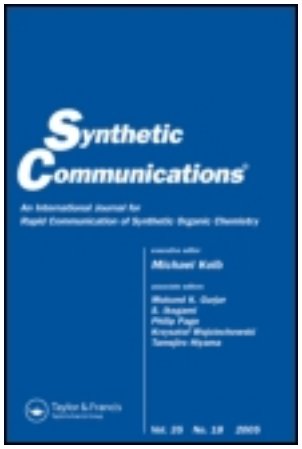

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Synthesis of 4H-Pyran Derivatives Under Solvent-Free and Grinding Conditions

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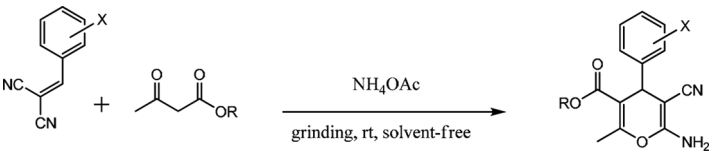
SYNTHESIS OF 4*H*-PYRAN DERIVATIVES UNDER SOLVENT-FREE AND GRINDING CONDITIONS

Rufus Smits, Sergey Belyakov, Aiva Plotniece, and Gunars Duburs

Latvian Institute of Organic Synthesis, Riga, Latvia

GRAPHICAL ABSTRACT



Abstract *Based on x-ray diffraction analysis, we have proved that the recently published results for ethyl 6-amino-5-cyano-4-aryl-1,4-dihydropyridine-3-carboxylate synthesis is in fact an environmentally friendly synthesis of 6-amino-5-cyano-4-aryl-4H-pyran derivatives using a multicomponent room-temperature grinding procedure of ethyl acetoacetate, [(2-aryl)methylene]malononitriles, and ammonium acetate.*

Keywords Green synthesis; grinding; 4*H*-pyran derivatives; multicomponent reactions; solvent-free; x-ray diffraction

INTRODUCTION

The work presented here is a correction of A. M. Zonouz et al., which was recently published in this journal[1] under the incorrect title of "Synthesis of 1,4-Dihydropyridine Derivatives Under Solvent-Free and Grinding Conditions." We have corrected the products from "1,4-dihydropyridine (1,4-DHP) derivatives" to 4*H*-pyran derivatives and included some additional synthesis and x-ray crystallographic proof.

On repeating the reported multicomponent grinding procedure with thiophene-2-carbaldehyde, malononitrile, and ammonium acetate to give the thiophenemalononitrile and subsequent addition of methyl acetoacetate to generate the expected methyl 6-amino-5-cyano-2-methyl-4-(thiophen-2-yl)-1,4-dihydropyridine-3-carboxylate, we were surprised that the x-ray single-crystal structure analysis of the recrystallized crystals (Fig. 1) proved that the compound was not a 1,4-DHP derivative, but a 4*H*-pyran derivative or methyl 6-amino-5-cyano-2-methyl-4-(thiophen-2-yl)-4*H*-pyran-3-carboxylate (Scheme 1).

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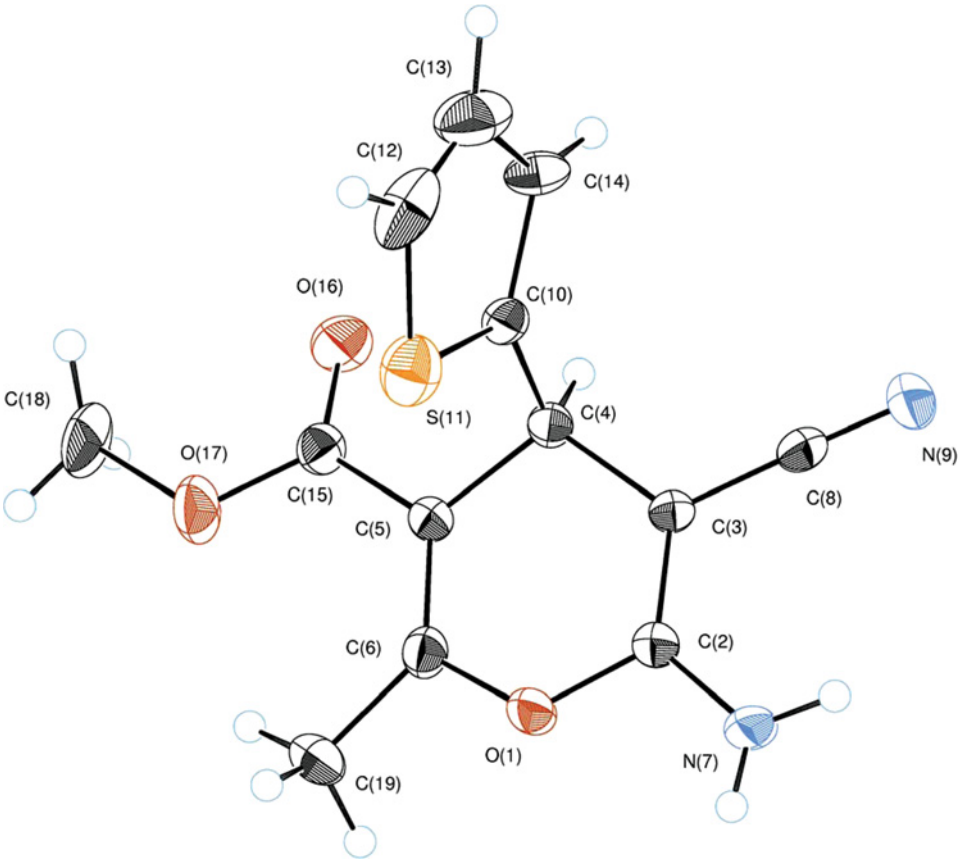
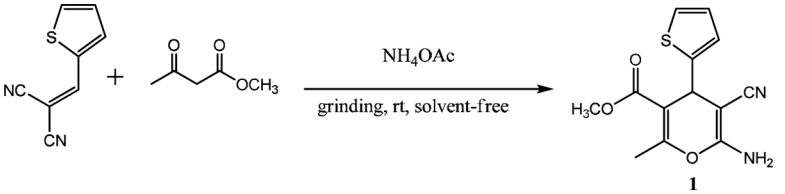


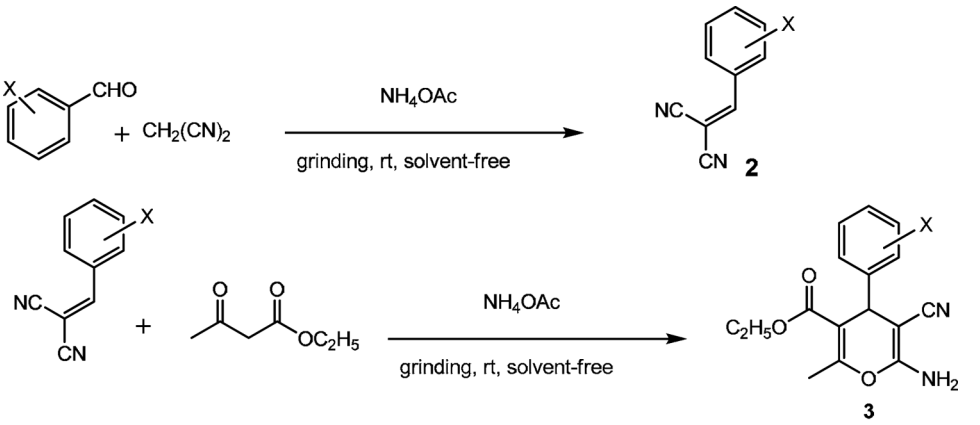
Figure 1. ORTEP representation of the molecular structure **1**. (Figure is provided in color online.)

We then carefully repeated the exact procedure with 3-nitrobenzaldehyde and ethyl acetoacetate according to the publication and again the product, which had the identical melting point of 187–188 °C and ^{1}H NMR spectrum when subjected to an x-ray single-crystal structure analysis, proved to be a 4*H*-pyran derivative. Further, the literature melting points for 1,4-DHP derivatives differ significantly from the 4*H*-pyran derivatives, in particular for this particular compound, by more than 30 °C.



1

Scheme 1. Synthesis of methyl 6-amino-5-cyano-2-methyl-4-(thiophen-2-yl)-4*H*-pyran-3-carboxylate (**1**).



(2a) X=H

(2b) X=2-NO_2

(2c) X=3-NO_2

(2d) X=4-NO_2

(2e) X=2-OMe

(2f) X=3-Me

(3a) X=H

(3b) X=2-NO_2

(3c) X=3-NO_2

(3d) X=4-NO_2

(3e) X=2-OMe

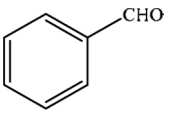
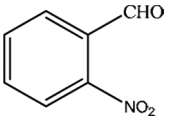
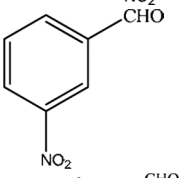
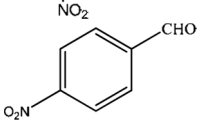
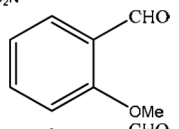
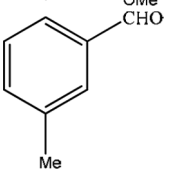
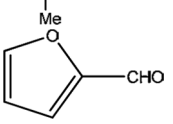
(3f) X=3-Me

Scheme 2. Synthesis of 6-amino-5-cyano-4-aryl-4*H*-pyrans **3a–f**.

The 4*H*-pyrans exhibit an extensive range of biological and pharmacological activities, such as spasmolytic, diuretic, anticoagulant, anticancer, and antianaphylactic properties. They are useful in treatment of neurodegenerative disorders, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and Parkinson's disease.[2] Polyfunctionalized 4*H*-pyrans also constitute a structural unit of many natural products,[3,4] having antiallergic,[5] antitumor,[6] and antibacterial[7–9] activities. 4*H*-Pyran derivatives are also potential calcium channel antagonists, which are structurally similar to the biologically active 1,4-dihydropyridines.[10]

Recent publications that have reported on the multicomponet synthesis of 4*H*-pyrans have used aryl aldehyde, malononitrile, ethyl acetoacetate, and magnesium oxide as a basic catalyst with grinding and without solvent,[9] the same ingredients but with silica nanoparticles as a catalyst and ethanol as solvent,[11] and Cu(II) oxymetasilicate as a reusable catalyst in methanol as solvent.[12] In these reactions the catalyst had to be separated from the reaction medium. In the present work ammonium acetate was used instead of any catalyst, and after completion of the reaction the ammonium acetate was simply washed away with ethanol and recrystallized to give good yields of the *4H*-pyran derivatives.

Table 1. Synthesis of 6-amino-5-cyano-4-aryl-4*H*-pyrans **3a–g** by grinding

Entry	Aldehyde	Product	Yield (%)	Mp (°C)
1		**3a**	78	190–192 (lit.[9] 195–196)
2		**3b**	57	178–179
3		**3c**	81	187–188 (lit.[9] 182–183)
4		**3d**	76	175–176 (lit.[9] 180–183)
5		**3e**	59	196–197
6		**3f**	68	176–177
7		**3g**	68	204–205

RESULTS AND DISCUSSION

Treatment of an aryl aldehyde (1 equiv.) with malononitrile (1 equiv.) in the presence of ammonium acetate (1.5 equiv.) under solvent-free conditions at room temperature on grinding gave benzylidene malononitrile derivatives **2** via the Knovenagel condensation without any purification. Ethyl acetoacetate (1 equiv.) was added to the same reaction vessel, followed by grinding (Scheme 2). After workup and purification, the 6-amino-5-cyano-4-aryl-4*H*-pyrans **3a–f** were obtained in good yields. The results with different aldehydes are depicted in Table 1.

The reaction products were characterized by their melting points, infrared (IR) (KBr), ^{1}H NMR, and ^{13}C NMR. The compound **3c** has been additionally characterized by single-crystal x-ray diffraction (XRD) study (Fig. 2).

In both structures the geometrical parameters of pyran systems are usual for 4*H*-pyran heterocycles with the envelope conformation. The deviations of C(4) atom from the O(1), C(2), C(3), C(5), and C(6) plane are equal 0.271(4) Å for

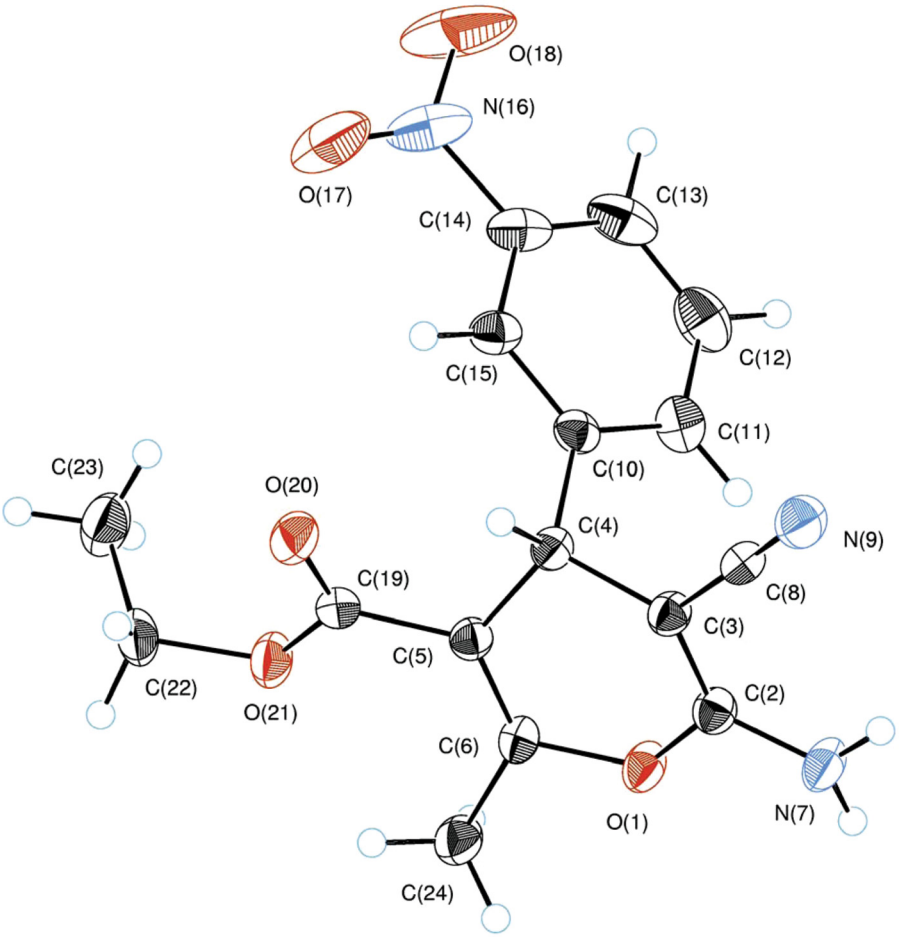
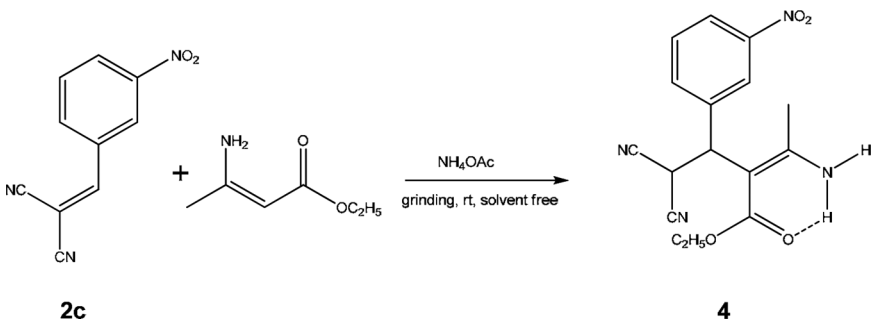


Figure 2. ORTEP representation of the molecular structure of **3c**. (Figure is provided in color online.)

methyl 6-amino-5-cyano-2-methyl-4-(thiophen-2-yl)-4*H*-pyran-3-carboxylate (**1**) and 0.359(3) Å for **3c**. Both crystal structures are characterized by intermolecular hydrogen bonds of NH···O and NH···N types. The hydrogen bond lengths in **1** are 2.904(4) Å [N(7)–H(7A)···O(16) bond] and 3.051(4) Å [N(7)–H(7B)···N(9) bond]. In **3c** these bonds are stronger and the lengths are 2.820(3) Å [N(7)–H(7A)···O(20) bond] and 2.987(3) Å [N(7)–H(7B)···N(9) bond].

Because initially we were interested in synthesizing 1,4-DHP derivatives, we tried a reaction where the ethyl acetoacetate in Scheme 2 was substituted with ethyl 3-aminobut-2-enoate. Analysis of the product by NMR revealed that the compound formed was an intermediate (**4**) with an acyclic structure and an intramolecular NH···O hydrogen bond (Scheme 3).

The generation of this intermediate with a strong internal NH···O bond in a six-membered ring configuration explains why no further reaction takes place at room temperature to produce the dihydropyridine derivative. Even when



2c 4

Scheme 3. Formation of intermediate **4**.

intermediate **4** was boiled in ethanol for 6 h with dimethylaminopyridine (DMAP) as catalyst, the starting material only slowly reacted to form a mixture of products, which was not further analyzed. From this reaction it is also apparent that ethyl acetatoacetate reacts first with compound **2c** and cyclizes to the 4*H*-pyran before it could form the enamine. The structure of intermediate was futher proved by single-crystal x-ray diffraction. In the crystal structure of intermediate **4** there are two independent molecules in the asymmetric unit. The bond lengths and valence angles in these molecules are near and correspond to standard values. However, these molecules differ by conformation: the torsion angle H7–C7–C17–H17 is equal 161° for molecule **A** and −41 ° for molecule **B**. Figure 3 illustrates a perspective view of these molecules.

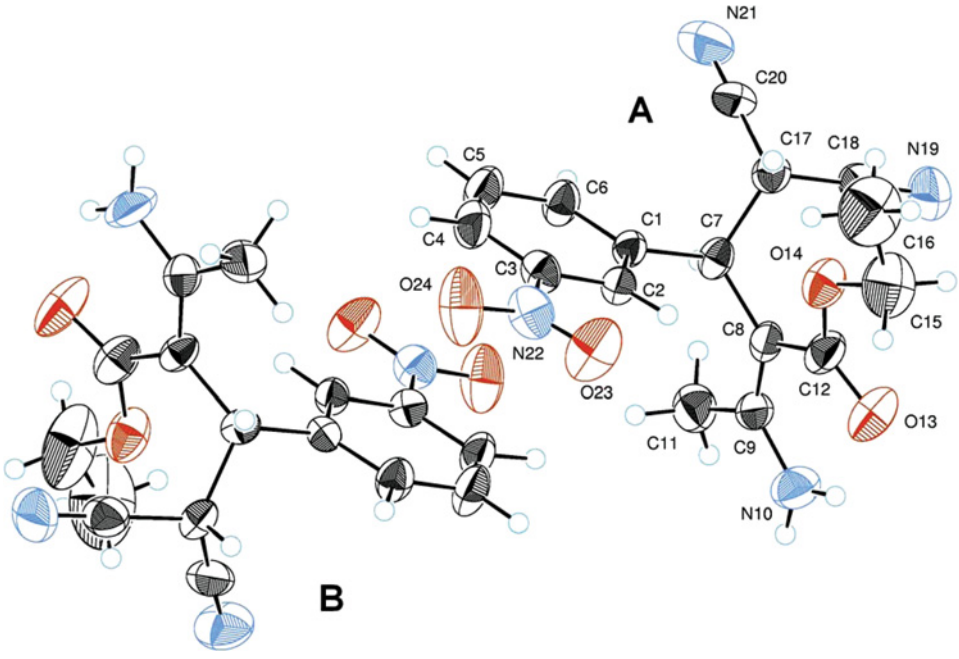
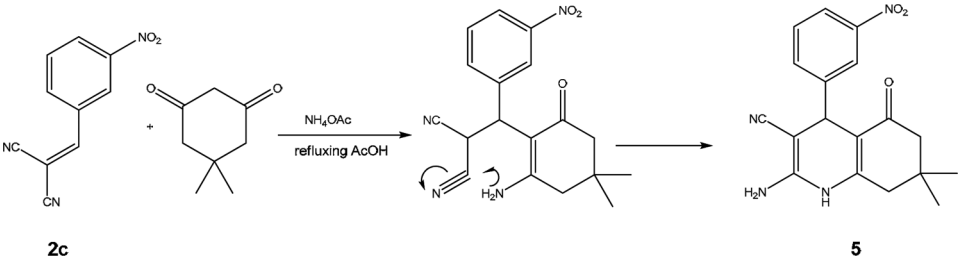


Figure 3. ORTEP representation of the structure of intermediate **4**. (Figure is provided in color online.)



2c 5

Scheme 4. Arylidinemalononitrile reaction with dimedone and ammonium acetate in refluxing glacial acetic acid to form 1,4-dihydropyridine derivative **5**.

When the possibility of internal hydrogen bonding is eliminated, as in the case of dimedone, the dihydropyridine structure is formed readily (Scheme 4).[13]

CONCLUSIONS

We have proved unequivocally using single-crystal x-diffraction analysis that the structures which A. M. Zonouz et al. recently published in this journal[1] as 1,4-dihydropyridine derivatives are in fact 4*H*-pyran derivatives. Consequently we have corrected all the incorrectly reported "1,4-dihydropyridine" derivatives to the correct 4*H*-pyran structures. Therefore, an efficient and environmentally friendly synthesis of 6-amino-5-cyano-4-aryl-4H-pyran and not 1,4-DHP derivatives has been developed using a multicomponent room-temperature grinding procedure of ethyl acetoacetate, [(2-aryl)methylene]malononitriles, and ammonium acetate.

EXPERIMENTAL

Preparation of Ethyl 6-Amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate (3a), Typical Procedure

A mixture of benzaldehyde (10 mmol, 1 ml), malononitrile (10 mmol, 0.66 g), and ammonium acetate (15 mmol, 1.15 g) was thoroughly mixed in a mortar by grinding until the completion of reaction as indicated by thin-layer chromatography (TLC) (15 min). The mixture solidified during the grinding. Then, ethyl acetoacetate (10 mmol, 1.26 ml) was added to the same vessel. The mixture, which initially was in a partially liquid state, solidified during the process of grinding (15 min). The pure product (**3a**) was obtained by recrystallized from ethanol (2.21 g, 78%).

Mp 190–192 °C; IR (KBr) $\nu = 3402$ (s), 3328 (s), 3223 (m), 2966 (w), 2189 (s), 1693 (s), 1259 (s), 1060 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.10$ (t, $J = 7.20$ Hz, 3H, CH_3 ester), 2.38 (s, 3H, $CH_{3\text{-}2}$), 4.05 (m, 2H, CH_2 ester), 4.45 [s, 1H, C(4)-H], 4.50 (br, s, 2H, NH_2), 7.17–7.35 (m, 5H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.86$ (CH_3 ester), 18.37 ($CH_{3\text{-}2}$), 38.75 (C-4), 60.64 (CH_2 ester), 62.58 (C-5), 108.00 (C-3), 118.80 (CN), 127.17 (C-4′), 127.50 (C-3′,5′), 128.56 (C-2′,6′), 143.72 (C-1′), 156.76, 157.39 (C-2, 6), 165.83 (CO) ppm.

Methyl 6-Amino-5-cyano-2-methyl-4(thiophen-2-yl)-4*H*-pyran-3-carboxylate (1)

This compound was synthesized by this procedure except 1.12 g (10 mmol) thiophene-2-carbaldehyde and 1.16 g (10 mmol) methyl acetoacetate instead of ethyl acetoacetate were used. At the end of the grinding procedure, the sticky yellow substance was recrystallized from ethanol to give white crystals (1.98 g, 72%). Mp 142–144 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.28$ (s, 3H, CH_3), 3.64 (s, 3H, CH_3 ester), 4.65 [s, 1H, C(4)-H], 6.85 (d, $J = 3.6$ Hz, 1H, Ar), 6.93 (dd, $J = 5.1$, 3.5, 1H, Ar), 7.05 (br, s, 2H, NH_2), 7.36 (d, $J = 5.1$, 1H, Ar) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 18.22$, 33.81, 51.69, 56.93, 107.61, 119.55, 123.55, 124.78, 126.97, 149.34, 156.90, 159.09, 165.76 ppm.

Ethyl 6-Amino-5-cyano-2-methyl-4-(2-nitrophenyl)-4*H*-pyran-3-carboxylate (3b)

Mp 177.5–178.5 °C; IR (KBr) $\nu = 3453$ (s), 3294 (s), 3215 (s), 3185 (s), 2984 (w), 2208 (s), 1719 (s), 1684 (s), 1601 (s), 1530 (s), 1381 (s), 1225 (s), 1062 (s), 786 (s), 726 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.99$ (t, $J = 7.20$ Hz, 3H, CH_3 ester), 2.41 (s, 3H, $CH_{3\text{-}2}$), 3.96 (m, 2H, CH_2 ester), 4.67 (br, s, NH_2), 5.26 [s, 1H, C(4)-H], 7.32–7.40 (m, 2H, Ar-H4′, H6′), 7.58 (dt, $J_1 = 7.50$ Hz, $J_2 = 1.20$ Hz, 1H, Ar-H5′), 7.82 (dd, $J_1 = 7.70$ Hz, $J_2 = 1.20$ Hz, 1H, Ar-H3′) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.66$ (CH_3 ester), 18.45 ($CH_{3\text{-}2}$), 32.97 (C-4), 60.95 (CH_2 ester), 63.50 (C-5), 107.30 (C-3), 118.21 (CN), 124.06 (C-3′), 127.91 (C-4′), 130.61 (C-6′), 133.23 (C-5′), 139.08 (C-1′), 149.09 (C-2′), 158.05, 158.24 (C-2, 6), 165.04 (CO) ppm.

Ethyl 6-Amino-5-cyano-2-methyl-4-(3-nitrophenyl)-4*H*-pyran-3-carboxylate (3c)

Mp 187–188 °C; IR (KBr) $\nu = 3402$ (s), 3328 (s), 3221 (m), 2987 (w), 2190 (s), 1672 (s), 1531 (s), 1344 (s), 1063 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.12$ (t, $J = 7.20$ Hz, 3H, CH_3 ester), 2.41 (s, 3H, $CH_{3\text{-}2}$), 4.05 (m, 2H, CH_2 ester), 4.58 [s, 1H, C(4)-H], 4.69 (br, s, NH_2), 7.49 (t, $J = 8.00$ Hz, 1H, Ar-H5′), 7.58 (td, $J_1 = 8.00$ Hz, $J_2 = 0.80$ Hz, Ar-H6′), 8.06 (t, $J = 1.60$ Hz, 1H, Ar-H2′), 8.11 (md, $J = 8.00$ Hz, 1H, Ar-H4′) ppm; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.01$ (t, $J = 7.20$ Hz, 3H, CH_3 ester), 2.07 (s, 2H, NH_2), 2.34 (s, 3H, $CH_{3\text{-}2}$), 3.95 (m, 2H, CH_2 ester), 4.52 [s, 1H, C(4)-H], 7.60–7.70 (m, 2H, Ar-H5′, H6′), 7.98 (s, 1H, Ar-H2′), 8.10 (dt, $J_1 = 7.50$ Hz, $J_2 = 1.92$ Hz, 1H, Ar-H4′) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.90$ (CH_3 ester), 17.64 ($CH_{3\text{-}2}$), 37.75 (C-4), 59.95 (CH_2 ester), 63.50 (C-5), 105.93 (C-3), 117.33 (CN), 121.39 (C-4′), 121.55 (C-2′), 128.51 (C-5′), 133.01 (C-6′), 145.10 (C-1′), 147.47 (C-3′), 159.77, 156.95 (C-2, 6), 164.26 (CO) ppm.

Ethyl 6-Amino-5-cyano-2-methyl-4-(4-nitrophenyl)-4*H*-pyran-3-carboxylate (3d)

Mp 175–176 °C; IR (KBr) $\nu = 3404$ (s), 3333 (s), 3204 (s), 2983 (w), 2200 (s), 1690 (s), 1650 (s), 1518 (s), 1345 (s), 1270 (s), 1060 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.11$ (t, $J = 7.20$ Hz, 3H, CH_3 ester), 2.42 (s, 3H, $CH_{3\text{-}2}$), 4.05

(q, $J = 7.20$ Hz, 2H, CH_2 ester), 4.57 [s, 1H, C(4)-H], 4.67 (br, s, NH_2), 7.39 (d, $J = 7.70$ Hz, 2H, Ar-H2,6′), 8.18 (d, $J = 7.70$ Hz, 1H, Ar-H3′,5′) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.92$ (CH_3 ester), 18.61 ($CH_{3\text{-}2}$), 38.82 (C-4), 60.86 (C-5), 60.97 (CH_2 ester), 106.79 (C-3), 118.28 (CN), 123.99 (C-2′,6′), 128.42 (C-3′,5′), 147.09 (C-1′), 151.09 (C-4′), 157.73, 158.05 (C-2, 6), 165.26 (CO) ppm.

Ethyl 6-Amino-5-cyano-2-methyl-4-(2-methoxyphenyl)-4*H*-pyran-3-carboxylate (3e)

Mp 196–197 °C; IR (KBr) $\nu = 3403$ (s), 3326 (s), 3220 (m), 2967 (w), 2933 (w), 2187 (s), 1693 (s), 1606 (m), 1256 (s), 1063 (s), 713 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.06$ (t, $J = 7.20$ Hz, 3H, CH_3 ester), 2.38 (s, 3H, $CH_{3\text{-}2}$), 3.84 (s, 3H, OCH_3), 4.00 (m, 2H, CH_2 ester), 4.41 (br, s, 2H, NH_2), 4.88 [s, 1H, C(4)-H], 6.82–6.92 (m, 2H, Ar-H5′, 3′), 7.06 (dd, $J_1 = 7.50$ Hz, $J_2 = 1.50$ Hz, 1H, Ar-H6′), 7.19 (dt, $J_1 = 7.50$ Hz, $J_2 = 1.50$ Hz, 1H, Ar-H4′) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.77$ (CH_3 ester), 18.31 ($CH_{3\text{-}2}$), 32.61 (C-4), 55.58 (OCH_3), 60.42 (CH_2 ester), 61.81 (C-5), 107.06 (C-3), 111.05 (C-3′), 119.10 (CN), 120.65 (C-5′), 128.24 (C-4′), 128.68 (C-6′), 131.79 (C-1′), 157.07 (C-2), 157.45 (C-2′), 157.94 (C-6), 166.08 (CO) ppm.

Ethyl 6-Amino-5-cyano-2-methyl-4-(3-methylphenyl)-4*H*-pyran-3-carboxylate (3f)

Mp 176–177 °C; IR (KBr) $\nu = 3401$ (s), 3330 (m), 3222 (m), 2981 (w), 2192 (s), 1697 (s), 1675 (s), 1647 (m), 1604 (m), 1372 (m), 1266 (s), 1058 (s), 721 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.11$ (t, $J = 6.90$ Hz, 3H, CH_3 ester), 2.33 (s, 3H, $CH_{3\text{-}2}$), 2.38 (s, 3H, CH_3), 4.05 (m, 2H, CH_2 ester), 4.41 [s, 1H, C(4)-H], 4.45 (br, s, NH_2), 6.92–7.25 (m, 4H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.86$ (CH_3 ester), 18.37 ($CH_{3\text{-}2}$), 21.45 (CH_3), 38.68 (C-4), 60.61 (CH_2 ester), 62.52 (C-5), 108.08 (C-3), 118.91 (CN), 124.62 (C-4′), 127.96, 128.20, 128.40 (C-2′,5′,6′), 138.07 (C-3′), 143.64 (C-1′), 156.61, 157.45 (C-2,6), 165.91 (CO) ppm.

Ethyl 6-Amino-5-cyano-2-methyl-4-(2-furyl)-4*H*-pyran-3-carboxylate (3g)

Mp 204–205 °C; IR (KBr) $\nu = 3393$ (m), 3370 (m), 3202 (m), 2963 (m), 2193 (s), 1693 (s), 1685 (s), 1261 (s), 1065 (s), 802 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.23$ (t, $J = 7.20$ Hz, 3H, CH_3 ester), 2.37 (s, 3H, $CH_{3\text{-}2}$), 4.16 (m, 2H, CH_2 ester), 4.53 (br, s, 2H, NH_2), 4.64 [s, 1H, C(4)-H], 6.102 (d, $J = 3.30$ Hz, 1H, Ar-H5′), 6.28 (m, 1H, Ar-H4′), 7.31 (s, 1H, Ar-H3′) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.00$ (CH_3 ester), 18.43 ($CH_{3\text{-}2}$), 32.37 (C-4), 59.53 (C-5), 60.78 (CH_2 ester), 105.71 (C-3), 105.93 (C-5′), 110.33 (C-4′), 118.62 (CN), 141.93 (C-3′), 155.13 (C-1′), 157.78, 158.54 (C-2,6), 165.63 (CO) ppm.

(Z)-Ethyl 3-Amino-2-(2,2-dicyano-1-(3-nitrophenyl)ethyl)but-2-enoate (4)

This intermediate was synthesized according to the typical grinding procedure using 3-nitrobenzaldehyde (10 mmol) and (*Z*)-ethyl 3-aminobut-2-enoate (1.29 g

10 mmol) instead of ethyl acetoacetate. The yellow sticky mixture was washed with ethanol and recrystallized to give light green needles (1.9 g, 58%).

Mp 142–144 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.02$ (t, $J = 7.0$ Hz, 3H, CH_3, ester), 2.17 (s, 3H, CH_3), 3.67–4.12 (m, 2H, CH_2, ester), 4.75 [d, $J = 11.4$ Hz, 1H, $CH(CN)_2$], 5.73 (d, $J = 11.4$ Hz, 1H, CH-Ar), 7.46 (br, s, 1H, NH), 7.58 (t, $J = 7.9$ Hz, 1H, Ar-H5), 7.73 (d, $J = 7.6$ Hz, 1H, Ar-H6), 8.07 (d, $J = 8.0$ Hz, 1H, Ar-H4), 8.14 (s, 1H, Ar-H2), 8.61 (br, s, 1H, NH···O) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 13.99$, 20.92, 26.69, 43.34, 58.45, 88.97, 113,79, 114.38, 121.92, 122.24, 129.47, 135.03, 141.99, 147.38, 163.10, 167.55 ppm.

Crystal Data

For ethyl 6-amino-5-cyano-2-methyl-4-(3-nitrophenyl)-4H-pyran-3-carboxylate (**3c**), methyl 6-amino-5-cyano-2-methyl-4-(thiophen-2-yl)-4*H*-pyran-3-carboxylate (**1**), and intermediate **4**, diffraction data were collected at −100 °C (for **3c** and **1**) and at room temperature for **4** on a Bruker-Nonius KappaCCD diffractometer using graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). Both crystal structures were solved by the direct method and refined by full-matrix least squares. All non hydrogen atoms were refined anisotropically.

Crystal Data for 1. $C_{13}H_{12}N_2O_3S$, triclinic, $a = 8.6311(2)$, $b = 9.0785(3)$, $c = 9.6055(3)$ Å, $\alpha = 96.548(2)$, $\beta = 115.097(2)$, $\gamma = 95.679(2)°$, $V = 668.02(3)$ Å^3, $Z = 2$, $\mu = 0.250\,\text{mm}^{-1}$, $D_{calc} = 1.374\,\text{g cm}^{-3}$, space group $P\bar{1}$. A total of 3256 independent reflection intensities were collected at room temperature. For structure refinement, 2055 reflections with $I > 3\sigma(I)$ were used. The final R factor is 0.059.

Crystal Data for 3c. $C_{16}H_{15}N_3O_5$, triclinic, $a = 8.3621(2)$, $b = 8.4736(3)$, $c = 12.0001(5)$ Å, $\alpha = 82.192(1)$, $\beta = 71.039(2)$, $\gamma = 76.176(2)°$, $V = 779.29(5)$ Å^3, $Z = 2$, $\mu = 0.106\,\text{mm}^{-1}$, $D_{calc} = 1.403\,\text{g cm}^{-3}$, space group $P\bar{1}$. A total of 3911 independent reflection intensities were collected at room temperature. For structure refinement, 2546 reflections with $I > 3\sigma(I)$ were used. The final R factor is 0.047.

Crystal Data for 4. $C_{16}H_{16}N_4O_4$, monoclinic, $a = 19.8757(7)$, $b = 8.4327(3)$, $c = 20.637(1)$ Å, $\beta = 106.330(1)°$, $V = 3319.3(2)$ Å^3, $Z = 8$, $\mu = 0.097\,\text{mm}^{-1}$, $D_{calc} = 1.314\,\text{g·cm}^{-3}$, space group $P2_1/n$. A total of 8959 independent reflection intensities were collected at room temperature. For structure refinement, 3496 reflections with $I > 3\sigma(I)$ were used. The final R factor is 0.074. For further details, see crystallographic data for these structures deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Numbers CCDC 865274 (for **1**), 865275 (for **3c**), and 870203 (for "intermediate"). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

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REFERENCES

1. Zonouz, A. M.; Moghani, D. Synthesis of 1,4-dihydropyridine derivatives under solvent-free and grinding conditions. *Synth. Commun.* **2011**, *41*, 2152–2160.
2. (a) Foye, W. O. *Principi di Chemico Farmaceutica*; Piccin: Padora, Italy, 1991; p. 416; (b) Andreani, L. L.; Lapi, E. On some esters of coumarin-3-carboxylic acid with balsamic bronchodilator action. *Bull. Chim. Farm.* **1960**, *99*, 583–586; (c) Zhang, Y. L.; Chen, B. Z.; Zeng, K. Q.; Xu, M. L.; Lei, X. H.; Yaoxue, X. B. Chemotherapeutic studies on schistosomiasis XXV: Derivatives of substituted coumarin-3-carboxylic esters and amides. *Chinese Acta Pharmaceutica Sinica* **1982**, *17*, 17; *Chem. Abstr.* **1982**, *96*, 135383e; (d) Bonsignore, L.; Loy, G.; Secci, D.; Calignano, A. Synthesis and pharmacological activity of 2-oxo-(2*H*) 1-benzopyran-3-carboxamide derivatives. *Eur. J. Med. Chem.* **1993**, *28*, 517–520.
3. Kuthan, J. Pyrans, thiopyrans, and selenopyrans. *Adv. Heterocycl. Chem.* **1983**, *34*, 145–303.
4. Hatakeyama, S.; Ochi, N.; Numata, H.; Takano, S. A new route to substituted 3-methoxycarbonyldihydropyrans enantioselective synthesis of (−)-methyl enolate. *J. Chem. Soc., Chem. Commun.* **1988**, 1202–1204.
5. Witte, E. C.; Neubert, P.; Roesch, A. Ger. Offen. Patent DE3427985, 1986.
6. Wang, J. L.; Liu, D.; Zhang, Z. J.; Shan, S.; Han, X.; Srinivasula, S. M.; Croce, C. M.; Alnemri, E. S.; Huang, Z. Structure-based discovery of an organic compound that binds Bcl-2 protein and induces apoptosis of tumor cells. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 7124–7129.
7. El-Saghier, A. M. M.; Naili, M. B.; Rammash, B. K.; Saleh, N. A.; Kreddan, K. M. Synthesis and antibacterial activity of some new fused chromenes. *Arkivoc.* **2007**, *16*, 83–91.
8. Kumar, R. R.; Perumal, S.; Senthilkumar, P.; Yogeeswari, P.; Sriram, D. An atom-efficient, solvent-free, green synthesis and antimycobacterial evaluation of 2-amino-6-methyl-4-aryl-8-[(*E*)-arylmethylidene]-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6459–6462.
9. Kumar, D.; Reddy, V. B.; Sharad, S.; Dube, U.; Kapur, S. A facile one-pot green synthesis and antibacterial activity of 2-amino-4*H*-pyrans and 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes. *Eur. J. Med. Chem.* **2009**, *44*, 3805–3809.
10. Suarez, M.; Slafran, E.; Verdecia, Y.; Ochoa, E.; Alba, L.; Martin, N.; Martinez, R.; Quinteiro, M.; Seoane, C.; Novoa, H.; Blaton, N.; Peeters, O. M.; De Ranter, C. X-ray and theoretical structural study of novel 5,6,7,8-tetrahydrobenzo-4*H*-pyrans. *Tetrahedron.* **2002**, *58*, 953–960.
11. Banerjee, S.; Horn, A.; Khatri, H.; Sereda, G. A green one-pot multicomponent synthesis of 4*H*-pyrans and polysubstituted aniline derivatives of biological, pharmacological, and optical applications using silica nanoparticles as reusable catalyst. *Tetrahedron. Lett.* **2011**, *52*, 1878–1881.
12. Heravi, M. M.; Beheshtiha, Y. S.; Piernia, Z.; Sadjadi, S.; Adibi, M. One-pot, three-component synthesis of 4*H*-pyrans using Cu(II) oxymetasilicate. *Synth. Commun.* **2009**, *39*, 3663–3667.
13. Suarez, M.; Verdecia, Y.; Ochoa, E.; Martin, N.; Martinez, R.; Quinteiro, M.; Seoane, C.; Soto, J. L.; Novoa, H.; Blaton, N.; Peeters, O. M.; De Ranter, C. Synthesis and structural study of novel 1,4,5,6,7,8-hexahydroquinolones. *J. Heterocycl. Chem.* **2000**, *37*, 735–742.