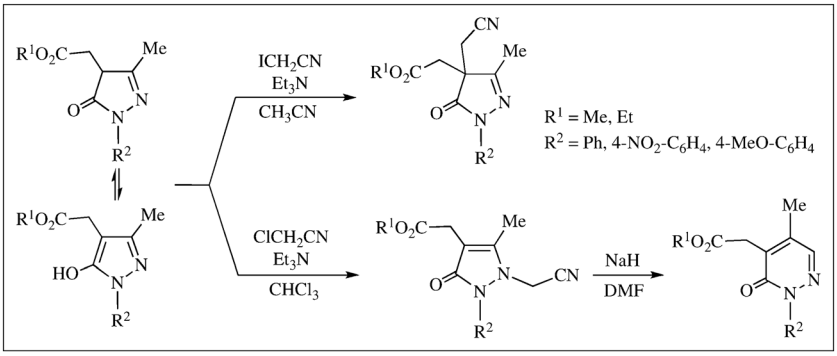
A Novel Synthesis of 4-Pyridazineacetic Acids *via* Ring Expansion of *N*-Cyanomethylated 3-Pyrazoline-4-acetic Acids

Eiichi Masumoto, Hiroshi Maruoka,* Fumi Okabe, Sho Nishida, Ryoko Tomita, Toshihiro Fujioka, and Kenji Yamagata

Faculty of Pharmaceutical Sciences, Fukuoka University, Jonan-ku, Fukuoka 814-0180, Japan
*E-mail: maruoka@fukuoka-u.ac.jp

Received January 30, 2011
DOI 10.1002/jhet.894
View this article online at wileyonlinelibrary.com.



A novel synthetic route to 4-pyridazineacetic acids **10**–**12** has been achieved by the ring-expansion reaction of *N*-cyanomethylated 3-pyrazoline-4-acetic acids **7**–**9**. 1*H*-Pyrazole-4-acetic acids **1**–**3** were reacted with iodoacetonitrile in the presence of triethylamine in refluxing acetonitrile to give the corresponding *C*-cyanomethylated 1*H*-pyrazole-4-acetic acids **4**–**6** as major products together with *N*-cyanomethylated 3-pyrazoline-4-acetic acids **7** and **8** as minor products. On the other hand, reactions of **1** and **3** with chloroacetonitrile in the presence of triethylamine in refluxing chloroform afforded the corresponding *N*-cyanomethylated 3-pyrazoline-4-acetic acids **7** and **9** as major products. Thermal treatment of **7**–**9** with sodium hydride in *N,N*-dimethylformamide caused ring expansion to yield the corresponding 4-pyridazineacetic acids **10**–**12**.

J. Heterocyclic Chem., **49**, 893 (2012).

INTRODUCTION

Nitrogen-containing heterocycles are of biological importance and design of newer strategies for their synthesis is an important area of research in organic chemistry. Pyrazole derivatives are well established in the literatures as important biologically effective heterocyclic compounds. These derivatives are the subject of many research studies due to their widespread potential pharmacological activities such as antitumor, analgesic, antidepressant, antibacterial, plant growth regulatory, anti-inflammatory, and antihyperglycemic activities [1–8]. Various methods have been reported for the synthesis of pyrazole derivatives [9–14].

On the other hand, pyridazine derivatives are also versatile pharmacophores in many biologically active molecules of contemporary interest. For example, these molecules have been previously reported to be platelet aggregation inhibitor, α-adrenoceptor antagonist, and antisecretory/antiulcer agent [15–20]. In this context, the synthesis of pyridazine derivatives continues to attract attention and provides an interesting challenge [21–29].

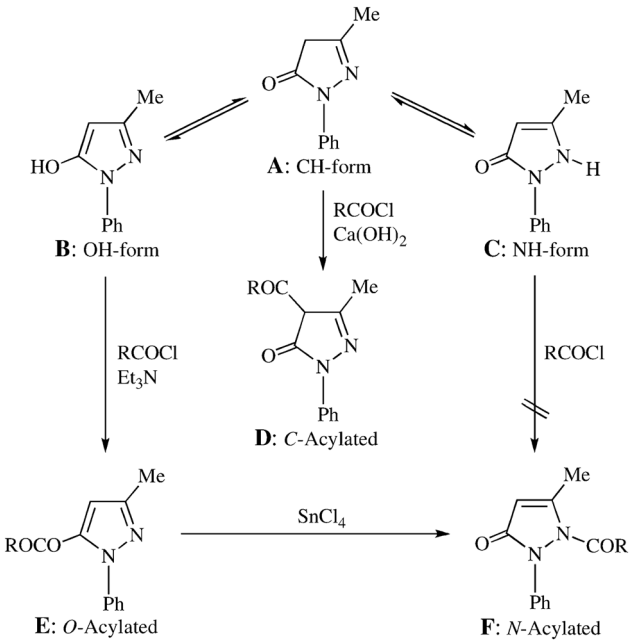
In connection with the synthesis and reactivity of pyrazole derivatives, it seems to us of interest to examine the chemical properties of 3*H*-pyrazol-3-one **A** (CH-form) as well as possible tautomerization including OH- and NH-forms **B** and **C** (Scheme 1). It is well known that under an appropriate reaction condition, an acylation of **A** provides the corresponding *C*- or *O*-acylated pyrazoles **D** and **E** [30], while we have reported the synthesis of *N*-acylated pyrazoles **F** through Lewis acid-mediated rearrangement of *O*-acylated pyrazoles **E** [31]. Furthermore, in our recent work, we achieved the synthesis of functionalized pyrazoles and dihydropyridazinones *via* a ring-opening reaction of spirocyclopropanepyrazoles [32]. In keeping with our interest in the chemical reactivity of functionalized pyrazoles [33,34], we focused our attention on the development of a new method for the preparation of pyridazine derivatives starting from 1*H*-pyrazole-4-acetic acids, because these derivatives are easily available by established synthetic procedures [35–37]. Thus, we, herein, wish to report our experimental results, a cyanomethylation and subsequent ring expansion of 1*H*-pyrazole-4-acetic acids in the presence of a base such as triethylamine and sodium hydride.

RESULTS AND DISCUSSION

The starting materials, 1*H*-pyrazole-4-acetic acids **1**–**3**, were easily prepared by the condensation reaction of

© 2012 HeteroCorporation

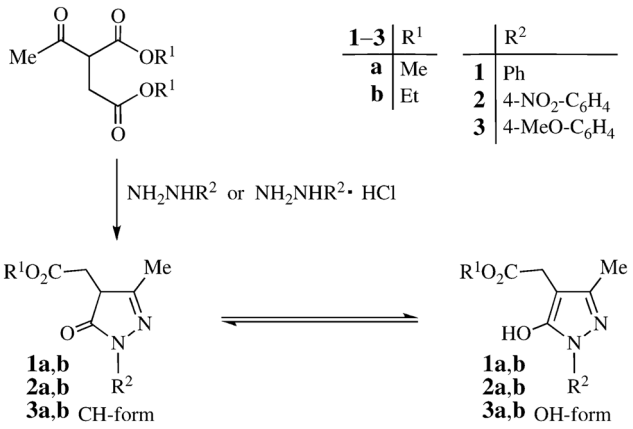
Scheme 1



dimethyl and/or diethyl acetylsuccinate with phenylhydrazines, such as phenylhydrazine, 4-nitrophenylhydrazine, and 4-methoxyphenyhydrazine hydrochloride, in moderate to good yields according to the procedure for the preparation of **1a** [35] and **1b** [36,37] reported in literature (Scheme 2, **1a**: 87%, **1b**: 88%, **2a**: 70%, **2b**: 80%, **3a**: 75%, and **3b**: 86%). The structures of **2a**,**b** and **3a**,**b** were confirmed by elemental analyses and spectroscopic data (IR, ^{1}H-NMR, ^{13}C-NMR, and mass). The ^{1}H-NMR spectra of **2a**,**b** and **3a** in deuteriochloroform indicate that **2a**,**b** exist almost exclusively as a single CH-form and **3a** exists as a single OH-form, whereas those of **1a**,**b** and **3b** show the presence of a tautomeric mixture of the CH-form and OH-form, with the following ratios observed: CH-form: OH-form = 1:1.2 for **1a**, 1:1.5 for **1b**, and 1:1.3 for **3b** (Experimental section). For example, the IR spectra of **2a,b** display bands near 1730 cm^{-1} due to two carbonyl groups, whereas that of **3a** shows bands at 3359 cm^{-1} due to a hydroxyl group and at 1730 cm^{-1} due to an ester carbonyl group. The ^{1}H-NMR spectra of **2a**,**b** exhibit a one-proton multiplet near δ 3.6 assignable to the H-4 methine proton of pyrazole ring, whereas that of **3a** shows a D_2O exchangeable signal at δ 10.62 attributable to the hydroxyl proton. The ^{13}C-NMR spectra of **2a**,**b** show a signal near δ 49 due to the C-4 methine carbon of pyrazole ring and a signal near δ 170 and 173 due to the two carbonyl carbons, whereas that of **3a** shows a signal at δ 97.2 due to the C-4 carbon of pyrazole ring and a signal at δ 157.2 due to the C-5 carbon of pyrazole ring.

In our initial studies, to check something about the reactivity of 1*H*-pyrazole-4-acetic acids **1**–**3**, we carried out

Scheme 2

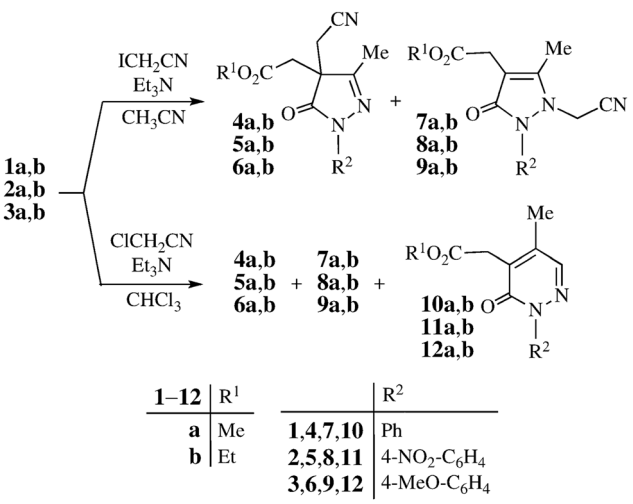


1–3	R^1
a	Me
b	Et

	R^2
1	Ph
2	4-NO_2-C_6H_4
3	4-MeO-C_6H_4

cyanomethylation reaction of **1**–**3**. Thus, we examined several reaction conditions, e.g., solvent, time, reagent, and substrate/base molar ratio. The best results are shown in Scheme 3 and Table 1. As a consequence, the reaction of **1a**,**b**, **2a**,**b**, and **3a**,**b** with iodoacetonitrile in the presence of triethylamine in refluxing acetonitrile led to the corresponding *C*-cyanomethylated 1*H*-pyrazole-4-acetic acids **4a**,**b**, **5a**,**b**, and **6a**,**b** as major products together with *N*-cyanomethylated 3-pyrazoline-4-acetic acids **7a**,**b** and **8a**,**b** as minor products. In this reaction, the *N*-cyanomethylated 3-pyrazoline-4-acetic acids **9a**,**b** were not detected at all (entries 5 and 6 in Table 1), while we found the reaction condition under which *N*-cyanomethylated 3-pyrazoline-4-acetic acids **7a**,**b**, **8b**, and **9a**,**b** could be isolated as major products (Scheme 3 and Table 2). Indeed, when **1a**,**b**, **2b**, and **3a**,**b** were treated with chloroacetonitrile in the presence of triethylamine in refluxing chloroform, the expected *N*-cyanomethylated products **7a**, **b**, **8b**, and **9a**,**b** were obtained in a somewhat better yields.

Scheme 3



1–12	R^1
a	Me
b	Et

	R^2
1,4,7,10	Ph
2,5,8,11	4-NO_2-C_6H_4
3,6,9,12	4-MeO-C_6H_4

Table 1

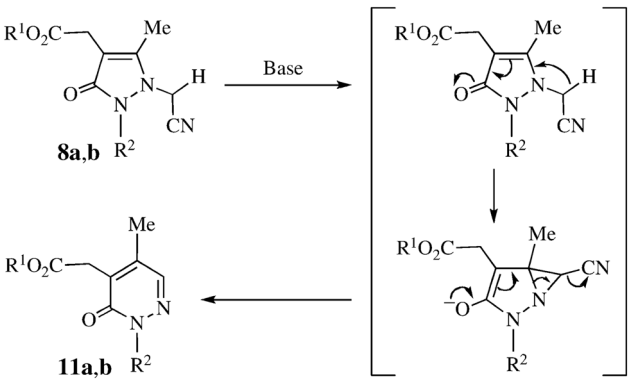
Reaction of **1–3** with iodoacetonitrile according to Scheme 3.

Entries	Substrate	R^1	R^2	Products	Yields (%)
1	**1a**	Me	Ph	**4a/7a**	65/28
2	**1b**	Et	Ph	**4b/7b**	69/9
3	**2a**	Me	4-NO_2-C_6H_4	**5a/8a**	62/15
4	**2b**	Et	4-NO_2-C_6H_4	**5b/8b**	61/12
5	**3a**	Me	4-MeO-C_6H_4	**6a/9a**	36/0
6	**3b**	Et	4-MeO-C_6H_4	**6b/9b**	29/0

In this reaction, the *C*-cyanomethylated 1*H*-pyrazole-4-acetic acids **4a**,**b** and **5a**,**b** were not isolated at all (entries 1–4 in Table 2). Interestingly, in the case of the reaction of **2a**,**b**, the 4-pyridazineacetic acid derivatives **11a**,**b** were produced in 8–18% low yields (entries 3 and 4 in Table 2). The reason for this change of behavior under the appropriate reaction conditions, such as an iodoacetonitrile/acetonitrile and chloroacetonitrile/chloroform combinations, is not very clear at present.

These products **4–9** and **11** gave satisfactory spectroscopic data consistent with their assigned structures (Experimental section). The IR spectra of **4–6** display a band in the range of 2251–2259 cm^{-1} due to a nonconjugated cyano group, whereas those of **7–9** show a band in the range of 2248–2253 cm^{-1} due to a nonconjugated cyano group. The ^{1}H-NMR spectra of **4–6** in deuteriochloroform exhibit two two-proton AB quartets near δ 2.7 and 3.0 assignable to the two methylene protons, whereas those of **7–9** show two two-proton singlets near δ 3.4 and 4.3 due to the two methylene protons. The ^{13}C-NMR spectra of **4–6** show a signal near δ 52 due to the C-4 carbon of pyrazole ring and a signal near δ 114 due to the cyano carbon, whereas those of **7–9** show a signal near δ 111 due to the C-4 carbon of pyrazole ring and a signal near δ 111 due to the cyano carbon. The ^{1}H-NMR spectra of **11a**,**b** in deuteriochloroform exhibit a one-proton singlet near δ 8.1 assignable to the H-6 proton of pyridazine ring. The ^{13}C-NMR spectra of **11a,b** show a signal near δ 119 due to the C-4 carbon of pyridazine ring and a signal near δ 146 due to the C-6 carbon of pyridazine ring.

Scheme 4



The formation of 4-pyridazineacetic acids **11a**,**b** could be explained by the possible mechanism presented in Scheme 4. This reaction probably proceeds through attack of a carbanion at position C-3 of pyrazole ring of **8a**,**b** with intramolecular Michael addition followed by ring expansion with loss of cyanide ion to yield **11a**,**b**.

To understand better the formation of 4-pyridazineacetic acids **10–11**, we examined the conversion of 3-pyrazoline-4-acetic acid **7a** into 4-pyridazineacetic acids **10a** in the presence of a base. After some optimization, the best result was obtained when **7a** was treated with sodium hydride in *N*,*N*-dimethylformamide at 80°C for 2 h, and the expected compound **10a** was isolated in 75% yield (entry 1 in Table 3). The use of several other bases, e.g., potassium carbonate and potassium *tert*-butoxide, resulted in lower yields (entries 2 and 3 in Table 3).

With the optimized reaction conditions in hand, we carried out the ring expansion of **7b**, **8a**,**b**, and **9a**,**b** under the sodium hydride/*N*,*N*-dimethylformamide combination. The results are listed in Table 4. In fact, the desired compounds **10b**, **11a**,**b**, and **12a**,**b** were obtained in moderate to good yields. These products **10a**,**b**, and **12a**,**b** were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, mass, and elemental analyses (Experimental section). In addition, compound **11a**,**b** was confirmed by direct comparison with authentic samples prepared from **2a**,**b** and chloroacetonitrile as described above.

Table 2

Reaction of **1–3** with chloroacetonitrile according to Scheme 3.

Entries	Substrate	R^1	R^2	Products	Yields (%)
1	**1a**	Me	Ph	**4a/7a/10a**	0/36/0
2	**1b**	Et	Ph	**4b/7b/10b**	0/34/0
3	**2a**	Me	4-NO_2-C_6H_4	**5a/8a/11a**	0/0/18
4	**2b**	Et	4-NO_2-C_6H_4	**5b/8b/11b**	0/12/8
5	**3a**	Me	4-MeO-C_6H_4	**6a/9a/12a**	9/21/0
6	**3b**	Et	4-MeO-C_6H_4	**6b/9b/12b**	6/24/0

Table 3

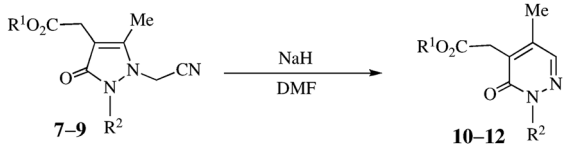
Ring expansion of **7a** into **10a** in the presence of bases.

7a —(Base, DMF)→ **10a**

Entries	Base (equiv.)	Conditions	Yield (%) of **10a**
1	NaH (1.0)	80°C, 2 h	75
2	K_2CO_3 (2.0)	120°C, 2 h	63
3	^{t}BuOK (2.0)	120°C, 2 h	55

Table 4

Ring expansion of **7–9** into **10–12** in the presence of sodium hydride.



Entries	Substrate	R^1	R^2	Products	Yield (%)
1	**7a**	Me	Ph	**10a**	75
2	**7b**	Et	Ph	**10b**	84
3	**8a**	Me	4-NO_2-C_6H_4	**11a**	61
4	**8b**	Et	4-NO_2-C_6H_4	**11b**	45
5	**9a**	Me	4-MeO-C_6H_4	**12a**	42
6	**9b**	Et	4-MeO-C_6H_4	**12b**	45

In conclusion, we have demonstrated the *C*- and *N*-cyanomethylation reaction of 1*H*-pyrazole-4-acetic acids **1–3**. Furthermore, we have developed a novel method for the construction of 4-pyridazineacetic acids **10–12** from *N*-cyanomethylated 3-pyrazoline-4-acetic acids **7–9** *via* a ring expansion. Functionalized pyrazole and pyridazine derivatives are important synthons in organic synthesis and for the preparation of biologically active compounds with interest in medicinal chemistry. Further synthetic applications for pyrazole and pyridazine derivatives are in progress.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a JASCO FTIR-4100 spectrometer. The ^{1}H and ^{13}C-NMR spectra were recorded on a JEOL JNM-A500 spectrometer at 500 and 125 MHz, respectively. The ^{1}H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane as internal standard. The positive FAB mass spectra were obtained on a JEOL JMS-700T spectrometer. The elemental analyses were performed on a YANACO MT-6 CHN analyzer. The starting compounds, 1*H*-pyrazole-4-acetic acids **1a** [35], **1b** [36,37], **2a**,**b**, and **3a**,**b**, were prepared in this laboratory according to the procedure reported in literature [35–37].

4,5-Dihydro-3-methyl-1-(4-nitrophenyl)-5-oxo-1*H*-pyrazole-4-acetic acid methyl ester (2a). This compound was obtained as yellow needles (70%), mp 155–156°C (acetone–petroleum ether); IR (potassium bromide): ν 1731, 1634 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 2.18 (s, 3H, 3-Me), 2.98–2.99 (m, 2H, C*H*$_2$CO$_2$Me), 3.57–3.60 (m, 1H, 4-H), 3.72 (s, 3H, CO_2Me), 8.13–8.16 (m, 2H, Ph-H), 8.25–8.28 ppm (m, 2H, Ph-H); ^{13}C-NMR (deuteriochloroform): δ 15.7 (3-Me), 31.3 (*C*H$_2$CO$_2$Me), 48.6 (C-4), 52.5 (CO$_2$*Me*), 117.9, 124.8, 143.1, 144.1 (Ph-C), 159.7 (C-3), 170.2 (*C*O$_2$Me), 172.7 ppm (C-5); ms: *m/z* 292 [M+H]$^+$. *Anal.* Calcd. for $C_{13}H_{13}N_3O_5$: C, 53.61; H, 4.50; N, 14.43. Found: C, 53.78; H, 4.72; N, 14.16.

4,5-Dihydro-3-methyl-1-(4-nitrophenyl)-5-oxo-1H-pyrazole-4-acetic acid ethyl ester (2b). This compound was obtained as brown needles (80%), mp 148–149°C (acetone–petroleum ether);IR (potassium bromide): ν 1734, 1632 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 1.22 (t, *J* = 7.0 Hz, 3H, CO_2CH_2*Me*), 2.18 (s, 3H, 3-Me), 2.93–3.02 (m, 2H, C*H*$_2$CO$_2$CH$_2$Me), 3.56–3.58 (m, 1H, 4-H), 4.16 (q, *J* = 7.0 Hz, 2H, CO_2*CH*$_2$Me), 8.04–8.16 (m, 2H, Ph-H), 8.25–8.28 ppm (m, 2H, Ph-H); ^{13}C-NMR (deuteriochloroform): δ 14.0 (CO_2CH_2*Me*), 15.7 (3-Me), 31.5 (*C*H$_2$CO$_2$CH$_2$Me), 48.7 (C-4), 61.6 (CO$_2$*C*H$_2$Me), 117.9, 124.8, 143.2, 144.0 (Ph-C), 159.8 (C-3), 169.6 (*C*O$_2$CH$_2$Me), 172.7 ppm (C-5); ms: *m/z* 306 [M+H]$^+$. *Anal.* Calcd. for $C_{14}H_{15}N_3O_5$: C, 55.08; H, 4.95; N, 13.76. Found: C, 55.15; H, 4.97; N, 13.71.

4,5-Dihydro-5-hydroxy-1-(4-methoxyphenyl)-3-methyl-1*H*-pyrazole-4-acetic acid methyl ester (3a). This compound was obtained as colorless needles (75%), mp 114–117°C (acetone–petroleum ether); IR (potassium bromide): ν 3359 (OH), 1730 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 2.22 (s, 3H, 3-Me), 3.45 (s, 2H, C*H*$_2$CO$_2$Me), 3.61 (s, 3H, CO_2Me), 3.75 (s, 3H, OMe), 6.81–6.84 (m, 2H, Ph-H), 741–7.43 (m, 2H, Ph-H), 10.62 ppm (br, 1H, OH); ^{13}C-NMR (deuteriochloroform): δ 10.6 (3-Me), 27.3 (*C*H$_2$CO$_2$Me), 52.1 (CO$_2$*Me*), 55.5 (OMe), 97.2 (C-4), 114.3, 124.6, 127.1 (Ph-C), 146.1 (C-3), 157.2 (C-5), 159.2 (Ph-C), 171.3 ppm (*C*O$_2$Me); ms: *m/z* 277 [M+H]$^+$. *Anal.* Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.85; H, 5.89; N, 10.15.

4,5-Dihydro-1-(4-methoxyphenyl)-3-methyl-5-oxo-1*H*-pyrazole-4-acetic acid ethyl ester and its isomer (3b). This compound was obtained as pale red needles (86%), mp 125–127°C (acetone–petroleum ether); IR (potassium bromide): ν 1725, 1623 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 1.22 (t, *J* = 7.3 Hz, 1.3H, CO_2CH_2*Me*), 1.28 (t, *J* = 7.3 Hz, 1.7H, CO_2CH_2*Me*), 2.116, 2.121 (s, 3H, 3-Me), 2.85–2.95 (m, 0.86H, C*H*$_2$CO$_2$CH$_2$Me), 3.40 (s, 1.14H, C*H*$_2$CO$_2$CH$_2$Me), 3.50–3.53 (m, 0.43H, 4-H), 3.79, 3.80 (s, 3H, OMe), 4.14–4.20 (m, 2H, CO_2*CH*$_2$Me), 6.85–6.88 (m, 1.14H, Ph-H), 6.90–6.93 (m, 0.86H, Ph-H), 7.26–7.52 (m, 1.14H, Ph-H), 7.53–7.76 (m, 0.86H, Ph-H), 9.61 ppm (br, 0.57H, OH); ^{13}C-NMR (deuteriochloroform): δ 11.8 (3-Me), 14.0 (CO_2CH_2*Me*), 15.6 (3-Me), 28.7, 31.7 (*C*H$_2$CO$_2$CH$_2$Me), 48.4 (C-4), 55.42, 55.45 (OMe), 61.4, 61.5 (CO$_2$*C*H$_2$Me), 95.3 (C-4), 114.0, 120.8, 123.0, 130.9, 131.5 (Ph-C), 147.0 (C-3), 156.4 (C-5), 157.1, 157.7 (Ph-C), 158.4 (C-3), 169.9 (*C*O$_2$CH$_2$Me), 171.9 (C-5), 173.3 ppm (*C*O$_2$CH$_2$Me); ms: *m/z* 291 [M+H]$^+$. *Anal.* Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 62.12; H, 6.28; N, 9.67.

General procedure for the preparation of *C*-cyanomethylated 1*H*-pyrazole-4-acetic acids 4–6 from 1–3 and iodoacetonitrile in the presence of triethylamine. A mixture of **1–3** (1 mmol), iodoacetonitrile (0.501 g, 3 mmol), and triethylamine (0.304 g, 3 mmol) in acetonitrile (5 mL) was refluxed for 3 h. To the reaction mixture, cold water was added with stirring and ice cooling. The resulting mixture was extracted with ethyl acetate (60 mL). The extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with chloroform as the eluent to give **4a**,**b**, **5a**,**b**, and **6a**,**b**. Further, the elution afforded **7a**,**b** and **8a**,**b** (see Table 1).

4-(Cyanomethyl)-4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazole-4-acetic acid methyl ester (4a). This compound was obtained as colorless prisms (0.185 g, 65%), mp 69–71°C (chloroform–petroleum ether); IR (potassium bromide): ν 2255 (CN), 1739, 1715 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 2.23 (s, 3H, 3-Me), 2.72 (AB q, *J* = 16.8 Hz, 2H, CH_2CN), 2.95 (AB q, *J* = 16.5 Hz, 2H, C*H*$_2$CO$_2$Me), 3.63 (s, 3H,

CO_2Me), 7.20–7.23 (m, 1H, Ph-H), 7.39–7.42 (m, 2H, Ph-H), 7.85–7.87 ppm (m, 2H, Ph-H); ^{13}C-NMR (deuteriochloroform): δ 14.3 (3-Me), 23.0 (*C*H_2CN), 36.9 (*C*H_2CO_2Me), 51.7 (C-4), 52.4 (CO_2*Me*), 114.4 (CN), 119.3, 125.7, 128.9, 137.5 (Ph-C), 158.6 (C-3), 168.3 (*C*O_2Me), 171.7 ppm (C-5); ms: *m/z* 286 $[M+H]^+$. *Anal.* Calcd. for $C_{15}H_{15}N_3O_5 \cdot 0.5H_2O$: C, 61.22; H, 5.48; N, 14.28. Found: C, 61.07; H, 5.21; N, 14.17.

4-(Cyanomethyl)-4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazole-4-acetic acid ethyl ester (4b). This compound was obtained as colorless scales (0.206 g, 69%), mp 93–95°C (chloroform-petroleum ether); IR (potassium bromide): ν 2252 (CN), 1733, 1715 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 1.15 (t, *J* = 7.0 Hz, 3H, CO_2CH_2*Me*), 2.25 (s, 3H, 3-Me), 2.72 (AB q, *J* = 16.8 Hz, 2H, CH_2CN), 2.95 (AB q, *J* = 16.5 Hz, 2H, C*H*$_2CO_2CH_2$Me), 4.03 (q, *J* = 7.0 Hz, 2H, CO_2C*H*$_2$Me), 7.20–7.26 (m, 1H, Ph-H), 7.39–7.42 (m, 2H, Ph-H), 7.86–7.89 ppm (m, 2H, Ph-H); ^{13}C-NMR (deuteriochloroform): δ 13.9 (CO_2CH_2*Me*), 14.4 (3-Me), 23.2 (*C*H_2CN), 37.3 (*C*$H_2CO_2CH_2$Me), 51.8 (C-4), 61.7 (CO_2*C*H_2Me), 114.5 (CN), 119.2, 125.7, 128.9, 137.5 (Ph-C), 158.7 (C-3), 167.7 (*C*O_2CH_2Me), 171.7 ppm (C-5); ms: *m/z* 300 $[M+H]^+$. *Anal.* Calcd. for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.21; H, 5.78; N, 14.03.

4-(Cyanomethyl)-4,5-dihydro-3-methyl-1-(4-nitrophenyl)-5-oxo-1*H*-pyrazole-4-acetic acid methyl ester (5a). This compound was obtained as yellow prisms (0.205 g, 62%), mp 160–162°C (chloroform-petroleum ether); IR (potassium bromide): ν 2259 (CN), 1736, 1719 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 2.28 (s, 3H, 3-Me), 2.77 (AB q, *J* = 16.8 Hz, 2H, CH_2CN), 3.02 (AB q, *J* = 17.1 Hz, 2H, C*H*$_2CO_2$Me), 3.65 (s, 3H, CO_2Me), 8.13–8.15 (m, 2H, Ph-H), 8.27–8.29 ppm (m, 2H, Ph-H); ^{13}C-NMR (deuteriochloroform): δ 14.4 (3-Me), 23.2 (*C*H_2CN), 37.1 (*C*H_2CO_2Me), 52.0 (C-4), 52.6 (CO_2*Me*), 114.0 (CN), 118.3, 124.9, 142.5, 144.5 (Ph-C), 160.0 (C-3), 168.3 (*C*O_2Me), 172.3 ppm (C-5); ms: *m/z* 331 $[M+H]^+$. *Anal.* Calcd. for $C_{15}H_{14}N_4O_5$: C, 54.55; H, 4.27; N, 16.96. Found: C, 54.35; H, 4.37; N, 16.83.

4-(Cyanomethyl)-4,5-dihydro-3-methyl-1-(4-nitrophenyl)-5-oxo-1*H*-pyrazole-4-acetic acid ethyl ester (5b). This compound was obtained as yellow prisms (0.210 g, 61%), mp 139–141°C (chloroform–petroleum ether); IR (potassium bromide): ν 2251 (CN), 1734, 1720 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 1.56 (t, *J* = 7.0 Hz, 3H, CO_2CH_2*Me*), 2.28 (s, 3H, 3-Me), 2.76 (AB q, *J* = 17.1 Hz, 2H, CH_2CN), 3.00 (AB q, *J* = 16.8 Hz, 2H, C*H*$_2CO_2CH_2$Me), 4.09 (q, *J* = 7.0 Hz, 2H, CO_2C*H*$_2$Me), 8.13–8.16 (m, 2H, Ph-H), 8.26–8.29 ppm (m, 2H, Ph-H); ^{13}C-NMR (deuteriochloroform): δ 13.9 (CO_2CH_2*Me*), 14.4 (3-Me), 23.2 (*C*H_2CN), 37.4 (*C*$H_2CO_2CH_2$Me), 52.1 (C-4), 61.9 (CO_2*C*H_2Me), 114.0 (CN), 118.3, 124.9, 142.5, 144.5 (Ph-C), 159.8 (C-3), 167.6 (*C*O_2CH_2Me), 172.4 ppm (C-5); ms: *m/z* 345 $[M+H]^+$. *Anal.* Calcd. for $C_{16}H_{16}N_4O_5 \cdot 0.3H_2O$: C, 54.95; H, 4.78; N, 16.02. Found: C, 54.96; H, 4.64; N, 15.97.

4-(Cyanomethyl)-4,5-dihydro-1-(4-methoxyphenyl)-3-methyl-5-oxo-1*H*-pyrazole-4-acetic acid methyl ester (6a). This compound was obtained as colorless scales (0.114 g, 36%), mp 138–140°C (chloroform–petroleum ether); IR (potassium bromide): ν 2259 (CN), 1720, 1703 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 2.26 (s, 3H, 3-Me), 2.73 (AB q, *J* = 17.1 Hz, 2H, CH_2CN), 2.94 (AB q, *J* = 16.8 Hz, 2H, C*H*$_2CO_2$Me), 3.64 (s, 3H, CO_2Me), 3.81 (s, 3H, OMe), 6.92–6.95 (m, 2H, Ph-H), 7.71–7.74 ppm (m, 2H, Ph-H); ^{13}C-NMR (deuteriochloroform): δ 14.3 (3-Me), 23.0 (*C*H_2CN), 37.0 (*C*H_2CO_2Me), 51.5 (C-4), 52.4 (CO_2*Me*), 55.5 (OMe), 114.2 (Ph-C), 114.5 (CN), 121.3, 130.8, 157.6 (Ph-C), 158.4 (C-3), 168.3 (*C*O_2Me), 171.4 ppm (C-5); ms: *m/z* 315 $[M+H]^+$. *Anal.* Calcd. for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.95; H, 5.47; N, 13.33.

4-(Cyanomethyl)-4,5-dihydro-1-(4-methoxyphenyl)-3-methyl-5-oxo-1*H*-pyrazole-4-acetic acid ethyl ester (6b). This compound was obtained as colorless scales (0.096 g, 29%), mp 95–97°C (chloroform–petroleum ether); IR (potassium bromide): ν 2253 (CN), 1725, 1704 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 1.16 (t, *J* = 7.3 Hz, 3H, CO_2CH_2*Me*), 2.30 (s, 3H, 3-Me), 2.72 (AB q, *J* = 17.1 Hz, 2H, CH_2CN), 2.93 (AB q, *J* = 16.5 Hz, 2H, C*H*$_2CO_2CH_2$Me), 3.81 (s, 3H, OMe), 4.09 (q, *J* = 7.3 Hz, 2H, CO_2C*H*$_2$Me), 6.92–6.94 (m, 2H, Ph-H), 7.73–7.75 ppm (m, 2H, Ph-H); ^{13}C-NMR (deuteriochloroform): δ 13.9 (CO_2CH_2*Me*), 14.3 (3-Me), 23.1 (*C*H_2CN), 37.3 (*C*$H_2CO_2CH_2$Me), 51.6 (C-4), 55.5 (OMe), 61.6 (CO_2*C*H_2Me), 114.1 (Ph-C), 114.5 (CN), 121.2, 130.8, 157.6 (Ph-C), 158.5 (C-3), 167.8 (*C*O_2CH_2Me), 171.4 ppm (C-5); ms: *m/z* 329 $[M+H]^+$. *Anal.* Calcd. for $C_{17}H_{19}N_3O_4$: C, 62.00; H, 5.81; N, 12.76. Found: C, 62.02; H, 5.81; N, 12.82.

2-(Cyanomethyl)-3-methyl-5-oxo-1-phenyl-3-pyrazoline-4-acetic acid methyl ester (7a). This compound was obtained as colorless prisms (0.079 g, 28%), mp 93–95°C (chloroform–petroleum ether); IR (potassium bromide): ν 2251 (CN), 1738, 1676 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 2.28 (s, 3H, 3-Me), 3.42 (s, 2H, C*H*$_2CO_2$Me), 3.70 (s, 3H, CO_2Me), 4.29 (s, 2H, NCH_2CN), 7.29–7.32 (m, 1H, Ph-H), 7.40–7.48 ppm (m, 4H, Ph-H); ^{13}C-NMR (deuteriochloroform): δ 11.4 (3-Me), 27.9 (*C*H_2CO_2Me), 37.4 (N*C*H_2CN), 52.2 (CO_2*Me*), 110.9 (C-4), 111.8 (CN), 123.3, 127.1, 129.5, 134.3 (Ph-C), 154.0 (C-3), 165.5 (C-5), 170.3 ppm (*C*O_2Me); ms: *m/z*286 $[M+H]^+$. *Anal.* Calcd. for $C_{15}H_{15}N_3O_5 \cdot 0.15H_2O$: C, 62.56; H, 5.35; N, 14.59. Found: C, 62.56; H, 5.23; N, 14.66.

2-(Cyanomethyl)-3-methyl-5-oxo-1-phenyl-3-pyrazoline-4-acetic acid ethyl ester (7b). This compound was obtained as colorless prisms (0.027 g, 9%), mp 109–111°C (chloroform–petroleum ether); IR (potassium bromide): ν 2251 (CN), 1734, 1677 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 1.26 (t, *J* = 7.0 Hz, 3H, CO_2CH_2*Me*), 2.28 (s, 3H, 3-Me), 3.40 (s, 2H, C*H*$_2CO_2CH_2$Me), 4.16 (q, *J* = 7.0 Hz, 2H, CO_2C*H*$_2$Me), 4.29 (s, 2H, NCH_2CN), 7.29–7.32 (m, 1H, Ph-H), 7.40–7.47 ppm (m, 4H, Ph-H); ^{13}C-NMR (deuteriochloroform): δ 11.4 (3-Me), 14.1 (CO_2CH_2*Me*), 28.1 (*C*$H_2CO_2CH_2$Me), 37.4 (N*C*H_2CN), 61.2 (CO_2*C*H_2Me), 111.0 (C-4), 111.8 (CN), 123.3, 127.1, 129.5, 134.3 (Ph-C), 154.0 (C-3), 165.6 (C-5), 170.0 ppm (*C*O_2CH_2Me); ms: *m/z* 300 $[M+H]^+$. *Anal.* Calcd. for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.19; H, 5.79; N, 14.06.

2-(Cyanomethyl)-3-methyl-1-(4-nitrophenyl)-5-oxo-1-phenyl-3-pyrazoline-4-acetic acid methyl ester (8a). This compound was obtained as pale yellow needles (0.050 g, 15%), mp 187–189°C (chloroform–petroleum ether); IR (potassium bromide): ν 2252 (CN), 1744, 1689 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 2.32 (s, 3H, 3-Me), 3.43 (s, 2H, C*H*$_2CO_2$Me), 3.72 (s, 3H, CO_2Me), 4.36 (s, 2H, NCH_2CN), 7.63–7.65 (m, 2H, Ph-H), 8.32–8.34 ppm (m, 2H, Ph-H); ^{13}C-NMR (deuteriochloroform): δ 11.6 (3-Me), 27.8 (*C*H_2CO_2Me), 38.2 (N*C*H_2CN), 52.3 (CO_2*Me*), 111.2 (CN), 111.6 (C-4), 121.6, 125.1, 139.9, 145.3 (Ph-C), 156.5 (C-3),

165.6 (C-5), 169.8 ppm (CO_2Me); ms: *m/z* 331 $[M+H]^+$. *Anal.* Calcd. for $C_{15}H_{14}N_4O_5$: C, 54.55; H, 4.27; N, 16.96. Found: C, 54.50; H, 4.31; N, 16.96.

2-(Cyanomethyl)-3-methyl-1-(4-nitrophenyl)-5-oxo-1-phenyl-3-pyrazoline-4-acetic acid ethyl ester (8b). This compound was obtained as colorless needles (0.040 g, 12%), mp 166–168°C (chloroform–petroleum ether); IR (potassium bromide): ν 2248 (CN), 1735, 1686 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 1.27 (t, *J* = 7.3 Hz, 3H, CO_2CH_2*Me*), 2.32 (s, 3H, 3-Me), 3.41 (s, 2H, C$H_2CO_2CH_2$Me), 4.17 (q, *J* = 7.3 Hz, 2H, CO_2CH_2Me), 4.34 (s, 2H, NCH_2CN), 7.63–7.65 (m, 2H, Ph-H), 8.32–8.34 ppm (m, 2H, Ph-H); ^{13}C-NMR (deuteriochloroform): δ 11.6 (3-Me), 14.1 (CO_2CH_2*Me*), 28.1 ($CH_2CO_2CH_2$Me), 38.2 (NCH_2CN), 61.4 (CO_2CH_2Me), 111.2 (CN), 111.8 (C-4), 121.6, 125.2, 140.0, 145.3 (Ph-C), 156.4 (C-3), 165.6 (C-5), 169.4 ppm (CO_2CH_2Me); ms: *m/z* 345 $[M+H]^+$. *Anal.* Calcd. for $C_{16}H_{16}N_4O_5$: C, 55.81; H, 4.68; N, 16.27. Found: C, 55.71; H, 4.73; N, 16.29.

General procedure for the preparation of *N*-cyanomethylated 3-pyrazoline-4-acetic acids 7–9 from 1–3 and chloroacetonitrile in the presence of triethylamine. A mixture of **1**–**3** (1 mmol), chloroacetonitrile (0.227 g, 3 mmol), and triethylamine (0.304 g, 3 mmol) in chloroform (5 mL) was refluxed for 3 h. To the reaction mixture, cold water was added with stirring and ice cooling. The resulting mixture was extracted with chloroform (60 mL). The extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with chloroform as the eluent to yield **7a**,**b**, **11a**, **8b**, and **6a**,**b**. Further, the elution provided **11b** and **9a**,**b** (see Table 2).

2-(Cyanomethyl)-1-(4-methoxyphenyl)-3-methyl-5-oxo-1-phenyl-3-pyrazoline-4-acetic acid methyl ester (9a). This compound was obtained as pale brown needles (0.067 g, 21%), mp 132–134°C (chloroform–petroleum ether); IR (potassium bromide): ν 2253 (CN), 1752, 1671 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 2.26 (s, 3H, 3-Me), 3.41 (s, 2H, CH_2CO_2Me), 3.70 (s, 3H, CO_2Me), 3.83 (s, 3H, OMe), 4.24 (s, 2H, NCH_2CN), 6.97–6.99 (m, 2H, Ph-H), 7.30–7.32 ppm (m, 2H, Ph-H); ^{13}C-NMR (deuteriochloroform): δ 11.3 (3-Me), 27.9 (CH_2CO_2Me), 37.0 (NCH_2CN), 52.2 (CO_2*Me*), 55.6 (OMe), 110.5 (CN), 111.9 (C-4), 115.0, 126.1, 126.8 (Ph-C), 153.2 (C-3), 159.1 (Ph-C), 165.7 (C-5), 170.4 ppm (CO_2Me); ms: *m/z* 316 $[M+H]^+$. *Anal.* Calcd. for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.80; H, 5.41; N, 13.57.

2-(Cyanomethyl)-1-(4-methoxyphenyl)-3-methyl-5-oxo-1-phenyl-3-pyrazoline-4-acetic acid ethyl ester (9b). This compound was obtained as colorless columns (0.079 g, 24%), mp 109–111°C (chloroform–petroleum ether); IR (potassium bromide): ν 2248 (CN), 1741, 1668, 1651 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 1.26 (t, *J* = 7.3 Hz, 3H, CO_2CH_2*Me*), 2.26 (s, 3H, 3-Me), 3.40 (s, 2H, C$H_2CO_2CH_2$Me), 3.83 (s, 3H, OMe), 4.16 (q, *J* = 7.3 Hz, 2H, CO_2CH_2Me), 4.24 (s, 2H, NCH_2CN), 6.97–6.99 (m, 2H, Ph-H), 7.30–7.32 ppm (m, 2H, Ph-H); ^{13}C-NMR (deuteriochloroform): δ 11.4 (3-Me), 14.1 (CO_2CH_2*Me*), 28.1 ($CH_2CO_2CH_2$Me), 37.0 (NCH_2CN), 55.6 (OMe), 61.2 (CO_2CH_2Me), 110.6 (C-4), 111.9 (CN), 114.9, 126.1, 126.9 (Ph-C), 153.2 (C-3), 159.1 (Ph-C), 165.7 (C-5), 170.0 ppm (CO_2CH_2Me); ms: *m/z* 330 $[M+H]^+$. *Anal.* Calcd. for $C_{17}H_{19}N_3O_4$: C, 62.00; H, 5.81; N, 12.76. Found: C, 62.00; H, 5.81; N, 12.78.

General procedure for the preparation of 4-pyridazineacetic acids 10–12 from 7–9 and sodium hydride. To an ice-cooled and stirred solution of **7**–**9** (1 mmol) in *N,N*-dimethylformamide (5 mL), 60% of sodium hydride (0.040 g, 1 mmol) was added. The stirring was continued at room temperature until evolution of gas ceased, and then the mixture was stirred at 80°C for 1 h. After the removal of the solvent *in vacuo*, cold water was added to the residue. The resulting mixture was extracted with chloroform (60 mL). The extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with chloroform as the eluent to afford **10a**,**b**, **11a**,**b**, and **12a**,**b**.

2,3-Dihydro-5-methyl-3-oxo-2-phenyl-4-pyridazineacetic acid methyl ester (10a). This compound was obtained as pale yellow oil (0.194 g, 75%); IR (neat): ν 1738, 1669 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 2.36 (s, 3H, 5-Me), 3.64 (s, 2H, CH_2CO_2Me), 3.71 (s, 3H, CO_2Me), 7.35–7.37 (m, 2H, Ph-H), 7.44–7.52 (m, 3H, Ph-H), 8.06 ppm (s, 1H, 6-H); ^{13}C-NMR (deuteriochloroform): δ 21.7 (5-Me), 31.5 (CH_2CO_2Me), 52.1 (CO_2*Me*), 119.0 (C-4), 126.6, 129.2, 129.5, 137.1 (Ph-C), 147.6 (C-6), 160.8 (C-3), 160.9 (C-5), 170.8 ppm (CO_2Me); ms: *m/z* 259 $[M+H]^+$. *Anal.* Calcd. for $C_{14}H_{14}N_2O_3 \cdot 0.2H_2O$: C, 64.21; H, 5.54; N, 10.70. Found: C, 64.28; H, 5.55; N, 10.73.

2,3-Dihydro-5-methyl-3-oxo-2-phenyl-4-pyridazineacetic acid ethyl ester (10b). This compound was obtained as pale yellow oil (0.228 g, 84%); IR (neat): ν 1732, 1667 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 1.26 (t, *J* = 7.0 Hz, 3H, CO_2CH_2*Me*), 2.36 (s, 3H, 5-Me), 3.63 (s, 2H, C$H_2CO_2CH_2$Me), 4.17 (q, *J* = 7.0 Hz, 2H, CO_2CH_2Me), 7.36–7.37 (m, 2H, Ph-H), 7.36–7.52 (m, 3H, Ph-H), 8.05 ppm (s, 1H, 6-H); ^{13}C-NMR (deuteriochloroform): δ 14.1 (CO_2CH_2*Me*), 21.7 (5-Me), 31.7 ($CH_2CO_2CH_2$Me), 60.9 (CO_2CH_2Me), 119.1 (C-4), 126.6, 129.1, 129.4, 137.1 (Ph-C), 147.5 (C-6), 160.8 (C-3), 160.9 (C-5), 170.3 ppm (CO_2CH_2Me); ms: *m/z* 273 $[M+H]^+$. *Anal.* Calcd. for $C_{15}H_{16}N_2O_3 \cdot 0.3H_2O$: C, 64.88; H, 6.03; N, 10.09. Found: C, 64.81; H, 5.96; N, 10.10.

2,3-Dihydro-5-methyl-1-(4-nitrophenyl)-3-oxo-2-phenyl-4-pyridazineacetic acid methyl ester (11a). This compound was obtained as pale brown needles (0.185 g, 61%), mp 183–185°C (chloroform–petroleum ether); IR (potassium bromide): ν 1737, 1676 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 2.38 (s, 3H, 5-Me), 3.64 (s, 2H, CH_2CO_2Me), 3.72 (s, 3H, CO_2Me), 7.61–7.63 (m, 2H, Ph-H), 8.07 (s, 1H, 6-H), 8.37–8.39 ppm (m, 2H, Ph-H); ^{13}C-NMR (deuteriochloroform): δ 21.7 (5-Me), 31.4 (CH_2CO_2Me), 52.2 (CO_2*Me*), 119.3 (C-4), 124.8, 127.7, 142.1 (Ph-C), 146.3 (C-6), 147.9 (Ph-C), 160.2 (C-3), 161.4 (C-5), 170.5 ppm (CO_2Me); ms: *m/z* 304 $[M+H]^+$. *Anal.* Calcd. for $C_{14}H_{13}N_3O_5 \cdot 0.2H_2O$: C, 54.79; H, 4.40; N, 13.69. Found: C, 54.79; H, 4.38; N, 13.75.

2,3-Dihydro-5-methyl-1-(4-nitrophenyl)-3-oxo-2-phenyl-4-pyridazineacetic acid ethyl ester (11b). This compound was obtained as pale yellow scales (0.143 g, 45%), mp 157–159°C (chloroform–petroleum ether); IR (potassium bromide): ν 1735, 1665 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 1.28 (t, *J* = 7.0 Hz, 3H, CO_2CH_2*Me*), 2.38 (s, 3H, 5-Me), 3.63 (s, 2H, C$H_2CO_2CH_2$Me), 4.19 (q, *J* = 7.0 Hz, 2H, CO_2CH_2Me), 7.27–7.62 (m, 2H, Ph-H), 8.06 (s, 1H, 6-H), 8.37–8.39 ppm (m, 2H, Ph-H); ^{13}C-NMR (deuteriochloroform): δ 14.2 (CO_2CH_2*Me*), 21.8 (5-Me), 31.6 ($CH_2CO_2CH_2$Me), 61.2 (CO_2CH_2Me), 119.5 (C-4), 124.8, 127.7, 142.2 (Ph-C), 146.3 (C-6), 147.9 (Ph-C), 160.2 (C-3), 161.4 (C-5), 170.0 ppm (CO_2CH_2Me); ms: *m/z* 318 $[M+H]^+$. *Anal.* Calcd. for $C_{15}H_{15}N_3O_5$: C, 56.78; H, 4.76; N, 13.24. Found: C, 56.69; H, 4.77; N, 13.29.

2,3-Dihydro-1-(4-methoxyphenyl)-5-methyl-3-oxo-2-phenyl-4-pyridazineacetic acid methyl ester (12a). This compound was obtained as colorless needles (0.120 g, 42%), mp 78–80°C (chloroform–petroleum ether); IR (potassium bromide): ν 1732, 1720, 1665 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 2.35 (s, 3H, 5-Me), 3.64 (s, 2H, C*H*$_2$CO$_2$Me), 3.71 (s, 3H, CO$_2$Me), 3.84 (s, 3H, OMe), 6.98–7.00 (m, 2H, Ph-H), 7.26–7.28 (m, 2H, Ph-H), 8.04 ppm (s, 1H, 6-H); ^{13}C-NMR (deuteriochloroform): δ 21.7 (5-Me), 31.5 (*C*H$_2$CO$_2$Me), 52.1 (CO$_2$*Me*), 55.6 (OMe), 114.7 (Ph-C), 118.9 (C-4), 127.7, 129.8 (Ph-C), 147.9 (C-6), 160.1 (Ph-C), 160.9 (C-3), 161.1 (C-5), 170.8 ppm (*C*O$_2$Me); ms: *m/z* 289 [M+H]$^+$. *Anal.* Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.38; H, 5.67; N, 9.68.

2,3-Dihydro-1-(4-methoxyphenyl)-5-methyl-3-oxo-2-phenyl-4-pyridazineacetic acid ethyl ester (12b). This compound was obtained as colorless needles (0.137 g, 45%), mp 82–84°C (chloroform–petroleum ether); IR (potassium bromide): ν 1727, 1665 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ 1.26 (t, *J* = 7.3 Hz, 3H, CO$_2$CH$_2$*Me*), 2.35 (s, 3H, 5-Me), 3.62 (s, 2H, C*H*$_2$CO$_2$CH$_2$Me), 3.84 (s, 3H, OMe), 4.17 (q, *J* = 7.3 Hz, 2H, CO$_2$*CH*$_2$Me), 6.98–7.00 (m, 2H, Ph-H), 7.26–7.28 (m, 2H, Ph-H), 8.03 ppm (s, 1H, 6-H); ^{13}C-NMR (deuteriochloroform): δ 14.1 (CO$_2$CH$_2$*Me*), 21.7 (5-Me), 31.7 (*C*H$_2$CO$_2$CH$_2$Me), 55.6 (OMe), 61.0 (CO$_2$*C*H$_2$Me), 114.7 (Ph-C), 119.1 (C-4), 127.7, 129.9 (Ph-C), 147.9 (C-6), 160.0 (Ph-C), 160.8 (C-3), 161.1 (C-5), 170.3 ppm (*C*O$_2$CH$_2$Me); ms: *m/z* 303 [M+H]$^+$. *Anal.* Calcd. for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.46; H, 6.02; N, 9.26.

Acknowledgments. The authors thank Hiroshi Hanazono and Yukiko Iwase for obtaining Mass and NMR spectra and to Junko Honda for her valuable help with elemental analyses.

REFERENCES AND NOTES

[1] Congiu, C.; Onnis, V.; Vesci, L.; Castorina, M.; Pisano, C. Bioorg Med Chem 2010, 18, 6238.

[2] Caruso, F.; Pettinari, C.; Marchetti, F.; Rossi, M.; Opazo, C.; Kumar, S.; Balwani, S.; Ghosh, B. Bioorg Med Chem 2009, 17, 6166.

[3] Ouyang, G.; Chen, Z.; Cai, X.-J.; Song, B.-A.; Bhadury, P. S.; Yang, S.; Jin, L.-H.; Xue, W.; Hu, D.-Y.; Zeng, S. Bioorg Med Chem 2008, 16, 9699.

[4] Kimata, A.; Nakagawa, H.; Ohyama, R.; Fukuuchi, T.; Ohta, S.; Suzuki, T.; Miyata, N. J Med Chem 2007, 50, 5053.

[5] Ismail, M. M. F.; Ammar, Y. A.; EI-Zahaby, H. S. A.; Eisa, S. I.; Barakat, S. E.-S. Arch Pharm Chem Life Sci 2007, 340, 476.

[6] Singh, P.; Paul, K.; Holzer, W. Bioorg Med Chem 2006, 14, 5061.

[7] Hiremath, S. P.; Rudresh, K.; Saundane, A. R. Indian J Chem 2002, 41B, 394.

[8] Ono, S.; Okazaki, K.; Sakurai, M.; Inoue, Y. J Phys Chem A 1997, 101, 3769.

[9] Cooper, M.; Receveur, J.-M.; Bjurling, E.; Nørregaard, P. K.; Nielsen, P. A.; Sköld, N.; Högberg, T. Bioorg Med Chem Lett 2010, 20, 26.

[10] Schmidt, D.; Smenton, A.; Raghavan, S.; Carballo-Jane, E.; Lubell, S.; Ciecko, T.; Holt, T. G.; Wolff, M.; Taggart, A.; Wilsie, L.; Krsmanovic, M.; Ren, N.; Blom, D.; Cheng, K.; McCann, P. E.; Waters, M. G.; Tata, J.; Colletti, S. Bioorg Med Chem Lett 2009, 19, 4768.

[11] Varvounis, G.; Fiamegos, Y.; Pilidis, G. Adv Heterocycl Chem 2008, 95, 27.

[12] Varvounis, G.; Fiamegos, Y.; Pilidis, G. Adv Heterocycl Chem 2004, 87, 141.

[13] Varvounis, G.; Fiamegos, Y.; Pilidis, G. Adv Heterocycl Chem 2001, 80, 73.

[14] Elguero, J. InComprehensive Heterocyclic Chemistry; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 5, p 167.

[15] Betti, L.; Zanelli, M.; Giannaccini, G.; Manetti, F.; Schenone, S.; Strappaghetti, G. Bioorg Med Chem 2006, 14, 2828.

[16] Betti, L.; Corelli, F.; Floridi, M.; Giannaccini, G.; Maccari, L.; Manetti, F.; Strappaghetti, G.; Botta, M. J Med Chem 2003, 46, 3555.

[17] Li, C. S.; Brideau, C.; Chan, C. C.; Savoie, C.; Claveau, D.; Charleson, S.; Gordon, R.; Greig, G.; Gauthier, J. Y.; Lau, C. K.; Riendeau, D.; Thérien, M.; Wong, E.; Prasit, P. Bioorg Med Chem Lett 2003, 13, 597.

[18] Barbaro, R.; Betti, L.; Botta, M.; Corelli, F.; Giannaccini, G.; Maccari, L.; Manetti, F.; Strappaghetti, G.; Corsano, S. J Med Chem 2001, 44, 2118.

[19] Corsano, S.; Vezza, R.; Scapicchi, R.; Foresi, S.; Strappaghetti, G.; Nenci, G. G.; Gresele, P. Eur J Med Chem 1995, 30, 627.

[20] Yamada, T.; Nobuhara, Y.; Shimamura, H.; Tsukamoto, Y.; Yoshihara, K.; Yamaguchi, A.; Ohki, M. J Med Chem 1983, 26, 373.

[21] El-Mobayed, M. M.; Hussein, A. M.; Mohlhel, W. M. J Heterocycl Chem 2010, 47, 534.

[22] Elnagdi, M. H.; Al-Awadi, N. A.; Abdelhamid, I. A. Adv Heterocycl Chem 2009, 97, 1.

[23] Wan, W.; Hou, J.; Jiang, H.; Wang, Y.; Zhu, S.; Deng, H.; Hao, J. Tetrahedron 2009, 65, 4212.

[24] Khattab, S. N.; Bekhit, A. A.; El-Faham, A.; Massry, A. M. E.; Amer, A. Chem Pharm Bull 2008, 56, 1717.

[25] Ferguson, G. N.; Valant, C.; Horne, J.; Figler, H.; Flynn, B. L.; Linden, J.; Chalmers, D. K.; Sexton, P. M.; Christopoulos, A.; Scammells, P. J. J Med Chem 2008, 51, 6165.

[26] Clapham, K. M.; Batsanov, A. S.; Greenwood, R. D. R.; Bryce, M. R.; Smith, A. E.; Tarbit, B. J Org Chem 2008, 73, 2176.

[27] Murphy, D. E.; Dragovich, P. S.; Ayida, B. K.; Bertolini, T. M.; Li, L.-S.; Ruebsam, F.; Stankovic, N. S.; Sun, Z.; Zhao, J.; Zhou, Y. Tetrahedron Lett 2008, 49, 811.

[28] Al-Mousawi, S. M.; EL-Apasery, M. A.; Elnagdi, M. H. Heterocycles 2008, 75, 1151.

[29] Albrecht, A.; Koszuk, J.; Kobuciński, M.; Janecki, T. Org Biomol Chem 2008, 6, 1197.

[30] Jensen, B. S. Acta Chem Scand 1959, 13, 1668.

[31] Maruoka, H.; Yamagata, K.; Okabe, F.; Tomioka, Y. J Heterocycl Chem 2006, 43, 859.

[32] Masumoto, E.; Maruoka, H.; Okabe, F.; Nishida, S.; Yoshimura, Y.; Fujioka, T.: Yamagata, K. J Heterocycl Chem 2011, 48, 96.

[33] Maruoka, H.; Masumoto, E.; Okabe, F.; Nishida, S.; Yoshimura, Y.; Fujioka, T.: Yamagata, K. J Heterocycl Chem 2009, 46, 782.

[34] Maruoka, H.; Kashige, N.; Okabe, F.; Tanaka, R.; Miake, F.; Yamagata, K. J Heterocycl Chem 2008, 45, 1883.

[35] Craig, G. W.; Eberle, M.; Lamberth, C.; Vettiger, T. J Prakt Chem 2000, 342, 504.

[36] Tietze, L. F.; Steinmetz, A.; Balkenhohl, F. Bioorg Med Chem Lett 1997, 7, 1303.

[37] Short, F. W.; Schoeb, E. J. J Heterocycl Chem 1969, 6, 723.