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Tetrahedron 64 (2008) 3372–3380
Tetrahedron
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Cyanamide: a convenient building block to synthesize 4-aryl-2-cyanoimino-3,4-dihydro-1*H*-pyrimidine systems via a multicomponent reaction

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Received 19 December 2007; received in revised form 21 January 2008; accepted 24 January 2008
Available online 31 January 2008

Abstract

4-Aryl-2-cyanoimino-3,4-dihydro-1*H*-pyrimidine derivatives were prepared using a multicomponent reaction by reacting a mixture of arene or heteroarenecarbaldehyde, 1,3-dicarbonyl compounds, and cyanamide under acidic conditions. The novelty of this approach derives from its use of cyanamide as a building block in a four-component Biginelli-type reaction. Varying the reaction conditions led to the formation of either *N*-(2-imino-6-phenyl-1,3,5-oxadiazinan-4-ylidene) cyanamide or 3,4-dihydropyrimidin-2(1*H*)-one. The type of heterocycle skeleton synthesized depends on the nature of the acid catalyst as well as the reaction conditions employed.

Keywords: Cyanamide; Building block; Multicomponent reaction; 4-Aryl-2-cyanoimino-3,4-dihydro-1*H*-pyrimidine

1. Introduction

In recent years, multicomponent reactions (MCRs) have emerged as a powerful strategy to construct structurally complex molecules from simple starting materials.[1] Molecules synthesized by this method continue attracting the attention of medicinal and synthetic chemists.[2] One of the most cited MCRs is the Biginelli reaction, which leads to the formation of 3,4-dihydropyrimidin-2(1*H*)-one (DHPM) derivatives using benzaldehyde, ethyl acetoacetate, and urea as starting materials.[3] This reaction has been widely extended to include variations in all of its components,[4] allowing access to a large number of multifunctionalized DHPM derivatives. For example, an interesting reaction is the four-component approach, recently reported by Orru and et al., to synthesize DHPMs that are properly functionalized at the N-3 position, providing a pool of structurally diverse compounds of biological interest.[5] Many of these derivative compounds have emerged as a class of therapeutic drugs with important pharmacological roles in medicinal chemistry, such as hexahydrotriazaacenaphthalenes (**1**),[6] SQ 32926 (**2**),[7] and HAP-1 (**3**).[8]

Although this reaction has been intensely explored, the construction of 4-aryl-2-cyanoimino-3,4-dihydro-1*H*-pyrimidine (aryl-CIDHPM) compounds (**4**) that are chemically analogous to the Biginelli compounds has not yet been reported. Interestingly, the above molecules possess the *N*-cyanoguanidinyl moiety in their structure, which is found in other biologically active molecules such as the potentially antimycotic agent *N*-cyanoiminopyrimidine (**5**),[9] pinacidil (**6**), a K_{ATP} channel activator[10] (Fig. 1), and other compounds containing the cyanoimino

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doi:10.1016/j.tet.2008.01.087

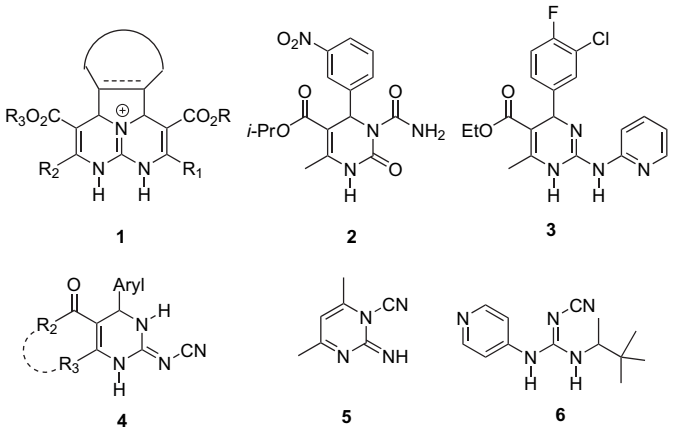
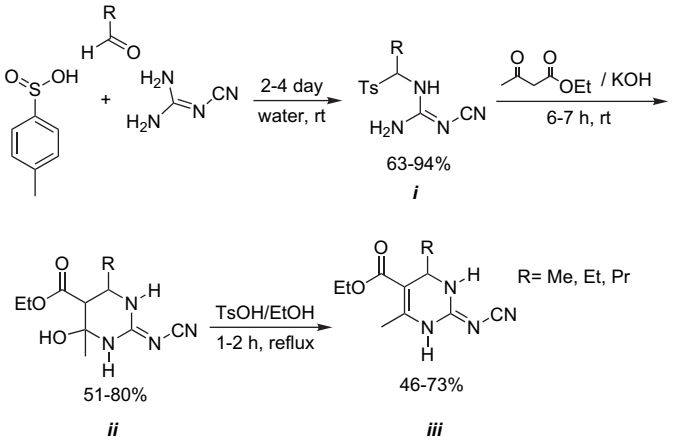


Figure 1. Biginelli-type and cyanoguanidine compounds with pharmacological activity.

functional group that have been found in pharmacologically active products.[11]

The most promising method to construct aryl-CIDHPMs is through the synthesis reported by Shutalev et al. for the obtention of 4-alkyl-2-cyanoimino-3,4-dihydro-1*H*-pyrimidines (alkyl-CIDHPMs).[12] This approach implies the preparation of α-tosyl-substituted *N*-cyanoguanidines **i**. A subsequent reaction with potassium enolates of ethyl acetoacetate results in 5-ethoxycarbonyl-2-cyanimino-4-hydroxyhexahydropyrimidines **ii**, which yield the alkyl-CIDHPMs **iii** after dehydration under acidic conditions (Scheme 1). However, some of the drawbacks of this approach involve a relatively long synthetic pathway, lengthy reaction times, and purification steps that considerably reduce the efficiency of the reaction and overall yields of these compounds.



Scheme 1. Shutalev synthesis of alkyl-CIDHPMs.

More relevant to the present work is the novel methodology employed to synthesize aryl-CIDHPMs by a four-component Biginelli-type reaction based on replacing the cyanoguanidine with 2 equiv of cyanamide. It is worth mentioning that this protocol explored the use of cyanamide as a precursor of new urea-type building blocks to obtain structurally diverse Biginelli compounds, whereas most of the previously reported Biginelli reactions involve urea, thiourea, isourea, or guanidine as building blocks.[13] Therefore, the application of this approach to prepare aryl-CIDHPMs, its scope and limitations via systematic variation of arene or heteroarenecarbaldehyde and 1,3-diketone components, and the influence of catalyst nature in the absence or presence of solvents are reported.

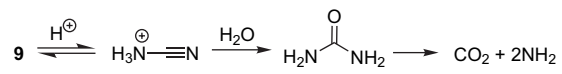
2. Results and discussion

The initial efforts to synthesize aryl-CIDHPMs were based on the preparation of *N*-arylidenecyanoguanidine, a Michael acceptor that was chemically convenient to replace α-tosyl-substituted *N*-cyanoguanidines, the key intermediate in the synthesis of alkyl-CIDHPMs. In agreement with the accepted Biginelli mechanism,[14] this species may form in situ under the Biginelli three-component reaction (B-3CR) conditions through the initial reaction of a mixture of arenecarbaldehyde and cyanoguanidine. The subsequent formation of the aryl-CIDHPMs theoretically could have been achieved by reacting the *N*-arylidenecyanoguanidine with an appropriate 1,3-dicarbonylic compound. Unfortunately, we were unable to prepare this compound using this method.

However, recently Fischer et al. reported the synthesis of 2-arylaminopyrimidine derivatives through *N*-arylguanidine. This intermediate was appropriately synthesized from a mixture of cyanamide and aryl amines under strongly acidic conditions.[15] The chemical explanation behind this process led us to attempt to form *N*-arylidenecyanoguanidine under similar conditions by replacing cyanoguanidine with 2 equiv of cyanamide in the presence of 1 equiv of arenecarbaldehyde, yielding the title compound after a subsequent reaction with a 1,3-dicarbonyl compound. The result was the development of a novel one-pot multicomponent reaction via a four-component approach to prepare aryl-CIDHPMs.

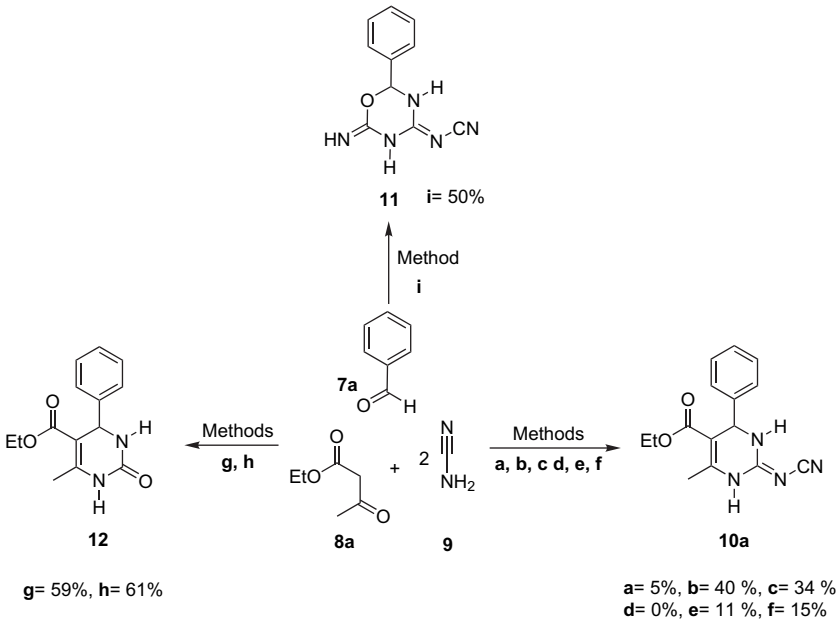
In this multicomponent approach, an exploratory reaction composed of benzaldehyde **7a**, ethyl acetoacetate **8a**, and cyanamide **9** (50% in water) were reacted in a 1:1:2 molar ratio, respectively, in the presence of concd hydrochloric acid (pH ~2) at reflux conditions (EtOH, 4 h). The desired 2-cyanoimino-5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro-1*H*-pyrimidine **10a** was obtained, although in very low yields (5%, Scheme 2, method a).

The result may be rationalized by considering the substantial formation of cyanamidium cations and its corresponding hydrolysis to urea, according to the following equation:[16]



This reaction is known to occur at pH <8.[17] Therefore, weak acidic conditions that shift the equilibrium toward the cyanamide would inhibit ureide formation and probably improve the yield.

Thus, the next catalytic system explored was a mixture of AcONa (1 equiv) and concd hydrochloric acid (in catalytic amount) at pH ~5, which substantially improved the overall yield (40%, Scheme 2, method b). Since this process implies the in situ formation of AcOH, the possibility of better yields



Scheme 2. Synthesis of compounds **10a**, **11**, and **12** through the 4-CR protocol using diverse reaction conditions. Reagents and conditions: method a: HCl/EtOH, method b: HCl/AcONa/EtOH, method c: AcOH/EtOH, method d: AcONa/EtOH, method e: acetate buffer (AcOH/AcONa/HCl, pH 5), method f: HCl/AcONa/H_2O, method g: TsOH/NH_4Cl/EtOH, method h: $AlCl_3$/EtOH, and method i: HCl/AcONa.

using AcOH alone was considered. However, the yield with AcOH was lower (34%, Scheme 2, method c) than that with method b, whereas no product was formed when the reaction was carried out in the absence of either AcOH or concd hydrochloric acid (0%, Scheme 2, method d). Since these experimental results show that the reaction is pH dependent, an acetate buffer was considered to be more appropriate. However, the yield of **10a** did not improve (11%, Scheme 2, Method e), and unwanted by-products were observed, perhaps due to a competing acid-catalyzed hydrolysis of cyanamide to urea, known to happen under acetate buffer conditions.[18]

On the other hand, when the reaction was promoted with pure cyanamide using the conditions of method b, the overall yield was not improved (30%) and the corresponding product was not observed as a precipitate at the end of the reaction (similar to the results from method b). To obtain the desired compound, it was necessary to concentrate and cool the mixture for 24 h at 0 °C.

To further improve the yield, other solvents, such as water and methyl sulfoxide, were used without obtaining better results. When EtOH was substituted with water, the yields were substantially lower (15%, Scheme 2, method f), which was probably a consequence of a lack of reagent solubility and the hydrolysis of cyanamide to urea, known to be more effective in hydrochloric acid aqueous solution,[18] while the reaction with methyl sulfoxide led to no detectable production of **10a**.

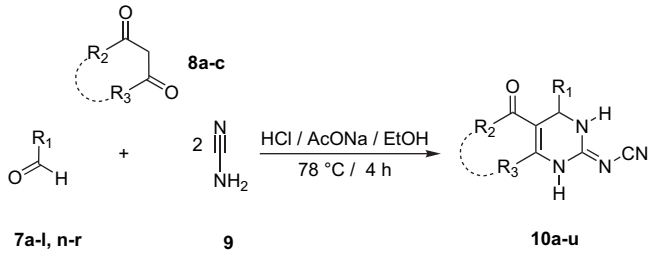
In an attempt to gain more complete understanding on the behavior of this reaction, we employed modified conditions, such as the use of TsOH/NH_4Cl or $AlCl_3$ as catalytic agent, as well as solventless conditions in the presence of concd hydrochloric acid and AcONa. In the former case, the Biginelli product, 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one **12**, was obtained at 59% with TsOH and 61% with $AlCl_3$ (Scheme 2, methods g and h). This compound was spectroscopically identical to a sample prepared through the typical B-3CR protocol.[3c] When concd hydrochloric acid/AcONa and solventless conditions were used, the isolated product was *N*-(2-imino-6-phenyl-1,3,5-oxadiazinan-4-ylidene) cyanamide **11** (50%, Scheme 2, method i). The proposed structure was consistent with the spectroscopic data obtained on the basis of NMR and MS experiments. The ^1H NMR spectrum showed the presence of four magnetically different protons that appear as two singlet signals at 10.47 and 9.68 ppm and two doublet signals at 8.63 ($^3J_{6,5}$=2.4 Hz) and 5.63 ($^3J_{5,6}$=2.4 Hz) ppm. These signals were appropriately assigned to the NH groups bonded to C-2, NH-3, NH-5, and H-6, respectively. The multiple signals observed between 7.45 and 7.34 ppm were attributed to the five protons of the phenyl moiety on C-6. The ^{13}C NMR spectrum showed signals assigned to two nonequivalent C=N groups at 156.6 (C-4) and 150.6 (C-2) ppm; carbons observed at 140.4 (C-1′), 128.9 (C-4′), 128.8 (C-3′), and 125.9 (C-2′) ppm were appropriately assigned to the phenyl group, and the signal that appeared at 63.3 ppm was attributed to the methine carbon (C-6).

Comparing the reaction conditions summarized in Scheme 2, it is clear that method b constitutes the most efficient method to prepare aryl-CIDHMs, while chemoselectivity depends on the reaction conditions.

In order to explore the scope and limitations of this novel protocol, as well as to identify the effect induced by other substrates on the formation of the aryl-CIDHPM, the reactions were performed using various arenecarbaldehyde, heteroarenecarbaldehyde, arenedicarbaldehydes, aliphatic aldehydes, β-ketoesters, and cyclic β-diketones, under the conditions of method b (Table 1).

A similar behavior was observed in the reactions of arenecarbaldehyde or heteroarenecarbaldehydes, **7b–u**, with the

Table 1
Synthesis of 4-aryl-2-cyanoimino-3,4-dihydro-1*H*-pyrimidine derivates (**10a–u**)[a]



Entry	R_1	R_2	R_3	Product	Yield[b] (%)
1	C_6H_5	C_2H_5O	CH_3	**10a**	40
2	4-NO_2–C_6H_4	C_2H_5O	CH_3	**10b**	68
3	2-NO_2–C_6H_4	C_2H_5O	CH_3	**10c**	68
4	3-F–C_6H_4	C_2H_5O	CH_3	**10d**	33
5	2-Cl–C_6H_4	C_2H_5O	CH_3	**10e**	38
6	Piperonyl	C_2H_5O	CH_3	**10f**	25
7	4-Br–C_6H_4	C_2H_5O	CH_3	**10g**	40
8	2-(CF_3)–C_6H_4	C_2H_5O	CH_3	**10h**	35
9	3-(CF_3)–C_6H_4	C_2H_5O	CH_3	**10i**	30
10	4-($OCHF_2$)–C_6H_4	C_2H_5O	CH_3	**10j**	45
11	2-($OCHF_2$)–C_6H_4	C_2H_5O	CH_3	**10k**	50
12	5-NO_2–2-($OCHF_2$)–C_6H_3	C_2H_5O	CH_3	**10l**	63
13	4-(NO_2)–C_6H_4	CH_3O	CH_3	**10m**	50
14	[c]	C_2H_5O	CH_3	**10n**	45
15	[d]	C_2H_5O	CH_3	**10o**	20
16	4-Pyridinyl	C_2H_5O	CH_3	**10p**	39
17	2-Furanyl	C_2H_5O	CH_3	**10q**	34
18	2-Thienyl	C_2H_5O	CH_3	**10r**	36
19	C_6H_5	$R_2\cdots R_3=(CH_2)_3$		**10s**	36
20	4-(NO_2)–C_6H_4	$R_2\cdots R_3=(CH_2)_3$		**10t**	25
21	2-(NO_2)–C_6H_4	$R_2\cdots R_3=(CH_2)_3$		**10u**	26

[a] Reaction conditions: **7** (24 mmol), **8** (24 mmol), **9** (48 mmol), AcONa (24 mmol), EtOH (20 mL), reflux, 4 h.
[b] Overall yields.
[c] 4-[4-(2-Cyanoimino-5-ethoxycarbonyl-6-methyl-3,4-dihydro-1*H*-pyrimidin-4-yl)-phenyl].
[d] 4-[3-(2-Cyanoimino-5-ethoxycarbonyl-6-methyl-3,4-dihydro-1*H*-pyrimidin-4-yl)-phenyl].

1,3-dicarbonylic compounds **8a–c** in the presence of cyanamide **9**. The overall yields obtained for the corresponding products **10b–u** range from modest to good (Table 1, entries 2–21). The highest yields of aryl-CIDHPMs corresponded to the reactions between arenecarbaldehyde containing electron-withdrawing substituents with ethyl acetoacetate (Table 1, entries 2 and 3). However, when cyclohexane-1,3-dione was used, the corresponding aryl-CIDHPMs **10t–u** yields were rather poor (Table 1, entries 20 and 21). Conversely, when the sterically more demanding isophthalaldehyde was used as reactant, the yield of **10o** was low (Table 1, entry 15). The use of aliphatic aldehydes failed to give useful yields of the desired products (data not shown). The reactivity trends found with the cyclic and acyclic 1,3-dicarbonylic compounds are most likely explained by their keto–enol tautomeric content. In this sense, ethyl acetoacetate is more easily enolized than cyclohexane-1,3-dione because the former is stabilized by a very favorable intramolecular hydrogen bond within a six-membered ring.

To determine the structural attributes of these products, several spectroscopic experiments were performed (NMR, MS, and IR). All the data are consistent with the aryl-CIDHPMs **10a–u** structure. Thus, only the most important signals of the 2-cyanoimino-3,4-dihydro-1*H*-pyrimidine fragment, which is common to all aryl-CIDHPMs, are described. The ^{1}H NMR spectrum of **10b** (taken as an example) showed two D_2O-exchangeable protons at δ 10.30 and 9.24 ppm. The former signal appeared as a doublet ($^3J_{1,3}$=1.4 Hz) and was assigned to NH-1, whereas the latter signal was observed as a doublet of doublets (^3J=1.4 and 3.6 Hz) and was assigned to NH-3. The doublet signal ($^3J_{4,3}$=3.6 Hz) observed at 5.37 ppm was assigned to H-4. The ^{13}C NMR spectrum displayed signals at 154.6, 116.2, and 53.0 ppm due to the imino, cyano, and methine, as well as at 100.1 and 147.1 ppm due to the carbons C-5 and C-6, respectively.

Further confirmation of the structure of this fragment is provided by gHMBC. Long-range correlations were observed between the carbon atom at 101.1 ppm (C-5) and the protons at 10.36 (H-1), 9.24 (H-3), 2.32 (CH_3), and 5.37 (H-4) ppm. In conclusion, the spectroscopic data lead to the unambiguous identification of 4-aryl-2-cyanoimino-3,4-dihydro-1*H*-pyrimidine as tautomer **A** and rule out the other two possible tautomeric forms **B** or **C** (Fig. 2).

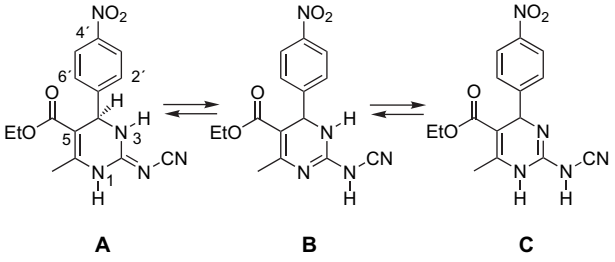
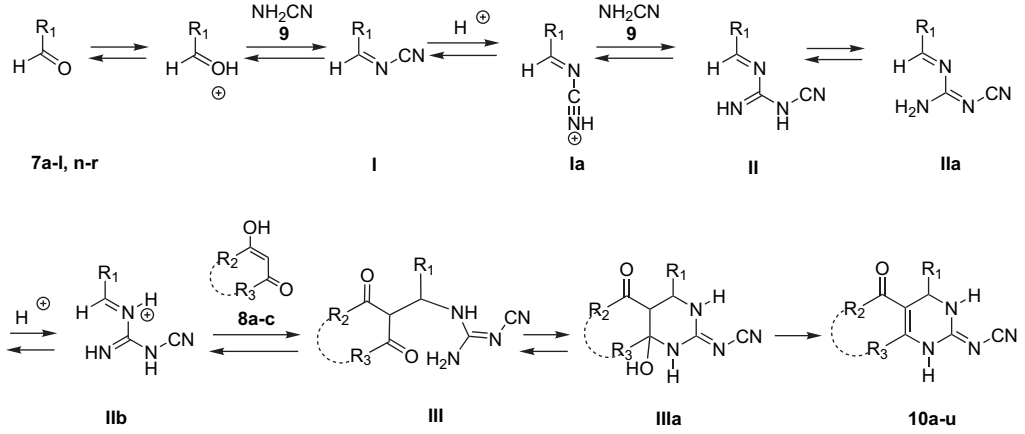


Figure 2. Possible tautomeric forms of **10b**.

Finally, a reasonable and appropriate mechanism is suggested for this MCR, as outlined in Scheme 3. The cyclocondensation reaction of **7a–u** and **8a–c** with **9** that produces the aryl-CIDHPM derivatives **10a–u** probably involves *N*-arylidenecyanoguanidinium **IIb** as the key intermediate. The nucleophilic addition of cyanamide to the arenecarbaldehyde leads to the aryl cyanoimino compound **I**, which forms the arylcyanoiminium species **Ia** after protonation. A subsequent reaction with a second molecule of cyanamide generates the intermediate **II**, which is in equilibrium with **IIa**. The cationic intermediate **IIb** may now undergo nucleophilic attack by the 1, 3-dicarbonyls **8a–c**, probably under its enol form, to yield the intermediate **III**, which finally cyclizes to the aryl-CIDHPMs **10a–u**.

The proposed mechanism assumes the presence of cyanamide as a nucleophile in a pH range of 5–6 and rules out the cyanamide hydrolysis to urea. This latter conclusion is supported by ^{13}C NMR experiments, as the ^{13}C signal of cyanamide at 116.5 ppm remains unchanged. If hydrolysis occurs, the carbon signal of the urea at 164.7 ppm would gradually appear. Also implicit in the proposed mechanism is that the



Scheme 3. Proposed mechanism to obtain aryl-CIDHPMs.

presence of the enol form of 1,3-dicarbonyl favors a conjugate attack on either the *N*-arylidenecyanoguanidine species **IIa** or the carbocationic form **IIb** to subsequently yield the corresponding aryl-CIDHPMs. In this regard, the postulation of **IIb** as an intermediate would also account for the lack of reactivity observed with aliphatic aldehydes. Compared to aromatic aldehydes, aliphatic aldehydes are less efficient in stabilizing the intermediate carbocation **IIb**, which ultimately results in a less efficient cyclocondensation reaction to generate aliphatic-CIDHPMs.

One important feature of the present protocol is the ability to tolerate variation in two of the four components, making it an MCR of moderate variability. Furthermore, cyclic β-diketone and aromatic aldehyde can also be employed as substrates, in addition to the β-ketoester and aryl dialdehyde or heterocyclic aldehyde, without causing a substantial decrease in the overall yield of aryl-CIDHPM. Interestingly, all aromatic aldehydes that carry either electron-donating or electron-withdrawing substituents reacted under this 4-CR protocol, allowing the production of aryl-CIDHPM in high purity and at low to moderate yields. An additional feature of this procedure is the tolerance of acid-sensitive aldehydes (e.g., furfural **7q**) and functional groups (e.g., acetal **7f**). Finally, many of the pharmacologically relevant substitution patterns on the 4-phenyl ring can be introduced with high efficiency.

3. Conclusion

A novel synthesis based on a four-component Biginelli-type reaction has been described. The novelty of this multicomponent reaction is the use of cyanamide as a convenient building block to obtain Aryl-CIDHPMs in a very simple and practical way. Furthermore, mild reaction conditions, tolerance of acid-sensitive functional groups, facile purification, moderate overall yields, and flexibility make this method an attractive tool to synthesize molecules featuring 2-cyanoimino-3,4-dihydro-1*H*-pyrimidinic moieties, which might be useful synthons in organic chemistry or important scaffolds in the synthesis of more elaborate compounds with interesting pharmacological properties.

4. Experimental section

4.1. General

Melting points (uncorrected) were determined with a Fisher–Johns apparatus. IR spectra were recorded on a Perkin–Elmer 1600 spectrophotometer. ^{1}H, ^{13}C, DEPT, COSY, HETCOR, and gHMBC spectra were recorded on a Varian Mercury 300 instrument in DMSO-d_6. Mass spectra (MS) and high-resolution mass spectrometry (HRMS) were obtained on an MStation JMS-700 JEOL spectrometer. Analytical thin-layer chromatography (TLC) was performed using Kieselgel 60 F_{254} silica gel plates (Merck, Darmstadt, Germany). All reagents, except 2-difluoromethoxy-5-nitrobenzaldehyde that was prepared according to protocols described previously,[10a] as well as solvents were of reagent grade from Aldrich and were used without further treatment.

4.2. General procedures

4.2.1. 2-Cyanoimino-dihydro-1H-pyrimidines (*10a–u*)

A suspension of the corresponding arenecarbaldehydes **7a–l**, **n–r** (24 mmol), 1,3-dicarbonyls **8a–c** (24 mmol), cyanamide **9** (50% in water, 48 mmol), sodium acetate (24 mmol), and concd hydrochloric acid (37%, 0.5 mL) in ethanol (20 mL) was stirred and heated at reflux for 4 h. After, the solvent was removed under vacuum, the crude product was filtered and the solid obtained was recrystallized from ethanol to give the pure products.

*4.2.1.1. 2-Cyanoimino-5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro-1H-pyrimidine (**10a**).* Yield 40%; mp 259–261 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.09 (t, J=7.0 Hz, 3H), 2.30 (s, 3H), 4.01 (q, J=7.0 Hz, 2H), 5.25 (s, 1H), 7.23–7.40 (m, 5H), 9.14 (s, 1H), 10.16 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 14.0, 17.3, 53.2, 59.7, 101.2, 116.5, 126.4, 127.9, 128.7, 143.2, 146.0, 154.8, 164.7; IR (KBr) 1641 (C=N), 1679 (C=O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 284; HRMS (EI, 70 eV) found: 284.1282, calcd for $C_{15}H_{16}O_2N_4$: 284.1273.

*4.2.1.2. 2-Cyanoimino-5-ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydro-1H-pyrimidine (**10b**).* Yield 68%; mp 263–265 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.08 (t, J=7.0 Hz, 3H), 2.32 (s, 3H), 4.0 (m, J=7.0 Hz, 2H), 5.37 (d, J=3.6 Hz, 1H), 7.53 (d, J=8.7 Hz, 2H), 8.24 (d, J=8.7 Hz, 2H), 9.23 (dd, J=3.0, 2.1 Hz, 1H), 10.31 (d, J=1.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 14.0, 17.4, 53.0, 59.9, 100.1, 116.2, 124.1, 128.0, 147.1, 150.1, 154.6, 164.4; IR (KBr) 1641 (C═N), 1679 (C═O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 329; HRMS (EI, 70 eV) found: 329.1127, calcd for $C_{15}H_{15}O_4N_5$: 329.1124.

*4.2.1.3. 2-Cyanoimino-5-ethoxycarbonyl-6-methyl-4-(2-nitrophenyl)-3,4-dihydro-1H-pyrimidine (**10c**).* Yield 68%; mp 205–207 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 0.93 (t, J=7.0 Hz, 3H), 2.32 (s, 3H), 3.87 (q, J=7.0 Hz, 2H), 6.04 (d, J=2.7 Hz, 1H), 7.50–7.60 (m, 2H), 7.76 (ddd, J=8.7, 7.8, 1.2 Hz, 1H), 7.95 (dd, J=8.4, 1.2 Hz, 1H), 9.16 (d, J=2.7 Hz, 1H), 10.27 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 13.7, 17.3, 48.6, 59.7, 100.1, 115.9, 124.4, 129.3, 129.4, 134.3, 137.8,147.0, 147.4, 153.9, 164.1; IR (KBr) 1641 (C═N), 1679 (C═O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 329; HRMS (EI, 70 eV) found: 329.1198, calcd for $C_{15}H_{15}O_4N_5$: 329.1124.

*4.2.1.4. 2-Cyanoimino-5-ethoxycarbonyl-6-methyl-4-(3-fluorophenyl)-3,4-dihydro-1H-pyrimidine (**10d**).* Yield 33%; mp 270–272 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.08 (t, J=7.2 Hz, 3H), 2.30 (s, 3H), 4.10 (q, J=7.2 Hz, 2H), 5.27 (s, 1H), 7.19 (d, J=8.4 Hz, 2H), 7.57 (d, J=8.0 Hz, 2H), 9.33 (br s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 14.0, 17.3, 52.8, 59.8, 100.5, 113.3 ($^2J_{CF}$=21.6 Hz), 114.7 ($^2J_{CF}$=20.4 Hz), 116.3, 122.4, 130.8 ($^3J_{CF}$=7.9 Hz), 145.9, 146.7, 154.7, 163.7 ($^1J_{CF}$=275.0 Hz), 164.5; IR (KBr) 1641 (C═N), 1679 (C═O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 302; HRMS (EI, 70 eV) found: 302.1197, calcd for $C_{15}H_{15}O_2N_4F$: 302.1179.

*4.2.1.5. 2-Cyanoimino-5-ethoxycarbonyl-6-methyl-4-(2-chlorophenyl)-3,4-dihydro-1H-pyrimidine (**10e**).* Yield 38%; mp 243–245 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.02 (t, J=7.0 Hz, 3H), 2.31 (s, 3H), 3.93 (q, J=7.0 Hz, 2H), 5.68 (d, J=0.9 Hz, 1H), 7.25–7.53 (m, 5H), 9.28 (br s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 13.9, 17.2, 51.4, 59.6, 79.2, 100.0, 116.2, 127.8, 129.7, 129.8, 131.9, 140.3, 146.5, 154.0, 164.4; IR (KBr) 1641 (C═N), 1679 (C═O), 2174 (C≡N), 3297 (NH) cm^{-1}; HRMS (EI, 70 eV) found: 318.0875, calcd for $C_{15}H_{15}O_2N_4Cl$: 318.0884.

*4.2.1.6. 2-Cyanoimino-5-ethoxycarbonyl-6-methyl-4-piperonyl-3,4-dihydro-1H-pyrimidine (**10f**).* Yield 25%; mp 264–266 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.09 (t, J=7.0 Hz, 3H), 2.30 (s, 3H), 4.01 (q, J=7.0 Hz, 2H), 5.17 (s, 1H), 6.00 (s, 1H), 6.68–6.90 (m, 3H), 9.08 (s, 1H), 10.15 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 14.0, 17.3, 52.9, 59.7, 101.1, 101.2, 106.8, 108.2, 116.5, 119.7, 137.0, 146.1, 146.9, 147.4, 154.6, 164.7; IR (KBr) 1641 (C═N), 1679 (C═O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 328; HRMS (EI, 70 eV) found: 328.1177, calcd for $C_{16}H_{16}O_4N_4$: 328.1172.

*4.2.1.7. 2-Cyanoimino-5-ethoxycarbonyl-6-methyl-4-(4-bromophenyl)-3,4-dihydro-1H-pyrimidine (**10g**).* Yield 40%; mp 264–265 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.08 (t, J=7.0 Hz, 3H), 2.30 (s, 3H), 4.10 (q, J=7.0 Hz, 2H), 5.23 (s, 1H), 7.19 (d, J=8.4 Hz, 2H), 7.57 (d, J=8.0 Hz, 2H), 9.17 (br s, 1H), 10.07 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 14.0, 17.3, 52.8, 59.8, 100.6, 116.3, 121.0, 128.7, 131.6, 142.5,146.4, 154.6, 164.5; IR (KBr) 1641 (C═N), 1679 (C═O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 362; HRMS (EI, 70 eV) found: 362.0381, calcd for $C_{15}H_{15}O_2N_4Br$: 362.0378.

*4.2.1.8. 2-Cyanoimino-5-ethoxycarbonyl-6-methyl-4-(2-trifluoromethylphenyl)-3,4-dihydro-1H-pyrimidine (**10h**).* Yield 35%; mp 210–211 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 0.91 (t, J=7.2 Hz), 2.38 (s, 3H,), 3.89 (q, J=7.2 Hz, 2H), 5.70 (s, 1H), 7.46–7.58 (m, 2H), 7.66–7.76 (m, 2H), 8.61 (s, 1H), 10.28 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 13.6, 17.8, 50.7, 60.5 101.4, 115.2, 124.2 ($^1J_{CF}$=272.1 Hz), 126.5 ($^3J_{CF}$=5.7 Hz), 127.1 ($^2J_{CF}$=30.6 Hz), 128.3, 128.9, 133.3, 139.2, 145.5, 154.2, 164.0; IR (KBr) 1641 (C═N), 1679 (C═O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 352; HRMS (EI, 70 eV) found: 352.1140, calcd for $C_{16}H_{15}O_2N_4F_3$: 352.1147.

*4.2.1.9. 2-Cyanoimino-5-ethoxycarbonyl-6-methyl-4-(3-trifluoromethylphenyl)-3,4-dihydro-1H-pyrimidine (**10i**).* Yield 30%; mp 267–268 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.05(t, J=7.0 Hz, 3H), 2.32 (s, 3H,), 3.99 (q, J=7.0 Hz, 2H), 5.35 (s, 1H), 7.50–7.71 (m, 4H), 9.22 (br s, 1H), 10.15 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 13.8, 17.3, 53.1, 59.8, 100.3, 116.2, 123.5 ($^3J_{CF}$=4.5 Hz), 124.1 ($^3J_{CF}$=3.45 Hz), 129.0 ($^2J_{CF}$=31.7 Hz), 130.1, 130.4, 144.5, 146.8, 154.6, 164.4; IR (KBr) 1641 (C═N), 1679 (C═O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 352; HRMS (EI, 70 eV) found: 352.1134, calcd for $C_{16}H_{15}O_2N_4F_3$: 352.1147.

*4.2.1.10. 2-Cyanoimino-5-ethoxycarbonyl-6-methyl-4-(4-difluoromethoxyphenyl)-3,4-dihydro-1H-pyrimidine (**10j**).* Yield 45%; mp 209–211 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.02 (t, J=6.9 Hz, 3H), 2.31 (s, 3H), 4.01 (q, J=7.0 Hz, 2H), 5.26 (br s, 1H), 7.18 (d, J=8.7 Hz, 2H), 7.22 (t, $^2J_{HF}$=74.1 Hz, 1H), 7.29 (d, J=8.7 Hz, 2H), 9.14 (br s, 1H), 10.20 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 14.0, 17.3, 52.6, 59.8, 100.9, 116.3 (t, $^1J_{CF}$=256.2 Hz), 116.4, 118.9, 128.2, 140.1, 146.3, 150.5, 154.7, 164.6; IR (KBr) 1641 (C═N), 1679 (C═O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 350; HRMS (EI, 70 eV) found: 350.1197, calcd for $C_{16}H_{16}O_3N_4F_2$: 350.1190.

*4.2.1.11. 2-Cyanoimino-5-ethoxycarbonyl-6-methyl-4-(2-difluoromethoxyphenyl)-3,4-dihydro-1H-pyrimidine (**10k**).* Yield 50%; mp 247–249 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.04 (t, J=6.9 Hz, 3H), 2.28 (s, 3H), 3.93 (q, J=7.0 Hz, 2H), 5.54 (s, 1H), 7.15–7.41 (m, 4H), 7.21 (dd,

$^2J_{HF}$=75.0, 72.9 Hz, 1H), 8.95 (br s, 1H), 10.14 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 13.8, 17.2, 49.9, 59.6, 99.5, 116.4, 116.5 (t, $^1J_{CF}$=255.1 Hz), 117.3, 125.0, 129.6, 130.1, 133.3, 146.3, 149.0, 154.2, 164.5; IR (KBr) 1641 (C=N), 1679 (C=O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 350; HRMS (EI, 70 eV) found: 350.1176, calcd for $C_{16}H_{16}O_3N_4F_2$: 350.1190.

*4.2.1.12. 2-Cyanoimino-5-ethoxycarbonyl-6-methyl-4-(2-difluoromethoxy-5-nitrophenyl)-3,4-dihydro-1H-pyrimidine (**10l**).* Yield 63%; mp 249–250 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.02 (t, *J*=6.9 Hz, 3H), 2.27 (s, 3H), 3.91 (q, *J*=7.0 Hz, 2H), 5.59 (s, 1H), 7.43 (d, *J*=9.0 Hz, 1H), 7.50 (dd, $^2J_{HF}$=73.5, 72.9 Hz, 1H), 8.08 (d, *J*=3.0 Hz, 1H), 8.29 (dd, *J*=9.0, 2.7 Hz, 1H), 8.97 (br s, 1H), 10.28 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 13.6, 17.1, 51.1, 59.5, 97.7, 115.7 (t, $^1J_{CF}$=257.3 Hz), 116.1, 117.0, 125.2, 125.9, 133.6, 143.1, 147.2, 153.9, 154.1, 164.1; IR (KBr) 1641 (C=N), 1679 (C=O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 395; HRMS (EI, 70 eV) found: 395.1041, calcd for $C_{16}H_{15}O_5N_5F_2$: 395.1041.

*4.2.1.13. 2-Cyanoimino-5-methoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydro-1H-pyrimidine (**10m**).* Yield 50%; mp 238–240 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 2.32 (s, 3H), 3.55 (s, 3H), 5.38 (s, 1H), 7.52 (d, *J*=8.4 Hz, 2H), 8.23 (d, *J*=8.7 Hz, 2H), 9.27 (s, 1H), 10.34 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 17.4, 51.3, 52.8, 99.9, 116.2, 124.1, 127.9, 147.1, 147.3, 149.9, 154.7, 164.9; IR (KBr) 1641 (C=N), 1679 (C=O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 315; HRMS (EI, 70 eV) found: 315.0954, calcd for $C_{14}H_{13}O_4N_5$: 315.0968.

*4.2.1.14. 2-Cyanoimino-4-[4-(2-cyanoimino-5-ethoxycarbonyl-6-methyl-3,4-dihydro-1H-pyrimidin-4-yl)-phenyl]-5-ethoxycarbonyl-6-methyl-3,4-dihydro-1H-pyrimidine (**10n**).* Yield 45%; mp 303–305 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.08 (t, *J*=7.2 Hz, 3H), 1.09 (t, *J*=7.2 Hz, 3H), 2.29 (s, 6H), 4.01 (q, *J*=7.2 Hz, 4H), 5.23 (s, 2H), 7.23 (s, 4H), 9.08 (s, 2H), 10. 13 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 14.6, 18.0, 53.7, 59.4, 101.7, 117.0, 143.5, 146.7, 155.4, 165.3; IR (KBr) 1641 (C=N), 1679 (C=O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 490; HRMS (EI, 70 eV) found: 490.2079, calcd for $C_{24}H_{26}O_4N_8$: 490.2077.

*4.2.1.15. 2-Cyanoimino-4-[3-(2-cyanoimino-5-ethoxycarbonyl-6-methyl-3,4-dihydro-1H-pyrimidin-4-yl)-phenyl]-5-ethoxycarbonyl-6-methyl-3,4-dihydro-1H-pyrimidine (**10o**).* Yield 20%; mp 315–320 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.05 (t, *J*=7.2 Hz, 3H), 1.09 (t, *J*=7.2 Hz, 3H), 2.29 (s, 6H), 3.99 (q, *J*=7.2 Hz, 4H), 5.23 (s, 2H), 7.23 (s, 4H), 9.12 (s, 2H), 10.15 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 14.0, 17.2, 53.2, 59.7, 101.1, 116.4, 124.3, 124.5, 126.0, 128.9, 143.7, 146.1, 154.7, 154.8, 164.5; IR (KBr) 1641 (C=N), 1679 (C=O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 490; HRMS (EI, 70 eV) found: 490.2069, calcd for $C_{24}H_{26}O_4N_8$: 490.2077.

*4.2.1.16. 2-Cyanoimino-5-ethoxycarbonyl-6-methyl-4-(4-pyridinyl)-3,4-dihydro-1H-pyrimidine (**10p**).* Yield 39%; mp 249–251 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.10 (t, *J*=7.0 Hz, 3H), 2.30 (s, 3H), 4.10 (q, *J*=7.0 Hz, 2H), 5.26 (s, 1H), 7.23 (d, *J*=4.8 Hz, 2H), 8.57 (d, *J*=4.8 Hz, 2H), 9.24 (s, 1H), 10.30 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 14.0, 17.4, 52.3, 59.9, 99.9, 116.2, 121.4, 147.2, 150.2, 151.1, 154.9, 164.5; IR (KBr) 1641 (C=N), 1679 (C=O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 285; HRMS (EI, 70 eV) found: 285.1215, calcd for $C_{14}H_{15}O_2N_5$: 285.1226.

*4.2.1.17. 2-Cyanoimino-5-ethoxycarbonyl-6-methyl-4-(2-furanyl)-3,4-dihydro-1H-pyrimidine (**10q**).* Yield 34%; mp 244–245 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.12 (t, *J*=7.0 Hz, 3H), 2.25 (s, 3H), 4.08 (q, *J*=7.0 Hz, 2H), 5.30 (d, *J*=2.7 Hz, 1H), 6.16 (d, *J*=3.3 Hz, 1H), 6.37 (dd, *J*=3.3, 1.8 Hz, 1H), 7.58 (dd, *J*=1.8, 0.6 Hz, 1H), 9.15 (d, *J*=2.7 Hz, 1H), 10.22 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 14.1, 17.3, 47.0, 59.8, 98.8, 106.4, 110.5, 116.3, 142.8, 147.0, 154.2, 155.3, 164.4; IR (KBr) 1641 (C=N), 1679 (C=O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 274; HRMS (EI, 70 eV) found: 274.1052, calcd for $C_{13}H_{14}O_3N_4$: 274.1066.

*4.2.1.18. 2-Cyanoimino-5-ethoxycarbonyl-6-methyl-4-(2-thienyl)-3,4-dihydro-1H-pyrimidine (**10r**).* Yield 36%; mp 255–256 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.15 (t, *J*=7.0 Hz, 3H), 2.28 (s, 3H), 4.08 (q, *J*=7.0 Hz, 2H), 5.52 (s, 1H), 6.92 (d, *J*=3.6 Hz, 1H), 6.97 (dd, *J*=4.8, 3.6 Hz, 1H), 7.42 (d, *J*=4.5 Hz, 1H), 9.31 (s, 1H), 10.31 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 14.1, 17.2, 48.5, 59.9, 101.7, 116.3, 124.3, 125.5, 127.0, 146.5,146.7, 155.0, 164.4; IR (KBr) 1641 (C=N), 1679 (C=O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 290; HRMS (EI, 70 eV) found: 290.0840, calcd for $C_{13}H_{14}O_2N_4S$: 290.0837.

*4.2.1.19. [5-Oxo-4-phenyl-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-ylidene]cyanamide (**10s**).* Yield 36%; mp 300 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.72–206 (m, 2H), 2.20–2.40 (m, 2H), 2.45–2.65 (m, 2H), 5.26 (d, *J*=3.6 Hz, 1H), 7.19–7.36 (m, 5H), 9.12 (d, *J*=3.6 Hz, 1H), 10.46 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 20.4, 25.4, 36.2, 50.9, 109.5, 116.2, 126.4, 127.7, 128.6, 143.0, 152.1, 154.7, 193.6; IR (KBr) 1641 (C=N), 1679 (C=O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 266; HRMS (EI, 70 eV) found: 266.1173, calcd for $C_{15}H_{14}ON_4$: 266.1168.

*4.2.1.20. [4-(4-Nitrophenyl)-5-oxo-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-ylidene]cyanamide (**10t**).* Yield 25%; mp 300 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.65–2.05 (m, 2H), 2.10–2.40 (m, 2H), 2.45–2.70 (m, 2H), 5.39 (s, 1H), 7.51 (d, *J*=9.0 Hz, 2H), 8.21 (d, *J*=8.7 Hz, 2H), 9.22 (s, 1H), 10.59 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 20.3, 25.5, 36.1, 50.9, 108.5, 115.9, 123.9, 127.9, 146.9, 150.0, 152.8, 154.6, 193.5; IR (KBr) 1641 (C=N), 1679 (C=O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 311;

HRMS (EI, 70 eV) found: 311.1006, calcd for $C_{15}H_{13}O_3N_5$: 311.1018.

*4.2.1.21. [4-(2-Nitrophenyl)-5-oxo-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-ylidene]cyanamide (**10u**).* Yield 26%; mp 270–275 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.65–2.0 (m, 2H), 2.05–2.35 (m, 2H), 2.41–2.65 (m, 2H), 6.01 (s, 1H), 7.19–7.36 (m, 5H), 9.13 (s, 1H), 10.56 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 20.4, 25.4, 36.0, 47.5, 108.5, 115.7, 124.1, 129.0, 129.7, 133.8, 137.2, 147.8, 152.4, 153.9, 193.4; IR (KBr) 1641 (C=N), 1679 (C=O), 2174 (C≡N), 3297 (NH) cm^{-1}; MS *m/z* 312; HRMS (EI, 70 eV) found: 312.1100, calcd for $C_{15}H_{14}O_3N_5$: 311.2954.

*4.2.2. N-(2-Imino-6-phenyl-1,3,5-oxadiazinan-4-ylidene)-cyanamide (**11**)*

Benzaldehyde **7a** (24 mmol), cyanamide **9** (50% in water, 48 mmol), sodium acetate (24 mmol), and concd hydrochloric acid (37%, 0.5 mL, pH ~5–6) were stirred and heated in the absence of solvent at 90 °C for 2 h. After being concentrated under vacuum, the residue was filtered, resuspended in hot ethanol, and cooled. The precipitate was filtered to yield the pure product: yield 50%; mp 300 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 5.63 (d, J=2.4 Hz, 1H), 7.30–7.47 (m, 5H), 8.63 (d, J=2.4 Hz, 1H), 9.68 (br s, 1H), 10.47 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 63.3, 115.7, 125.9, 128.8, 128.9, 140.4, 150.6, 156.6; MS *m/z* 215; HRMS (EI, 70 eV) found: 215.0809, calcd for $C_{10}H_9ON_5$: 215.0807.

*4.2.3. 5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**12**)*

Benzaldehyde **9a** (24 mmol), cyanamide **9** (50% in water, 48 mmol), ammonium chloride (24 mmol), and *p*-toluenesulfonic acid (24 mmol) in ethanol (20 mL) were stirred and heated to reflux for 2 h. Subsequently, ethyl acetate **8a** (24 mmol) was added to the mixture, which was heated and stirred for 3 h, and then concentrated, cooled, and filtered. The residue was washed with either isopropyl alcohol or ethanol and ether. The solid was suspended in acetone and filtered. The product was collected after elimination of acetone and recrystallized from ethanol obtaining the pure product: yield 59%; mp 203–205 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS): δ 1.08 (t, J=6.9 Hz, 3H), 2.24 (s, 3H), 3.97 (q, J=7.2 Hz, 2H), 5.13 (d, J=3.3 Hz, 1H), 7.0–7.50 (m, 5H), 7.77 (dd, J=3.3 and 2.1 Hz, 1H), 9.22 (d, J=1.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS): δ 14.1, 17.8, 53.9, 59.2, 99.2, 126.2, 127.3, 128.4, 144.8, 148.4, 152.1, 165.3; MS (EI, 70 eV) *m/z* 260.2908.

Acknowledgements

F.D. would like to acknowledge CONACyT (Grant 44038-Q) and SIP/IPN (Grant 20060055, 20070617) for financial support. R.H. is grateful to CONACyT for a graduate scholarship and a Research Fellowship IN1-69, FESC-UNAM. I.V.-H. is a fellow of the EDI/IPN and COFAA/IPN programs. The authors are grateful to Ms. Ana P. Contreras Rojas (McGill University, Montreal Canada) for reviewing the manuscript.

References and notes

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