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ORIGINAL PAPER

Ionic liquid and Lewis acid combination in the synthesis of novel (*E*)-1-(benzylideneamino)-3-cyano-6-(trifluoromethyl)-1*H*-2-pyridones

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Abstract In this work, a new catalytic system to synthesize a series of new (*E*)-1-(benzylideneamino)-3-cyano-6-(trifluoromethyl)-1*H*-2-pyridones from the cyclocondensation reaction of benzylidene cyanoacetohydrazide with 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones [$CF_3C(O)C(R^2) = C(R^1)(OR)$, where R = Me, Et; R^1 = H, Me, Pr, Bu, Ph, 4-Me-Ph, 4-F-Ph, 4-Cl-Ph, 4-Br-Ph; R^2 = H, Me and R^1,R^2 = $–(CH_2)_4–$] is presented. The products were obtained at room temperature in moderate to good yields (42–87%). Comparison of the catalytic system with a conventional method was not possible, because the products were obtained only when the new catalyst system—consisting of triethylamine and Lewis acid in ionic liquid [BMIM][BF_4]—was used.

Keywords 2-Pyridones · Enones · Benzylidene cyanoacetohydrazide · Ionic liquid · Catalysis

Introduction

Many naturally occurring and synthetic compounds containing the 2-pyridone [1] scaffold possess interesting pharmacological properties. Pyridone L-697,661 has been identified as a specific non-nucleoside reverse transcriptase inhibitor of human immunodeficiency virus-1 (HIV-1) [2], while milrinone, amrinone [3, 4], and their analogs [5–7] have been shown to be cardiotonic agents for the treatment of heart failure (Fig. 1). In addition, 2-pyridones can be used as starting materials for synthesizing more complex molecules, such as dienes in the Diels–Alder reaction [8], and also as intermediates for the preparation of arylazo dyes [9].

The main synthetic route to 2-pyridones involves the reaction of cyanoacetamide or cyanoacetohydrazide and 1,3-dielectrophilic reactants, such as 1,3-dicarbonyl compounds [10, 11], α,β-unsaturated ketones [12–14], ketene dithioacetals [15], malonitrile [16] and its derivatives, and 2-arylvinamidinium salts [17]. The preparation of 2-pyridones in this way involves a base-catalyzed reaction, and a few protocols for this are reported in the literature [10–17]. In earlier methods, the use of polar and toxic solvents such as acetonitrile as well as high reaction temperatures was required. Most of these base-catalyzed reactions, especially those involving cyanoacetohydrazide, furnished a limited scope of products. There is still a lack of reports on 2-pyridones that possess a trifluoromethyl group attached to their structure, for example. Data from the literature have demonstrated that the most convenient method to construct trifluoromethylated heterocycles is from trifluoromethyl-containing building blocks used as starting reactants [18–20]. Our research group has systematically synthesized 4-alkoxy-1,1,1-trihalo-3-alken-2-ones and demonstrated their importance as versatile building blocks in the construction of trifluoromethyl-heterocyclic rings (e.g., isoxazoles, pyrazoles, pyrazolium chlorides, pyrrolidinones, pyrimidines, pyrimidinones, pyrazolo[1,5-*a*]pyrimidines, pyridines, thiazolopyrimidinones, selenazoles, quinolines, and diazepines) [18–20].

For these applications, synthetic chemistry relies heavily on the use of molecular solvents. Many of these solvents

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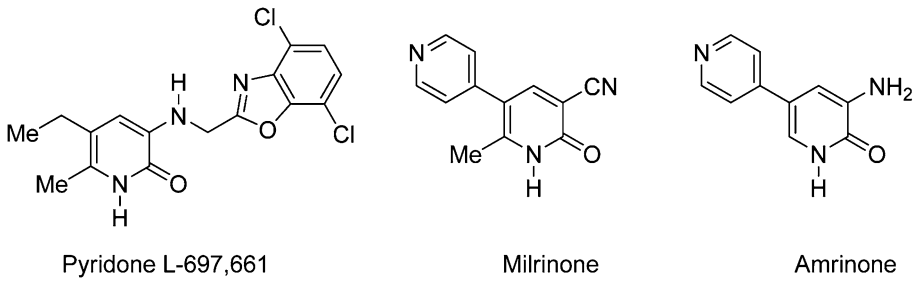
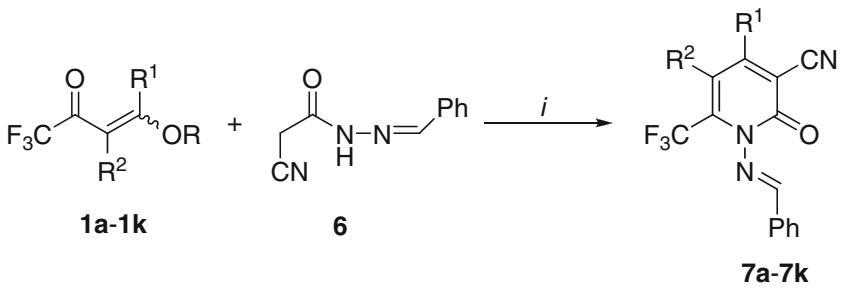
Fig. 1 2-Pyridones possessing pharmacological properties



Scheme 1



i: Et_3N (10 mol%), $BF_3{\cdot}OEt_2$, [BMIM][BF_4] (1 equiv), r.t., 24-48 h

have been found to be environmentally unfriendly, which has generated interest in alternative reaction media [21]. One potential answer to these problems lies in the use of ionic liquids (ILs). Ionic liquids have earned themselves a reputation as excellent reaction media [22, 23]. Furthermore, ionic liquids have the potential to be recycled and reused many times [24, 25], greatly reducing waste and environmental impacts. Therefore, it is desirable to find novel catalytic procedures, especially ones that avoid the use of molecular and toxic solvents, that represent efficient routes to such highly useful organic products as 2-pyridones. The combination of a classical base-catalyzed route and ionic liquids could afford a new green methodology to synthesize 2-pyridones. In this context, and in connection with our ongoing interest in the synthesis and evaluation of new trifluoromethylated heterocyclic compounds, we report herein an environmentally friendly and efficient reaction of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones and cyanoacetohydrazide using a new and interesting catalytic system of base/Lewis acid and [BMIM][BF_4] as a recyclable solvent (Scheme 1).

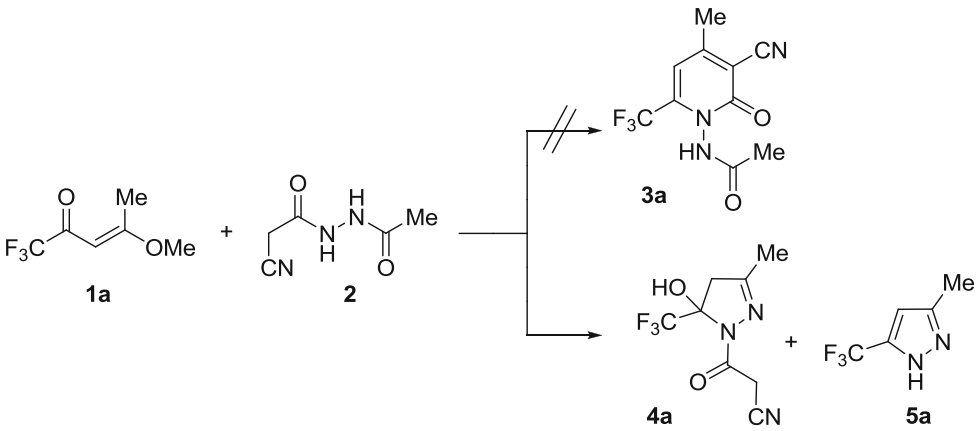
Results and discussion

Recently, we reported that the reaction of cyanoacetohydrazide under basic conditions led to the formation of a mixture of 1-cyanoacetyl-4,5-dihydro-1*H*-pyrazole and a dehydro-pyrazole [26]. Thus, we first performed a protection reaction in order to block one of the nitrogens of cyanoacetohydrazide. The N-acylation was performed in ethyl acetate under reflux for 5 h, and furnished the desired product acylcyanoacetohydrazide **2** in excellent yield (90%). The mixture of acylcyanoacetohydrazide **2** and enone **1a** was submitted to different reaction conditions, using various basic catalysts and ethanol as solvent (Table 1).

Unfortunately, all attempts to produce the desired product failed; only 1-cyanoacetyl-4,5-dihydro-1*H*-pyrazole **4a**, NH-pyrazole **5a**, or a mixture of these was attained. These products form due to a deprotection reaction that occurred with acylcyanoacetohydrazide **2**, which freed both nitrogen atoms to react with the enone, leading to the pyrazole derivatives.

In a second attempt, we performed another protection reaction on cyanoacetohydrazine, converting it to a hydrazone (a stronger protection group) in 96% yield. This was obtained from the reaction of benzaldehyde and cyanoacetohydrazide in ethanol for 16 h with stirring at room temperature. Benzylidene cyanoacetohydrazide (**6**) was submitted to different reaction conditions with enone **1a** in order to find the best conditions for the synthesis of 2-pyridones. Initially, we evaluated the same conditions that were used with acylcyanoacetohydrazide **2**. However, in all cases, only the starting material was recovered, together with by-products that have not been identified. Due to its special properties, the ionic liquid [BMIM][BF_4] was used in these cyclocondensation reactions, since it has been demonstrated to be an excellent alternative medium for heterocyclic synthesis [22]. In a first attempt, enone **1a** was reacted with **6** in the presence of triethylamine in [BMIM][BF_4] at room temperature for 24 h. From the

Table 1 Reaction conditions of enone **1a** with acylcyanoacetohydrazide **2**



Entry	*T*/°C	Base	Product molar ratio **4a**:**5a**	Yield/%
1	r.t.	KOH	5:1	14
2	r.t.	Piperidine	1:2	51
3	−78 to r.t.	Piperidine	1:3	40
4	Reflux	Et_3N	0:1	34

All reactions were carried out in ethanol for 16 h

Table 2 Reaction conditions of enones **1a–1k** with **6**

Enone	R	R^2	R^1	Product	$BF_3{\cdot}OEt_2$/equiv.	Time/h	Yield/%[a]
1a	Me	H	Me	**7a**	1.2	48	50
1b	Me	H	Pr	**7b**	1.2	30	47
1c	Me	H	Bu	**7c**	1.2	27	42
1d	Me	H	2-MeO-PhCH_2	**7d**	0.6	24	79
1e	Me	H	Ph	**7e**	–	24	80
1f	Me	H	4-Me-Ph	**7f**	–	24	70
1g	Me	H	4-F-Ph	**7g**	–	24	86
1h	Me	H	4-Cl-Ph	**7h**	–	24	87
1i	Me	H	4-Br-Ph	**7i**	–	24	68
1j	Et	Me	H	**7j**	1.2	24	73
1k	Me	–$(CH_2)_4$–		**7k**	2.4	27	63

[a] Yield of isolated compounds after column chromatography

NMR spectroscopy and GC-MS data, we observed the formation of the 2-pyridone **7a**. However, this was obtained as a mixture of products (hydroxyl, dehydrated, and/or deprotected 2-pyridones). Thus, we rationalized that the enone activation could require a Lewis acid, and a basic catalyst may be required for anion formation in **6**. We therefore decided to use a catalytic system consisting of $BF_3{\cdot}OEt_2$, triethylamine, and [BMIM][BF_4], which gave the desired product **7a** in moderate yield. The Lewis acid $BF_3{\cdot}OEt_2$ was chosen because it allowed activation under mild conditions; stronger catalysts can cause the deprotection reaction of the starting material **6**. In order to show the efficacy of this new synthetic route, other trifluoromethylated enones were submitted to these reaction conditions with **6**, as shown in Scheme 1. The reaction time and amount of $BF_3{\cdot}OEt_2$ were specific to each enone, as demonstrated in Table 2. Considering the results, we can see that aryl enones were more reactive than alkyl enones, since the reactions of aryl enones did not require the addition of a Lewis acid catalyst. All products were obtained in moderate-to-good yields after purification by column chromatography. This purification step was required to remove any remaining starting material.

All isolated products were well characterized by their melting points, ^1H and ^{13}C NMR, and MS data. In some cases, the 2-pyridones were barely soluble in any deuterated solvents, so it was necessary to analyze them via ^{13}C CPMAS-NMR. 2-Pyridone **7e** was also identified by

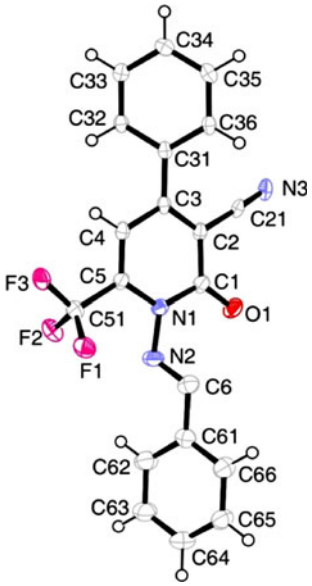


Fig. 2 Crystal structure of (*E*)-1-(benzylideneamino)-1,2-dihydro-2-oxo-4-phenyl-6-(trifluoromethyl)-3-pyridinecarbonitrile (**7e**) obtained using ORTEP

X-ray diffraction. Using these data, the double-bond configurations for the pyridones **7a**-**7k** were determined. ORTEP (Fig. 2) demonstrated that the benzylidene group [C(6)-C(61-66)] is *trans* in relation to the 1-amino-2-pyridone ring [N(2)-N(1)], and that the compound has the *E* configuration.

A probable mechanism for the formation of benzylideneamino-2-pyridones **7a**-**7k** involves a Guareschi–Thorpe reaction [27] that begins with the removal of a proton from the benzylidene cyanoacetohydrazide, promoted by the base, which leads to carbanion formation. This carbanion attacks the β-carbon atom of the enone, which is activated by the Lewis acid, resulting in the elimination of the OR group. In the next step, the enaminoketone intermediate formed undergoes cyclization through the addition of the sp^3 nitrogen of the benzylidene cyanoacetohydrazide to the carbonyl carbon, giving the benzylideneamino-2-pyridones **7a**-**7k** . Due to the neutral nature of the ionic liquid used in this reaction [28], its role is probably to stabilize the carbanion intermediate [29]. Because of the polar nature of the ionic liquid, it is also generally accepted that the activation barrier to the reactions can be reduced by stabilizing the polar transition states or reaction intermediate in polar ionic liquids [30].

In summary, we have developed an efficient synthetic route to a series of eleven new trifluoromethyl-2-pyridones based on the cyclocondensation reaction of enones and benzylidene cyanoacetohydrazide using the catalytic system $BF_3{\cdot}OEt_2$/triethylamine/[BMIM][BF_4].

Experimental

Unless otherwise indicated, all common reactants and solvents were used as obtained from commercial suppliers without further purifications. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 (^{1}H at 400.13 MHz and ^{13}C at 100.62 MHz) in 5 mm sample tubes at 298 K (digital resolution ± 0.01 ppm) in $CDCl_3$/TMS solutions. CPMAS-NMR spectra have been obtained with a Bruker WB-400 spectrometer at 300 K with a wide-bore 4-mm DVT probehead. Samples were carefully packed in ZrO_2 rotors. ^{13}C spectra were originally referenced to a glycine sample and then the chemical shifts were recalculated to the TMS [for the carbonyl atom δ (glycine)1/4 176.1 ppm]. Mass spectra were registered on a HP 5973 MSD connected to a HP 6890 GC and interfaced with a Pentium PC. The GC was equipped with a split-splitless injector and autosampler, crosslinked to a HP-5 capillary column (30 m, 0.32 mm internal diameter), and helium was used as the carrier gas. Elemental analyses were performed on a PerkinElmer 2400 CHN elemental analyzer. Melting points were determined on a Microquímica MQAPF-302 melting point apparatus.

*Typical procedure for the synthesis of benzylideneamino-2-pyridones **7a-7k***

In a round-bottomed flask, benzylidene cyanoacetohydrazide (**6**, 1.2 mmol), [BMIM][BF_4] (1 mmol), and triethylamine (10 mol%) were mixed. The mixture was kept at room temperature under magnetic stirring until complete homogenization. Then, a mixture of enones **1a**–**1k** (1 mmol) and $BF_3{\cdot}OEt_2$ was added dropwise. The amount of $BF_3{\cdot}OEt_2$ used was different for each enone, as detailed in Table 2. The mixture was maintained at room temperature under magnetic stirring for 24–48 h. After this period, dichloromethane was added and the reaction mixture was washed with 10% hydrochloric acid solution (3×10 cm^3). Then the organic phase was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The products **7a**-**7k** were purified by CC using 10% hexane/ethyl acetate as eluent.

(E)-1-(Benzylideneamino)-1,2-dihydro-4-methyl-2-oxo-6-(trifluoromethyl)-3-pyridinecarbonitrile (**7a**, $C_{15}H_{10}F_3N_3O$)

Yield 50%; m.p.: 154–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.56$ (s, 3H, Me), 6.69 (s, 1H, H5), 7.47–7.57 (m, 3H, Ar–H), 7.84–7.86 (m, 2H, Ar–H), 9.18 (m, 1H, H8) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.4$ (Me), 107.6 (q, $^3J = 5.4$ Hz, C5), 109.3 (C3), 113.6 (CN), 118.9 (q, $^1J = 286$ Hz, CF_3), 129.1, 129.3, 131.9, 133.1 (C–Ar), 137.2 (q, $^2J = 34$ Hz, C6), 156.7 (C4), 157.0 (C8), 167.6 (C=O) ppm; GC/MS (CI): $m/z = 334$ ($M + C_2H_7^+$, 7), 306 (MH^+, 63), 243 (14), 203 (28), 104 (100).

(E)-1-(Benzylideneamino)-1,2-dihydro-2-oxo-4-propyl-6-(trifluoromethyl)-3-pyridinecarbonitrile
(**7b**, $C_{17}H_{14}F_3N_3O$)
Yield 47%; oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.06$ (t, 3H, Me), 1.76 (sex, 2H, CH_2), 2.79 (t, 2H, CH_2), 6.68 (s, 1H, H5), 7.47–7.57 (m, 3H, H–Ar), 7.84–7.87 (m, 2H, H–Ar), 9.20 (s, 1H, H8) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.7$ (C11), 22.6 (C10), 37.1 (C9), 106.6 (q, $^3J = 5.4$ Hz, C5), 109.2 (C3), 113.6 (CN), 119.1 (q, $^1J = 286$ Hz, CF_3), 129.0, 129.3, 132.2, 133.1 (C–Ar), 137.6 (q, $^2J = 34$ Hz, C6), 157.0 (C4), 161.1 (C8), 167.4 (C=O) ppm; GC/MS (CI): $m/z = 334$ (MH^+, 2), 259 (14), 231 (57), 104 (100).

(E)-1-(Benzylideneamino)-4-butyl-1,2-dihydro-2-oxo-6-(trifluoromethyl)-3-pyridinecarbonitrile
(**7c**, $C_{18}H_{16}F_3N_3O$)
Yield 42%; m.p.: 98–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.90$–0.97 (t, 3H, Me), 1.36–1.47 (m, 2H, CH_2), 1.63–1.71 (m, 2H, CH_2), 2.81–2.88 (t, 2H, CH_2), 6.41 (s, 1H, H5), 7.52–7.58 (m, 3H, H–Ar), 7.86–7.90 (m, 2H, H–Ar), 8.90 (s, 1H, H8) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.6$ (CH_3), 22.3 (C11), 29.4 (C10), 33.4 (C9), 99.2 (C3), 100.8 (q, $^3J = 5.4$ Hz, C5), 112.4 (CN), 120.8 (q, $^1J = 286$ Hz, CF_3), 129.1, 129.4, 131.5, 133.5 (C–Ar), 144.2 (q, $^2J = 34$ Hz, C6), 157.3 (C4), 157.6 (C8), 169.9 (C=O) ppm; GC/MS (CI): $m/z = 392$ ($M^+ + CH_5^+ + C_2H_7^+$, 14), 374 ($MH^+ + CH_5$, 29), 332 (100), 273 (40), 236 (91), 196 (25).

(E)-1-(Benzylideneamino)-1,2-dihydro-4-(2-methoxybenzyl)-2-oxo-6-(trifluoromethyl)-3-pyridinecarbonitrile (**7d**, $C_{22}H_{16}F_3N_3O_2$)
Yield 69%; m.p.: 147–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.85$ (s, 3H, OMe), 4.11 (s, 2H, CH_2), 6.69 (s, 1H, H5), 6.90–6.98 (m, 3H, H–Ar), 7.47–7.62 (m, 3H, H–Ar), 7.82–7.89 (m, 3H, H–Ar), 9.18 (s, 1H, H8) ppm; ^{13}C CPMAS-NMR (100 MHz): $\delta = 35.3$ (CH_2), 55.7 (MeO), 106.4 (C5), 107.7 (C3), 113.3 (CN), 114.7, 121.7, 124.0, 126.7, 128.8, 129.2, 131.2, 156.5 (C–Ar), 134.6 (C6), 154.6 (C4), 159.4 (C8), 166.8 (C=O) ppm.

(E)-1-(Benzylideneamino)-1,2-dihydro-2-oxo-4-phenyl-6-(trifluoromethyl)-3-pyridinecarbonitrile
(**7e**, $C_{20}H_{12}F_3N_3O$)
Yield 80%; m.p.: 198–201 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.91$ (s, 1H, H5), 7.51–7.69 (m, 8H, Ar–H), 7.87–7.91 (m, 2H, Ar–H), 9.28 (s, 1H, H8) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 106.8$ (q, $^3J = 5.4$ Hz, C5), 114.4 (C3), 114.9 (CN), 118.9 (q, $^1J = 276$ Hz, CF_3), 128.1, 129.0, 129.2, 129.3, 131.5, 132.0, 133.2, 134.3 (Ar–C), 137.6 (q, $^2J = 34$ Hz, C6), 156.8 (C4), 157.4 (C8), 167.6 (C=O) ppm; GC/MS (CI): $m/z = 367$ (M^+, 100), 297 (5).

Crystallographic data for **7e** have been deposited with the Cambridge Crystallographic Data Center (CCDC 767836). Copies of the data can be obtained, free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

(E)-1-(Benzylideneamino)-1,2-dihydro-4-(4-methylphenyl)-2-oxo-6-(trifluoromethyl)-3-pyridinecarbonitrile (**7f**, $C_{21}H_{14}F_3N_3O$)
Yield 70%; m.p.: 213–215 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.46$ (s, 1H, Me), 6.89 (s, 1H, H5), 7.50–7.63 (m, 7H, Ar–H), 7.87–7.90 (m, 2H, Ar–H), 9.28 (s, 1H, H8) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$ (Me), 106.3 (C3), 106.7 (q, $^3J = 5.7$ Hz, C5), 114.5 (CN), 119.1 (q, $^1J = 286$ Hz, CF_3), 125.5, 126.8, 128.1, 129.0, 129.2, 130.0, 131.4, 132.1, 133.1 (C–Ar), 137.5 (q, $^2J = 34$ Hz, C6), 156.7 (C4), 157.6 (C8), 167.3 (C=O) ppm; GC/MS (CI): $m/z = 381$ (M^+, 3), 285 (100).

(E)-1-(Benzylideneamino)-4-(4-fluorophenyl)-1,2-dihydro-2-oxo-6-(trifluoromethyl)-3-pyridinecarbonitrile
(**7g**, $C_{20}H_{11}F_4N_3O$)
Yield 86%; m.p.: 211–214 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.86$ (s, 1H, H5), 7.24–7.27 (m, 2H, H–Ar), 7.49–7.61 (m, 3H, H–Ar), 7.69–7.72 (m, 2H, H–Ar), 7.86–7.89 (m, 2H, H–Ar), 9.26 (s, 1H, H8) ppm; ^{13}C CPMAS-NMR (100 MHz): $\delta = 104.9$ (C5), 113.8 (C3), 115.5 (CN), 127.8, 132.9, 130.4, 135.3, 162.6 (C–Ar), 135.3 (C6), 154.4 (C8), 165.3 (C4), 165.3 (C=O) ppm; GC/MS (CI): $m/z = 298$ ($M^+ - CF_3 - F$, 11), 104 (22), 57 (100).

(E)-1-(Benzylideneamino)-4-(4-chlorophenyl)-1,2-dihydro-2-oxo-6-(trifluoromethyl)-3-pyridinecarbonitrile
(**7h**, $C_{20}H_{11}ClF_3N_3O$)
Yield 87%; m.p.: 209–212 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.86$ (s, 1H, H5), 7.51–7.62 (m, 7H, H–Ar), 7.87–7.90 (m, 2H, H–Ar), 9.25 (s, 1H, H8) ppm; ^{13}C CPMAS-NMR (100 MHz): $\delta = 104.1$ (C5), 105.7 (C3), 107.4 (CN), 119.0, 129.0, 131.1, 132.1, 141.9 (C–Ar), 137.1 (C6), 155.0 (C8), 156.9 (C4), 168.6 (C=O) ppm; GC/MS (CI): $m/z = 132$ ($M^+ - 2Ph - CF_3$, 5), 104 (53), 57 (100).

(E)-1-(Benzylideneamino)-4-(4-bromophenyl)-1,2-dihydro-2-oxo-6-(trifluoromethyl)-3-pyridinecarbonitrile
(**7i**, $C_{20}H_{11}BrF_3N_3O$)
Yield 68%; m.p.: 208–210 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.85$ (s, 1H, H5), 7.49–7.58 (m, 5H, H-Ar), 7.70–7.87 (m, 2H, H–Ar), 7.87–7.90 (m, 2H, H–Ar), 9.25

(s, 1H, H8) ppm; ^{13}C CPMAS-NMR (100 MHz): $\delta =$ 103.4 (C5), 105.2 (C3), 107.0 (CN), 117.3, 131.5, 136.7 (C–Ar), 136.7 (C6), 155.5 (C4), 156.5 (C8), 167.1 (C=O) ppm; GC/MS (CI): *m/z* = 207 ($M^+ - Ph - Br - CF_3$, 5), 149 (31), 57 (100).

(E)-1-(Benzylideneamino)-1,2-dihydro-5-methyl-2-oxo-6-(trifluoromethyl)-3-pyridinecarbonitrile
(**7j**, $C_{15}H_{10}F_3N_3O$)
Yield 73%; m.p.: 147–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.39$ (q, 3H, $^5J = 4.4$ Hz, Me), 7.45–7.58 (m, 3H, H–Ar), 7.69 (s, 1H, H4), 7.85–7.88 (m, 2H, H–Ar), 8.89 (s, 1H, H8) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.8$ (q, $^4J = 5.0$ Hz, Me), 109.7 (C5), 116.1 (CN), 114.0 (C3), 120.2 (q, $^1J = 274$ Hz, CF_3), 129.1, 129.4, 131.8, 133.3 (C–Ar), 135.9 (q, $^2J = 32.7$ Hz, C6), 149.6 (C4), 155.3 (C8), 169.4 (C=O) ppm; GC/MS (CI): *m/z* = 306 (MH^+, 1), 264 (5), 202 (100).

(E)-2-(Benzylideneamino)-2,3,5,6,7,8-hexahydro-3-oxo-1-(trifluoromethyl)-4-isoquinolinecarbonitrile
(**7k**, $C_{18}H_{14}F_3N_3O$)
Yield 63%; m.p.: 176–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.74$–1.79 (m, 2H, CH_2), 1.82–1.88 (m, 2H, CH_2), 2.72 (t, 2H, CH_2), 2.88 (t, 2H, CH_2), 7.47–7.51 (m, 2H, H–Ar), 7.56–7.61 (m, 1H, H–Ar), 7.86–7.88 (m, 2H, H–Ar), 8.83 (s, 1H, H8) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.9$ (C6), 21.3 (C5), 24.3 (q, $^4J = 4.4$ Hz, C8), 28.3 (C7), 100.3 (C4), 112.0 (C8a), 113.0 (CN), 121.5 (q, $^1J = 278$ Hz, CF_3), 128.1, 129.0, 129.4, 131.5, 133.3 (C–Ar), 142.6 (q, $^2J = 35$ Hz, C1), 153.3 (C4a), 156 (C10), 170.1 (C=O) ppm; GC/MS (CI): *m/z* = 419 ($M^+ + CH_5^+ + 2C_2H_7^+$, 21), 392 ($M^+ + CH_5^+ + C_2H_7^+$, 100), 243 (29), 104 (38).

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