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Facile synthesis of 1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-dione derivatives by a one-pot, three-component reactions

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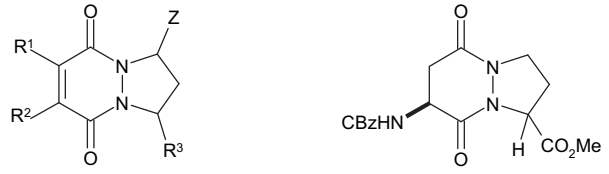
ABSTRACT

Protonation of the highly reactive 1:1 intermediate produced in the reaction between alkyl or aryl isocyanides and electron-deficient acetylenic esters with 3,6-dihydroxypyridazine, leads to a vinylisonitrilium cation, which undergoes an addition reaction with the conjugate base of the 3,6-dihydroxypyridazine to produce dialkyl 3-(alkyl or arylamino)-5,8-dioxo-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-1,2-dicarboxylates in good yields at room temperature.

1. Introduction

The design and development of convergent strategies to synthesize diverse arrays of drug-like compounds for biological screening is an important objective in contemporary chemical biology and medicinal chemistry. In this context, multicomponent reactions (MCRs) are attractive to many organic and pharmaceutical chemists, as these reactions allow construction of basic and important compounds that serve as molecular skeletons for many naturally occurring products and biologically active substances in a single step.[1]

Nitrogen-containing heterocycles have received a great deal of interest in the biological and medicinal sciences and this justifies continuing efforts in the development of new efficient and mild synthetic strategies.[2–6] Among a large variety of nitrogen-containing heterocyclic compounds, heterocycles containing a bridgehead hydrazine functionality have received considerable attention because of their pharmacological properties and clinical applications.[7–19] For example, 1-hydroxy-, 1-amino- and 1-hydrazino-2,3-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-diones **1** were reported to possess *anti*-inflammatory, analgesic, *anti*-hypoxic and *anti*-pyretic properties.[19] Furthermore, pyrazolidine compounds have been converted into azaproline amino acids, which have been studied upon incorporation into traditional peptides as well as small molecule peptidomimetics **2** (Scheme 1).[20,21] To the best of our knowledge, there are only a few reports[19,22,23] on cycloaddition entries into the fused 1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-dione ring system involving ring synthesis by formation of two bonds from [3+2] atom fragments ([CCC+NN]). All these cycloaddition reactions employ a two-component condensation between maleic hydrazide and an α,β-unsaturated aldehyde. To date, we know of no published report concerning the synthesis of pyrazolo[1,2-*a*]pyridazine ring systems, which proceed via the formation of three new bonds (one C=C and two C–N bonds) by a [C+CC+NN] annulation strategy.



1 **2**

Scheme 1. Some biologically active 1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-diones.

Extensive work has been done by many groups on the reactivities of 1,4-dipoles derived from activated acetylenic compounds and isocyanides.[24–26] Recently, these highly reactive

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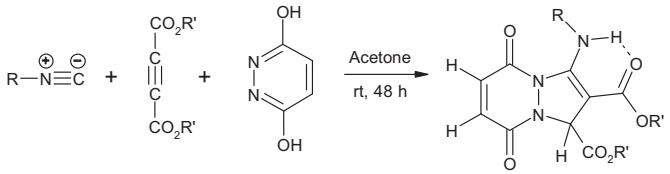
Table 1
Three-component condensation reactions of isocyanides, dialkyl acetylenedicarboxylates, and 3,6-dihydroxypyridazine



3 4 5 6

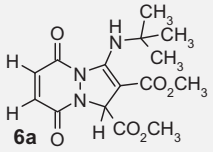
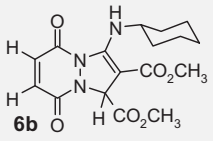
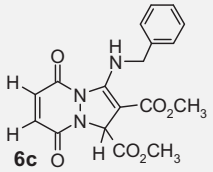
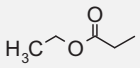
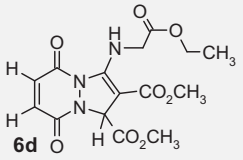
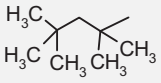
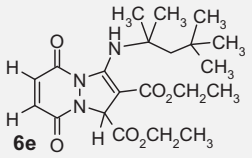
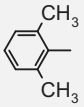
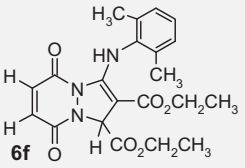
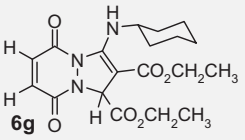
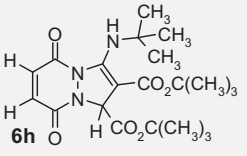
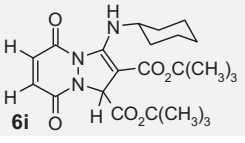
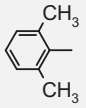
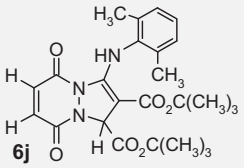
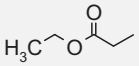
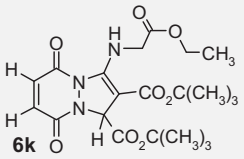
Entry	R	R′	Product	Yield[a] (%)
1			 **6a**	83
2			 **6b**	86
3			 **6c**	81
4			 **6d**	72
5			 **6e**	80
6			 **6f**	81
7			 **6g**	83
8			 **6h**	76
9			 **6i**	79

Table 1 (*continued*)

Entry	R	R′	Product	Yield[a] (%)
10			 **6j**	84
11			 **6k**	70

[a] Refers to purified yield.

1,4-dipolar intermediates have been captured by suitable CH–,[24] NH–,[25] and OH-acids[26] substrates. These studies have led to a number of interesting carbon–carbon bond forming reactions and heterocyclic constructions.

Indeed, our group has long had an interest in developing new reactions as well as expanding the scope of existing MCRs to rapidly access drug-like motifs. In connection with our recent interest aimed at the development of efficient protocols for the preparation of biologically active heterocycles via isocyanide-based multicomponent reactions involving acidic substrates,[27] in this report the facile synthesis of some new pyrazolopyridazine heterocycles is described.

3,6-Dihydroxypyridazine is a very interesting heterocyclic compound, which has two rather acidic protons.[28] In the present study, this was used advantageously in the formation of polyfunctional pyrazolopyridazine derivatives incorporating the 1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-dione substructure via a three-component condensation reaction of isocyanides.

2. Results and discussion

The one-pot, three-component condensation reactions of alkyl or aryl isocyanides **3** with dialkyl acetylenedicarboxylates **4** in the presence of 3,6-dihydroxypyridazine **5** proceeded at room temperature in dry acetone and were complete after 48 h to afford corresponding dialkyl 3-(alkyl or arylamino)-5,8-dioxo-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-1,2-dicarboxylates **6** in 70–86% yields and the full results are summarized in Table 1. ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of fused pyrazolopyridazine **6**. Any other products could not be detected by NMR spectroscopy.

The structures of the products **6a**–**k** were deduced from their elemental analyses and IR, ^{1}H NMR and ^{13}C NMR spectra. For example, the ^{1}H NMR spectrum of **6a** exhibited four single sharp lines readily recognized as arising from *tert*-butyl (δ_H 1.44 ppm), two methoxy protons (δ_H 3.70 and 3.76 ppm), and allylic methine (δ_H 5.60 ppm) along with two doublets for the two vinylic methines of pyridazine residue (δ_H 6.86 and 6.94 ppm, J=10.1 Hz). A fairly broad singlet (δ_H 8.55 ppm) was observed for the NH group. The presence of an amine proton was confirmed by exchange with D_2O. The chemical shift of the NH group indicates that this moiety must have participated in a six-membered intramolecular hydrogen bond formation with the vicinal carbonyl group as shown in Table 1.

The ^{1}H decoupled ^{13}C NMR spectrum of **6a** showed 13 distinct resonances, which confirmed the proposed structure. The characteristic signal due to the allylic methine carbon was discernible at δ_C 81.3 ppm and four carbonyl groups were resonated at δ_C 153.1, 156.9, 163.3 and 168.9 ppm. Partial assignment of these resonances is given in Experimental section.

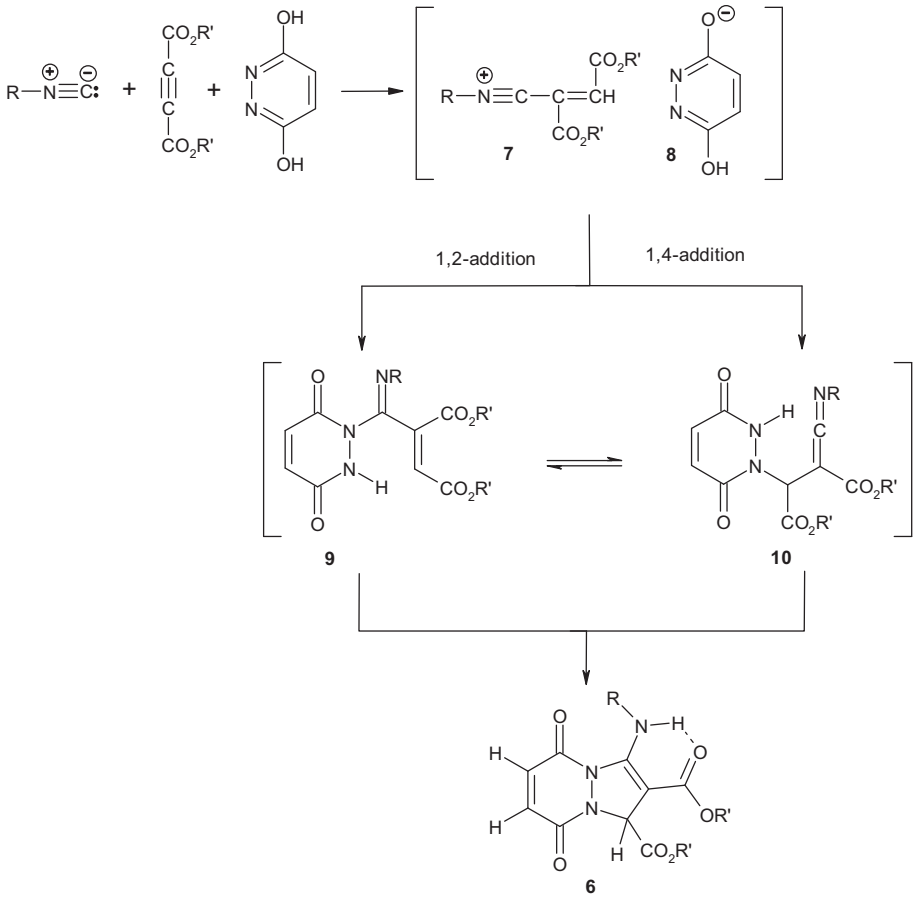
The structural assignments made on the basis of the ^{1}H and ^{13}C NMR spectra of compounds **6a** was supported by measurement of its IR spectra. The IR spectrum of **6a** showed strong absorptions at 1749, 1706, 1683 and 1657 cm^{-1} due to the carbonyls and the amino group at 3150 cm^{-1} as a weak broad band.

The scope and limitations of this three-component reaction were explored by using three dialkyl acetylenedicarboxylates and six alkyl or aryl isocyanides. The results show that the three-component reaction is quite general with dialkyl acetylenedicarboxylates affording the expected pyrazolopyridazines **6** in good yields. Note that even moderate yields are synthetically useful because these reactions form complex structures and a number of bonds are formed. Also, we examined the scope of reactive isocyanides in the three-component reaction. As shown in Table 1, a variety of structurally diverse alkyl or aryl isocyanides are used in this protocol with excellent results.

The mechanism of this reaction has not been established experimentally, a likely mechanism for the formation of these heterocycles **6** is shown in Scheme 2. In a first step, nucleophilic attack of the isocyanide on to the acetylenic ester and subsequent protonation of the highly reactive 1:1 zwitterionic intermediate by OH-acid (3,6-dihydroxypyridazine) affords the vinylisonitrilium cation **7**. Then, vinylisonitrilium cation **7** could undergone addition reactions with the nitrogen atom of the conjugate base of the OH-acid **8** on the two possible electrophilic sites (1,2-addition and 1,4-conjugate addition) to produce two possible intermediates **9** and **10** in equilibrium with each other. These intermediates can then cyclise under the reaction conditions employed to produce the dialkyl 3-(alkyl or arylamino)-5,8-dioxo-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-1,2-dicarboxylates **6**.

3. Conclusion

In summary, the one-pot, three-component condensation reaction of isocyanides with dialkyl acetylenedicarboxylates in presence of 3,6-dihydroxypyridazine can be successfully applied to the synthesis of dialkyl 3-(alkyl or arylamino)-5,8-dioxo-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-1,2-dicarboxylates derivatives. The method is simple, starts from readily accessible commercial reagents, and provides biologically interesting pyrazolopyridazine derivatives in good yields without any other additive to promote the reaction. Moreover, it is worth noting that two C–N and one C=C bonds were formed with concomitant creation of a fused pyrazolopyridazine ring in this one-pot, three-component process.



Scheme 2.

4. Experimental

4.1. General

Melting points were measured on a Büchi 535 apparatus and are uncorrected. Elemental analyses were performed using an elementar vario EL III instrument. FTIR Spectra were recorded on a *Bruker Equinox-55* spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 Avance spectrometer at 400.13 and 100.77 MHz, respectively, with $CDCl_3$ as solvent. *Chemical shifts are reported in parts per million relative to TMS as internal reference.* The solvents, 3,6-dihydroxypyridazine, dimethyl and diethyl acetylenedicarboxylates, cyclohexyl and 1,1,3,3-tetramethylbutyl isocyanides used in this work were purchased from Merck and the 2,6-dimethylphenyl, *tert*-butyl isocyanide, and di-*tert*-butylacetylenedicarboxylate were obtained from Fluka (Buchs, Switzerland). The benzyl isocyanide and ethyl isocyanoacetate were obtained from Aldrich chemical company. All reagents were used without further purification.

4.2. Typical procedure for preparation of dimethyl 3-(*tert*-butylamino)-5,8-dioxo-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-1,2-dicarboxylate (6a)

To a magnetically stirred solution of 3,6-dihydroxypyridazine (0.056 g, 0.5 mmol) and *tert*-butyl isocyanide (0.042 g, 0.5 mmol) in dry acetone (40 mL) was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.071 g, 0.5 mmol) in acetone (2 mL) at room temperature over 10 min via a syringe. The reaction mixture was stirred at room temperature for 48 h. The solvent was removed under reduced pressure and the solid residue was washed with diethyl ether and crystallized from CH_2Cl_2:*n*-hexane (1:4) to give **6a** as yellow powder (0.140 g, 83%). Mp 164–166 °C (dec); R_f (30% EtOAc/*n*-hexane) 0.55; IR (KBr) (ν_{max}, cm^{-1}): 3150 (N–H), 1749, 1706, 1683 and 1657 (C=O), 1597 and 1554 (C=C); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 3.70 and 3.76 (6H, 2 s, OCH_3), 5.60 (1H, s, NCH), 6.86 and 6.94 (2H, 2 d, J=10.2 Hz, CH=CH), 8.55 (1H, br s, NH···O=C); δ_C (100.6 MHz, $CDCl_3$) 168.9 and 163.3 (2×CO_2Me), 156.9 and 153.1 (2×N–C=O), 149.1 (N–*C*=C), 135.9 and 134.8 (CH=CH), 81.3 (N–C=*C*), 62.8 (N–CH), 57.4 (*C*Me_3), 53.1 and 51.2 (2×OCH_3), 29.9 (C*Me*$_3$); Anal. Calcd for $C_{15}H_{19}N_3O_6$ (337.32): C, 53.41; H, 5.68; N, 12.46%. Found: C, 53.46; H, 5.71; N, 12.43%.

*4.2.1. Dimethyl 3-(cyclohexylamino)-5,8-dioxo-5,8-dihydro-1H-pyrazolo[1,2-a]pyridazine-1,2-dicarboxylate (**6b**).* Yellow powder (0.160 g, 86%); mp 182–184 °C (dec); R_f (30% EtOAc/*n*-hexane) 0.53; IR (KBr) (ν_{max}, cm^{-1}): 3073 (N–H), 1744, 1707, 1682 and 1655 (C=O), 1600 and 1550 (C=C); δ_H (400 MHz, $CDCl_3$) 1.22–1.70 (10H, m, 5 CH_2), 3.70 and 3.78 (6H, 2 s, 2 °CH_3), 4.40 (1H, m, NHC*H*), 5.57 (1H, s, NCH), 6.90 and 6.96 (2H, 2 d, J=10.1 Hz, CH=CH), 8.50 (1H, d, J=5.1 Hz, NH···O=C); δ_C (100.6 MHz, $CDCl_3$) 169.1 and 162.8 (2×*C*O_2Me), 156.8 and 153.0 (2×N–C=O), 149.2 (N–*C*=C), 135.6 and 135.1 (CH=CH), 77.9 (N–C=*C*), 62.8 (N–CH), 53.9 (NH–CH), 53.0 and 51.3 (2×OCH_3), 33.7, 33.1, 25.4, 24.2 and 24.1 (5×CH_2); Anal. Calcd for $C_{17}H_{21}N_3O_6$ (363.36): C, 56.19; H, 5.83; N, 11.56%. Found: C, 56.26; H, 5.80; N, 12.01%.

*4.2.2. Dimethyl 3-(benzylamino)-5,8-dioxo-5,8-dihydro-1H-pyrazolo[1,2-a]pyridazine-1,2-dicarboxylate (**6c**).* Yellow powder (0.151 g, 81%); mp 190–192 °C (dec); R_f (30% EtOAc/*n*-hexane) 0.56; IR (KBr) (ν_{max}, cm^{-1}): 3132 (N–H), 1748, 1710, 1680 and 1660 (C=O), 1609 and 1558 (C=C); δ_H (400 MHz, $CDCl_3$) 3.74 and 3.81 (6H, 2 s,

2 °CH_3), 4.38 and 4.42 (2H, AB system, J=14.8 Hz, NHCH_2Ph), 5.61 (1H, s, NCH), 6.88 and 6.95 (2H, 2 d, J=10.0 Hz, CH=CH), 7.28–7.41 (5H, m, C_6H_5), 8.54 (1H, br s, NH···O=C); δ_C (100.6 MHz, $CDCl_3$) 169.3 and 162.7 (2×CO_2Me), 156.9 and 152.8 (2×N–C=O), 149.0 (N–*C*=C), 138.1 and 135.4 (CH=CH), 135.1 (C_{ipso}), 128.4 (C_{meta}), 127.3 (C_{para}), 127.1 (C_{ortho}), 77.8 (N–C=*C*), 62.9 (N–CH), 53.5 and 51.2 (2×OCH_3), 43.5 (NH–CH_2); Anal. Calcd for $C_{18}H_{17}N_3O_6$ (371.34): C, 58.22; H, 4.61; N, 11.32%. Found: C, 58.30; H, 4.58; N, 11.35%.

*4.2.3. Dimethyl 3-[(ethoxycarbonyl)methylamino]-5,8-dioxo-5,8-dihydro-1H-pyrazolo[1,2-a]pyridazine-1,2-dicarboxylate (**6d**).* Yellow powder (0.133 g, 72%); mp 153–155 °C (dec); R_f (30% EtOAc/*n*-hexane) 0.63; IR (KBr) (ν_{max}, cm^{-1}): 3204 (N–H), 1741, 1736, 1701, 1667 and 1661 (C=O), 1602 and 1554 (C=C); δ_H (400 MHz, $CDCl_3$) 1.20 (3H, t, J=7.1 Hz, CH_2CH_3), 3.72 and 3.79 (6H, 2 s, 2 °CH_3), 4.15–4.22 (4H, m, CH_2CH_3 and NHCH_2CO), 5.66 (1H, s, NCH), 6.89 and 6.94 (2H, 2 d, J=10.1 Hz, CH=CH), 8.89 (1H, br s, NH···O=C); δ_C (100.6 MHz, $CDCl_3$) 169.8, 168.5 and 163.8 (2×CO_2Me and CO_2Et), 156.9 and 153.2 (2×N–C=O), 148.8 (N–*C*=C), 136.0 and 133.7 (CH=CH), 82.3 (N–C=*C*), 62.1 (N–CH), 61.9 (OCH_2), 53.2 and 51.5 (2×OCH_3), 44.2 (NH–CH_2), 14.1 (CH_3); Anal. Calcd for $C_{15}H_{17}N_3O_8$ (367.31): C, 49.05; H, 4.66; N, 11.44%. Found: C, 48.97; H, 4.70; N, 11.45%.

*4.2.4. Diethyl 5,10-dioxo-3-[(1,1,3,3-tetramethylbutyl)amino]-5,8-dihydro-1H-pyrazolo[1,2-a]pyridazine-1,2-dicarboxylate (**6e**).* Yellow powder (0.169 g, 80%); mp 190–192 °C (dec); R_f (30% EtOAc/*n*-hexane) 0.55; IR (KBr) (ν_{max}, cm^{-1}): 3180 (N–H), 1744, 1706, 1678 and 1660 (C=O), 1588, 1548 (C=C); δ_H (400 MHz, $CDCl_3$) 1.06 (9H, s, $C(CH_3)_3$), 1.21 and 1.26 (6H, 2 t, $^3J_{HH}$=7.0 Hz, 2 °CH_2CH_3), 1.48 and 1.53 (6H, 2 s, $C(CH_3)_2$), 1.78 and 2.03 (2H, AB system, $^2J_{HH}$=15.1 Hz, CH_2), 4.15–4.21 (4H, m, 2 ABX_3 overlapping systems, 2 OCH_2CH_3), 5.58 (1H, s, NCH), 6.89 and 6.97 (2H, 2 d, J=10.1 Hz, CH=CH), 8.51 (1H, s, NH···O=C); δ_C (100.6 MHz, $CDCl_3$) 169.9 and 163.3 (2×CO_2Et), 157.1 and 153.2 (2×N–C=O), 149.5 (N–*C*=C), 136.5 and 134.7 (CH=CH), 81.9 (N–C=*C*), 62.6 (N–CH), 62.2 and 62.1 (2×OCH_2), 60.1 (CMe_2), 50.0 (CH_2), 31.8 (CMe_2), 30.8 (CMe_3) 29.1 (CMe_3) 14.5 and 14.1 (2×CH_3); Anal. Calcd for $C_{21}H_{31}N_3O_6$ (421.48): C, 59.84; H, 7.41; N, 9.97%. Found: C, 59.90; H, 7.39; N, 10.00%.

*4.2.5. Diethyl 3-[(2,6-dimethylphenyl)amino]-5,8-dihydro-1H-pyrazolo[1,2-a]pyridazine-1,2-dicarboxylate (**6f**).* Yellow powder (0.167 g, 81%); mp 205–207 °C (dec); R_f (30% EtOAc/*n*-hexane) 0.51; IR (KBr) (ν_{max}, cm^{-1}): 3170 (N–H), 1736, 1710, 1681 and 1657 (C=O), 1594, 1540 (C=C); δ_H (400 MHz, $CDCl_3$) 1.22 and 1.25 (6H, 2 t, $^3J_{HH}$=7.0 Hz, 2 °CH_2CH_3), 2.19 (6H, s, 2 CH_3), 4.16–4.22 (4H, m, 2 ABX_3 overlapping systems, 2 OCH_2CH_3), 5.68 (1H, s, NCH), 6.87 and 6.98 (2H, 2 d, J=10.0 Hz, CH=CH), 8.61 (1H, br s, NH···O=C); δ_C (100.6 MHz, $CDCl_3$) 168.8 and 162.2 (2×CO_2Et), 156.7 and 152.8 (2×N–C=O), 149.1 (N–*C*=C), 135.6 and 134.9 (CH=CH), 131.4, 130.8, 129.7 and 123.1 (aromatic carbons), 81.0 (N–C=*C*), 62.9 (N–CH), 62.2 and 60.2 (2×OCH_2), 18.7 ($C_6H_3Me_2$), 14.3 and 13.9 (2×CH_3); Anal. Calcd for $C_{21}H_{23}N_3O_6$ (413.42): C, 61.01; H, 5.61; N, 10.16%. Found: C, 60.96; H, 5.63; N, 10.20%.

*4.2.6. Diethyl 3-(cyclohexylamino)-5,8-dihydro-1H-pyrazolo[1,2-a]pyridazine-1,2-dicarboxylate (**6g**).* Yellow powder (0.163 g, 83%); mp 218–220 °C (dec); R_f (30% EtOAc/*n*-hexane) 0.60; IR (KBr) (ν_{max}, cm^{-1}): 3125 (N–H), 1744, 1708, 1670 and 1614 (C=O), 1588, 1533 (C=C); δ_H (400 MHz, $CDCl_3$) 1.21–2.18 (10H, m, 5 CH_2), 1.21 and 1.23 (6H, 2 t, $^3J_{HH}$=7.0 Hz, 2 °CH_2CH_3), 4.10–4.23 (4H, m, 2 ABX_3 overlapping systems, 2 OCH_2CH_3), 4.38 (1H, m, NHC*H*), 5.59 (1H, s, NCH), 6.86 and 6.93 (2H, 2 d, J=10.0 Hz, CH=CH), 8.57 (1H, d, J=5.0 Hz, NH···O=C); δ_C (100.6 MHz, $CDCl_3$) 170.0 and 162.7 (2×CO_2Et), 156.8 and 152.8 (2×N–C=O), 149.1 (N–*C*=C), 135.6 and 135.0 (CH=CH), 78.0 (N–C=*C*), 62.5 (N–CH), 62.1 and 60.4 (2×OCH_2), 51.3 (NH–CH), 33.7, 33.1, 25.4, 24.2 and 24.1 (5×CH_2), 14.3 and 14.1 (2×CH_3); Anal. Calcd for $C_{19}H_{25}N_3O_6$ (391.41): C, 58.30; H, 6.44; N, 10.74%. Found: C, 58.34; H, 6.47; N, 10.80%.

*4.2.7. Di-tert-butyl 3-(tert-butylamino)-5,8-dioxo-5,8-dihydro-1H-pyrazolo[1,2-a]pyridazine-1,2-dicarboxylate (**6h**).* Yellow powder (0.160 g, 76%); mp 157–159 °C (dec); R_f (30% EtOAc/*n*-hexane) 0.64; IR (KBr) (ν_{max}, cm^{-1}): 3142 (N–H), 1744, 1712, 1661 and 1623 (C=O), 1604, 1543 (C=C); δ_H (400 MHz, $CDCl_3$) 1.18 (9H, s, $NC(CH_3)_3$), 1.25 and 1.40 (18H, s, 2×$OC(CH_3)_3$), 5.60 (1H, s, NCH), 6.93 and 6.96 (2H, 2 d, J=10.1 Hz, CH=CH), 8.50 (1H, br s, NH···O=C); δ_C (100.6 MHz, $CDCl_3$) 168.8 and 162.8 (2×$CO_2{}^t$Bu), 156.7 and 152.4 (2×N–C=O), 149.0 (N–*C*=C), 135.7 and 134.7 (CH=CH), 80.3 (N–C=*C*), 79.8 and 79.3 (2×$OCMe_3$), 62.5 (N–CH), 57.3 ($NCMe_3$), 30.3 ($NCMe_3$), 29.9 and 29.8 (2×$OCMe_3$); Anal. Calcd for $C_{21}H_{31}N_3O_6$ (421.48): C, 59.84; H, 7.41; N, 9.97%. Found: C, 59.90; H, 7.45; N, 9.95%.

*4.2.8. Di-tert-butyl 3-(cyclohexylamino)-5,8-dioxo-5,8-dihydro-1H-pyrazolo[1,2-a]pyridazine-1,2-dicarboxylate (**6i**).* Yellow powder (0.177 g, 79%); mp 205–207 °C (dec); R_f (30% EtOAc/*n*-hexane) 0.61; IR (KBr) (ν_{max}, cm^{-1}): 3201 (N–H), 1735, 1709, 1648 and 1620 (C=O), 1587, 1550 (C=C); δ_H (400 MHz, $CDCl_3$) 1.17–2.06 (10H, m, 5 CH_2), 1.30 and 1.46 (18H, 2 s, 2×$OC(CH_3)_3$), 4.38 (1H, m, NHC*H*), 5.58 (1H, s, NCH), 6.94 and 6.97 (2H, 2 d, J=10.1 Hz, CH=CH), 8.54 (1H, br s, NH···O=C); δ_C (100.6 MHz, $CDCl_3$) 169.2 and 163.1 (2×$CO_2{}^t$Bu), 156.6 and 151.9 (2×N–C=O), 148.8 (N–*C*=C), 135.6 and 134.6 (CH=CH), 80.2 (N–C=*C*), 80.0 and 79.7 (2×$OCMe_3$), 62.4 (N–CH), 51.5 (NH–CH), 33.7, 33.2, 25.3, 24.3, 24.1 (5×CH_2), 29.9 and 29.7 (2×$OCMe_3$); Anal. Calcd for $C_{23}H_{33}N_3O_6$ (447.52): C, 61.73; H, 7.43; N, 9.39%. Found: C, 61.68; H, 7.40; N, 9.41%.

*4.2.9. Di-tert-butyl 3-[(2,6-dimethylphenyl)amino]-5,8-dioxo-5,8-dihydro-1H-pyrazolo[1,2-a]pyridazine-1,2-dicarboxylate (**6j**).* Yellow powder (0.197 g, 84%); mp 214–216 °C (dec); R_f (30% EtOAc/*n*-hexane) 0.60; IR (KBr) (ν_{max}, cm^{-1}): 3176 (N–H), 1745, 1714, 1681 and 1648 (C=O), 1588, 1501 (C=C); δ_H (400 MHz, $CDCl_3$) 1.24 and 1.41 (18H, s, 2×$OC(CH_3)_3$), 2.21 (6H, s, 2×CH_3), 5.58 (1H, s, NCH), 6.84 and 6.92 (2H, 2 d, J=10.1 Hz, CH=CH), 8.53 (1H, br s, NH···O=C); δ_C (100.6 MHz, $CDCl_3$) 169.2 and 163.1 (2×$CO_2{}^t$Bu), 156.6 and 152.1 (2×N–C=O), 148.9 (N–*C*=C), 135.6 and 135.0 (CH=CH), 131.4, 131.0, 129.8 and 123.2 (aromatic carbons), 80.4 (N–C=*C*), 80.1 and 79.9 (2×$OCMe_3$), 62.5 (N–CH), 29.9 and 29.7 (2×$OCMe_3$), 18.8 ($C_6H_3Me_2$); Anal. Calcd for $C_{25}H_{31}N_3O_6$ (469.53): C, 63.95; H, 6.65; N, 8.95%. Found: C, 64.02; H, 6.60; N, 9.00%.

*4.2.10. Di-tert-butyl 3-[(ethoxycarbonyl)methylamino]-5,8-dioxo-5,8-dihydro-1H-pyrazolo[1,2-a]pyridazine-1,2-dicarboxylate (**6k**).* Yellow powder (0.158 g, 70%); mp 170–172 °C (dec); R_f (30% EtOAc/*n*-hexane) 0.67; IR (KBr) (ν_{max}, cm^{-1}): 3180 (N–H), 1748, 1734, 1705, 1672 and 1652 (C=O), 1602 and 1532 (C=C); δ_H (400 MHz, $CDCl_3$) 1.19 (3H, t, J=7.1 Hz, CH_2CH_3), 1.25 and 1.41 (18H, s, 2×$OC(CH_3)_3$), 4.16–4.22 (4H, m, CH_2CH_3 and NHCH_2CO), 5.63 (1H, s, NCH), 6.88 and 6.96 (2H, 2 d, J=10.1 Hz, CH=CH), 8.70 (1H, br s, NH···O=C); δ_C (100.6 MHz, $CDCl_3$) 169.5, 168.3 and 163.8 (2×$CO_2{}^t$Bu and CO_2Et), 156.1 and 152.9 (2×N–C=O), 148.7 (N–*C*=C), 135.7 and 133.7 (CH=CH), 81.9 (N–C=*C*), 80.5 and 80.0 (2×$OCMe_3$), 62.3 (N–CH), 62.0 (OCH_2), 43.9 (NH–CH_2), 29.9 and 29.8 (2×$OCMe_3$), 14.1 (CH_3); Anal. Calcd for $C_{21}H_{29}N_3O_8$ (451.47): C, 55.87; H, 6.47; N, 9.31%. Found: C, 55.93; H, 6.50; N, 9.34%.

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