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Article

Infrared Irradiation-Assisted Multicomponent Synthesis of 2-Amino-3-cyano-4*H*-pyran Derivatives

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Abstract. A simple, versatile, and efficient synthesis of 4*H*-pyran derivative compounds is achieved via a three-component cyclocondensation of aldehydes, malononitrile, and ethyl acetoacetate, using ammonium hydroxide as the catalyst, promoted by infrared irradiation. The present method offers several advantages, such as high yields, non hazardous reaction conditions as well as short reaction times.
Key words: Infrared Irradiation, three-component reaction, MCR, 4*H*-pyrans.

Resumen. Se informa una síntesis sencilla, versátil y eficiente de derivados de 4*H*-piranos, a través de una ciclocondensación de tres componentes entre aldehídos, malononitrilo y acetoacetato de etilo, empleando hidróxido de amonio como catalizador y promovida por irradiación infrarroja como fuente de activación alterna. Este método ofrece varias ventajas, tal como: elevados rendimientos, condiciones no peligrosas y cortos tiempos de reacción.
Palabras clave: Irradiación infrarroja, reacción de tres componentes, RMC, 4*H*-piranos.

Introduction

Multicomponent reactions (MCRs) have greatly contributed to the convergent synthesis of complex and structurally interesting organic molecules from simple and readily available starting materials, and have emerged as a powerful tool for drug discovery [1]. In the other hand**,** 4*H*-pyrans are an important class of heterocycles because the core fragment is constituted by a great variety of natural products and biologically active compounds. The latter compounds, which have many pharmacological properties and play important roles in biochemical processes [2], include a selective inhibitor of excitatory amino acid transporter subtype 1 [3], IKCa channel blockers [4], A3 adenosine receptor antagonists as potential anti-inflammatory agents [5], and pro-apoptotic activity against cancer cells (administered alone or in combination with chemo- and radio-therapy) [6]. In addition, they can be used as cognitive enhancers for the treatment of neurodegenerative diseases [7]. Therefore, the synthesis of 4*H*-pyrans and their derivatives has attracted much attention in organic synthesis [8].

The typical procedure to synthesize pyran derivatives is usually a two-step reaction carried out between a Michael acceptor (arylidenemalononitriles) and β-dicarbonyl compounds in the presence of a base as the catalyst (piperidine, morpholine or metal alkoxides) in ethanol or other solvents (DMSO, DMF). A variety of methods have been used to prepare 4*H*-pyrans, which involve several catalysts such as KF/Al$_2$O$_3$ [8c], Baker´s yeast [8e], hexadecyldimethylbenzyl ammonium bromide (HDMBAB) [9], InBr$_3$ [10], and H$_6$P$_2$W$_{18}$O$_{62}$·18H$_2$O [11]. In addition to the employment of alternative activating sources, such as microwave irradiation [12, 13], combined microwave and ultrasound irradiation [14], and electro-oxidation [15], sometimes an ionic liquid is employed [12]. Although these methods are

valuable, they suffer from one or more disadvantages, such as hazardous reagents, high temperature, long reaction time, low yields, and tedious workup. Hence, it is important to continue to search for simpler and more efficient protocols.

One of the objectives in modern synthetic organic chemistry is to carry out reactions with effective, clean, economical, and environmentally safer methodologies [16]. In this sense, the synthetic reactions using infrared irradiation, as a source of heating, constitutes a significant advance in the development of environmentally benign methods [17], being one of the main focuses of our research group. In this context, numerous reactions have been included in our studies, among them the Knoevenagel condensation [18], the Biginelli reaction [19], the direct conversion of aromatic aldehydes into the corresponding nitriles [20], the Fischer indole reaction [21], the formation of *N*-benzylideneanilines [22], and more recently, the molecular rearrangement of perezone into isoperezone [23].

In keeping with our interest in the application of infrared irradiation in organic synthesis, we herein disclose a simple and efficient synthesis of 4*H*-pyran derivatives via a three-component cyclocondensation reaction of aldehydes, malononitrile, and ethyl acetoacetate using ammonium hydroxide as the catalyst. To the best of our knowledge, this is the first time that this cyclocondensation has been promoted by infrared irradiation.

Results and discussion

Initially, we carried out the cyclocondensation reaction of benzaldehyde (**1a**), malononitrile (**2**), ethyl acetoacetate (**3**) and commercial ammonium hydroxide (1:1:1 equiv. mol and 28 mol%, respectively) at reflux temperature for 1 h, which led to a poor yield (45%) of 4*H*-pyran **4a** (Table 1, entry 1). In spite

Table 1. Infrared irradiation-promoted cyclocondensation of **1a**, **2** and **3** in the presence of different bases at distinct percentages of NH_4OH and different solvents.[a]
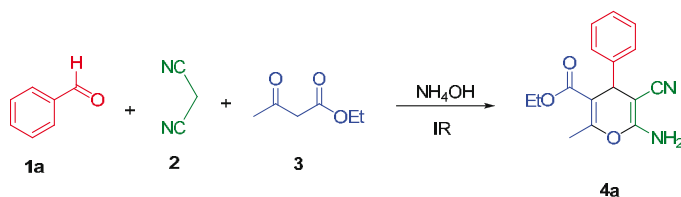
Entry	Base (%)	Solvent	Reaction time (min)	Yield (%)[b]
1	NH_4OH[c]	H_2O	60	45
2	NH_4OH[c]	H_2O	10	98
3	NH_4OH[d]	H_2O	10	50
4	NH_4OH[e]	H_2O	10	85
5	TEA[c]	H_2O	10	63
6	morpholine[c]	H_2O	10	82
7	NaOH[c]	H_2O	10	76
8	NH_4Cl[c]	H_2O	10	80
9	NH_4OH[c]	DMF	10	45
10	NH_4OH[c]	EtOH	10	98
11	NH_4OH[c]	1,4-dioxane	10	39

[a] All entries were carried out under IR irradiation, except entry 1. [b] Isolated yields, after recrystallization. [c] 28 mol%. [d] 10 mol%. [e] 20 mol%.

of increasing the reaction time to 2 h, no appreciable increment was observed in the yield of the desired product.

Therefore, an attempt was made to promote the target reaction by employing infrared irradiation as the source of heating, by taking into account that we have previously demonstrated that Knoevenagel adducts can be easily prepared by using infrared irradiation for the condensation of benzaldehydes and malononitrile in solvent-free conditions [18]. Interestingly, when this protocol was applied to the condensation of benzaldehyde (**1a**), malononitrile (**2**), ethyl acetoacetate (**3**), and commercial ammonium hydroxide, the 4*H*-pyran derivative **4a** (Table 1, entry 2) was isolated in excellent yield (98%) after only 10 min of reaction.

Thus, we evaluated the amount of ammonium hydroxide required for this transformation. By using 10, 20 and 40 mol% of the base under same reaction conditions, we obtained 50%, 85% and 97% yields, respectively. The highest yield was obtained (98%) when the reaction was loaded with 28 mol% of the base (Table 1, entries 2-4). Increasing this catalyst beyond that concentration did not affect the yield. It is important to note that in order to obtain the product **4a** in pure form, a simple filtration and recrystallization were carried out.

A series of organic and inorganic bases were then tested and compared to ammonium hydroxide. As shown in Table 1 (entries 5-8), good yields were obtained with triethylamine, morpholine, sodium hydroxide or ammonium chloride as a

base. However, afterwards the purification of the desired product was more difficult in comparison with the use of amonium hydroxide.

Finally, we examined the effect of the solvent on the reaction. When using protic and aprotic solvents, EtOH afforded the product in excellent yield (98%), whereas DMF and dioxane gave only moderate yields (Table 1, entries 9, 10 and 11).

According to these results, we decided to perform the reaction with the mixture of **1a**, **2**, and **3** (1:1:1 equiv. mol), and NH_4OH (28 mol%). This mixture was irradiated with an infrared lamp (OSRAM R-20 bulb, 127 V, 250 W, λ = 1255.6 nm) [24, 25, 26] at reflux temperature for 10 min, under solvent-free conditions (Table 1, entry 2). After this time, the conversion of the substrates into **4a** was very efficient, leading to the desired 4*H*-pyran **4a** in high yield (98%).

To validate this new method and to assess the effect of different substituents on the formation of the 4*H*-pyrans, both electron-poor and electron-rich aromatic aldehydes, as well as heteroaromatic and aliphatic aldehydes were employed. In all cases, almost the same result of cyclocondensation was observed, giving the desired adduct (Table 2). Aliphatic aldehydes gave the corresponding 4*H*-pyrans in lower yield (45-58%) (entries 12-13) than aromatic and heterocyclic aldehydes. However, no obvious correlation was found between the nature of the substituent on the aromatic or heterocyclic ring and the yield of this conversion. One of the major advantages of this

Table 2. Synthesis of 4*H*-pyrans promoted by infrared irradiation, in solvent-free conditions.[a]
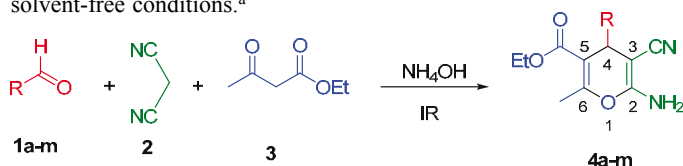

Entry	R	Reaction Time (min)	Product	Yield[b] (%)
1	C_6H_5	10	**4a**	98
2	C_6H_4-4-OMe	10	**4b**	80
3	C_6H_4-4-NO_2	10	**4c**	98
4	$NO_2C_6H_4$-2-NO_2	10	**4d**	88
5	C_6H_4-4-CHO	10	**4e**	92
6	C_6H_4-3-CHO	10	**4f**	40
7	C_6H_4-3-Cl	10	**4g**	57
8	C_6H_4-4-F	10	**4h**	80
9	4-pyridyl	10	**4i**	86
10	2-furyl	10	**4j**	95
11	2-thienyl	10	**4k**	80
12	H	10	**4l**	45
13	propyl	10	**4m**	58

[a]All entries were carried out under IR irradiation, using NH_4OH (28 mol%) and solvent-free conditions. [b]Isolated yields, after recrystallization.

protocol is the isolation and purification of the products, which have been achieved by simple washing and crystallization of the crude products.

The structural elucidation of products **4a-m** was made on the basis of their spectroscopic data. Thus, for instance, infrared (IR) spectra of **4c** exhibited bands at 3335 (NH_2), 2194 (CN), and 1676 (C=O) cm^{-1}. The ^1H NMR spectrum of **4c** showed the presence of: (i) four aromatic protons at 7.42-8.16 ppm attributed to system AA´-BB´; (ii) a triplet and quartet at 1.01 and 3.97 ppm integrating for three and two protons of the ethoxycarbonyl group, respectively; and (iii) three singlet at 2.38, 4.47 and 6.86 ppm identified as the methine (C-4), methyl (CH_3), and NH_2 protons. The ^{13}C NMR spectrum displayed: (i) a signal at 169.1 ppm due to the carbonyl group, and at 117.4 ppm due to cyano; (ii) four signals for the vinyl carbons at 158.2 (C-2), 156.1 (C-6), 104.3 (C-5), and 54.7 ppm (C-3); and (iii) four signal for aromatic carbons at 150.6-121.7 ppm. The attributions of the signals were supported on 2D experiments such as HMQC and HMBC. A single-crystal determination for compounds **4b** and **4c** allowed us to confirm their molecular structure (Figure 1). The X-ray structures show that the aryl group in C-4 and the heterocyclic ring are almost orthogonal. A torsion angle C(3)-C(4)-C(1')-C(2') of 91.38° (18) was found for **4b** and another C(3)-C(4)-C(1')-C(6') of -96.99° (15) for **4c**. [27]

The formation of **4** can be explained by the possible mechanism presented in Scheme 1. The reaction can occur via the initial formation of the α,β-unsaturated compound **A**, from the Knoevenagel condensation reaction between aldehyde **1** and malononitrile (**2**), which undergoes nucleophilic attack of the anion of ethyl acetoacetate (**3**) to give the Michael adduct **B**. Then, the latter promotes the cyclization to intermediate **C,** and subsequent tautomerization to afford the polyfunctionalized 4*H*-pyrans **4**. However, an alternative mechanism cannot be ruled out, in which the pathway starts from the reaction between **1** and **3** to generate the α,β-unsaturated compound **E**, which in turn undergoes the conjugated addition of the anion of malononitrile to afford adduct **B**. This latter possible mechanism follows the same sequence of reactions shown in the first case, giving rise to adduct **4**.
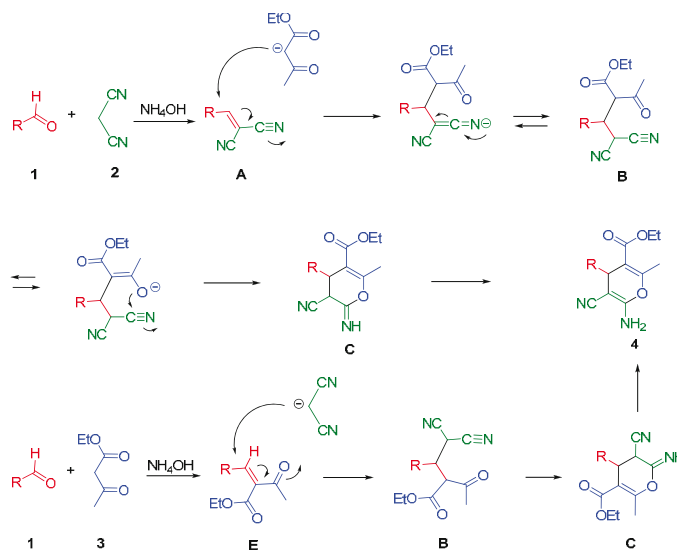
Scheme 1. Proposed mechanisms for the synthesis of pyrans **4**.

To test of the proposed mechanism, the reaction between benzylidenemalononitriles **5a-d**, ethyl acetoacetate (**3**) and NH_4OH (28 mol%) was carried out under infrared irradiation. The target compounds **4a-c** and **4h** were obtained in slightly lower yields than those obtained by the three-component reaction (Table 3). In contrast, when we attempted to test the second mechanistic route, starting from benzaldehyde (**1a**) and ethyl acetoacetate (**3**), the product of the Knoevenagel reaction, **E**, was not formed, leading to a complex mixture of products.
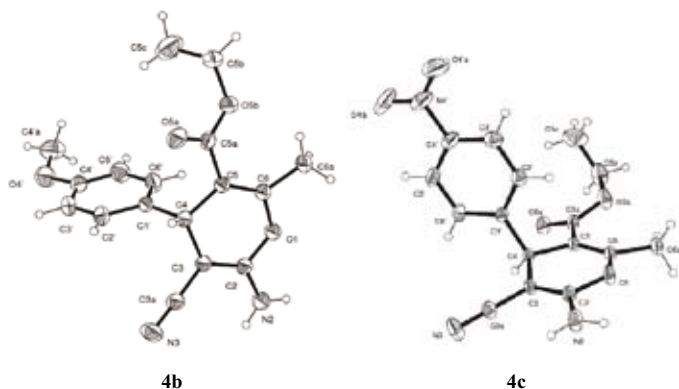
Conclusion

A novel and efficient three-component method for the synthesis of 4*H*-pyran derivatives, catalyzed with NH_4OH and promoted by infrared irradiation is described. Compared with other procedures, this method has the advantage of being a single step and

Fig. 1. Molecular structure of **4b** and **4c** with thermal ellipsoids at the 30% probability level.

Table 3. Synthesis of pyrans **4a-c** and **4h** by a condensation reaction between **5a-d**, **3** and NH_4OH.[a]

Entry	R	Time (min)	Product	Yield[b]
1	H	15	**4a**	70
2	OMe	35	**4b**	68
3	NO_2	10	**4c**	90
4	F	20	**4h**	76

[a] All entries were carried out under IR irradiation, and solvent free conditions. [b] After recristallization.

easy operation with short reaction times, mild and non-hazardous (environmentally friendly) reaction conditions, and good yields of potentially active compounds. Moreover, this method further expands the application of a new and efficient source of energy, infrared irradiation, in organic synthesis.

Experimental section

General Procedure. Melting points were determined on a Fisher-Johns melting point apparatus and were uncorrected. The progress of the reaction and the purity of compounds were monitored by TLC with E. Merck silica gel 60-F_{254} coated aluminum sheets, in *n*-hexane/ethyl acetate (7:3), and visualized by a 254 nm UV lamp. IR spectra were recorded on a Perkin-Elmer 2000 spectrophotometer. NMR spectra were recorded, for solutions in DMSO-d_6 and CDCl$_3$ with Me$_4$Si as internal standard, on Varian Gemini (200 MHz) and Varian VNMR System (500 MHz) instruments. High-resolution mass spectra (HRMS) were obtained with a JSM-GCMate II mass spectrometer, and electron impact techniques (70 eV) were employed. X-ray diffraction data were collected on an Oxford Diffraction Xcalibur S single-crystal X-ray diffractometer.

General procedures for the preparation of 2-amino-3-cyano-4H-pyrans derivatives (4a-m). Method A. A mixture of aldehyde **1a-m** (3.0 mmol), malononitrile **2** (3.0 mmol), ethyl acetoacetate **2** (3.0 mmol) and ammonium hydroxide solution 28% w/w (373 mg, 3.0 mmol) was placed in a 25 mL round-bottom flask equipped with a condenser. The mixture was irradiated with an infrared lamp at reflux temperature for ~10 min, under solvent-free conditions, until the consumption of the substrates. The reaction was monitored by ^{1}H NMR or *tlc*. After cooling, the product mixture was directly submitted to recrystallization from water/ethanol (90:10), affording the corresponding pure 4H-pyran derivates **4a-m**.

Method B. A mixture of the benzylidenemalononitriles **5a-d** (1 mol-equiv.), ethyl acetoacetate **3** (1 mol-equiv.) and an aqueous solution of ammonium hydroxide, 28% w/w (373 mg, 3.0 mmol) was placed in a 25 mL round-bottom flask equipped with a condenser. The mixture was irradiated with an infrared lamp [24] for ~5-30 min, under solvent-free conditions, until the consumption of the substrates. After cooling, the product mixture was directly submitted to recrystallization from water/ethanol (90:10), affording the corresponding pure 4H-pyran derivates **4a-c** and **4h**.

The target compounds were fully characterized by their physical and spectral data. In the case of known compounds, their physical and spectroscopic data were compared with those reported in the literature and found to be related. **4a**, mp 195-196 °C (lit. [28a]), **4b** mp 142-144 °C **4c**, mp 182-183 °C (lit.[28a]), (lit.[28c]), **4d**, mp 178-179 °C (lit.[28a], **4f**, mp 225-227 °C (lit. [28c]), **4g**, mp 153-156 °C (lit. [28a],]), **4h**, mp 154-157 °C (lit. [28a]), **4i**, mp 162-163 °C (lit. [28c]), **4j**, mp 280 °C (lit. [28c]), **4k**, mp 135-137 °C (lit. [28c]).

2-Amino-3-cyano-5-ethoxycarbonyl-6-methyl-4-phenyl-4H-pyran (4a). Following **General Method A**, the reac-

tion between **1a** (319 mg, 3.0 mmol), malononitrile (**2**) (198 mg, 3.0 mmol), ethyl acetoacetate (**3**) (390 mg, 3.0 mmol) and ammonium hydroxide 28% w/w (373 mg, 3.0 mmol) was irradiated with infrared irradiation for 5 min. The crude product was recrystallized from water/ethanol, giving 766 mg (90%) of **4a** as a white solid; mp 182-184 °C.

Method B. A mixture of benzylidenemalononitrile **5a** (462 mg, 3.0 mmol), ethyl acetoacetate (**3**) (390 mg, 3.0 mmol) and ammonium hydroxide 28% w/w (373 mg, 3.0 mmol) was irradiated with infrared irradiation for 15 min. The crude product was recrystallized from water/ethanol, giving 596 mg (70%) of **4a**; FT-IR (KBr) v_{max} 3404, 2190, 1688 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.03 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$), 2.31 (s, 3H, C*H*$_3$), 3.87 (qd, *J* = 7.0, 1.4 Hz, 2H, OC*H*$_2$CH$_3$), 4.29 (s, 1H, H-4), 6.78 (br s, 2H, NH$_2$), 7.12-7.31 (m, 5H, H-Ar); ^{13}C (50 MHz, DMSO-d_6) δ 13.6 (OCH$_2$*C*H$_3$), 18.1 (*C*H$_3$), 38.2 (C-4), 57.3 (C-3), 60.0 (O*C*H$_2$CH$_3$), 107.2 (C-5), 119.6 (*C*≡N), 126.6 (C-4′), 127.1 (C-2′ and C-6′), 128.2 (C-3′ and C-5′), 144.8 (C-1′), 156.5 (C-6), 158.3 (C-2), 165.3 (*C*=O). HRMS (EI$^+$) calcd for C$_{16}$H$_{16}$N$_2$O$_3$ 284.1161, found (M$^+$) 284.1158.

2-Amino-3-cyano-5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-4H-pyran (4b). Following **General Method A**, the reaction between **1b** (408 mg, 3.0 mmol), malononitrile (**2**) (198 mg, 3.0 mmol), ethyl acetoacetate (**3**) (390 mg, 3.0 mmol) and ammonium hydroxide 28% w/w (373 mg, 3.0 mmol) was irradiated with infrared irradiation for 10 min. The crude product was recrystallized from water/ethanol, giving 753 mg (80%) of **4b** as a yellow solid; yield; mp 135-137 °C.

Method B. A mixture of benzylidenemalononitrile **5b** (552 mg, 3.0 mmol), ethyl acetoacetate (**3**) (390 mg, 3.0 mmol) and ammonium hydroxide 28% w/w (373 mg, 3.0 mmol) was irradiated with infrared irradiation for 35 min. The crude product was recrystallized from water/ethanol, giving 642 mg (68%) of **4b**; IR (KBr) v_{max} 3400, 2191, 1682 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.11 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 2.34 (s, 3H, C*H*$_3$), 3.77 (s, 3H, OC*H*$_3$), 4.02 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$CH$_3$), 4.39 (s, 1H, H-4), 4.56 (br s, 2H, N*H*$_2$), 6.82 (d, *J* = 8.6 Hz, 2H, H-3′ and H-5′), 7.12 (d, *J* = 8.6 Hz, 2H, H-2′ and H-6′); ^{13}C (50 MHz, DMSO-d_6) δ 13.9 (OCH$_2$*C*H$_3$), 18.3 (*C*H$_3$), 37.9 (C-4), 55.2 (O*C*H$_3$), 60.6 (O*C*H$_2$CH$_3$), 62.3 (C-3), 108.19 (C5), 113.9 (C-3′ and C-5′), 119.1 (*C*≡N), 128.6 (C-2′ and C-6′), 136.1 (C-1′), 156.3 (C-4′), 157.4 (C-6), 158.6 (C-2), 160.1 (*C*=O). HRMS (EI$^+$) calcd for C$_{17}$H$_{18}$N$_2$O$_4$ 314.1267, found (M$^+$) 314.1268.

2-Amino-3-cyano-5-ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-4H-pyran (4c). Following **General Method A**, the reaction between **1c** (453 mg, 3.0 mmol), malononitrile (**2**) (198 mg, 3.0 mmol), ethyl acetoacetate (**3**) (390 mg, 3.0 mmol) and ammonium hydroxide 28% w/w (373 mg, 3.0 mmol) was irradiated with infrared irradiation for 5 min. The crude product was recrystallized from water/ethanol, giving 967 mg (98%) of **4c** as a yellow solid; yield; mp 178-180 °C.

Method B. A mixture of benzylidenemalononitrile **5c** (597 mg, 3.0 mmol), ethyl acetoacetate (**3**) (390 mg, 3.0 mmol) and ammonium hydroxide 28% w/w (373 mg, 3.0 mmol) was irradiated with infrared irradiation for 10 min. The crude product

was recrystallized from H_2O, giving 888 mg (90%) of **4c**; IR (KBr) v_{max} 3335, 2194, 1676 cm^{-1}; ^{1}H NMR (200 MHz DMSO-d_6) δ 1.01 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H$_3$*), 2.38 (s, 3H, C*H$_3$*), 3.97 (q, *J* = 7.0 Hz, 2H, OC*H$_2$*CH$_3$), 4.47 (s, 1H, H-4), 6.86 (br s, 2H, N*H$_2$*), 7.42 (d, *J* = 8.8 Hz, 2H, H-2′ and H-6′), 8.16 (d, *J* = 8.8 Hz, 2H, H-3′and H-5′); ^{13}C (50 MHz DMSO-d_6) δ 11.95 (OCH$_2$*C*H$_3$), 16.6 (*C*H$_3$), 36.6 (C-4), 54.7 (C-3), 58.4 (O*C*H$_2$CH$_3$), 104.3 (C-5), 117.4 (*C*≡N), 121.7 (C-2′ and C-6′), 126.5 (C-3′ and C-5′), 146.6 (C-4′), 150.6 (C-1′), 156.1 (C-6), 158.2 (C-2), 169.1 (*C*=O). HRMS (EI$^+$) calcd for $C_{16}H_{15}N_3O_5$ 329.1012, found (M$^+$) 329.1025.

2-Amino-3-cyano-5-ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-4*H*-pyran (4d). Following **General Method A**, the reaction between **1d** (453 mg, 3.0 mmol), malononitrile (**2**) (198 mg, 3.0 mmol), ethyl acetoacetate (**3**) (390 mg, 3.0 mmol) and ammonium hydroxide 28% w/w (373 mg, 3.0 mmol) was irradiated with infrared irradiation for 5 min. The crude product was recrystallized from water/ethanol, giving 868 mg (88%) of **4d** as a yellow solid; yield; mp 179-181 °C; IR (KBr) v_{max} 3455, 2209, 1689 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 0.90 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H$_3$*), 2.33 (s, 3H, C*H$_3$*), 3.85 (q, *J* = 7.2 Hz, 2H, OC*H$_2$*CH$_3$), 5.01 (s, 1H, H-4), 7.09 (br s, 2H, NH$_2$), 7.45 (m, 2H, H-4′ and H-6′), 7.69 (t, *J* = 8.0 Hz, 1H, H-5′), 7.84 (d, *J* = 8.0 Hz, 1H, H-3′); ^{13}C (50 MHz, DMSO-d_6) δ 13.1 (OCH$_2$*C*H$_3$), 17.9 (*C*H$_3$), 32.5 (C-4), 55.5 (C-3), 58.9 (O*C*H$_2$CH$_3$), 105.9 (C-5), 118.5 (*C*≡N), 123.3 (C-3′), 127.6 (C-4′), 130.0 (C-2′), 133.3 (C-3′), 139.1 (C-1′), 148.0 (C-6′), 157.8 (C-6), 158.5 (C-2), 164.8 (*C*=O). HRMS (EI$^+$) calcd for $C_{16}H_{15}N_3O_5$ 329.1012, found (M$^+$) 329.1013.

1,4-bis-(2-Amino-3-cyano-5-ethoxycarbonyl-6-methyl-4*H*-pyran-4-yl)benzene (4e). Following **General Method A**, the reaction between **1e** (402 mg, 3.0 mmol), malononitrile (**2**) (396 mg, 3.0 mmol), ethyl acetoacetate (**3**) (780 mg, 3.0 mmol) and ammonium hydroxide 28% w/w (373 mg, 3.0 mmol) was irradiated with infrared irradiation for 10 min. The crude product was recrystallized from water/ethanol, giving 1,352 mg (92%) of **4e** as a yellow solid; yield; mp 1909-191 °C; IR (KBr) v_{max} 3396, 2192, 1689 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.97 (t, *J* = 7.2 Hz, 6H, 2OCH$_2$C*H$_3$*), 2.30 (s, 6H, 2C*H$_3$*), 3.95 (m, 4H, 2OC*H$_2$*CH$_3$), 4.25 (s, 2H, 2H-4), 6.90 (br s, 4H, 2NH$_2$), 7.06 (s, 4H); ^{13}C (75.4 MHz, DMSO-d_6) δ 13.6 (OCH$_2$*C*H$_3$), 18.0 (*C*H$_3$), 38.3 (C-4′), 57.0 (C-3′), 60.0 (O*C*H$_2$CH$_3$), 107.1 (C-5′), 119.7 (*C*≡N), 127.2 (C-2 and C3), 143.3 (C-1 and C-4), 156.6 (C-6′), 158.4 (C-2′), 165.3 (*C*=O). HRMS (EI$^+$) calcd for $C_{26}H_{26}N_4O_6$ 490.1852, found (M$^+$) 490.1853.

1,3-bis-(2-Amino-3-cyano-5-ethoxycarbonyl-6-methyl-4*H*-pyran-4-yl)benzene (4f). Following **General Method A**, the reaction between **1f** (402 mg, 3.0 mmol), malononitrile (**2**) (396 mg, 3.0 mmol), ethyl acetoacetate (**3**) (780 mg, 3.0 mmol) and ammonium hydroxide 28% w/w (373 mg, 3.0 mmol) was irradiated with infrared irradiation for 10 min. The crude product was recrystallized from water/ethanol, giving 588 mg (40%) of **4f** as a yellow solid; yield; mp 166-167 °C; IR (KBr) v_{max} 3410, 2193, 1678 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.02 (t, *J* = 7.2 Hz, 6H, 2OCH$_2$C*H$_3$*), 2.30 (s, 6H, 2C*H$_3$*), 3.85 (m, 4H, 2OC*H$_2$*CH$_3$), 4.26 (s, 2H, 2H-4′), 6.89 (s, 1H, H-2) 6.92

(br s, 4H, 2NH$_2$), 6.99 (dd, *J* = 7.8, 1.2 Hz, 2H, H-4 and H-6), 7.26 (t, *J* = 7.8 Hz, 1H, H-5); ^{13}C (75.4 MHz, DMSO-d_6) δ 13.6 (OCH$_2$*C*H$_3$), 18.0 (*C*H$_3$), 38.5 (C-4′), 57.0 (C-3′), 60.0 (O*C*H$_2$CH$_3$), 107.1 (C-5′), 119.6 (*C*≡N), 125.5 (C-2), 125.6 (C-4 and C-6), 128.8 (C-5), 144.9 (C-1 and C-3), 156.6 (C-6′), 158.5 (C-2′), 165.3 (*C*=O). HRMS (EI$^+$) calcd for $C_{26}H_{26}N_4O_6$ 490.1852, found (M$^+$) 490.1851.

2-Amino-4-(3-chlorophenyl)-3-cyano-5-ethoxycarbonyl-6-methyl-4*H*-pyran (4g). Following **General Method A**, the reaction between **1g** (420 mg, 3.0 mmol), malononitrile (**2**) (198 mg, 3.0 mmol), ethyl acetoacetate (**3**) (390 mg, 3.0 mmol) and ammonium hydroxide 28% w/w (373 mg, 3.0 mmol) was irradiated with infrared irradiation for 10 min. The crude product was recrystallized from water/ethanol, giving 543 mg (57%) of **4g** as a yellow solid; yield; mp 175-177 °C; IR (KBr) v_{max} 3331, 2193, 1676 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.08 (t, *J* = 7.4 Hz, 3H, OCH$_2$C*H$_3$*), 2.37 (s, 3H, C*H$_3$*), 4.02 (m, 2H, OC*H$_2$*CH$_3$), 4.38 (s, 1H, H-4), 7.06 (br s, 2H, NH$_2$), 7.16 (m, 4H, H-2′, H-4′, H-5′, H-6′); ^{13}C (50 MHz, DMSO-d_6) δ 13.6 (OCH$_2$*C*H$_3$), 18.2 (*C*H$_3$), 38.5 (C-4), 56.6 (C-3), 60.2 (O*C*H$_2$CH$_3$), 106.5 (C-5), 119.5 (*C*≡N), 126.0 (C-2′), 126.8 (C-6′), 127.0 (C-3′), 130.4 (C-4′), 132.9 (C-5′), 147.4 (C-1), 157.2 (C-6), 158.5 (C-2), 165.2 (*C*=O). HRMS (EI$^+$) calcd for $C_{16}H_{15}N_2O_3Cl$ 318.0771, found (M$^+$) 318.0774.

2-Amino-3-cyano-5-ethoxycarbonyl-4-(4-flourophenyl)-6-methyl-4*H*-pyran (4h). Following **General Method A**, the reaction between **1h** (372 mg, 3.0 mmol), malononitrile (**2**) (198 mg, 3.0 mmol), ethyl acetoacetate (**3**) (390 mg, 3.0 mmol) and ammonium hydroxide 28% w/w (373 mg, 3.0 mmol) was irradiated with infrared irradiation for 10 min. The crude product was recrystallized from water/ethanol, giving 725 mg (80%) of **4h** as a white solid; mp 170-172 °C.

Method B. A mixture of benzylidenemalononitrile **5d** (516 mg, 3.0 mmol), ethyl acetoacetate (**3**) (390 mg, 3.0 mmol) and ammonium hydroxide 28% w/w (373 mg, 3.0 mmol) was irradiated with infrared irradiation for 20 min. The crude product was recrystallized from H_2O, giving 688 mg (76%) of **4h**; IR (KBr) v_{max} 3403, 2193, 1691 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.11 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H$_3$*), 2.35 (s, 3H, C*H$_3$*), 4.05 (q, *J* = 7.0 Hz, 2H, OC*H$_2$*CH$_3$), 4.39 (s, 1H, H-4), 5.89 (br s, 2H, NH$_2$), 6.92-7.21 (AA'BB' system, 4H, H-2′, H-3′, H-5′, and H-6′); ^{13}C (50 MHz, DMSO-d_6), δ 13.8 (OCH$_2$*C*H$_3$), 18.4 (*C*H$_3$), 38.2 (C-4), 59.2 (C-3), 60.3 (O*C*H$_2$CH$_3$), 107.5 (C-5), 115.2 (*J* = 21.3 Hz, C-3′ and C-5′), 119.5 (*C*≡N), 129.0 (*J* = 7.9 Hz, C-2′ and C-6′), 140.3 (C-1), 158.3 (C-2), 161.0 (*J* = 243.5 Hz, C-4′), 165.8 (*C*=O). HRMS (EI$^+$) calcd for $C_{16}H_{15}N_2O_3F$ 302.1067, found 302.1069.

2-Amino-3-cyano-5-ethoxycarbonyl-6-methyl-4-(pyridin-4-yl)-4*H*-pyran (4i). Following **General Method A**, the reaction between **1i** (322 mg, 3.0 mmol), malononitrile (**2**) (198 mg, 3.0 mmol), ethyl acetoacetate (**3**) (390 mg, 3.0 mmol) and ammonium hydroxide 28% w/w (373 mg, 3.0 mmol) was irradiated with infrared irradiation for 5 min. The crude product was recrystallized from water/ethanol, giving 735 mg (86%) of **4i** as a white solid; mp 164-166 °C; IR (KBr) v_{max} 3327, 2192, 1675 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.01 (t, *J* = 7.0

Hz, 3H, OCH$_2$C*H$_3$*), 2.35 (s, 3H, C*H$_3$*), 3.94 (q, *J* = 7.0 Hz, 2H, OC*H$_2$*CH$_3$), 4.32 (s, 1H, H-4), 7.08 (br s, 2H, NH$_2$), 7.18 (d, *J* = 5.8 Hz, 2H, H-2′ and H-6′), 8.50 (d, *J* = 5.8 Hz, 2H, H-3′ and H-5′); ^{13}C (50 MHz, DMSO-*d$_6$*) δ 13.6 (OCH$_2$*C*H$_3$), 18.2 (*C*H$_3$), 38.3 (C-4), 52.9 (C-3), 60.3 (O*C*H$_2$CH$_3$), 105.0 (C-5), 119.3 (C≡N), 122.3 (C-2′ and C-6′), 149.8 (C-3′ and C-5′), 153.3 (C-1′), 158.0 (C-6), 158.6 (C-2), 165.1 (*C*=O). HRMS (EI$^+$) calcd for C$_{15}$H$_{15}$N$_3$O$_3$ 285.1113, found (M$^+$) 285.1113.

2-Amino-3-cyano-5-ethoxycarbonyl-4-(furan-2-yl)-6-methyl-4*H*-pyran (4j). Following **General Method A**, the reaction between **1j** (288 mg, 3.0 mmol), malononitrile (**2**) (198 mg, 3.0 mmol), ethyl acetoacetate (**3**) (390 mg, 3.0 mmol) and ammonium hydroxide 28% w/w (373 mg, 3.0 mmol) was irradiated with infrared irradiation for 5 min. The crude product was recrystallized from water/ethanol, giving 780 mg (95%) of **4j** as an orange solid; mp 189-190 °C; IR (KBr) ν$_{max}$ 3329, 2192, 1687 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-*d$_6$*) δ 1.13 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H$_3$*), 2.29 (s, 3H, C*H$_3$*), 4.07 (m, 2H, OC*H$_2$*CH$_3$), 4.46 (s, 1H, H-4), 6.07 (d, *J* = 3.1 Hz, 1H, H-4′), 6.35 (m, 1H, H-5′), 7.03 (br s, 2H, NH$_2$), 7.52 (d, *J* = 1.6 Hz, 1H, H-3′); ^{13}C (50 MHz DMSO-*d$_6$*) δ 13.8 (OCH$_2$*C*H$_3$), 18.2 (*C*H$_3$), 32.4 (C-4), 54.1 (C-3), 60.3 (O*C*H$_2$CH$_3$), 105.0 (C-5′), 105.3 (C-5), 110.4 (C-4′), 119.5 (*C*≡N), 142.1 (C-3′), 155.9 (C-1′), 157.6 (C-6), 159.5 (C-2), 165.2 (*C*=O). HRMS (EI$^+$) calcd for C$_{14}$H$_{14}$N$_2$O$_4$ 274.0954, found (M$^+$) 274.0956.

2-Amino-3-cyano-5-ethoxycarbonyl-4-(thiophen-2-yl)-6-methyl-4*H*-pyran (4k). Following **General Method A**, the reaction between **1k** (335 mg, 3.0 mmol), malononitrile (**2**) (198 mg, 3.0 mmol), ethyl acetoacetate (**3**) (390 mg, 3.0 mmol) and ammonium hydroxide 28% w/w (373 mg, 3.0 mmol) was irradiated with infrared irradiation for 10 min. The crude product was recrystallized from water/ethanol, giving 696 mg (80%) of **4k** as a pale yellow solid; mp 180-182; IR (KBr) ν$_{max}$ 3394, 2192, 1669 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-*d$_6$*) δ 1.14 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H$_3$*), 2.28 (s, 3H, C*H$_3$*), 4.08 (dq, *J* = 7.2, 1.4 Hz, 2H, OC*H$_2$*CH$_3$), 4.61 (s, 1H, H-4), 6.82 (dd, *J* = 7.2, 1.4 Hz 1H, H-5′), 6.91 (m, 1H, H-4′), 7.05 (br s, 2H, NH$_2$), 7.36 (dd, *J* = 7.2, 1.4 Hz, 1H, H-3′); ^{13}C (50 MHz DMSO-*d$_6$*) δ 13.8 (OCH$_2$*C*H$_3$), 18.1 (*C*H$_3$), 33.8 (C-4), 56.9 (C-3), 60.4 (O*C*H$_2$CH$_3$), 107.6 (C-5), 119.5 (*C*≡N), 124.0 (C-5′), 124.7 (C-3′), 126.8 (C-4′), 149.3 (C-1′), 156.7 (C-6), 159.05 (C-2), 165.2 (*C*=O). HRMS (EI$^+$) calcd for C$_{14}$H$_{14}$N$_2$O$_3$S 290.0725, found (M$^+$) 290.0724.

2-Amino-3-cyano-5-ethoxycarbonyl-6-methyl-4*H*-pyran (4l). Following **General Method A**, the reaction between **1l** (90 mg, 3.0 mmol), malononitrile (**2**) (198 mg, 3.0 mmol), ethyl acetoacetate (**3**) (390 mg, 3.0 mmol) and ammonium hydroxide 28% w/w (373 mg, 3.0 mmol) was irradiated with infrared irradiation for 10 min. The crude product was recrystallized from water/ethanol, giving 280 mg (45%) of **4l** as a pale yellow solid; mp 252-254 °C; IR (KBr) ν$_{max}$ 3432, 2214, 1648 cm^{-1}, ^{1}H NMR (200 MHz, DMSO-*d$_6$*) δ 1.21 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H$_3$*), 2.19 (s, 3H, C*H$_3$*), 3.28 (s, 2H, H-4), 4.18 (q, *J* = 7.0 Hz, 2H, OC*H$_2$*CH$_3$), 7.48 (br s, 2H, NH$_2$). ^{13}C (50 MHz DMSO-*d$_6$*) δ 14.1 (OCH$_2$*C*H$_3$), 17.8 (*C*H$_3$), 31.7 (C-4), 58.6 (C-3), 69.7 (O*C*H$_2$CH$_3$), 97.2 (C-5′), 116.8 (*C*≡N), 143.6 (C-6′),

146.0 (C-2′), 167.1 (*C*=O). HRMS (EI$^+$) calcd for C$_{10}$H$_{12}$N$_2$O$_3$ 208.0848, found (M$^+$) 208.0855.

2-Amino-3-cyano-5-ethoxycarbonyl-6-methyl-4-propyl-4*H*-pyran (4m). Following **General Method A**, the reaction between **1m** (216 mg, 3.0 mmol), malononitrile (**2**) (198 mg, 3.0 mmol), ethyl acetoacetate (**3**) (390 mg, 3.0 mmol) and ammonium hydroxide 28% w/w (373 mg, 3.0 mmol) was irradiated with infrared irradiation for 10 min. The crude product was recrystallized from water/ethanol, giving 435 mg, (58%) of **4m** as a white solid; mp 163-165 °C; IR (KBr) ν$_{max}$ 3406, 2951, 2186, 1696 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ 0.92 (t, *J* = 7.0 Hz, 3H, H-3′), 1.05-1.45 (m, 7H, H-1′, H-2′, OCH$_2$CH$_3$), 2.20 (s, 3H, C*H$_3$*), 3.20 (m, 1H, H-4), 4.20 (m, 2H, OC*H$_2$*CH$_3$), 6.82 (br s, 2H, NH$_2$). ^{13}C (50 MHz, DMSO-*d$_6$*) δ 13.7 (C-3′), 13.8 (OCH$_2$*C*H$_3$), 17.6 (C-3′), 18.0 (*C*H$_3$), 18.09 (C-2′), 32.2 (C-4), 38.2 (C-1′), 54.5 (C-3), 60.1 (O*C*H$_2$CH$_3$), 107.8 (C-5), 120.3 (*C*≡N)), 157.1 (C-6), 160.1 (C-2), 165.8 (*C*=O). HRMS (EI$^+$) calcd for C$_{13}$H$_{18}$N$_2$O$_3$ 250.1320, found (M$^+$) 250.1318.

X-ray Structure Study of 4b and 4c. Single crystals were obtained by slow evaporation of concentrated solutions of **4b** (EtOH/H$_2$O, white crystals) and **4c** (EtOH/H$_2$O, yellow crystals), which were mounted on glass fibers. Crystallographic measurements were performed on an Oxford Diffraction Xcalibur S single-crystal X-ray diffractometer using Mo KR radiation (graphite crystal monochromator, λ = 71073 A°) at room temperature. Three standard reflections, which were monitored periodically, showed no change during data collection. Unit cell parameters were obtained from least-squares refinement of 26 reflections in the range 2° < 2θ <20°. Intensities were corrected for Lorentz and polarization effects. No absorption correction was applied. Anisotropic temperature factors were introduced for all non-hydrogen atoms. Hydrogen atoms were placed in idealized positions and their atomic coordinates refined. Structures were solved using the SHELXTL [29], SHELX97 [30], or SIR92 [31] programs as implemented in the WinGX suite [32] and refined using SHELXTL or SHELX97 within WinGX, on a personal computer. In all cases ORTEP and packing diagrams were made with PLATON and ORTEP-3 [33].

Acknowledgements

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27. This material is available free of charge via the Internet at the Cambridge Crystallographic Data Centre (e-mail: deposit@ccdc.cam.ac.uk; or http//www.ccdc.cam.ac.uk) as supplementary publication: CCDC 858874 (**4b**), and CCDC 858875 (**4c**).

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