A Novel One-Pot, Three-Component Synthesis of 5-Imino-2,3,5,8-tetrahydropyrazolo[1,2-*a*]pyridazin-1-one Derivatives

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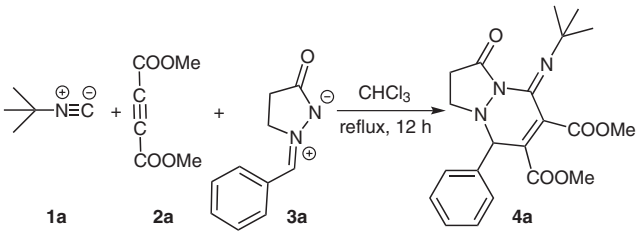
Abstract: It was found that the zwitterionic intermediate obtained from the addition of isocyanides to dimethyl acetylenedicarboxylate could react with 1,3-dipolar compounds under mild conditions to produce 5-imino-2,3,5,8-tetrahydropyrazolo[1,2-*a*]pyridazin-1-one derivatives in high yields. A plausible mechanism was also discussed for this process.

Key words: isocyanide, dimethyl acetylenedicarboxylate, multicomponent reactions, 1,3-dipolar compounds, 5-imino-2,3,5,8-tetrahydropyrazolo[1,2-*a*]pyridazin-1-one



Scheme 1

Multicomponent reactions (MCRs) have become increasingly important in the last 150 years. Compared with two-component reactions, multicomponent reactions are especially valuable. They have attracted considerable interest owing to their simple experimental procedures, one-pot character, and exceptional synthetic efficiency. Particularly, the isocyanide multicomponent reaction (IMCR) has occupied a major position in multicomponent reactions in recent years.[1–3] There are many reactions reported in the literature that involve isocyanides and dimethyl acetylenedicarboxylate.[4–9] The reactive 1:1 zwitterionic intermediate, formed by the addition of an isocyanide to dimethyl acetylenedicarboxylate, has since been identified.[10] In studying the reactions of zwitterionic intermediates, we found that zwitterionic intermediates obtained from isocyanide **1a** and dimethyl acetylenedicarboxylate (**2a**) could react with 1,3-dipolar compound **3a** to produce **4a** in good yield (80%, Scheme 1). This one-pot, three-component reaction gave a new and convenient way for the synthesis of 5-imino-2,3,5,8-tetrahydropyrazolo[1,2-*a*]pyridazin-1-one derivatives and pyrazolo[1,2-*a*]pyridazine ring systems[11] under mild conditions. In this paper, we presented our detailed investigations on this type of reaction.

Firstly, we conducted the reaction in various solvents at different temperatures to increase the product yield and reduce the reaction time. Of all of the solvents tested, such as dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, acetonitrile, and toluene, chloroform was found to be the best. The reaction could also take place at room temperature, but the yield was lower than that at reflux (Table 1, entries 4 and 5). Therefore, all the following reactions were carried out in chloroform at reflux.

Table 1 Reaction of *tert*-Butyl Isocyanide (**1a**) with Dimethyl Acetylenedicarboxylate (**2a**) and 2-Benzylidene-5-oxopyrazolidin-2-ium-1-ide (**3a**) under Various Conditions[a]

Entry	Temp	Solvent	Yield[b] (%)
1	reflux	CCl_4	33
2	reflux	toluene	50
3	reflux	CH_2Cl_2	60
4	r.t.	$CHCl_3$	52
5	reflux	$CHCl_3$	80
6	reflux	THF	0
7	reflux	MeCN	0

[a] Reaction conditions: *t*-BuNC (1.0 equiv), DMAD (1.0 equiv), 2-benzylidene-5-oxopyrazolidin-2-ium-1-ide (1.0 equiv).
[b] Isolated yield.

In subsequent research, it was found that aromatic aldehydes, regardless of electron-donating or electron-withdrawing substituents on the phenyl ring, participated in this process with high efficiency (Table 2). The products **4** were obtained in good or excellent yields. We also found that electron-deficient aldehydes performed much better than electron-rich ones. For example, the reaction of 4-methylbenzaldehyde and 4-methoxybenzaldehyde resulted in lower yields of the corresponding products (Table 2, entries 7 and 8). The position of the substituents on the aromatic ring has no significant effect on this transformation. Reactions of aromatic aldehydes, such as 4-chlorobenzaldehyde and the sterically congested 3-bromobenzaldehyde could also produce the corresponding products in high yields (Table 2, entries 2 and 6). To ex-

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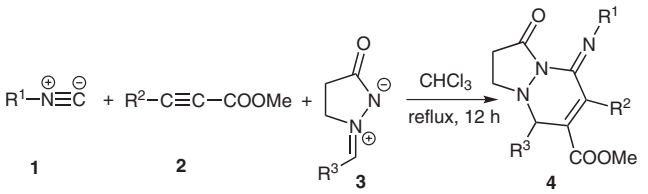
plore the scope of this reaction further, other isocyanides were utilized and the results were acceptable (Table 2, entries 11–14). Other acetylenic esters were also tried, but no conversion was observed in their reactions (Table 2, entries 15 and 16).

Table 2 Reaction of Isocyanides **1** with Acetylenic Esters **2** and 1,3-Dipolar Compounds **3**[a]



Entry	R^1	R^2	R^3	Product	Yield[b] (%)
1	*t*-Bu	CO_2Me	Ph	**4a**	80
2	*t*-Bu	CO_2Me	4-ClC_6H_4	**4b**	77
3	*t*-Bu	CO_2Me	4-BrC_6H_4	**4c**	72
4	*t*-Bu	CO_2Me	4-$O_2NC_6H_4$	**4d**	67
5	*t*-Bu	CO_2Me	3-ClC_6H_4	**4e**	85
6	*t*-Bu	CO_2Me	3-BrC_6H_4	**4f**	79
7	*t*-Bu	CO_2Me	4-MeC_6H_4	**4g**	35
8	*t*-Bu	CO_2Me	4-$MeOC_6H_4$	**4h**	33
9	*t*-Bu	CO_2Me	3-MeC_6H_4	**4i**	70
10	*t*-Bu	CO_2Me	3-$MeOC_6H_4$	**4j**	69
11	Cy	CO_2Me	Ph	**4k**	71
12	Cy	CO_2Me	4-$O_2NC_6H_4$	**4l**	70
13	Bn	CO_2Me	Ph	**4m**	63
14	Bn	CO_2Me	4-$O_2NC_6H_4$	**4n**	68
15	*t*-Bu	H	Ph	**4o**	–[c]
16	*t*-Bu	Ph	Ph	**4p**	–[c]

[a] Reagents and conditions: R^1NC **1** (1.0 equiv), acetylenic ester **2** (1.0 equiv), 1,3-dipolar compound **3** (1.0 equiv), $CHCl_3$, reflux, 12 h.
[b] Isolated yield.
[c] No reaction.

The structures of **4** were deduced from their IR, ^1H NMR, and ^{13}C NMR spectra and elemental analysis. In addition, the NMR-based structure was further confirmed by X-ray crystallographic analysis of **4a** (Figure 1).[12]

Although we have not established the mechanism of this reaction in an experimental manner, a possible explanation is proposed in Scheme 2. On the basis of the well-established chemistry of isocyanides,[1–3,13,14] it is reasonable to assume that the functionalized pyrazoles **4** may result from initial addition of the isocyanide **1** to acetylenedicarboxylate **2** and subsequent formation of the 1:1 adduct **5**,

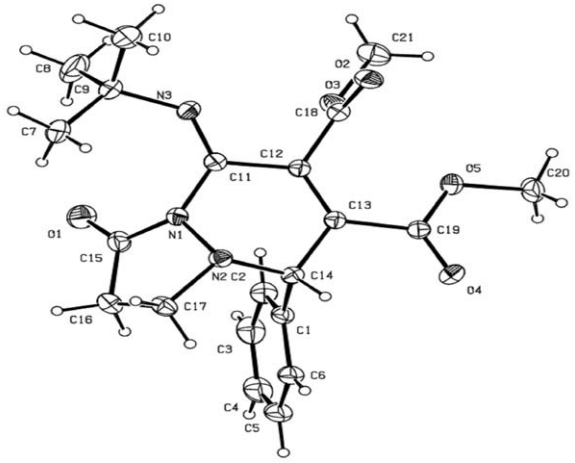
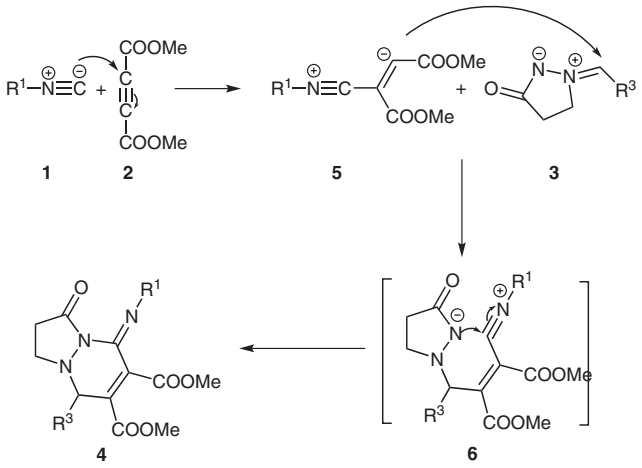


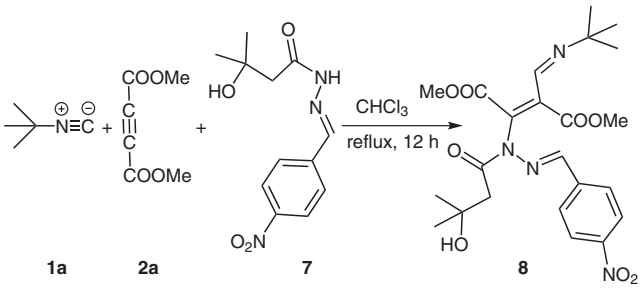
Figure 1 X-ray crystal structure of **4a**



Scheme 2

followed by attack of the 1,3-dipolar compound **3** resulting in the formation of **6**, which can produce the heterocyclic system **4**.

Another reaction using 3-hydroxy-3-methyl-*N*′-(4-nitrobenzylidene)butanehydrazide (**7**), an acyclic acylhydrazone was also tried. Unfortunately, the product with a cyclic structure was not obtained, but a linear compound dimethyl 2-[(*tert*-butylimino)methyl]-3-[1-(3-hydroxy-3-methylbutanoyl)-2-(4-nitrobenzylidene)hydrazinyl]fumarate (**8**) was formed (Scheme 3).



Scheme 3

The structure of **8** was deduced from its IR, ^{1}H NMR, and ^{13}C NMR spectra and elemental analysis. In addition, the NMR-based structure was further confirmed by X-ray crystallographic analysis of **8** (Figure 2).[15]

In conclusion, we have developed a novel one-pot, three-component synthesis of 5-imino-2,3,5,8-tetrahydropyrazolo[1,2-*a*]pyridazin-1-one derivatives. The simple starting materials, no need for catalysts, and good yields of the products are the main advantages of this method. Our future studies will focus on the application of these products.

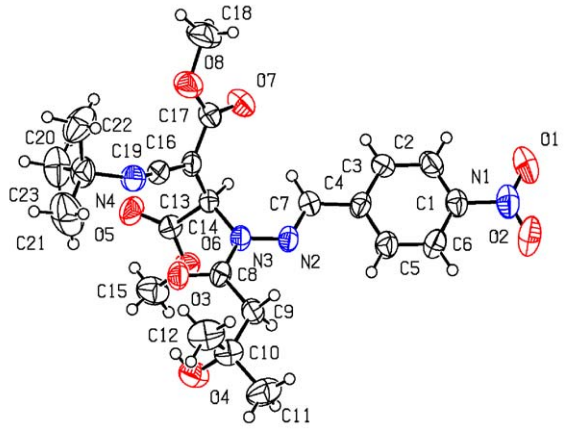


Figure 2 X-ray crystal structure of **8**

The acetylenecarboxylates were commercially available. Isocyanides and 1,3-dipolar compounds were prepared by literature procedures.[16,17] Melting points were determined on a microscopic apparatus and without correction. Column chromatography was carried out on silica gel; petroleum ether = PE. ^{1}H NMR spectra were recorded at 300 MHz or 400 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded at 75 MHz or 100 MHz in $CDCl_3$. A Nicolet AVATAR 360 FT-IR spectrophotometer was used for IR spectra.

Dimethyl 8-Imino-1-oxo-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-6,7-dicarboxylates 4a–n; General Procedure

To a magnetically stirred soln of acetylenedicarboxylate **2** (3 mmol) and 1,3-dipolar derivative **3** (3 mmol) in anhyd $CHCl_3$ (4 mL) was added a soln of the appropriate isocyanide **1** (3 mmol) in anhyd $CHCl_3$ (6 mL) at r.t. over 5 min. The mixture was then stirred and heated at reflux for 12 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, PE–EtOAc) to give final products.

Dimethyl 8-(*tert*-Butylimino)-1-oxo-5-phenyl-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-6,7-dicarboxylate (4a)

Recrystallization (PE–EtOAc); yellow solid; mp 113 °C.

IR (KBr): 3367, 2954, 1729, 1204, 1093 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (s, 1 H), 7.40–7.39 (m, 3 H), 7.27–7.24 (m, 2 H), 3.66 (s, 3 H), 3.51–3.46 (t, *J* = 7.5 Hz, 2 H), 3.42 (s, 3 H), 2.34–2.30 (t, *J* = 6.0 Hz, 2 H), 1.39 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.1, 167.4, 167.2, 149.8, 146.5, 133.5, 128.9, 128.7, 127.8, 114.1, 90.6, 54.8, 51.4, 51.3, 46.5, 30.5, 30.3.

Anal. Calcd for $C_{21}H_{25}N_3O_5$: C, 63.14; H, 6.31; N, 10.52. Found: C, 63.13; H, 6.33; N, 10.51.

Crystal data:[12] $C_{21}H_{25}N_3O_5$, *Mw* = 399.44, *T* = 294(2) K, λ = 0.71073 Å, $P2_1/c$, *a* = 9.6832(19) Å, *b* = 11.0308(19) Å, *c* = 12.041(2) Å, α = 68.267(3)°, β = 85.804(3)°, γ = 64.363(2)°, *V* = 1071.3(3) Å^3, *Z* = 2, D_{calcd} = 1.238 mg/m^3, μ = 0.089 mm^{-1}, *F*(000) = 424. Crystal size 0.28 × 0.25 × 0.22 mm, independent reflections 3953 [R_{int} = 0.0159], reflections collected 5669, refinement method, full-matrix least-squares on F^2, goodness-of-fit on F^2 1.234, final *R* indices [$I > 2\sigma(I)$] *R*1 = 0.0455, *wR*2 = 0.1026, *R* indices (all data) *R*1 = 0.0687, *wR*2 = 0.1132, extinction coefficient 0.012(2), Largest diff. peak and hole 0.179 and –0.149 e·Å^{-3}.

Dimethyl 8-(*tert*-Butylimino)-5-(4-chlorophenyl)-1-oxo-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-6,7-dicarboxylate (4b)

White solid; mp 135 °C.

IR (KBr): 3317, 2923, 1730, 1274, 1088 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (s, 1 H), 7.39–7.37 (d, *J* = 8.0 Hz, 2 H), 7.20–7.18 (d, *J* = 8.0 Hz, 2 H), 3.66 (s, 3 H), 3.49–3.47 (m, 2 H), 3.45 (s, 3 H), 2.33–2.30 (t, *J* = 6.0 Hz, 2 H), 1.39 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8, 167.2, 167.0, 149.8, 145.0, 134.8, 131.9, 129.0, 114.7, 90.3, 54.9, 52.3, 51.4, 51.3, 46.5, 30.4, 30.1.

Anal. Calcd for $C_{21}H_{24}ClN_3O_5$: C, 58.13; H, 5.58; N, 9.68. Found: C, 58.15; H, 5.57; N, 9.65.

Dimethyl 5-(4-Bromophenyl)-8-(*tert*-butylimino)-1-oxo-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-6,7-dicarboxylate (4c)

White solid; mp 139–140 °C.

IR (KBr): 3326, 2988, 1717, 1239, 1090 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (s, 1 H), 7.45–7.43 (d, *J* = 8.0 Hz, 2 H), 7.20–7.18 (d, *J* = 8.0 Hz, 2 H), 3.77 (s, 3 H), 3.37–3.35 (m, 2 H), 3.33 (s, 3 H), 1.96–1.93 (t, *J* = 6.0 Hz, 2 H), 1.28 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 165.5, 163.5, 149.8, 145.0, 134.6, 132.4, 131.9, 122.9, 90.2, 59.0, 52.2, 45.9, 38.8, 38.6, 31.7, 30.4.

Anal. Calcd for $C_{21}H_{24}BrN_3O_5$: C, 52.73; H, 5.06; N, 8.78. Found: C, 52.74; H, 5.05; N, 8.75.

Dimethyl 8-(*tert*-Butylimino)-5-(4-nitrophenyl)-1-oxo-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-6,7-dicarboxylate (4d)

Orange solid; mp 102–104 °C.

IR (KBr): 3380, 2922, 1734, 1203, 1094 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40 (s, 1 H), 8.29–8.27 (d, *J* = 6.0 Hz, 2 H), 7.46–7.44 (d, *J* = 6.0 Hz, 2 H), 3.67 (s, 3 H), 3.49–3.45 (m, 5 H), 2.36–2.32 (t, *J* = 6.0 Hz, 2 H), 1.40 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.8, 167.1, 166.8, 150.2, 147.8, 143.6, 140.1, 129.0, 124.1, 116.1, 89.7, 55.1, 51.7, 51.5, 46.8, 30.5, 30.1.

Anal. Calcd for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44; N, 12.61. Found: C, 56.75; H, 5.43; N, 12.59.

Dimethyl 8-(*tert*-Butylimino)-5-(3-chlorophenyl)-1-oxo-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-6,7-dicarboxylate (4e)

White solid; mp 138–140 °C.

IR (KBr): 3312, 2956, 1738, 1278, 1066 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (s, 1 H), 7.62–7.60 (d, *J* = 6.0 Hz, 1 H), 7.60–7.58 (d, *J* = 6.0 Hz, 1 H), 7.32–7.23 (m, 1 H), 4.54 (s, 1 H), 4.21–4.19 (m, 1 H), 4.02–3.94 (m, 1 H), 3.90 (s, 3 H), 3.79

(s, 3 H), 2.84–2.80 (t, *J* = 6.0 Hz, 1 H), 2.63–2.57 (m, 1 H), 1.06 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.2, 163.3, 159.2, 145.7, 139.7, 139.0, 137.9, 134.8, 131.0, 129.7, 127.4, 125.8, 53.5, 53.4, 52.8, 50.4, 37.6.

Anal. Calcd for $C_{21}H_{24}ClN_3O_5$: C, 58.13; H, 5.58; N, 9.68. Found: C, 58.14; H, 5.59; N, 9.66.

Dimethyl 5-(3-Bromophenyl)-8-(*tert*-butylimino)-1-oxo-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-6,7-dicarboxylate (4f)
White solid; mp 142–144 °C.

IR (KBr): 3310, 2957, 1735, 1276, 1067 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 7.71–7.69 (d, *J* = 6.0 Hz, 1 H), 7.39–7.24 (m, 2 H), 4.52 (s, 1 H), 4.19–4.13 (m, 1 H), 3.98–3.90 (m, 1 H), 3.85 (s, 3 H), 3.74 (s, 3 H), 2.83–2.75 (t, *J* = 12.0 Hz, 1 H), 2.58–2.52 (m, 1 H), 1.00 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.2, 163.2, 159.1, 145.8, 140.0, 138.9, 138.1, 133.9, 130.4, 129.9, 126.3, 122.9, 53.6, 53.4, 52.9, 50.5, 37.6.

Anal. Calcd for $C_{21}H_{24}ClN_3O_5$: C, 52.73; H, 5.06; N, 8.78. Found: C, 52.75; H, 5.04; N, 8.77.

Dimethyl 8-(*tert*-Butylimino)-1-oxo-5-(4-tolyl)-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-6,7-dicarboxylate (4g)
Yellow solid; mp 80–83 °C.

IR (KBr): 3328, 2955, 1730, 1269, 1039 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.20 (m, 4 H), 4.88 (s, 1 H), 3.83 (s, 3 H), 3.62–3.36 (m, 5 H), 2.35 (s, 3 H), 1.81–1.78 (t, *J* = 6.0 Hz, 2 H), 1.36 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 169.0, 161.5, 138.7, 130.0, 129.3, 129.2, 127.6, 127.0, 86.1, 63.1, 59.0, 52.3, 46.2, 33.4, 29.4, 29.1, 21.2.

Anal. Calcd for $C_{22}H_{27}N_3O_5$: C, 63.91; H, 6.58; N, 10.16. Found: C, 63.93; H, 6.56; N, 10.17.

Dimethyl 8-(*tert*-Butylimino)-5-(4-methoxyphenyl)-1-oxo-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-6,7-dicarboxylate (4h)
Yellow solid; mp 92–94 °C.

IR (KBr): 3319, 2957, 1709, 1275, 1066 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.27 (m, 2 H), 6.93–6.89 (m, 2 H), 4.88 (s, 1 H), 3.86 (s, 3 H), 3.80 (s, 3 H), 3.66–3.36 (m, 5 H), 3.36–3.32 (m, 1 H), 1.83–1.73 (m, 1 H), 1.36 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 164.7, 159.9, 131.2, 130.5, 129.4, 128.4, 124.7, 114.0, 90.8, 62.8, 59.1, 55.2, 52.3, 46.2, 35.4, 30.5, 29.1.

Anal. Calcd for $C_{22}H_{27}N_3O_6$: C, 61.53; H, 6.34; N, 9.78. Found: C, 61.50; H, 6.35; N, 9.79.

Dimethyl 8-(*tert*-Butylimino)-1-oxo-5-(3-tolyl)-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-6,7-dicarboxylate (4i)
Yellow solid; mp 83–84 °C.

IR (KBr): 3279, 2955, 1728, 1269, 1039 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 2 H), 7.07–7.02 (m, 2 H), 3.86 (s, 1 H), 3.66 (s, 3 H), 3.50–3.46 (t, *J* = 8.0 Hz, 2 H), 3.42 (s, 3 H), 2.36 (s, 3 H), 2.34–2.30 (t, *J* = 8.0 Hz, 2 H), 1.37 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.1, 167.4, 167.3, 149.8, 146.8, 138.5, 133.5, 129.6, 128.6, 124.8, 114.0, 90.8, 54.8, 52.3, 51.4, 51.3, 46.6, 30.5, 21.4.

Anal. Calcd for $C_{22}H_{27}N_3O_5$: C, 63.91; H, 6.58; N, 10.16. Found: C, 63.92; H, 6.60; N, 10.15.

Dimethyl 8-(*tert*-Butylimino)-5-(3-methoxyphenyl)-1-oxo-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-6,7-dicarboxylate (4j)
Yellow solid; mp 88–90 °C.

IR (KBr): 3280, 2952, 1731, 1207, 1094 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.39 (m, 2 H), 7.29–7.22 (m, 2 H), 7.16–7.14 (d, *J* = 8.0 Hz, 1 H), 3.84 (s, 3 H), 3.55–3.36 (m, 5 H), 3.18–3.16 (m, 2 H), 2.35 (s, 3 H), 1.43 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0, 163.5, 161.5, 142.6, 140.8, 138.3, 137.6, 129.5, 128.5, 127.7, 124.2, 86.0, 58.2, 52.5, 37.6, 33.5, 30.1, 29.5, 27.65.

Anal. Calcd for $C_{22}H_{27}N_3O_6$: C, 61.53; H, 6.34; N, 9.78. Found: C, 61.52; H, 6.32; N, 9.80.

Dimethyl 8-(Cyclohexylimino)-1-oxo-5-phenyl-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-6,7-dicarboxylate (4k)
Yellow solid; mp 113 °C.

IR (KBr): 3425, 2927, 1723, 1270, 1070 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 5 H), 4.94 (s, 1 H), 3.90 (s, 3 H), 3.64–3.53 (m, 5 H), 3.25–3.17 (t, *J* = 12.0 Hz, 1 H), 2.04–1.97 (m, 2 H), 1.86–1.71 (m, 2 H), 1.57–1.26 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 165.7, 163.5, 138.5, 138.3, 133.1, 131.4, 129.5, 129.3, 63.6, 60.7, 54.2, 52.7, 52.4, 34.7, 33.4, 33.1, 25.8, 23.8, 23.7.

Anal. Calcd for $C_{23}H_{27}N_3O_5$: C, 64.93; H, 6.40; N, 9.88. Found: C, 64.90; H, 6.38; N, 9.90.

Dimethyl 8-(Cyclohexylimino)-5-(4-nitrophenyl)-1-oxo-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-6,7-dicarboxylate (4l)
Orange solid; mp 90 °C.

IR (KBr): 3266, 2932, 1729, 1214, 1098 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.79–8.76 (d, *J* = 9.0 Hz, 1 H), 8.28–8.26 (d, *J* = 6.0 Hz, 2 H), 7.46–7.43 (d, *J* = 9.0 Hz, 2 H), 3.67 (s, 3 H), 3.52–3.46 (m, 5 H), 2.39–2.35 (t, *J* = 6.0 Hz, 2 H), 2.04–2.01 (m, 3 H), 1.76–1.50 (m, 4 H), 1.42–1.30 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 167.2, 167.0, 149.9, 147.7, 140.6, 140.2, 129.2, 124.0, 115.6, 84.0, 53.4, 51.6, 51.2, 46.3, 33.2, 30.0, 25.3, 24.3.

Anal. Calcd for $C_{23}H_{27}N_4O_7$: C, 58.72; H, 5.57; N, 11.91. Found: C, 58.73; H, 5.56; N, 11.93.

Dimethyl 8-(Benzylimino)-1-oxo-5-phenyl-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-6,7-dicarboxylate (4m)
Yellow solid; mp 156 °C.

IR (KBr): 3430, 2950, 1726, 1272, 1081 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.20 (m, 10 H), 4.96 (s, 2 H), 4.67 (s, 1 H), 3.91 (s, 3 H), 3.63–3.58 (m, 4 H), 3.44–3.36 (m, 1 H), 2.03–1.94 (m, 1 H), 1.25–1.00 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0, 165.4, 163.4, 142.2, 140.0, 132.8, 129.7, 129.3, 128.2, 127.1, 126.4, 63.9, 56.7, 52.7, 46.1, 29.7.

Anal. Calcd for $C_{24}H_{23}N_3O_5$: C, 66.50; H, 5.35; N, 9.69. Found: C, 66.35; H, 5.30; N, 9.76.

Dimethyl 8-(Benzylimino)-5-(4-nitrophenyl)-1-oxo-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-6,7-dicarboxylate (4n)
Orange solid; mp 86–88 °C.

IR (KBr): 3287, 2950, 1730, 1214, 1101 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.28–8.25 (d, *J* = 9.0 Hz, 2 H), 7.59–7.57 (d, *J* = 6.0 Hz, 2 H), 7.35–7.24 (m, 5 H), 5.05–4.95 (m, 2 H), 4.76 (s, 1 H), 3.92 (s, 3 H), 3.62–3.41 (m, 5 H), 2.17–2.04 (m, 1 H), 1.26–1.01 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3, 164.9, 163.1, 148.5, 141.5, 139.6, 130.3, 128.2, 127.1, 126.6, 124.2, 63.3, 56.7, 52.8, 46.1, 29.4.

Anal. Calcd for $C_{24}H_{22}N_4O_7$: C, 60.25; H, 4.63; N, 11.71. Found: C, 60.44; H, 4.71; N, 11.58.

3-Hydroxy-3-methyl-*N*′-(4-nitrobenzylidene)butanehydrazide (7)

4-Nitrobenzaldehyde (167 mg, 1.1 mmol) was added to a soln of 5,5-dimethylpyrazolidin-3-one (105 mg, 0.9 mmol) in MeOH (5 mL). The mixture was stirred at r.t. for 2 h. The precipitate was filtered and washed with acetone to give the product (146 mg, 55%) as a yellow solid; mp 140 °C.

IR (KBr): 3399, 2972, 1665, 1519, 1343 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.37 (s, 1 H), 8.29–8.27 (d, *J* = 8.0 Hz, 2 H), 7.95 (s, 1 H), 7.85–7.83 (t, *J* = 8.0 Hz, 2 H), 4.27 (s, 1 H), 3.01 (s, 2 H), 1.39 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.1, 148.6, 142.0, 139.3, 127.8, 124.1, 69.6, 43.3, 29.6.

Dimethyl 2-[(*tert*-Butylimino)methyl]-3-[1-(3-hydroxy-3-methylbutanoyl)-2-(4-nitrobenzylidene)hydrazinyl]fumarate (8)

To a magnetically stirred soln of acetylenedicarboxylate **2a** (3 mmol) and butanehydrazide **7** (3 mmol) in anhyd $CHCl_3$ (4 mL) was added a soln of the appropriate isocyanide **1a** (3 mmol) in anhyd $CHCl_3$ (6 mL) at r.t. in 5 min. The mixture was then stirred and heated at reflux for 12 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel PE–EtOAc) to give the final product (56%), which was recrystallized (PE–EtOAc) to give a yellow solid; mp 120 °C.

IR (KBr): 3451, 2977, 2072, 1681, 1344 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.29–8.26 (d, *J* = 9.0 Hz, 2 H), 7.89–7.86 (d, *J* = 9.0 Hz, 2 H), 5.68 (s, 1 H), 4.23 (s, 1 H), 3.76–3.74 (d, *J* = 6.0 Hz, 6 H), 3.22–3.17 (d, *J* = 15.0 Hz, 1 H), 2.96–2.91 (d, *J* = 15.0 Hz, 1 H), 1.49–1.45 (d, *J* = 12.0 Hz, 9 H), 1.34 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9, 170.6, 167.4, 161.0, 148.3, 140.2, 139.3, 127.9, 123.9, 69.5, 62.5, 58.9, 53.4, 52.8, 51.8, 43.9, 30.0, 29.5, 29.1.

Anal. Calcd for $C_{23}H_{30}N_4O_8$: C, 56.32; H, 6.16; N, 11.42. Found: C, 56.31; H, 6.18; N, 11.41.

Crystal data:[15] $C_{23}H_{30}N_4O_8$, *Mw* = 490.51, *T* = 296(2) K, λ = 0.71073 Å, $P2_1/c$, *a* = 8.7460(10) Å, *b* = 12.8442(15) Å, *c* = 24.154(3) Å, α = 94.182(6)°, β = 99.607(5)°, γ = 97.892(6)°, *V* = 2637.2(5) $Å^3$, *Z* = 4, D_{calcd} = 1.235 mg/m^3, μ = 0.094 mm^{-1}, *F*(000) = 1040. Crystal size 0.24 × 0.23 × 0.21 mm, independent reflections 9524 [R_{int} = 0.0284], reflections collected 13760, refinement method, full-matrix least-squares on F^2, goodness-of-fit on F^2 0.873, final *R* indices [$I > 2\sigma(I)$] *R*1 = 0.0502, *wR*2 = 0.1301, *R* indices (all data) *R*1 = 0.1274, *wR*2 = 0.1615, extinction coefficient 0.012(2), Largest diff. peak and hole 0.160 and –0.175 e·$Å^{-3}$.

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