57 (m, 2H), 1.30–1.22 (m, 10H), 0.86 (t, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 199.4, 171.6, 165.0, 100.1, 62.6, 61.6, 34.1, 31.8, 26.8, 22.7, 14.5, 14.3, 14.2; MS (ESI) (m/z) 259 $[M+H]^+$, 180, 135 (base peak); 281 $[M+Na]^+$.

Diethyl 2-decanoylmalonate (3m)

R_f=0.3 (15% ethyl acetate in hexanes); pale yellow oil; IR (neat, NaCl) 2927, 1735, 1602, 1243, 1037 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.36, 4.43 (br s, br s, total 1H), 4.28–4.19 (m, 4H), 2.59 (t, *J*=7.3 Hz, 1H), 2.41 (t, *J*=7.3 Hz, 1H), 1.64–1.57 (m, 2H), 1.31–1.21 (m, 18H), 0.86 (t, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 199.4, 171.6, 165.1, 100.1, 62.6, 61.5, 34.2, 32.2, 29.8, 29.6, 27.2, 25.4, 23.8, 23.0, 14.6, 14.4, 14.3; MS (ESI) (m/z) 315 $[M+H]^+$, 202, 161 (base peak), 104; 337 $[M+Na]^+$.

Diethyl 2-(3-phenylpropionyl)malonate (3n)

R_f=0.5 (20% ethyl acetate in hexanes); pale yellow oil; IR (neat, NaCl) 3449, 3063, 1733, 1604, 1245, 1039 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.50, 4.44 (br s, br s, total 1H), 7.31–7.17 (m, 5H), 4.28–4.17 (m, 4H), 2.99–2.59 (m, 4H), 1.33–1.21 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 198.5, 171.6, 164.9, 141.0, 140.9, 140.8, 128.9, 128.7, 126.7, 100.4, 62.7, 61.4, 36.3, 31.4, 14.6, 14.3; MS (ESI) (m/z) 293 $[M+H]^+$, 247, 161 (base peak), 104; 315 $[M+Na]^+$.

Ethyl 5-methyl-2-[4-methylphenylsulfonyl]-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxylate (5)

To a solution of diethyl 2-acetylmalomate (1.0 g, 5.0 mmol), *p*–toluenesulfonyl hydrazide (1.0 g, 5.0 mmol) in ethanol (6 mL) was added acetic acid (1 mL), and the mixture was refluxed for 16 h. The reaction mixture was concentrated under reduced pressure, and the residue was treated with ethanol/ether (5 mL, *v/v*, 1:9). The solid was filtered and washed with ether (6 mL) to give **5** (1.3 g, 81%). R_f=0.1 (10% methanol in dichloromethane); mp 155°C ($EtOH:Et_2O$, 1:10, *v/v*); IR (nujol, NaCl) 3271, 2953, 1687, 1462, 1377, 1170 cm^{-1}; ^1H NMR (DMSO–d_6) δ 9.92 (br s, 1H), 7.75–7.39 (m, 4H), 4.12 (q, *J*=7.1 Hz, 2H), 2.31 (s, 3H), 2.24 (s, 3H), 1.21 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (DMSO–d_6) δ 164.3, 161.7, 145.1,

138.7, 135.2, 130.7, 129.0, 128.7, 126.4, 95.7, 59.7, 21.8, 15.2, 13.0; HRMS Calcd for $C_{14}H_{17}N_2O_5S$: 325.0853 $[M+H]^+$, Found: 325.0851.

General Procedure for the Preparation of *N*-Substituted 3-Pyrazolin-5-one Derivatives (6a–e)

Method A. A solution of ethyl chloroformate (2.39 g, 22.0 mmol) in dichloromethane (5 mL) was added dropwise to a suspension of pyrazolin-5-one compounds (10.0 mmol) and triethylamine (2.43 g, 24.0 mmol) in dry dichloromethane (50 mL) at 10°C under an argon atmosphere. The reaction mixture was stirred at rt for 3 h. The mixture was filtered and the filtrate was washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (2–5% methanol in dichloromethane) to give products.

Method B. To a stirred solution of pyrazolin-5-one compounds (10.0 mmol), triethylamine (1.11 g, 11.0 mmol or 2.23 g, 22.0 mmol) in chloroform (50 mL) was added dropwise a solution of *p*-toluenesulfonyl chloride (2.10 g, 11.0 mmol or 4.19 g, 22.0 mmol) in dried chloroform (5 mL) at 5 °C under an argon atmosphere. The reaction mixture was stirred at rt for 3 h. The mixture was extracted with dichloromethane and washed with 5% *aq*. HCl solution (20 mL) and sat'd $NaHCO_3$ solution (20 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (2–5% methanol in dichloromethane) to give white crystals.

Diethyl 5-methyl-3-oxo-1*H*-pyrazole-1,2(3*H*)-dicarboxylate (6a)

Yield; 83%; R_f=0.7 (5% methanol in dichloromethane); oil; IR (neat, NaCl) 2984, 1769, 1754, 1580, 1239 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.01 (br s, 1H), 4.44 (q, *J*=7.1 Hz, 2H), 4.26 (q, *J*=7.1 Hz, 2H), 2.51 (s, 3H), 1.41 (t, *J*=7.1 Hz, 3H), 1.31 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 157.2, 152.3, 150.3, 146.6, 110.0, 102.2, 65.8, 64.8, 15.0, 14.6; MS (ESI) (m/z) 243 $[M+H]^+$, 171, 98 (base peak); 265 $[M+Na]^+$; HRMS Calcd for $C_{10}H_{14}N_2O_5Na$: 265.0795 $[M+Na]^+$, Found: 265.0793.

5-Methyl-1-[4-methylphenylsulfonyl]-1,2-dihydro-3*H*-pyrazol-3-one (6b)

Yield; 65%; R_f=0.3 (2% methanol in dichloromethane); mp 109°C [purified by FC (CH_2Cl_2:MeOH, 98:2, *v/v*)]; IR (nujol, NaCl) 3195, 2924, 1579, 1461, 1197 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.24 (br s, 1H), 7.76 (d, *J*=8.3 Hz, 2H), 7.27 (d, *J*=8.1 Hz, 2H), 5.67 (s, 1H), 242 (s, 3H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.2, 156.9, 141.0, 135.8, 130.3, 125.4, 95.3, 21.8, 20.9; HRMS Calcd for $C_{11}H_{12}N_2O_3NaS$: 275.0461 $[M+Na]^+$, Found: 275.0454.

Ethyl 5-methyl-1-[4-methylphenylsulfonyl]-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxylate (6c)

Yield; 67%; R_f=0.5 (5% methanol in dichloromethane); mp 134°C [purified by FC (CH_2Cl_2:MeOH, 98:2, *v/v*)]; IR (nujol, NaCl) 2923, 1692, 1457, 1377 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.14 (br s, 1H), 7.82 (d, *J*=8.3 Hz, 2H), 7.26 (d, *J*=8.3 Hz, 2H), 4.22 (q, *J*=7.1 Hz, 2H), 2.43 (s, 3H), 2.41 (s, 3H), 1.31 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 162.4, 153.5, 146.6, 146.0, 133.4, 130.1, 128.9, 102.5, 60.7, 22.1, 14.6, 12.4; HRMS Calcd for $C_{14}H_{17}N_2O_5S$: 325.0853 $[M+H]^+$, Found: 325.0841. Anal. Calcd for C, 51.84; H, 4.97; N, 8.64. Found: C, 52.10; H, 4.87; N, 8.65.

1,2,4-Triethoxycarbonyl-3-methylpyrazolin-5-one (6d)

Yield; 80%; R_f=0.6 (2% methanol in dichloromethane); mp 40°C [purified by FC (CH_2Cl_2:MeOH, 98:2, *v/v*)]; IR (nujol, NaCl) 2985, 1776, 1717, 1584, 1237 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.45–4.21 (m, 6H), 2.83 (s, 3H), 1.41–1.24 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 161.7, 155.9, 152.1, 151.8, 149.8, 106.9, 66.0, 65.5, 61.0, 14.5, 14.4, 13.9; HRMS Calcd for $C_{13}H_{18}N_2O_7Na$: 337.1006 $[M+Na]^+$, Found: 337.1001. Anal. Calcd for C, 49.68; H, 5.77; N, 8.91. Found: C, 49.99; H, 5.61; N, 8.93.

Ethyl 5-methyl-1,2-bis[4-methylphenylsulfonyl]-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxylate (6e)

Yield; 77%; R_f=0.8 (5% methanol in dichloromethane); mp 79°C [purified by FC (CH_2Cl_2:MeOH, 95:5, *v/v*)]; IR (nujol, NaCl) 2922, 1723, 1462, 1377 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78–7.75 (m, 4H), 7.34–7.25 (m, 4H), 4.28 (q, *J*=9.1 Hz, 2H), 2.82 (s, 3H), 2.48 (s, 3H), 2.46 (s, 3H), 1.33 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 162.7, 146.9, 130.5, 130.0, 129.2, 128.7, 61.5, 22.2, 14.5, 12.7; HRMS Calcd for $C_{21}H_{22}N_2O_7S_2Na$: 501.0760 $[M+Na]^+$, Found: 501.0771.

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

To a solution of 3-methyl-3-pyrazolin-5-one (0.5 g, 5.1 mmol) and pyridine (1.6 g, 20.4 mmol) in dichloromethane (20 mL) was added *N*–bromosuccinimide (2.7 g, 15.3 mmol) under an argon atmosphere, and the mixture was stirred at rt for 5 h. The reaction mixture was filtered and washed with dichloromethane (10 mL). The filtrate was washed with water (12 mL) and brine (12 mL), and the organic solution was separated, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give dibromopyrazolone, which was recrystallized by dichloromethane/ether to afford **7** (0.42 g, 32%) as pale yellow crystals. R_f=0.6 (5% methanol in dichloromethane); mp 130°C ($EtOH:Et_2O$:hexane, 1:2:4, *v/v*); (lit.,[20] mp 132–133°C); IR (nujol, NaCl) 3350, 2923, 1721, 1377, 1286 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.99 (br s, 1H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4, 156.4, 45.7, 13.6; HRMS Calcd for $C_4H_5N_2OBr_2$: 254.8763 $[M+H]^+$, Found: 254.8759.

General Procedure for the Preparation of 4-Bromo-3-pyrazolin-5-one Derivatives (8a–b)

To a solution of pyrazolones (8.0 mmol) in tetrahydrofuran (10 mL) was added sodium hydride (0.34 g, 8.4 mmol, 60%, washed with dry hexane). *N*-bromosuccinimide (1.50 g, 8.4 mmol) was added portionwise to the suspension at 0°C under an argon atmosphere. The reaction mixture was stirred at rt for 3 h. The mixture was filtered and washed with dichloromethane (10 mL). The organic residue was concentrated under reduced pressure to give bromo pyrazolone, which was purified by flash column chromatography using eluent, 5% methanol in dichloromethane to afford white crystals.

4-Bromo-5-methyl-1,2-dihydro-3*H*-pyrazol-3-one (8a)

Yield; 78%; R_f=0.3 (5% methanol in dichloromethane); mp 191°C (EtOH:Et_2O:hexane, 1:2:4, *v/v*); (lit.,[21] 192–194°C); IR (nujol, NaCl) 3366, 2924, 1614, 1461, 1171 cm^{-1}; ^1H NMR (DMSO–d_6) δ 11.15 (br s, 2H), 2.07 (s, 3H); ^{13}C NMR (DMSO–d_6) δ 158.6, 138.8, 78.4, 11.2; MS (ESI) (m/z) 176 $[M+H]^+$ (base peak), 140, 99; 198 $[M+Na]^+$.

4-Bromo-5-methyl-1-[4-methylphenylsulfonyl]-1,2-dihydro-3*H*-pyrazol-3-one (8b)

Yield; 86%; R_f=0.6 (5% methanol in dichloromethane); mp 103°C (EtOH:Et_2O:hexane, 1:2:4, *v/v*); IR (nujol, NaCl) 3176, 2942, 1594, 1377 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.90 (br s, 1H), 7.79 (d, *J*=8.3 Hz, 2H), 7.46 (d, *J*=8.3 Hz, 2H), 2.49, (s, 3H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.7, 151.7, 140.3, 133.1, 130.9, 129.2, 84.2, 22.0, 11.0; MS (ESI) (m/z) 330 $[M+H]^+$, 293, 252 (base peak), 218; HRMS Calcd for $C_{11}H_{12}BrN_2O_3S$: 330.9747 $[M+H]^+$, Found: 330.9739.

General Procedure for the Preparation of Bicyclic Pyrazolone Compounds: Diels-Alder Reactions

To a stirred solution of 3-methyl-3-pyrazolin-5-one (**4a**, 0.98 g, 10.0 mmol) or 4-ethoxycarbonyl-3-methylpyrazolin-5-one (**4b**, 1.70 g, 10.0 mmol) and 1,3-dienes (10.0 mmol) in dichloromethane (50 mL) was added portionwise lead(IV) acetate (4.66 g, 10.5 mmol) at –10°C under an argon atmosphere. The reaction mixture was stirred at rt for 3 h. The mixture was diluted with dichloromethane (20 mL) and washed with 5% *aq*. sodium carbonate solution (20 mL), water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using 3–10% methanol in dichloromethane to give products.

3,6-Dimethyl-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (10a)/3,7-dimethyl-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (11a)

R_f=0.5 (10% methanol in dichloromethane); mp 116°C (EtOH:Et_2O:hexane, 1:2:4, *v/v*); IR (nujol, NaCl) 2927, 2853, 1700, 1686, 1258 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.04 (d, *J*=19.3 Hz, 1H), 4.59 (s, 1H), 3.45 (s, 2H), 3.37 (s, 2H), 1.56 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.8, 151.2, 127.9, 114.5, 95.8, 48.7, 42.9, 19.8, 11.5; MS (ESI) (m/z) 165 $[M+H]^+$, (base peak), 142; 187 $[M+Na]^+$.

5-Methoxy-3-methyl-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (10b)/8-methoxy-3-methyl-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (11b)

R_f=0.3 (3% methanol in dichloromethane); oil; IR (nujol, NaCl) 2933, 1644, 1417, 1076 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.04 (s, 2H), 5.75 (s, 1H), 5.35 (s, 1H), 4.23 (d, *J*=15.8 Hz, 1H), 3.70 (d, *J*=16.0 Hz, 1H), 3.43 (s, 3H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.1, 155.9, 124.5, 123.5, 120.6, 99.4, 57.3, 46.6, 12.5; HRMS Calcd for $C_9H_{13}N_2O_2$: 181.0972 $[M+H]^+$, Found: 181.0973.

3,6,7-Trimethyl-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (10c)

R_f=0.4 (4% methanol in dichloromethane); mp 51–52°C [purified by FC (CH_2Cl_2:MeOH, 96:4, *v/v*)]; IR (nujol, NaCl) 2918, 1602, 1291, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.24 (s, 1H), 4.02 (s, 2H), 3.81 (s, 2H), 2.11 (s, 3H), 1.71 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 166.4, 151.4, 121.6, 119.6, 97.3, 49.3, 45.7, 16.4, 16.2, 12.3; HRMS Calcd for $C_{10}H_{15}N_2O$: 179.1179 $[M+H]^+$, Found: 179.1176.

3,5,5,8,8-Pentamethyl-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (10d)

R_f=0.5 (5% methanol in dichloromethane); oil; IR (nujol, NaCl) 2976, 1675, 1569, 1142 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.35 (d, *J*=5.8 Hz, 1H), 5.32 (d, *J*=5.8 Hz, 1H), 5.05 (s, 1H), 2.18 (s, 3H), 1.83 (s, 3H), 1.77 (s, 3H), 1.49 (s, 3H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.7, 157.8, 154.5, 142.9, 117.7, 93.2, 63.6, 26.6, 24.5, 21.4, 19.0, 15.6; HRMS Calcd for $C_{12}H_{19}N_2O$: 207.1492 $[M+H]^+$, Found: 207.1520.

5,8-Diphenyl-3-methyl-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (10e)

R_f=0.5 (5% methanol in dichloromethane); mp 166–167°C (CH_2Cl_2:Et_2O:hexane, 1:2:6, *v/v*); IR (nujol, NaCl) 2924, 1663, 1645, 1151 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36–7.26 (m, 10H), 6.08 (dq, *J*=2.0, *J*=2.2 Hz, 1H), 5.90 (br s, 1H), 5.80 (d, *J*=10.1 Hz, 1H), 5.36 (br s, 1H), 5.14 (d, *J*=2.1 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.4, 155.0, 139.8, 129.8, 129.1, 128.2, 127.4, 126.4, 124.0, 100.5, 62.1, 54.8, 14.7; HRMS Calcd for $C_{20}H_{19}N_2O$: 303.1492 $[M+H]^+$, Found: 303.1493.

6,7-Dibenzyl-3-methyl-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-1-one (10f)

R_f=0.5 (5% methanol in dichloromethane); oil; IR (nujol, NaCl) 3059, 2848, 1642, 1453, 1269 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.19 (m, 10H), 5.27 (s, 1H), 4.15 (s, 2H), 3.86 (s, 2H), 3.69 (s, 2H), 3.67 (s, 2H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.7, 162.7, 152.2, 138.1, 129.3, 129.2, 128.9, 128.7, 127.3, 127.2, 124.6, 98.1, 48.0, 44.6, 36.9, 36.7, 12.3; HRMS Calcd for $C_{22}H_{23}N_2O$: 331.1805 $[M+H]^+$, Found: 331.1808.

Ethyl 3,7-dimethyl-1-oxo-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazin-2-carboxylate (10g)/ethyl 3,6-dimethyl-1-oxo-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-2-carboxylate (11g)

R_f=0.6 (10% methanol in dichloromethane); mp 118°C [purified by FC (CH_2Cl_2:MeOH, 96:4, *v/v*)]; IR (nujol, NaCl) 2924, 1701, 1637, 1459, 1178 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.68 (d, *J*=23.6 Hz, 1H), 4.32 (d, *J*=14.9 Hz, 2H), 4.09 (q, *J*=7.1 HZ, 2H), 3.97 (d, *J*=17.5 Hz, 2H), 2.42 (s, 3H), 1.79 (s, 3H), 1.19 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.1, 162.9, 153.6, 128.0, 114.7, 96.7, 59.4, 46.6, 43.4, 20.5, 15.3, 12.1; MS (ESI) (m/z) 237 $[M+H]^+$, (base peak), 191, 82; 259 $[M+Na]^+$; HRMS Calcd for $C_{12}H_{17}N_2O_3$: 237.1234 $[M+H]^+$, Found: 237.1228.

Ethyl 8-acetyloxy-3-methyl-1-oxo-7,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazin-2-carboxylate (10h) ethyl 5-acetyloxy-3-methyl-1-oxo-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-2-carboxylate (11h)

R_f=0.5 (5% methanol in dichloromethane); semisolid; IR (nujol, NaCl) 2935, 1714, 1696, 1633, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.89 (s, 1H), 6.14 (s, 2H), 4.29–4.20 (m, 4H), 2.55 (s, 3H), 1.98 (s, 3H), 1.33 (t, 3H, *J*=7.03); ^{13}C NMR ($CDCl_3$) δ 167.0, 163.9, 162.7, 158.8, 124.6, 121.5, 99.8, 71.2, 60.5, 45.2, 21.1, 14.8, 12.3; HRMS Calcd for $C_{13}H_{17}N_2O_5$: 281.1132 $[M+H]^+$, Found: 281.1133.

Ethyl 3,6,7-trimethyl-1-oxo-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-2-carboxylate (10i)

R_f=0.4 (5% methanol in dichloromethane); mp 187–188°C (EtOH:Et_2O, 1:10, *v/v*); IR (nujol, NaCl) 2924, 1715, 1619, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.27 (q, *J*=7.1 Hz, 2H), 4.08 (br s, 4H), 2.50 (s, 3H), 1.76 (s, 6H), 1.33 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.5, 164.1, 152.4, 121.4, 118.4, 98.6, 60.2, 48.1, 46.0, 16.4, 16.3, 14.9, 11.9; HRMS Calcd for $C_{13}H_{19}N_2O_3$: 251.1390 $[M+H]^+$, Found: 251.1392. Anal. Calcd for C, 62.38; H, 7.25; N, 11.19. Found: C, 62.17; H, 7.28; N, 11.12.

Ethyl 3,5,5,8,8-pentamethyl-1-oxo-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-2-carboxylate (10j)

R_f=0.5 (5% methanol in dichloromethane); mp 78°C (CH_2Cl_2:Et_2O:hexane, 1:2:6, *v/v*); IR (nujol, NaCl) 2926, 1705, 1570, 1134 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.48 (d, *J*=7.2 Hz, 1H), 5.42 (d, *J*=7.2 Hz, 1H), 4.21 (q,

J=6.9 Hz, 2H), 2.39 (s, 3H), 1.84 (s, 3H), 1.78 (s, 3H), 1.53 (s, 3H), 1.29 (t, *J*=7.1 Hz, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.4, 162.7, 158.6, 156.1, 143.7, 117.0, 94.8, 64.0, 60.0, 26.6, 24.6, 21.7, 19.1, 15.7, 14.9; HRMS Calcd for $C_{15}H_{23}N_2O_3$: 279.1703 $[M+H]^+$, Found: 279.1688. Anal. Calcd for C, 64.73; H, 7.97; N, 10.06. Found: C, 64.74; H, 8.20; N, 10.06.

Ethyl 3-methyl-1-oxo-5,8-diphenyl-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-2-carboxylate (10k)

R_f=0.4 (5% methanol in dichloromethane); mp 186–187°C (MeOH:Et_2O:hexane, 1:2:4, *v/v*); IR (nujol, NaCl) 2924, 1715, 1637, 1104 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.32–7.18 (m, 10H), 5.99 (br s, 2H), 5.66 (d, *J*=15.7 Hz, 2H), 4.24 (q, *J*=7.1 Hz, 2H), 2.27 (s, 3H), 1.28 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.6, 163.0, 154.5, 138.7, 129.9, 129.1, 128.4, 128.0, 126.1, 124.4, 123.9, 99.5, 60.3, 59.3, 56.8, 14.9, 12.8; HRMS Calcd for $C_{23}H_{23}N_2O_3$: 375.1703 $[M+H]^+$, Found: 375.1704. Anal. Calcd for C, 73.78; H, 5.92; N, 7.48. Found: C, 73.85; H, 5.85; N, 7.42.

Ethyl 6,7-dibenzyl-3-methyl-1-oxo-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-2-carboxylate (10l)

R_f=0.5 (5% methanol in dichloromethane); mp 149–150°C (MeOH:Et_2O:hexane, 1:2:4, *v/v*); IR (nujol, NaCl) 3061, 2923, 1700, 1627, 1147 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33–7.15 (m, 10H), 4.27 (q, *J*=7.1 Hz, 2H), 4.19 (s, 2H), 4.11 (s, 2H), 3.70 (s, 4H), 2.49 (s, 3H), 1.33 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.4, 163.3, 162.7, 153.0, 137.8, 137.6, 129.4, 129.2, 128.8, 128.7, 127.5, 127.3, 127.0, 123.6, 99.0, 60.2, 46.8, 44.9, 36.9, 36.7, 14.8, 11.9; HRMS Calcd for $C_{25}H_{27}N_2O_3$: 403.2016 $[M+H]^+$, Found: 403.2030. Anal. Calcd for C, 74.60; H, 6.51; N, 6.96. Found: C, 74.36; H, 6.44; N, 6.93.

Diethyl 3,5-dimethyl-1,7-dioxo-1*H*, 7*H*-pyrazolo[1,2-*a*]pyrazole-2,6-dicarboxylate (13)/diethyl 3,7-dimethyl-1,5-dioxo-1*H*, 5*H*-pyrazolo[1,2-*a*]pyrazole-2,6-dicarboxylate (14)

To a stirred solution of 4-ethoxycarbonyl-3-methylpyrazolin-5-one (0.34 g, 2.0 mmol) in dichloromethane (40 mL) was added portionwise lead(IV) acetate (0.98 g, 2.2 mmol) at 0^{o}C under an argon atmosphere. The reaction mixture was stirred at rt for 6 h. The mixture was diluted with dichloromethane (20 mL) and washed with 5% *aq*. sodium carbonate solution (20 mL), water (15 mL) and brine (20 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using 5% methanol in dichloromethane to afford **13** (74 mg, 12%) and **14** (74 mg, 12%), respectively. Compound (**13**); R_f=0.3 (5% methanol in dichloromethane); mp 259 ^{o}C (Et_2O); IR (nujol, NaCl) 2922, 2854, 1772, 1702, 1461, 1377 cm^{-1}; ^{1}H NMR (DMSO–d_6) δ 4.25 (q, *J*=7.1 Hz, 2H), 2.80 (s, 3H), 1.27 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (DMSO–d_6) δ 161.4, 156.1, 154.4, 108.2, 60.8, 14.4, 13.3; MS (ESI) (m/z) 309 $[M+H]^+$,

(base peak), 256, 143; HRMS Calcd for $C_{14}H_{17}N_2O_6$: 309.1081 $[M+H]^+$, Found: 309.1087. Anal. Calcd for $C_{14}H_{17}N_2O_6$: C, 54.54; H, 5.23; N, 9.09. Found: C, 54.62; H, 5.16; N, 8.94. Compound (**14**); R_f=0.4 (5% methanol in dichloromethane); mp 171°C (Et_2O); IR (nujol, NaCl) 2923, 2853, 1746, 1695, 1462, 1366 cm^{-1}; ^1H NMR (DMSO–d_6) δ 4.33 (q, *J*=7.1 Hz, 2H), 2.91 (s, 3H), 1.36 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (DMSO–d_6) δ 161.7, 157.7, 156.0, 107.1, 61.5, 14.6, 12.7; MS (ESI) (m/z) 309 $[M+H]^+$, (base peak), 269, 143; HRMS Calcd for $C_{14}H_{17}N_2O_6$: 309.1081 $[M+H]^+$, Found: 309.1073. Anal. Calcd for C, 54.54; H, 5.23; N, 9.09. Found: C, 54.54; H, 5.18; N, 8.98.

3-Methyl-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (15)

To a stirred solution of pyridazins (**10b** or **11b**, 0.5 g, 2.8 mmol) in methanol (12 mL) potassium carbonate (2.2 g, 16.8 mmol) was added and the reaction mixture was refluxed for 2 h. The mixture was cooled to rt and diluted with dichloromethane (10 mL) and filtered through a pad of celite 545 and then concentrated under reduced pressure. The residue was purified by flash column chromatography to give pale yellow solid (66 mg, 16%). R_f=0.3 (5% methanol in dichloromethane); mp 113–114 °C (Et_2O:hexane, 10:1, *v/v*); (lit.,[18] 115–117 °C); IR (nujol, NaCl) 3059, 2848, 1642, 1453, 1269 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50 (d, *J*=7.5 Hz, 1H), 7.01 (d, *J*=7.0 Hz, 1H), 5.77 (dd, *J*=6.0, 7.0 Hz, 1H), 5.74 (dd, *J*=6.5, 6.0 Hz, 1H), 5.56 (s, 1H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.9, 134.7, 121.9, 120.8, 106.0, 103.4, 94.3, 11.2; HRMS Calcd for $C_8H_9N_2O$: 149.0710 $[M+H]^+$, Found: 149.0710.

7-Methoxy-3-methyl-7,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (16a)/6-methoxy-3-methyl-5,6-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (16b) Yield: 42%; R_f=0.4 (5% methanol in dichloromethane); pale yellow oil; IR (nujol, NaCl) 2940, 1645, 1431, 1308, 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.58 (dd, *J*=2.0, 8.2 Hz, 1H), 5.70 (d, *J*=3.6 Hz, 1H), 5.23 (s, 1H), 5.16–5.01 (m, 1H), 3.31 (s, 3H), 2.54–2.50 (m, 2H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.2, 148.9, 118.5, 100.0, 97.3, 80.9, 55.8, 28.6, 11.7; GC-MS 181 $[M+H]^+$, 149 (base peak), 122, 81, 54; HRMS Calcd for $C_9H_{12}N_2O_2Na$: 203.0796 $[M+ Na]^+$, Found: 203.0800.

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