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ORIGINAL PAPER

The clean synthesis and confirmatory structural characterization of new 2-amino-4,8-dihydropyrano[3,2-*b*]pyran-3-cyano based on Kojic acid

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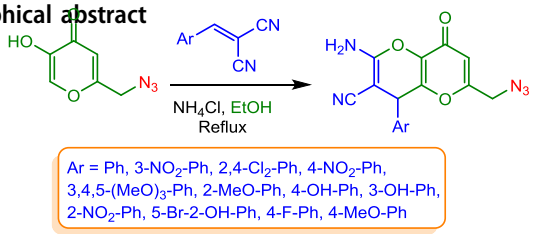
Abstract

A valuable and clean method was developed for the synthesis of the group of different novel 2-amino-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitriles containing a 2-aminopyran moiety by using of azido kojic acid and various 2-arylidinemalononitriles in the presence of NH_4Cl as a catalyst in a green solvent (ethanol) with excellent yields. All structures were analyzed by FT-IR, ^1H, ^{13}C NMR spectroscopy, and representatively, one compound was analyzed by X-ray crystallography technique. Crystallographic analyses indicated that of this compound a dimer formed via two weak intermolecular hydrogen bonds with $d_{(N\cdots O)}$ distances of 2.927 Å and made a 14-membered ring with centrosymmetric (C_i) form.

Graphical abstract



Keywords Kojic acid · Azido kojic acid · Michael addition · Pyran · 2-Amino-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile

Introduction

Pyrans are one of the main series of heterocyclic six-membered compounds including oxygen. Pyran products constitute a key structural motif of numerous biologically active natural and synthetic compounds which own a wide ranging of pharmacological [1] and biological activities and endure attracting attention [2–4]. Pyrans and poly-substituted pyrans due to their numerous medicinal and biological actions such as antioxidant [5], anticancer [6, 7], anti-inflammatory and antiviral [8], antibacterial [9], antimicrobial [10], anti-HIV [11], antifungal [12], and calcium channel antagonist activities [13] have received far interest.

A number of 2-aminopyrans are utilized in pigments [14] and photoactive resources [15] and also used as potentially bio-decomposable agrochemicals [16, 17]. Polyfunctionalized 2-amino-4*H*-pyran-3-cyano derivatives are the main heterocyclic compounds, which often show a range of biological actions [18–28]. Bispyrans show great colorability, as well as moral fatigue resistance and also are used as new photochromic dyes for the preparation of

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resources with uses in the modulation of fluorescence, filter, and display [29].

Kojic acid is a by-product of the fermentation of the saccharose, glucose, starch, etc., by different microorganisms (*Aspergillus*, *Penicillium*, and *Acetobacter*) in an aerobic process [30–32]. Kojic acid (KA) and some of its derivatives are an important category of the structural motif of many compounds (natural and synthetic), which possess high activity outline due to their wide series of biological actions as tyrosinase inhibitory activities [33, 34], antimelanogenic [35], antimicrobial [36], whitening agent [37], anti-inflammatory [38], antineoplastic [39], antiviral and anticonvulsant [40], antifungal and antibacterial [41], antioxidant [42], and depigmenting [43]. Pyrano[3,2-*b*]pyrans are of more notice in the synthesis of organic compounds, and numerous ways consuming diverse homogeneous and heterogeneous catalysts have been described for the manufacture of derivatives of KA [9, 19, 44–52].

Recently, some approaches have been published for the efficient and facile synthesis of polysubstituted 2-amino-4*H*-pyran-3-cyano supports [53]. Among these compounds, probable biological activity, great reactivity, and the ready accessibility of kojic acid make it a nice-looking molecule in pharmacological chemistry and synthetic reactions [20, 54]. The blend of two main structures such as pyran and kojic acid can lead to novel and substitute drug nominees with an enhanced pharmacological outline. In association with our attention in the product of heterocyclic derivatives [42, 55] and the wide spectrum of uses of pyrans, 2-aminopyrans, 2-amino-4*H*-pyran-3-cyano, bispyrans, and kojic acid as biologically active compounds, we became concerned in the synthesis of different 2-amino-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitriles from azido kojic acid with various alkenes (2-arylidenemalononitrile). Also, we present a safe, efficient, and clean method for the construction of new 2-amino-6-(azidomethyl)-8-oxo-4-aryl-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile derivatives from azido kojic acid with various alkenes in ethanol as a clean solvent.

Results and discussion

Initially, the reaction of KA (**1**) with $SOCl_2$ (thionyl chloride) at room temperature formed chloro kojic acid [2-(chloromethyl)-5-hydroxy-4*H*-pyran-4-one] [56], then followed 2-(azidomethyl)-5-hydroxy-4*H*-pyran-4-one (**2**) in the reaction with sodium azide (NaN_3) in dry DMF [57]. A strong absorption band at 2109 cm^{-1} matching to the azide group in the FT-IR spectra of the azide compound **2** was displayed (Scheme 1).

The reaction of **2** with Knoevenagel adducts **3** afforded 2-amino-6-(azidomethyl)-8-oxo-4-aryl-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitriles **4**. ^{1}H NMR spectra and X-ray crystallographic analysis data (see later) confirmed the formation of **4** (Scheme 1 and experimental data).

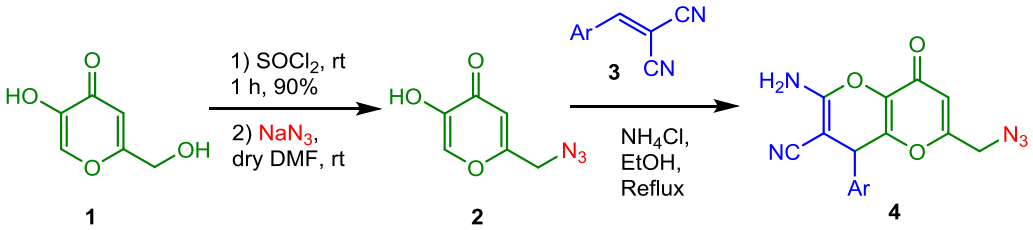
Representatively, FT-IR spectrum of **4a** showed broad peaks at the frequencies of 3387 and 3314 cm^{-1} that corresponded to NH_2 functional group, respectively, and two sharp peaks at 2193 and 2112 cm^{-1} were of nitrile and azide groups. A sharp peak at 1643 cm^{-1} corresponded to pyrone carbonyl group. ^{1}H NMR spectrum of this compound showed doublet of doublet at δ = 4.23–4.37 ppm which corresponded to diastereotopic methylene protons connected to azide substituent. A singlet at 4.82 ppm is of benzylic methine proton in the chiral center. The peak of amino protons is overlapped at aromatic peaks region. Other proton's peaks had good agreement with the assigned structure. ^{13}C NMR spectrum of **4a** showed 14 distinct peaks that confirmed the proposed structure. Two peaks at δ = 56.077 and 50.209 ppm corresponded to methylene and methine carbon atoms, respectively (see experimental section and Supplementary data). A possible mechanism for the production of 2-amino-6-(azidomethyl)-8-oxo-4-phenyl-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitriles **4a**–**4l** is shown in Scheme 2 [21, 58, 59].

First, enolate of azido kojic acid **2** corresponding to Knoevenagel adduct **3** is added via Michael addition which formed intermediate **A**. The 1,3-proton shift formed intermediate **B** and then, with a nucleophilic attack of oxygen enolate anion of intermediate **B** to nitrile group formed intermediate **C**. Finally, 1,3-proton shift to the nitrogen anion obtained more stable compounds **4**.

As shown in Table 1, in the item of alkenes with electron-withdrawing groups such as **4b**, **4c**, **4d**, **4i**, and **4k**, the time of reaction was short and the yields of the reaction were excellent. In contrast, in the case of alkenes with electron-donating groups such as **4e**, **4f**, **4g**, **4h**, **4j**, and **4l**, the time of reaction was long and the yields of the reaction were good. We performed the reaction of azido KA **2** with the Knoevenagel adducts **5**–**7** in which derived from the condensation reaction of malononitrile and ethyl cyanoacetate with various aromatic aldehydes. No expected compounds **8** and **9** were observed. In the case of the alkenes **6** and **10**, there was no product due to the high resonance of alkene double bond [60] that would not allow Michael addition (Fig. 1).

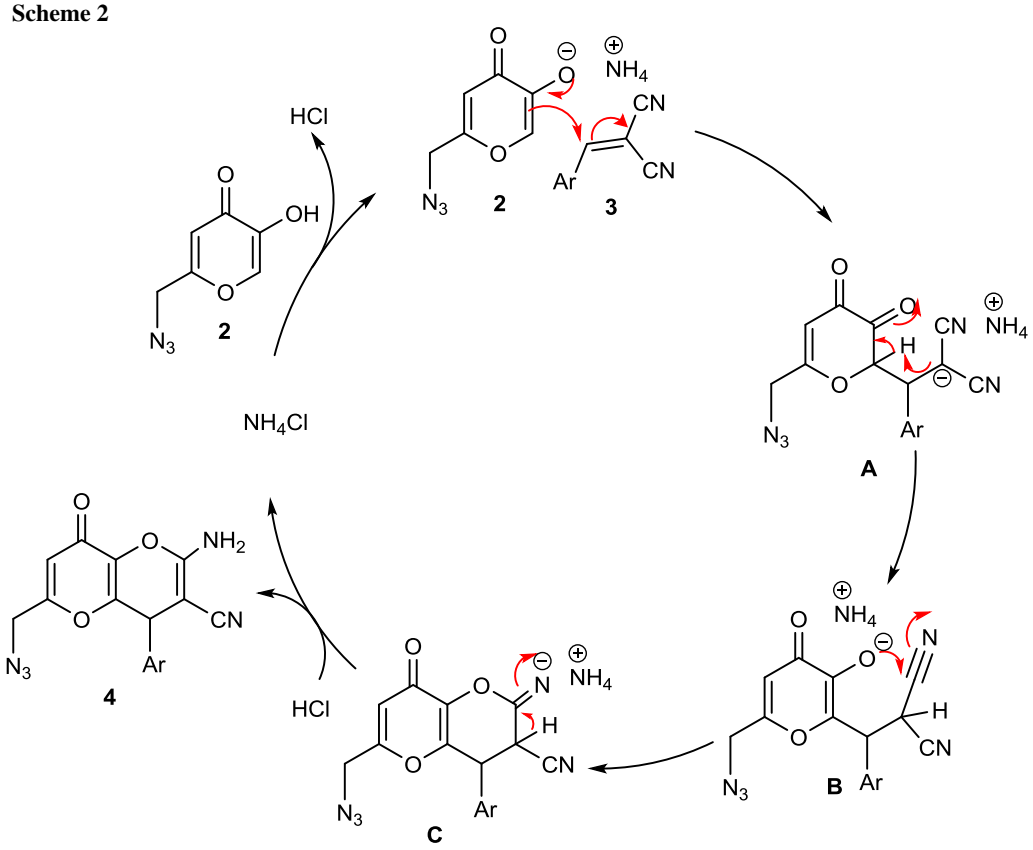
For the more investigation of the synthetic compound structure, the crystal structure analysis of **4c** was undertaken. The ORTEP diagram and crystal packing chart of **4c** are, respectively, shown in Figs. 2 and 3. Crystallographic data, angles, torsion angles, and selected bond lengths are, respectively, displayed in Tables 2 and 3.

Scheme 1



Ar = Ph (**a**), 3-NO_2-Ph (**b**), 2,4-Cl_2-Ph (**c**), 4-NO_2-Ph (**d**), 3,4,5-$(MeO)_3$-Ph (**e**), 2-MeO-Ph (**f**), 4-OH-Ph (**g**), 3-OH-Ph (**h**), 2-NO_2-Ph (**i**), 5-Br-2-OH-Ph (**j**), 4-F-Ph (**k**), 4-MeO-Ph (**l**)

Scheme 2



In 2-amino-4,8-dihydropyrano[3,2-*b*]pyran-3-cyano fused ring of compound **4c**, the 4*H*-pyran-4-one ring moiety was planar and the fused 4*H*-pyran ring was distorted and had little boat form. For instance, the torsion angles O3–C7–C8–C10 and O3–C5–C6–C10 were equal to 6.3(4)° and 2.4(3)°, respectively (Table 3, entries 21 and 22). These observations were indicated the non-planarity of 2-amino-4,8-dihydropyrano[3,2-*b*]pyran-3-cyano fused ring. Amino group had resonance with the cyano group on the 4*H*-pyran ring moiety due to the conjugation. The C=C double bond distances confirmed this resonance with judging to the double-bond distances of C7=C8, C5=C6, and C2=C3. As it could be seen, the bond distance of C7=C8 (1.362(3) Å) was longer than that of C5=C6 (1.342(3) Å) which indicated the resonance and conjugation of cyano and amino groups. Other evidence for this resonance effect was the near planarity of $–NH_2$ group with the –CN group on the double bond. The dihedral angle of N4–C7–C8–C9 equals to 6.8 (4)° (Table 3, entry 24). The bond distance of C2=C3 (1.340(4) Å) was shorter than that

Table 1 Reaction time and yields for the synthesis of **4**

Compd.	Time/h	Yield/%
4a	16	99
4b	12	99
4c	14	97
4d	12	98
4e	24	90
4f	20	96
4g	20	92
4h	20	92
4i	12	98
4j	17	90
4k	12	97
4l	20	94

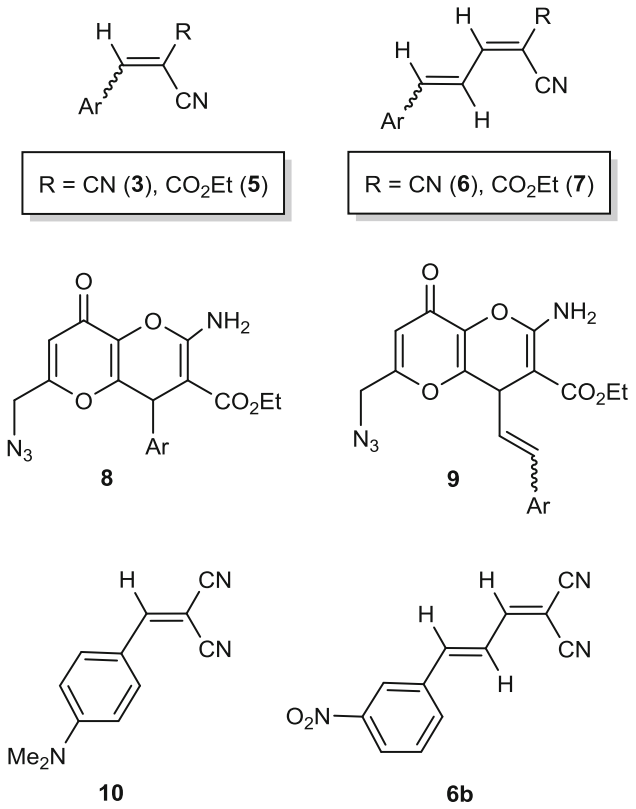


Fig. 1 Formula structures of Knoevenagel adducts **3**, **5**–**7**, and **10** and unfavored compounds **8** and **9**

of two other C=C double bonds and indicated no resonance of this bond (Table 3 and supplementary data). The phenyl ring was not perpendicular with the 4*H*-pyran ring moiety. The dihedral angle of C8–C10–C11–C16 was equal to − 34.4 (3)° (Table 3, entry 25). The azido group (N1–N2–N3) did not lie linear due to the angle of 168.8(4)° (Table 3, entry 13). One of the interesting phenomena in this structure was the existence of two intermolecular hydrogen bonds between two structures. The hydrogen bond of C4=O2···H4B–N4 and donor-acceptor ($d_{N\cdots O}$) distances were respectively obtained 2.104 and 2.927 Å. Based on bar chart of $d_{(O\cdots O)}$ distances (d, Å) in organic compounds, subdivided into hydrogen bond strength subclasses, the $d_{(N\cdots O)}$ distances of 2.927 Å is attributed to weak intermolecular hydrogen bond [61, 62]. The compound 4c formed a dimer form via two intermolecular hydrogen bonds between C4=O2···H4B–N4 atoms with $d_{(N\cdots O)}$ distances of 2.927 Å and made a 14-membered ring with centrosymmetric (C_i) form (Fig. 4, Table 4).

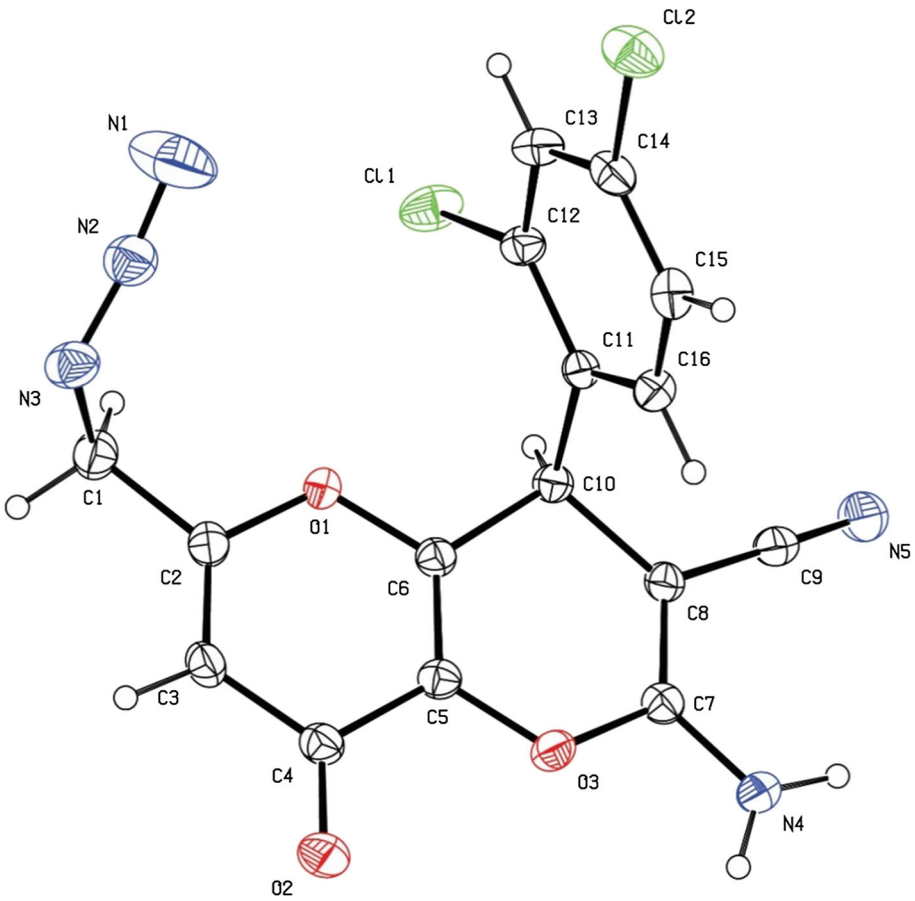
Conclusion

In the current study, we have reported a safe, efficient, and clean process for the synthesis of 2-amino-6-(azidomethyl)-4-(4-aryl)-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile by the use of different alkenes with 2-(azidomethyl)-5-hydroxy-4*H*-pyran-4-one in excellent yields. It was established that the usage of alkenes with electron-withdrawing groups in ethanol as a green solvent via Michael addition of 2-(azidomethyl)-5-hydroxy-4*H*-pyran-4-one rises the reaction yield and decreases the reaction time in comparison to the same reaction with other alkenes with electron releasing groups. Representatively, crystallographic analyses of compound **4c** showed two weak intermolecular hydrogen bonds between two structures and formed a 14-membered ring with centrosymmetric (C_i) form.

Experimental

All used material were purchased from Fluka or Merck companies. The structure of compounds was drawn and nomenclature by ChemDraw Ultra 15 version software. Melting points were evaluated with an Electro-thermal (numerical melting point device). FT-IR spectra of the synthetic compound were confirmed by making KBr pills in area 400–4000 cm^{-1} on a NEXUS 670 FT-IR spectrometer (Urmia University, Urmia, Iran). The ^{1}H and ^{13}C NMR spectra were documented at 300 and 75 MHz on Bruker 300 FT-NMR, one-to-one (Urmia University, Urmia, Iran). ^{1}H and ^{13}C NMR spectra were achieved on a solution in $CDCl_3$ and DMSO-d_6 as solvents using TMS as an internal standard. The information is informed as bs = broad singlet, m = multiplet or unresolved, t = triplet, d = doublet, and s = singlet, coupling constant(s) in Hz, integration. All reactions were controlled by TLC (silica gel-converted plates). Mass data were measured on Agilent Technology (HP), MS model: 5973 Network Mass Selective Detector, ion source: electron impact (EI) 70 eV, ion source temperature: 230 °C, analyzer: quadrupole, analyzer temperature: 230 °C.

Fig. 2 ORTEP diagram of **4c**



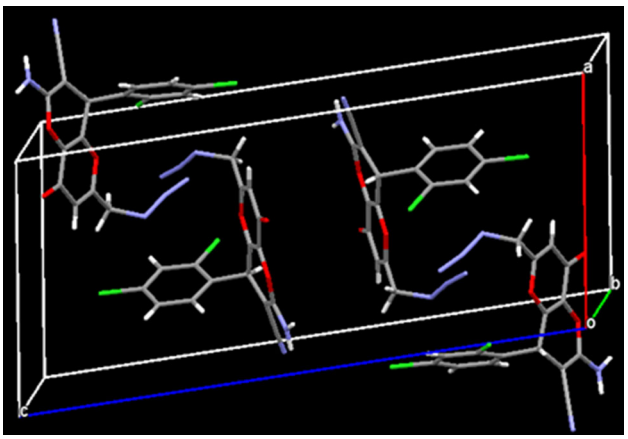


Fig. 3 Crystal packing diagram of **4c**

2-(Azidomethyl)-5-hydroxy-4H-pyran-4-one **(2, $C_6H_5N_3O_3$)** To a suspension of 0.39 g sodium azide (6 mmol) in 4 cm^3 dry DMF, 1 g 2-(chloromethyl)-5-hydroxy-4*H*-pyran-4-one (6 mmol) was added and the mixture for 24 h under inert gas at room temperature was stirred. Then, cold water was added to a reaction mixture. As the water increased, the colored cream precipitates were formed. The filtered precipitates were dried under vacuum. The rudimentary product with ethyl acetate was recrystallized to give azide compound **2** as yellow solid, with 0.73 g (70%) yield. M.p.: 131–132 °C. The analytical data are matching with the one previously described [57].

General procedure for the preparation of various Knoevenagel adducts of 2-benzylidenemalononitrile and ethyl 2-cyano-3-aryl acrylate (3 and 5–7)

To a solution of 1 mmol ethyl cyanoacetate or malononitrile and 20 cm^3 NaOH (2%), a solution of various aldehydes (1 mmol) in 5 cm^3 ethanol was added. Then, the mixture of the reaction was heated at 60 °C. The resulting precipitate was filtrated and dried under reduced pressure to give the crude product **3** and **5–7** which was purified by recrystallization from EtOH.

General procedure for the synthesis of 2-amino-6-(azidomethyl)-8-oxo-4-aryl-4,8-dihydropyrano [3,2-*b*]pyran-3-carbonitriles 4a–4l

Azido kojic acid **2** (1 mmol) and various Knoevenagel adducts **3** (1 mmol) in 5 cm^3 dry ethanol were solved. After adding ammonium chloride (30 mol%), the mixture was refluxed for 12–24 h. After achievement of the reaction, the mixture was evaporated with rotary set and the

Table 2 Crystallographic data for **4c**

Chemical formula	$C_{16}H_9Cl_2N_5O_3$
M_r	390.18
Crystal system, space group	Monoclinic, $P2_1/n$
T/K	298
a, b, c /Å	10.557(2), 6.7419(13), 23.419(5)
β/°	100.32(3)
V/Å^3	1639.9(6)
Z	4
Radiation type	Mo $K\alpha$, λ = 0.71073 Å
μ/mm^{-1}	0.43
Crystal size/mm	0.40 × 0.40 × 0.20
F(000)	792
D_x	1.580 Mg m^{-3}
Data collection	
Diffractometer	STOE *IPDS* 2T
T_{min}, T_{max}	0.849, 0.920
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	10513, 4380, 2742
R_{int}	0.063
(sin $\theta/\lambda)_{max}$ /Å^{-1}	0.686
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.047, 0.157, 0.98
No. of reflections	4380
No. of parameters	241
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$/e Å^{-3}	0.37, − 0.41

Table 3 Selected bond lengths (d/Å), angles (θ/°), and torsion angles (φ/°) for **4c**

Entry	Atom	d/Å, θ/°, φ/°
1	O1–C2	1.357(3)
2	O1–C6	1.353(3)
3	O2–C4	1.233(3)
4	O3–C7	1.371(3)
5	C8–C9	1.421(4)
6	C2–C3	1.340(4)
7	C5–C6	1.342(3)
8	C7–C8	1.362(3)
9	N1–N2	1.121(4)
10	N2–N3	1.217(3)
11	N5–C9	1.141(4)
12	N4–C7	1.332(3)
13	N1–N2–N3	168.8(4)
14	N2–N3–C1	115.7(3)
15	C8–C10–C11	114.1(2)
16	C6–C10–C8	107.0(2)
17	C6–O1–C2	119.3(2)
18	N3–C1–C2	112.1(2)
19	O1–C2–C3–C4	− 1.6(4)
20	O1–C6–C10–C8	− 167.63(18)
21	O3–C7–C8–C10	6.3(4)
22	O3–C5–C6–C10	− 2.4(3)
23	N3–C1–C2–O1	− 89.2(3)
24	N4–C7–C8–C9	6.8(4)
25	C8–C10–C11–C16	− 34.4(3)
26	C10–C11–C12–C13	173.6(2)

resultant precipitate was recrystallized for purification in methanol:acetonitrile (1:1).

2-Amino-6-(azidomethyl)-8-oxo-4-phenyl-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (4a, $C_{16}H_{11}N_5O_3$) Cream solid; yield 0.32 g (99%); m.p.: 207–209 °C; FT-IR (KBr): $\bar{\nu}$ = 3387 and 3314 (–NH_2), 3204, 3068, 2929, 2331, 2193 (–CN), 2112 (–N_3), 1643 (pyrone-CO), 1601, 1426, 1271, 1210, 1082, 1011, 860, 704 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.23–4.37 (dd, 2H, –CH_2N_3), 4.82 (s, 1H, –CH-chiral), 6.46 (s, 1H, pyrone-H), 7.24–7.41 (m, 7H, NH_2, H-Ph) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 50.2 (C-chiral), 56.0 (–CH_2N_3), 114.5, 119.6, 128.2, 129.4, 136.9, 140.9, 150.0, 159.6, 162.5, 169.8 (pyrone-CO) ppm; MS: m/z (%) = 321 (M^+, 100), 244 (97), 216 (40).

2-Amino-6-(azidomethyl)-4-(3-nitrophenyl)-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (4b, $C_{16}H_{10}N_6O_5$) Yellow solid; yield 0.36 g (99%); m.p.: 213–215 °C; FT-IR (KBr): $\bar{\nu}$ = 3380 and 3321 (–NH_2), 3206, 3074, 2916, 2316, 2190 (–CN), 2107 (–N_3), 1645 (pyrone-CO), 1547, 1427, 1345, 1306, 1211, 1086, 1022, 879, 680 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.19–4.38 (dd, 2H, –CH_2N_3), 5.17 (s, 1H, –CH-chiral), 6.47 (s, 1H, pyrone-H), 7.40 (s, 2H, NH_2), 7.68–7.73 (m, 1H, H-Ph), 7.82–7.85(m, 1H, H-Ph), 8.20 (s, 2H, H-Ph) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 50.0 (C-chiral), 55.0 (–CH_2N_3), 114.6,

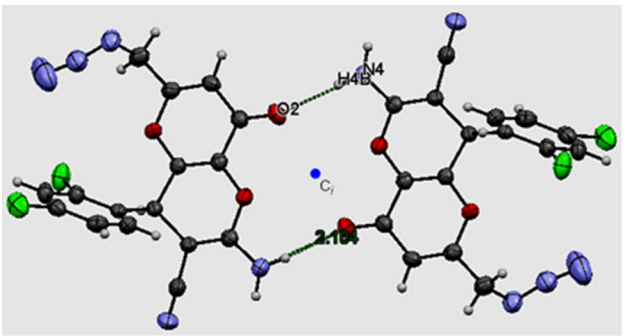


Fig. 4 Two intermolecular hydrogen bonds of **4c**. Formation of the 14-membered ring with centrosymmetric C_i form and assigned with a dense dot (blue circle) (color figure online)

Table 4 Hydrogen bond geometries in the crystal structure of **4c**

D–H···A	*d*(D–H)	*d*(H···A)	*d*(D···A)	< (DHA)	Directionality
N(4)–H(4B)···O(2)[a]	0.828	2.104	2.927	173.36	Weak

[a]Symmetry code: $-x, 2-y, -z$

119.4, 122.3, 124.4, 137.1, 142.9, 148.5, 159.8, 162.6, 169.8 (pyrone-CO) ppm; MS: *m/z* (%) = 366 (M^+, 77), 244 (100), 216 (50).

2-Amino-6-(azidomethyl)-4-(2,4-dichlorophenyl)-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (4c, $C_{16}H_9Cl_2N_5O_3$)- Cream solid; yield 0.38 g (97%); m.p.: 203–205 °C; FT-IR (KBr): $\bar{\nu}$ = 3390 and 3313 (–NH_2), 3189, 2308, 2197 (–CN), 2108 (–N_3), 1645 (pyrone-CO), 1421, 1212, 1094, 1024, 861, 674 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.21–4.36 (dd, 2H, –CH_2N_3), 5.32 (s, 1H, –CH-chiral), 6.48 (s, 1H, pyrone-H), 7.34 (s, 2H, NH_2), 7.43–7.5 (m, 2H, H-Ph), 7.6 (s, 1H, H-Ph) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 50.0 (C-chiral), 54.5 (–CH_2N_3), 114.6, 119.1, 128.5, 131.1, 133.9, 134.1, 136.6, 137.5, 148.5, 159.8, 162.6, 169.7 (pyrone-CO) ppm; MS: *m/z* (%) = 390 (M^+, 21), 389 (55), 244 (100), 216 (50).

2-Amino-6-(azidomethyl)-4-(4-nitrophenyl)-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (4d, $C_{16}H_{10}N_6O_5$) Orange solid; yield 0.36 g (98%); m.p.: 193–195 °C; FT-IR (KBr): $\bar{\nu}$ = 3398 and 3295 (–NH_2), 3190, 2854, 2322, 2198 (–CN), 2101 (–N_3), 1643 (pyrone-CO), 1597, 1424, 1349, 1216, 1013, 861, 628 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.22–4.37 (dd, 2H, –CH_2N_3), 5.11 (s, 1H, –CH-chiral), 6.49 (s, 1H, pyrone-H), 7.37 (s, 2H, NH_2), 7.62–7.65 (d, *J* = 8.7 Hz, 2H, H-Ph), 8.24–8.27 (d, *J* = 8.7 Hz, 2H, H-Ph) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 50.1 (C-chiral), 55.1 (–CH_2N_3), 114.7, 119.3, 123.5, 125.5, 129.9, 131.2, 137.3, 147.6, 159.7, 162.6, 169.8 (pyrone-CO) ppm.

2-Amino-6-(azidomethyl)-8-oxo-4-(3,4,5-trimethoxyphenyl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (4e, $C_{19}H_{17}N_5O_6$)- Cream solid; yield 0.37 g (90%); m.p.: 202–204 °C; FT-IR (KBr): $\bar{\nu}$ = 3398 and 3319 (–NH_2), 3185, 2943, 2842, 2314, 2195 (–CN), 2109 (–N_3), 1645 (pyrone-CO), 1598, 1428, 1331, 1216, 1127, 1012, 863, 684 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.64 (s, 3H, –OMe), 3.75 (s, 6H, –OMe), 4.28–4.39 (dd, 2H, –CH_2N_3), 4.79 (s, 1H, –CH-chiral), 6.46 (s, 1H, pyrone-H), 6.56 (s, 2H, NH_2), 7.22 (s, 2H, H-Ph) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 50.2 (C-chiral), 55.8 (–CH_2N_3), 56.8 (–OCH_3), 105.5, 114.5, 119.7, 136.3, 149.7, 153.6, 159.6, 162.4, 169.9 (pyrone-CO) ppm; MS: *m/z* (%) = 411 (M^+, 100), 346 (25), 216 (54).

2-Amino-6-(azidomethyl)-4-(2-methoxyphenyl)-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (4f, $C_{17}H_{13}N_5O_4$) Brown solid; yield 0.34 g (96%); m.p.: 197–199 °C; FT-IR (KBr): $\bar{\nu}$ = 3382 and 3316 (–NH_2), 3205, 2945, 2846, 2330, 2192 (–CN), 2111 (–N_3), 1648 (pyrone-CO), 1598, 1424, 1265, 1209, 1108, 1021, 859, 629 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.74 (s, 3H, –OMe), 4.23–4.36 (dd, 2H, –CH_2N_3), 5.03 (s, 1H, –CH-chiral), 6.46 (s, 1H, pyrone-H), 6.92–7.37 (7H, –NH_2, H-Ph) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 50.1 (C-chiral), 55.6 (–CH_2N_3), 56.7 (–OCH_3), 114.5, 119.7, 128.5, 129.1, 130.6, 137.4, 150.5, 157.5, 159.9, 162.3, 169.8 (pyrone-CO) ppm.

2-Amino-6-(azidomethyl)-4-(4-hydroxyphenyl)-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (4g, $C_{16}H_{11}N_5O_4$) Yellow solid; yield 0.31 g (92%); m.p.: 209–211 °C; FT-IR (KBr): $\bar{\nu}$ = 3317 (–NH_2), 3177, 2676, 2321, 2203 (–CN), 2111 (–N_3), 1645 (pyrone-CO), 1604, 1427, 1365, 1262, 1216, 1019, 864, 661 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.25–4.38 (dd, 2H, –CH_2N_3), 4.67 (s, 1H, –CH-chiral), 6.45 (s, 1H, pyrone-H), 6.74–6.77 (d, *J* = 8.4, 2H, H-Ph), 7.06–7.09 (d, *J* = 8.4, 2H, H-Ph), 7.17 (s, 2H, NH_2), 9.47 (s, 1H, OH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 50.1 (C-chiral), 55.6 (–CH_2N_3), 116.1, 119.7, 131.2, 136.6, 150.5, 157.5, 159.5, 162.4, 169.8 (pyrone-CO) ppm.

2-Amino-6-(azidomethyl)-4-(3-hydroxyphenyl)-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (4h, $C_{16}H_{11}N_5O_4$) Yellow solid; yield 0.31 g (92%); m.p.: 209–211 °C; FT-IR (KBr): $\bar{\nu}$ = 3372 (–NH_2), 3211, 2858, 2313, 2192 (–CN), 2105 (–N_3), 1638 (pyrone-CO), 1589, 1425, 1358, 1276, 1215, 1020, 860, 627 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.26–4.39 (dd, 2H, –CH_2N_3), 4.69 (s, 1H, –CH-chiral), 6.47 (s, 1H, pyrone-H), 6.66–6.71 (m, 3H, H-Ph), 7.14–7.19 (m, 1H, H-Ph), 7.25 (s, 2H, NH_2), 9.51 (s, 1H, OH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 50.1 (C-chiral), 56.1 (–CH_2N_3), 114.7, 119.6, 129.4, 131.2, 136.8, 142.47, 150.3, 158.2, 159.6, 162.5, 169.8 (pyrone-CO) ppm; MS: *m/z* (%) = 337 (M^+, 100), 272 (35), 244 (91), 216 (40).

2-Amino-6-(azidomethyl)-4-(2-nitrophenyl)-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (4i, $C_{16}H_{10}N_6O_5$) Orange solid; yield 0.36 g (98%); m.p.: 194–196 °C; FT-IR (KBr): $\bar{\nu}$ = 3400 and 3318 (–NH_2), 3198, 3069, 2929, 2376, 2194 (–CN), 2118 (–N_3), 1649 (pyrone-CO), 1520, 1431, 1358, 1209, 1086, 1017, 864, 709 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.17–4.33 (dd, 2H, –CH_2N_3), 5.51 (s, 1H, –CH-chiral), 6.48 (s, 1H, pyrone-H), 6.66–6.71 (m, 3H, H-Ph), 7.39 (s, 2H, NH_2), 7.57–7.62 (m, 2H, H-Ph), 7.74–7.79 (m, 1H, H-Ph), 7.96–7.98 (m, 1H, H-Ph) ppm;

^{13}C NMR (75 MHz, DMSO-d_6): δ = 49.5 (C-chiral), 54.3 (–CH_2N_3), 114.8, 119.1, 128.7, 131.4, 137.3, 148.6, 149.6, 159.9, 162.5, 169.8 (pyrone-CO) ppm.

2-Amino-6-(azidomethyl)-4-(5-bromo-2-hydroxyphenyl)-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (4j, $C_{16}H_{10}BrN_5O_4$) Brown solid; yield 0.38 g (91%); m.p.: 205–207 °C; FT-IR (KBr): $\bar{\nu}$ = 3430 and 3326 (–NH_2), 3240, 3071, 2308, 2191(–CN), 2103 (–N_3), 1650 (pyrone-CO), 1410, 1228, 1030, 983, 879, 675 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.23–4.34 (dd, 2H, –CH_2N_3), 5.25 (s, 1H, –CH-chiral), 6.41 (s, 1H, pyrone-H), 7.02–7.04 (m, 1H, H-Ph), 7.17 (s, 2H, NH_2), 7.25 (s, 1H, H-Ph), 7.45–7.48 (m, 1H, H-Ph), 9.30 (s, 1H, OH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 50.0 (C-chiral), 55.0 (–CH_2N_3), 112.7, 116.6, 120.0, 122.1, 130.8, 131.7, 142.2, 148.9, 151.1, 161.9, 174.0 (pyrone-CO) ppm; MS: *m/z* (%) = 417 (M^++1, 26), 416 (M^+, 16), 373 (73), 289 (21), 249 (100), 223 (43), 167 (44), 143 (33), 114 (64), 69 (33).

2-Amino-6-(azidomethyl)-4-(4-fluorophenyl)-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (4k, $C_{16}H_{10}FN_5O_3$) Orange solid; yield 0.33 g (97%); m.p.: 195–197 °C; FT-IR (KBr): $\bar{\nu}$ = 3317 and 3203 (–NH_2), 3054, 2862, 2289, 2201 (–CN), 2110 (–N_3), 1644 (pyrone-CO), 1602, 1421, 1271, 1214, 1011, 853, 586 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.23–4.38 (dd, 2H, –CH_2N_3), 4.88 (s, 1H, –CH-chiral), 6.47 (s, 1H, pyrone-H), 7.18–7.23 (m, 2H, H-Ph), 7.28 (s, 2H, NH_2), 7.33–7.37 (m, 2H, H-Ph) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 50.1 (C-chiral), 55.9 (–CH_2N_3), 114.2, 114.9, 115.1, 116.3, 117.2, 119.5, 129.7, 131.1, 131.9, 136.9, 149.7, 159.5, 160.5, 162.5, 169.8 (pyrone-CO) ppm; MS: *m/z* (%) = 339 (M^+, 100), 244 (33), 216 (8).

2-Amino-6-(azidomethyl)-4-(4-methoxyphenyl)-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (4l, $C_{17}H_{13}N_5O_4$) Yellow solid; yield 0.33 g (94%); m.p.: 188–190 °C; FT-IR (KBr): $\bar{\nu}$ = 3375 and 3327 (–NH_2), 3208, 3075, 2925, 2338, 2200 (–CN), 2105 (–N_3), 1642 (pyrone-CO), 1510, 1428, 1209, 1078, 1017, 848, 538 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.74 (s, 3H, –OMe), 4.24–4.37 (dd, 2H, –CH_2N_3), 4.75 (s, 1H, –CH-chiral), 6.45 (s, 1H, pyrone-H), 6.92–6.95 (m, 2H, –NH_2), 7.19–7.20 (m, 4H, H-Ph) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 50.1 (C-chiral), 56.3 (–CH_2N_3, –OCH_3), 114.2, 119.6, 128.4, 130.2, 132.9, 136.7, 150.3, 159.5, 162.5, 169.8 (pyrone-CO) ppm; MS: *m/z* (%) = 351 (M^+, 100), 286 (35), 244 (26), 216 (24).

X-ray crystallographic analysis of 4c

A plate, colorless single crystal size was designated 0.40 × 0.40 × 0.20 mm and mounted on a STOE IPDS II diffractometer with graphite monochromatized Mo Kα radiation (λ = 0.71073 Å). Data collection: X-AREA 1.31 [63], cell refinement: X-AREA [63], data reduction: X-AREA [63], program(s) used to solve structure: SHELXS97 [64], program(s) applied to refine the synthetic compound structure: SHELXL97 [64], molecular graphics: ORTEP-3 for Windows and software applied to prepare material for publication: WinGX. Crystallographic data were deposited in the CCDC 1823236 registration number. These information could be earned free of charge from The Cambridge Crystallographic Data Center via request to CCDC, 12 Union Road, Cambridge, UK or www.ccdc.cam.ac.uk/data_request/cif (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk).

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