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Regiocontrolled synthesis of 3-substituted-6-trifluoromethyl-4(3*H*)-pyrimidinones

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Abstract—Direct reaction of a variety of *N*-monosubstituted benzamidines with 4,4,4-trifluoroacetoacetate esters substituted at the 2-position with methyl, ethyl or methoxy afforded moderate to good yields of herbicidal 3-substituted-6-trifluoromethyl-4(3*H*)-pyrimidinones. Lower yields were obtained with the corresponding 4,4-difluoroacetoacetate esters and the reaction failed with nonfluorinated β-ketoesters. In addition to benzamidines, 3- and 4-pyridylcarboxamidines reacted successfully. The reaction tolerated propyl, allyl, propargyl and phenyl substituents on the amidine nitrogen.

1. Introduction

Pyrimidinones of general structure **1** (Fig. 1) bearing an aromatic or heteroaromatic group at R^2 and a propargyl group at R^3 are inhibitors of zeta-carotene desaturase[1] and possess interesting herbicidal activity.[2] Among this class of compounds, analogs with difluoromethyl and, especially, trifluoromethyl groups at the 6-position of the pyrimidinone ring, e.g. **1a** (Scheme 1) proved to possess superior herbicidal activity. Our original route to **1a** (Method A) is shown in Scheme 1. Reaction of benzamidine hydrochloride (**3**) with ethyl 2-trifluoroacetylbutanoate (**4a**) proceeded in satisfactory yield to afford **5a**.[3] An extensive effort to optimize the propargylation of **5a** was undertaken but the best ratio, based on ^{1}H NMR and GC of the crude product, of the desired *N*-propargyl compound **1a** to the undesired *O*-propargyl compound **6a** that could be obtained was ca. 1:4.[4,5] This result was obtained using propargyl bromide as alkylating agent, sodium methoxide as base and methanol as solvent.[6] Under these conditions, propargylation of **5a** was incomplete and separation of **1a** from the unreacted **5a** and from **6a** required careful chromatography. Therefore, we sought an alternate route to **1a** which would be suitable for the preparation of 500 g quantities.

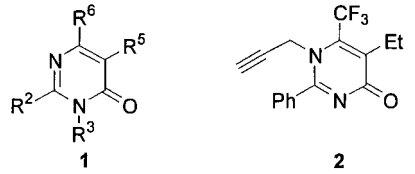

Figure 1. 2-Aryl-4(3*H*)-pyrimidinone regioisomers.

2. Results and discussion

Incorporation of the propargyl group into the benzamidine building block prior to reaction with the β-keto ester appeared to offer an alternative route to pyrimdininones including **1a**, avoiding the troublesome propargylation reaction (Scheme 2). However, examination of the literature was not encouraging. Sitte and Paul reported in 1969 that reaction of a concentrated solution of *N*-propylbenzamidine (**7c**) and methyl acetoacetate (**4c**) in methanol at room temperature for two weeks afforded the pyrimidinone **1c** (R^2=Ph, R^3=*n*-Pr, R^5=H, R^6=Me) in 64% yield (Scheme 3) but, they stated that the reaction failed when the β-keto ester used was substituted with an alkyl group at the α-position.[7] To provide the most herbicidally active compounds which bear an ethyl group at R^5 an α-ethyl-β-ketoester is required. Our own investigations of the reactions between *N*-propyl benzamidine (**7c**) or *N*-propargyl benzamidine (**7a**) and various β-ketoesters, including **4b** and **4c** (Scheme 4), confirmed Sitte and Paul's findings. Presumably, formation of enamine intermediate **9** (Scheme 5) required for ring closure is disfavored for steric reasons when R^5 is a non-hydrogen substituent leading to failure of the reaction. Somewhat more encouraging results were reported by Huber et al. who successfully reacted the cyclic amidine 2-iminopiperidine (**7n**, Scheme 7) with a cyclic β-keto ester to afford a fused tricyclic pyrimidinone.[8] Presumably, the cyclic nature of both of the reactants in this example enforced conformations favoring ring closure over other possible reactions.

Furthermore, during the course of investigating the

Keywords: pyrimidones; amidines; keto acids and derivatives; herbicides.

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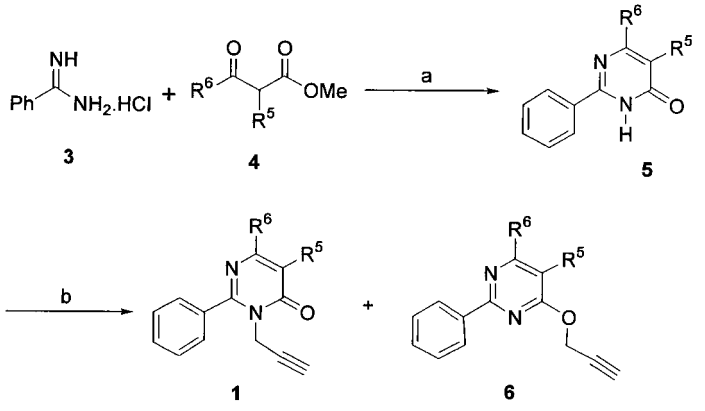
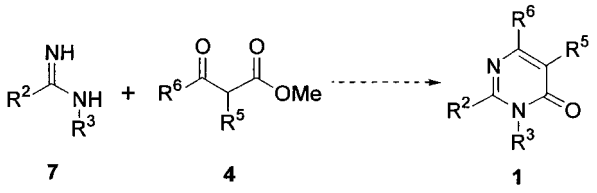
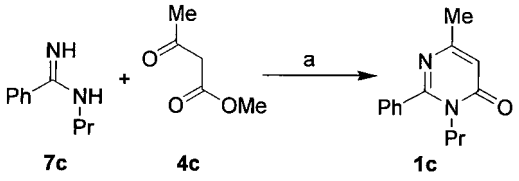


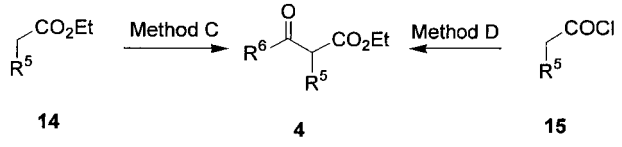
Scheme 1. Synthesis of **1a** and **1b** by base catalyzed propargylation (Method A). **1a** R^5=Et, R^6=CF_3, **1b** R^5=Et, R^6=Et. (a) NaOAc, xylenes, reflux, Dean Stark trap. (b) HC≡CCH_2Br, NaOMe, MeOH, reflux.



Scheme 2. Direct synthesis of pyrimidinones (Method B).



Scheme 3. Sitte and Paul pyrimidinone synthesis (see Ref. 7).

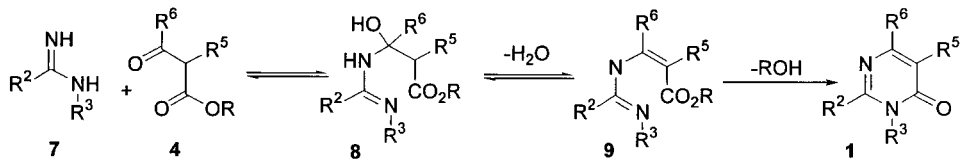


Scheme 4. β-Ketoesters used and their preparation. Method C: R^6CO_2Et, NaH, toluene, reflux. Method D: (i) $(R^6CO)_2O$, pyridine, 10°C, (ii) EtOH. **4a** R^5=Et, R^6=CF_3, Method C or D; **4b** R^5=Et, R^6=Et, Reference 18; **4c** R^5=Me, R^6=H, Commercially available; **4d** R^5=Me, R^6=CF_3, Method; **4e** R^5=H, R^6=CF_3, Commercially available; **4f** R^5=OMe, R^6=CF_3, Method C; **4g** R^5=Cl, R^6=CF_3, Commercially available; **4h** R^5=Et, R^6=CHF_2, Method D; **4i** R^5=H, R^6=CHF_2, Method C; **4j** R^5=OMe, R^6=CHF_2, Method C; **4k** R^5=Me, R^6=CO_2Et, Commercially available.

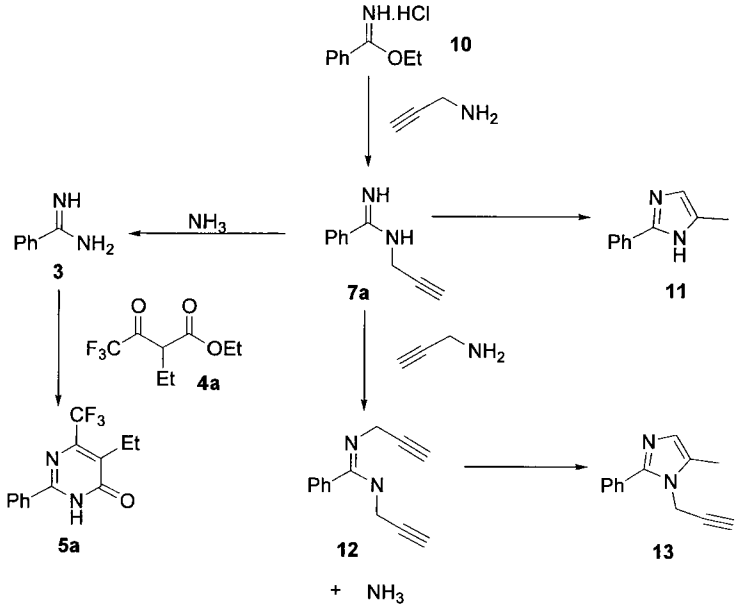
preparation[9] and reactions of *N*-propargylbenzamidine (**7a**), we discovered that it began to decompose over the course of several days at room temperature, and more rapidly when heated or exposed to acid, to afford imidazole **11**,[10] directly from **7a**, and **13**, presumably via **12** (Scheme 6).[11] The imidazoles **11** and **13** were both isolated and characterized; however, the putative intermediate *N*,*N*′-bis(propargyl)-benzamidine (**12**) was not isolated. Similar reactions of *N*-propargylamidines have been reported previously by Deryckere et al.[12]

Despite these discouraging results, we reasoned that when the β-ketoester used is a trifluoromethyl ketone, e.g. **4a**, direct pyrimidinone synthesis (Scheme 2) might be workable. The well-known electrophilicity of trifluoromethyl ketones might shift the equilibria in the first two steps of ring formation (Scheme 5) to the right in favor of formation of enamine **9** (R^6=CF_3), despite the unfavorable steric interactions present in this intermediate, and allow the desired reaction to occur under conditions mild enough to avoid rapid decomposition of **7a**. We were pleased to find that on our first attempt, reaction of **7a** (generated in situ from ethyl benzimidate hydrochloride (**10**) and propargylamine, Scheme 7, Method B1) with **4a** in THF at 50°C for 24 h afforded **1a** in 26% yield. The crude reaction product also contained the imidazoles **11** and **13** and the unpropargylated pyrimidinone **5a**. A plausible route for the formation **5a** is shown in Scheme 6. This version of Method B, in which the amidine **7** was generated in situ from an imidate, is referred to as Method B1 below.

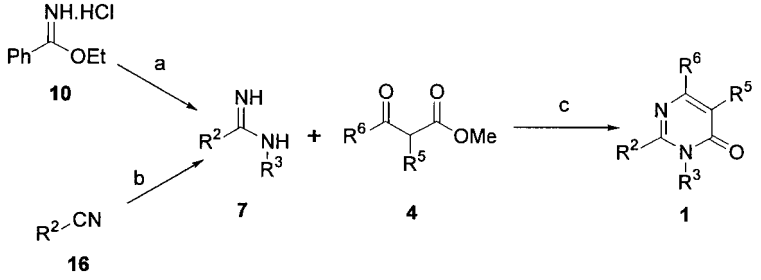
In principle, reaction of **7a** with **4a** could also produce the regioisomer **2** (Fig. 1). In our work, only a single regioisomer was ever detected. The structure **1a** was initially assigned based on the precedent of the work of Sitte and Paul.[7] The fact that the same product is also produced by propargylation of **5a** also favors structure **1a** over **2**, since alkylation of pyrimidinones typically occurs at the 3-position to a greater extent than at the 1 position.[4a,b] The carbonyl group of **1a** absorbs at 1674 cm^{-1} which is typical



Scheme 5. Proposed mechanism of the reaction of *N*-monosubstituted amidines with β-ketoesters.



Scheme 6. Side reactions of *N*-propargylbenzamidine.



Scheme 7. Synthesis of **1** by Methods B, B1 and B2 (for definitions of R^2, R^3, R^5 and R^6 in **1** see Table 2). Method B: c. CH_2Cl_2 or THF, 40–60°C, 3 d. Method B1: a. R^3NH_2, $NaHCO_3$, 25°C, 4 h, CH_2Cl_2. c. CH_2Cl_2, reflux, 3 d. Method B2: b. (i) 0.1 equiv. NaOMe, MeOH, 25°C. (ii) R^3NH_2.HCl. c. CH_2Cl_2 or THF, 40–60°C, 3 d. **7a** R^2=Ph, R^3=$CH_2C{\equiv}CH$, Method B1; **7b** R^2=Ph, R^3=$CH_2CH{=}CH_2$, Method B1; **7c** R^2=Ph, R^3=$CH_2CH_2CH_3$, Method B1; **7d** R^2=3-Cl-Ph, R^3=$CH_2C{\equiv}CH$, Method B2; **7e** R^2=3-F-Ph, R^3=$CH_2C{\equiv}CH$, Method B2; **7f** R^2=3,5-diCl-Ph, R^3=$CH_2C{\equiv}CH$, Method B2; **7g** R^2=3,5-diF-Ph, R^3=$CH_2C{\equiv}CH$, Method B2; **7h** R^2=2-pyridyl, R^3=$CH_2C{\equiv}CH$, Method B2; **7i** R^2=3-pyridyl, R^3=$CH_2C{\equiv}CH$, Method B2; **7j** R^2=5-Br-3-pyridyl, R^3=$CH_2C{\equiv}CH$, Method B2; **7k** R^2=4-pyridyl, R^3=$CH_2C{\equiv}CH$, Method B2; **7l** R^2=2-Cl-4-pyridyl, R^3=$CH_2C{\equiv}CH$, Method B2; **7m** R^2=2,6-diCl-4-pyridyl, R^3=$CH_2C{\equiv}CH$, Method B2; **7n** R^2-R^3=$-(CH_2)_4-$, Method B; **7o** R^2=Ph, R^3=Ph, Method B.

of N^3 alkylated pyrimidinones. The carbonyl groups of N^1 alkylated pyrimidinones typically occur below 1670 cm^{-1}.[4a] An X-ray crystal structure of the closely related compound **1b**, which has very similar spectral characteristics to **1a**, was obtained and confirmed the presence of the propargyl group at N^3.

Extensive efforts to optimize the synthesis of **1a** by Method B1 were undertaken and selected results are shown in Table 1. Five solvents were studied for the cyclization step (Entries 1–5). The best yields (50–60%) of **1a** with the smallest amounts of **5a** were obtained with CH_2Cl_2 and acetonitrile. Significantly lower yields of **1a** and greater

Table 1. Effect of varying conditions on the yield and purity of **1a**

Entry	Solvent	Additives	T (°C)	t (h)	Yield **1a**[a] (%)	Yield **5a**[b] (%)
1	CH_2Cl_2	–	40	72	60	5
2	MeCN	–	40	72	57	4
3	DMF	–	40	72	47	3
4	MeOH	–	40	72	38	5
5	EtOAc	–	40	72	29	2
6	MeCN	–	60	26	53	5
7	MeCN	–	80	8	40	5
8	CH_2Cl_2	4 Å sieves	40	72	63	6
9	CH_2Cl_2	H_2O	40	72	56	7

[a] After chromatography.
[b] Estimated by integration of the ^1H NMR signals for the ortho protons on the phenyl rings of **1a** and **5a**.

amounts of **5a** were produced when DMF, methanol and especially ethyl acetate were used as solvents. Acetonitrile was employed as solvent to examine the effect of temperature. At 80°C, no further product was produced after 8 h and the yields of **1a** and **5a** were 40 and 5%, respectively (Entry 7) while at 40°C, the reaction required 72 h to reach a point at which no further product was produced and the yields of **1a** and **5a** were 57 and 4%, respectively (Entry 2). The crude products from Entries 1–7 all appeared to contain some unreacted **7a** and **4a** at the end of the reaction. Reasoning that water and ethanol produced in the course of the reaction might be preventing the reaction from proceeding further by forming the hydrate and/or hemiacetal of **4a**, 4 Å molecular sieves were added to the reaction mixture to remove water and this did effect a slight increase in yield (Entry 8), while deliberate addition of water appeared to cause a slight decrease in yield (Entry 9). In large scale runs, a moisture trap was employed to remove water. The presence of residual trifluoroacetic acid in some batches of **4a** had a deleterious effect on the yield. The final conditions selected for the large scale preparation of **1a** were as follows: ethyl benzimidate hydrochloride and propargylamine were reacted in CH_2Cl_2 in the presence of $NaHCO_3$ to afford a solution of **7a**. An excess of β-keto ester **4a** (1.25–1.5 equiv.) was immediately added and the mixture was placed in a 40°C oil bath and stirred for 72 h with a moisture trap. The reaction mixture was diluted with ether and washed with aqueous HCl to remove the imidazole by-products **11** and **13** and any unreacted **7a** and **10**. Unreacted **4a** could be recovered by trituration of the crude product with hexanes. Washing the crude product with aqueous sodium hydroxide failed to remove **5a** from the crude product, presumably due to the insolubility of the sodium salt of **5a** in water; instead, flash chromatography on activity III basic alumina was employed and afforded **1a** that was 90–95% pure. This procedure routinely afforded 50–55% yields of **1a** on a 1 mol scale.

Once this methodology was established for **1a**, preparation of a variety of related analogs allowed us to investigate the scope of the reaction (Table 2). Two general methods were employed to prepare the β-ketoesters **4a**, **4f**, **4h**–**4j** that were not commercially available (Scheme 4). In Method C, the appropriate ethyl ester **14** was reacted with ethyl trifluoroacetate or ethyl difluoroacetate using 2.2 equiv. of sodium hydride.[13] This was the preferred method when working at a 0.5 mol or smaller scale. Because of the hazards of sodium hydride, for larger scale work a modification of the method of Zard et al. using the acid chloride and either trifluoroacetic anhydride or difluoroacetic anhydride was employed (Method D).[14] Distillation of the crude products from Methods C and D effected partial purification, but in general, β-ketoesters **4** were difficult to separate from esters **14** (unreacted in Method C or produced in situ from ethanolysis of **15** in Method D). In addition, the keto–enol equilibria in **4** complicated the interpretation of

Table 2. Pyrimidinones **1** synthesized

Pyrimidinone	Precursors		R^2	R^3	R^5	R^6	Method	Yield (%)
	β-Ketoester	Amidine (nitrile or imidate)						
1a	**4a**	**7a** (**10**)	Ph	$CH_2C{\equiv}CH$	Et	CF_3	B1	53[a]
1b	**4b**	**7a** (**10**)	Ph	$CH_2C{\equiv}CH$	Et	Et	B1	0[a]
1c	**4a**	**7b** (**10**)	Ph	$CH_2CH{=}CH_2$	Et	CF_3	B1	55[a]
1d	**4a**	**7g** (**10**)	3,5-di-F-Ph	$CH_2C{\equiv}CH$	Et	CF_3	B2	53[b]
1e	**4a**	**7i** (**16g**)	3-Pyridyl	$CH_2C{\equiv}CH$	Et	CF_3	B2	25[b]
1f	**4a**	**7j** (**16j**)	5-Br-3-pyridyl	$CH_2C{\equiv}CH$	Et	CF_3	B2	23[b]
1g	**4a**	**7k** (**16k**)	4-Pyridyl	$CH_2C{\equiv}CH$	Et	CF_3	B2	36[b]
1h	**4a**	**7l** (**16l**)	2-Cl-4-pyridyl	$CH_2C{\equiv}CH$	Et	CF_3	B2	14[b]
1i	**4a**	**7m** (**16m**)	2,6-di-Cl-4-pyridyl	$CH_2C{\equiv}CH$	Et	CF_3	B2	14[b]
1j	**4d**	**7a** (**10**)	Ph	$CH_2C{\equiv}CH$	Me	CF_3	B1	59[a]
1k	**4d**	**7c** (**10**)	Ph	n-Pr	Me	CF_3	B1	72[a]
1l	**4d**	**7o**	Ph	Ph	Me	CF_3	B	44[c]
1m	**4d**	**7l** (**16l**)	2-Cl-4-pyridyl	$CH_2C{\equiv}CH$	Me	CF_3	B2	33[b]
1n	**4d**	**7m** (**16m**)	2,6-di-Cl-4-pyridyl	$CH_2C{\equiv}CH$	Me	CF_3	B2	41[b]
1o	**4d**	**7n**	$-(CH_2)_4-$		Me	CF_3	B	83[c]
1p	**4d**	**7e** (**16e**)	3-F-Ph	$CH_2C{\equiv}CH$	H	CF_3	B2	22[b]
1q	**4e**	**7f** (**16f**)	3,5-diCl-Ph	$CH_2C{\equiv}CH$	H	CF_3	B2	32[b]
1r	**4e**	**7j** (**16j**)	5-Br-3-pyridyl	$CH_2C{\equiv}CH$	H	CF_3	B2	30[b]
1s	**4e**	**7l** (**16l**)	2-Cl-4-pyridyl	$CH_2C{\equiv}CH$	H	CF_3	B2	46[b]
1t	**4e**	**7m** (**16m**)	2,6-diCl-4-pyridyl	$CH_2C{\equiv}CH$	H	CF_3	B2	33[b]
1u	**4f**	**7l** (**16l**)	2-Cl-4-pyridyl	$CH_2C{\equiv}CH$	OMe	CF_3	B2	45[b]
1v	**4h**	**7a** (**10**)	Ph	$CH_2C{\equiv}CH$	Et	CHF_2	B1	12[b]
1w	**4h**	**7e** (**16e**)	3-F–Ph	$CH_2C{\equiv}CH$	Et	CHF_2	B2	12[b]
1x	**4i**	**7m** (**16m**)	2,6-diCl-4-pyridyl	$CH_2C{\equiv}CH$	H	CHF_2	B2	3[b]
1y	**4j**	**7a** (**10**)	Ph	$CH_2C{\equiv}CH$	OMe	CHF_2	B1	29[a]
1z	**4j**	**7m** (**16m**)	2,6-di-Cl-4-pyridyl	$CH_2C{\equiv}CH$	OMe	CHF_2	B2	11[b]
1aa	**4g**	**7a** (**10**)	Ph	$CH_2C{\equiv}CH$	Cl	CF_3	B1	0[a]
1ab	**4g**	**7o**	Ph	Ph	Cl	CF_3	B	0[c]
1ac	**4e**	**7h** (**16h**)	2-Pyridyl	$CH_2C{\equiv}CH$	H	CF_3	B2	0[b]
1ad	**4k**	**7a** (**10**)	Ph	$CH_2C{\equiv}CH$	Me	CO_2Et	B1	0[a]

[a] Yield calculated based on ethyl benzimidate hydrochloride (**10**).
[b] Yield calculated based on the nitrile precursor **16**.
[c] Yield based on amidine precursor **7**.

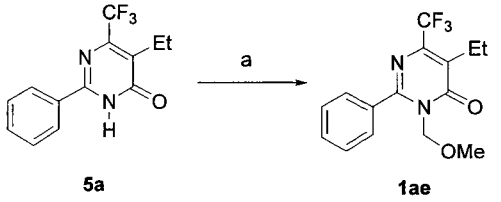
their ^{1}H NMR spectra; however, the major peaks in the spectra corresponded to those expected based on the literature values for the keto forms.[15] The purity of these intermediates was estimated by GC.

Two different methods were also employed to prepare the desired *N*-monosubstituted amidines **7a**–**m** (Scheme 7); **7n** and **7o** were commercially available. In Method B1, Step 1, benzamidines **7a**–**c** without any substituents on the benzene ring were prepared from ethyl benzimidate by treatment with the appropriate amine as described above.[9] These amidines were used immediately without isolation or characterization. In Method B2, Step 1, benzamidines with electron withdrawing substituents **7e**–**g** and pyridinecarboxamidines **7h**–**m** were prepared in one pot from the corresponding nitriles **16** as follows: the appropriate nitrile **16** was first treated with a catalytic quantity of sodium methoxide in methanol to convert it to the imidate and then with a slight excess of amine hydrochloride to afford the amidine.[16] The nitriles used were either commercially available or prepared from the corresponding carboxylic acids via the carboxamides using standard methods.[17] Since 2-chloropyridines are susceptible to displacement by methoxide, it was found to be important to hold the time for the generation of the imidate to a minimum with nitrile **16m**. A reaction time of 2 h was found satisfactory. The *N*-substituted pyridine carboxamidines **7h**–**7m** were found to be qualitatively more stable than the benzamidines **7a**–**g** and they could be stored for a few days before use. Amidines **7d**–**m** were characterized by ^{1}H NMR spectroscopy but no attempt was made to rigorously purify them.

The reactions of **4** and **7** to produce **1** shown in Table 2 were run at 40–60°C in THF or methylene chloride for 3 d. In certain instances, the reactions were terminated earlier if ^{1}H NMR of an aliquot of the crude reaction mixture indicated that the starting amidine had been consumed. Yields were calculated based on ethyl benzimidate hydrochloride (**10**) for pyrimidinones made by Method B1, on nitriles **16** for compounds made by Method B2 or on the commercially available amidine in the cases of **7n** and **7o**. The clearest trend apparent in Table 2 is that yields were lower when the less electrophilic difluoromethyl ketoesters **4h** and **4i** were employed than with the corresponding trifluoromethyl ketoesters **4a** and **4e** (**1a** vs **1v**; **1t** vs **1x**). As expected, the reaction failed when ethyl 2-propionylbutanoate (**4b**, Scheme 4) was used.[7] It also failed when diethyl oxalopropionate (**4k**, Scheme 4) was employed despite the electron withdrawing carboethoxy group at R^6 in this β-ketoester (**1ad**). Somewhat better yields were obtained when the α-methoxyketoesters **4f** and **4j** were used than with the corresponding α-methyl or ethyl keto esters **4d**, **4a** or **4h** (**1u** vs **1m**, **1h**; **1y** vs **1v**). The reaction failed to give the desired pyrimidinones when the α-chloro ketoester **4g** was used (**1aa**, **1ab**). Presumably, the introduction of an additional electrophilic site into the ketoester component leads to the predominance of alternate reaction pathways. The overall yields of the pyrimidinone product were lower with the electron withdrawing chloropyridyl amidines **7l** and **7m** than with **7a** (**1h**, **1i** vs **1a**; **1z** vs **1y**); however, it is unclear whether the yield of amidine formation or of ring formation is responsible for this drop. Interestingly, the reaction failed entirely when pyridine-2-(*N*-propargylcarboxamidine) **7h** was employed (**1ac**). Possibly intramolecular hydrogen bonding between the pyridine nitrogen and one of the amidine NHs lowers the reactivity of **7h**. The effects of variations in R^3 on product yields are unclear from these reactions although the increased yield observed with **7c** (R^3=propyl) compared to **7a** (R^3=propargyl) is consistent with the role of the decomposition of *N*-propargyl benzamidine **7a** depicted in Scheme 6 (**1k** vs **1j**). As expected from the work of Huber et al.,[8] excellent results were obtained when the cyclic amidine 2-iminopiperidine (**7n**) was employed (**1o**).

Table 3. ^{1}H NMR of aromatic protons in selected pyrimidinones

Compound (aromatic region)	R^3	^{1}H NMR
1a	$CH_2C{\equiv}CH$	7.48–7.56 (3H), 7.64–7.74 (2H)
1b	$CH_2{\equiv}CH$	7.48–7.56 (3H), 7.64–7.74 (2H)
1c	$CH_2CH{=}CH2$	7.40–7.60 (5H)
1k	$CH_2CH_2CH_3$	7.40–7.60 (5H)
1ae	CH_2OCH_3	7.45–7.55 (3H), 7.60–7.70 (2H)
6a	n/a	7.45–7.55 (3H), 8.40–8.50 (2H)



5a **1ae**

Scheme 8. Methoxymethylation. (a) P_2O_5, $(MeO)_2CH_2$, $CHCl_3$, rt, 18 h.

In the ^{1}H NMR spectra of **1a** and **1b** (R^3=propargyl), the ortho protons on the phenyl ring appear 0.15 ppm downfield from the meta and para protons (Table 3). By contrast, in **1c** (R^3=allyl) and **1k** (R^3=propyl) the ortho protons are coincident with the *meta* and *para* protons. We attributed this difference to the slightly greater steric demands of the allyl (sp^2 CH at β-position) and propyl (sp^3 CH_2 at β-position) groups compared to the propargyl group (sp C at β-position) forcing the phenyl ring to rotate further out of the plane of the pyrimidinone rings thus moving the ortho protons further into the shielding cone of the heterocyclic ring. The X-ray structure of **1b** showed a 43.9° angle between the plane of the phenyl and pyridmidinone rings. In the *O*-propargyl compound **6a**, in which the phenyl and pyrimidinone rings are expected to be coplanar, the ortho protons are separated from the *meta* and *para* protons by 0.95 ppm. In **1ae** (R^3=CH_2OMe, sp^3 O at β-position, preparation shown in Scheme 8), the ^{1}H NMR of the aromatic region is very similar to that of **1a** and **1b**. It is possible that this subtle conformational effect plays a role in the level of herbicidal activity of these pyrimidinones: **1a**, **1b** and **1ae** are substantially more active than **1c** or **1k**.[20]

3. Conclusions

We have developed a method for the regiocontrolled synthesis of 3-substituted-6-trifluoromethyl-4(3*H*)-pyrimidinones

from *N*-monosubstituted amidines and trifluoroacetoacetate esters in moderate yields under mild conditions (Scheme 7). This method is more convenient and affords better yields of this type of compound than alkylation of a 3-unsubstituted pyrimidinone precursor (Scheme 1). Not unexpectedly, reaction yields are lower when amidines with electron withdrawing substituents are employed. The main limitation encountered in the trifluoroacetate reactant was the lack of tolerance for a chlorine at the α-position.

4. Experimental

4.1. General

Unless otherwise state all reagents were purchased from commercial sources and used without further purification. All reactions were conducted under a nitrogen atmosphere. Solvents were removed on a rotary evaporator under house vacuum (20–50 mm Hg). Melting points were determined on a Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectroscopy was performed on a Bruker DPX300 or a Varian XL200. Chemical shifts are reported in ppm downfield from internal tetramethylsilane. ^{13}C and ^{19}F NMR were performed on a Bruker DPX300. ^{13}C NMR chemical shifts are referenced to the central line of $CDCl_3$ at 77.0 ppm and ^{19}F NMR chemical shifts are referenced to CCl_3F at 0 ppm. Infra red spectra were recorded on a Perkin–Elmer Model BMC spectrophotometer or a Mattson Genesis-II FTIR. Mass spectra were obtained on a Hewlett Packard 5970 GC–MS. Elemental analyses were performed by Robertson–Microlit Labs.

4.1.1. 5-Ethyl-2-phenyl-3-(prop-2-ynyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1a) via 5-ethyl-2-phenyl-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (5a). *Method A*. A stirred mixture of benzamidine hydrochloride (23.7 g, 0.15 mol), ethyl 2-(trifluoroacetyl)butanoate (30.00 g, 0.15 mol), anhydrous sodium acetate (13.60 g, 0.16 mol) and xylenes (30 mL) was heated at reflux with a Dean–Stark trap for 7.5 h. The mixture was poured onto ice and allowed to stand overnight. The mixture was filtered and the solid collected was washed with water and dried in a vacuum oven to afford **5a** (17.7 g, 44%) as a light brown solid, mp 250°C (dec). ^{1}H NMR (300 MHz, d_6 DMSO) δ 1.12 (t, 3H, J=7.4 Hz), 2.61 (q, 2H, J=7.4 Hz), 7.6–7.8 (3H), 8.1–8.2 (2H), 13.3 (1H); ^{19}F NMR (282 MHz, d_6 DMSO) δ −64.3; IR (nujol) 1650. Anal. Calcd for $C_{13}H_{11}F_3N_2O$: C, 58.21; H, 4.13; N, 10.44. Found: C, 58.32; H, 3.94; N, 10.19.

To a stirred suspension of **5a** (16.2 g, 60 mmol) in methanol (200 mL) was added 25% by weight sodium methoxide in methanol (20.9 mL, 91.4 mmol), followed by 80% propargyl bromide in toluene by weight (13.5 mL, 120 mmol). The mixture was heated at reflux for 5.5 h. The bulk of the solvent was removed under reduced pressure and the residue was suspended in 1 M aqueous sodium hydroxide (200 mL) and extracted with ether (4×100 mL). The combined ether extracts were dried over $MgSO_4$ and evaporated under reduced pressure to afford a light brown solid (17.7 g). This material was redissolved in ether (350 mL) and washed with aqueous sodium hydroxide (3×75 mL) and brine (2×75 mL). The ether layer was dried over $MgSO_4$ and evaporated to dryness under reduced pressure to leave a solid (8.9 g) which was purified by flash chromatography on a silica gel column eluted with 20% ethyl acetate in hexanes to afford **6a** (2.4 g, 13%) as an off-white solid, mp 83–87°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20 (t, 3H, J=7.5 Hz), 2.53 (t, 1H, J=2.5 Hz), 2.79 (q, 2H, J=7.5 Hz), 5.20 (d, 2H, J=2.5 Hz), 7.45–7.55 (3H), 8.40–8.50 (2H); IR (nujol mull) 3280. Anal. Calcd for $C_{16}H_{13}F_3N_2O$: C, 62.74; H, 4.28; N, 9.15. Found: C, 62.68; H, 4.15; N, 8.80. Additional **6a** present in mixed fractions was not isolated. Further elution of the column afforded **1a** (1.9 g, 10%), mp 113–115°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, 3H, J=7.4 Hz), 2.42 (t, 1H, J=2.3 Hz), 2.77 (q, 2H, J=7.4 Hz), 4.61 (d, 2H, J=2.3 Hz), 7.50–7.60 (3H), 7.70–7.80 (2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 19.8, 37.7, 73.8, 77.8, 121.9 (q), 128.7, 129.3, 131.5, 133.7, 146.4 (q), 158.3, 162.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.5; IR ($CDCl_3$) 3308, 1674, 1549. Anal. Calcd for $C_{16}H_{13}F_3N_2O$: C, 62.74; H, 4.28; N, 9.15. Found: C, 62.49; H, 4.10; N, 9.03.

4.1.2. 5,6-Diethyl-2-phenyl-3-(prop-2-ynyl)-4(3*H*)-pyrimidinone (1b) via 5,6-diethyl-2-phenyl-4(3*H*)-pyrimidinone (5b). A stirred mixture of benzamidine hydrochloride (21.7 g, 0.14 mol), ethyl 2-propionylbutanoate (21.64 g, 0.13 mol),[18] anhydrous sodium acetate (11.30 g, 0.14 mol) and xylenes (350 mL) was heated at reflux with a Dean–Stark trap for 5.5 h. The mixture was poured onto ice and allowed to stand overnight. The mixture was filtered and the solid collected was washed with water and dried in a vacuum oven to afford **5b** (14.5 g, 49%) as an off-white solid, mp 170–173°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.06 (t, 3H, J=7.4 Hz), 1.22 (t, 3H, J=7.5 Hz), 2.51 (q, 2H, J=7.4 Hz), 2.60 (q, 2H, J=7.5 Hz), 7.5–7.6 (3H), 8.1–8.2 (2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3, 11.7, 16.4, 25.2, 121.3, 125.8, 126.1, 126.9, 129.5, 131.0, 151.9, 161.6; IR (nujol) 1650. Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.58; H, 6.93; N, 12.35.

Sodium metal (1.65 g, 71.7 mmol) was dissolved in methanol (200 mL) and **5b** (13.60 g, 59.6 mmol) was added followed by 80% propargyl bromide in toluene by weight (9.76 mL, 87.6 mmol). The mixture was heated at reflux for 2 h and the bulk of the solvent was removed under reduced pressure. The residue was taken up in ethyl acetate (200 mL), washed with 1 M aqueous NaOH (3×100 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure left a yellow solid (14.4 g). Flash chromatography on silica gel (250 g) eluting with methylene chloride afforded **1b** (5.7 g, 36%) as an off-white solid, mp 101–103°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, 3H, J=7.5 Hz), 1.26 (t, 3H, J=7.6 Hz), 2.33 (t, 1H, J=2.4 Hz), 2.63 (q, 2H, J=7.5 Hz), 2.64 (q, 2H, J=7.6 Hz), 4.56 (d, 2H, J=2.4 Hz), 7.48–7.56 (3H), 7.64–7.74 (2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 13.7, 19.7, 28.0, 36.9, 72.9, 78.8, 124.4, 128.5, 129.2, 130.7, 134.9, 157.0, 162.4, 162.9; IR (nujol) 3205, 1650. Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.69; H, 6.77; N, 10.53. Found: C, 76.25; H, 6.65; N, 10.34.

4.1.3. General procedure used for optimization of the synthesis of 1a by method B1. *Method B1*. All reactions

summarized in Table 1 were run using ethyl benzimidate hydrochloride (**10**, 1.86 g, 10.0 mmol) and powdered sodium bicarbonate (0.84 g, 10.0 mmol) in the solvent specified (6 mL). The mixture was stirred for 0.5 h at room temperature and propargylamine (0.70 mL, 10.2 mmol) was added. The mixture was stirred for 3–4 h to afford a solution containing **7a**. Ethyl 2-trifluoroacetylbutanoate (**4a**, 3.18 g, ~12.5 mmol assuming 85% purity) was added. The mixture was stirred in an oil bath at the specified temperature *T* for *t* h (see Table 1). The progress of the reactions was monitored by reverse phase HPLC using a C-18 column eluted with 70% acetonitrile and 30% water containing 25 mM ammonium acetate with UV detection at 254 nm. Compounds **1a**, **5a** and **13** were separated and detected under these conditions. *N*-propargylbenzamidine (**7a**) and imidazole **11** were detected but were not resolved from each other under these conditions. Ethyl 2-trifluoroacetylbutanoate (**4a**) and propargylamine were not detected. Reactions were run until no further change in the HPLC trace could be discerned. The reaction mixtures were diluted with ether, washed with 5% aqueous HCl and 5% aqueous NaOH and dried over $MgSO_4$. The crude neutral products obtained in this way were examined by ^{1}H NMR. The % of **5a** in the crude product was estimated based on comparison of the integration of the ortho protons of the phenyl rings of **5a** and **1a**. The crude neutral product was subjected to flash chromatography on activity III neutral alumina (30 g) eluting with ether (200 mL). Ca. 25 mL fractions were collected and fractions containing **1a** were pooled and evaporated under reduced pressure to afford **1a** whose purity was confirmed by ^{1}H NMR. No attempt was made to isolate or quantify the basic products from these runs.

4.1.4. 5-Ethyl-2-phenyl-3-(prop-2-ynyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1a) from 4a and 10. A 1 L 4-neck flask, equipped with a condenser, mechanical stirrer and thermometer, maintained under a slight positive nitrogen pressure, was charged with ethyl benzimidate hydrochoride (**10**, 46.54 g, 0.25 mol) and methylene chloride (150 mL). To the stirred suspension was added powdered sodium bicarbonate (21.03 g, 0.25 mol). The mixture was stirred for 0.5 h and propargylamine (17.0 mL, 0.25 mol) was added rapidly. A 10°C exotherm occurred. The mixture was stirred for 3.75 h at room temperature to afford a solution containing **7a** and ethyl 2-trifluoroacetylbutanoate (**4a**, 81.20 g, 0.38 mol) was added. A 10°C exotherm occurred. The mixture was placed in an oil bath maintained at 40°C and stirred for 3 d. The mixture was diluted with ether (800 mL) and washed with 5% aqueous HCl (2×250 mL) and with saturated aqueous $NaHCO_3$ (250 mL), and dried over $MgSO_4$. Removal of the solvent under reduced pressure with a room temperature water bath afforded a mixture of **1a**, unreacted **4a** and residual solvents as a pasty yellow solid (95.15 g). The crude product was triturated with hexanes (2×100 mL) to afford crude **1a** (45.59 g). The mother liquors were evaporated under reduced pressure with a room-temperature water bath to leave a yellow liquid, which was taken up in hexanes (20 mL) and placed in the freezer overnight. Filtration of this mixture afforded additional crude **1a** (3.46 g). The filtrate was evaporated under reduced pressure with a room-temperature water bath to leave recovered **4a** (30.91 g) as an orange oil. The combined crude **1a** (49.05 g) was purified by flash chromatography on a column of activity III neutral alumina (100 g) packed in ether. The column was eluted with ether to afford **1a** (37.3 g, 53%) as a white solid, mp 113–115°C.

The following compounds were prepared following Method B1 as described above.

4.1.5. 5-Ethyl-2-phenyl-3-(prop-2-enyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1c). Mp 73–76°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, 3H, J=7.4 Hz), 2.76 (dq, 2H, J=1.6, 7.4 Hz), 4.55 (dt, 2H, J=5.3, 1.4 Hz), 4.96 (dd, 1H, J=17.2, 0.9 Hz), 5.22 (dd, 2H, J=9.4, 0.9 Hz), 5.88 (m, 1H), 7.40–7.60 (5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 19.8, 49.6, 118.7, 122.1 (q), 128.5, 129.0, 129.2, 131.0, 131.7, 134.3, 146.9 (q), 158.9, 162.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.4; IR ($CDCl_3$) 1660. Anal. Calcd for $C_{16}H_{15}F_3N_2O$: C, 62.33; H, 4.90; N, 9.09. Found: C, 61.98; H, 4.94; N, 8.89.

4.1.6. 5-Methyl-2-phenyl-3-(prop-2-ynyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1j). Mp 143–145°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (q, 3H, J=2.1 Hz), 2.42 (t, 1H, J=2.4 Hz), 4.63 (d, 2H, J=2.4 Hz), 7.50–7.60 (3H), 7.70–7.78 (2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.9, 37.3, 73.4, 77.5, 121.4 (q), 123.2, 128.2, 128.7, 130.9, 133.1, 146.2 (q), 157.6, 162.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.8; IR ($CDCl_3$) 3300, 1670. Anal. Calcd for $C_{15}H_{11}F_3N_2O$: C, 61.65; H, 3.79; N, 9.59. Found: C, 61.44; H, 3.56; N, 9.63.

4.1.7. 5-Methyl-2-phenyl-3-(propyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1k). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (t, 3H, J=7.5 Hz), 1.64 (m, 2H), 2.30 (q, 3H, J=2.1 Hz), 3.90 (m, 2H), 7.42–7.56 (5H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.3, 10.4, 21.0, 47.8, 121.2 (q), 122.4, 127.4, 128.1, 129.7, 133.7, 145.4 (q), 157.8, 162.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.8; IR ($CDCl_3$) 1660, 1540; MS (EI) *m/z* 296, 295, 254. Anal. Calcd for $C_{15}H_{15}F_3N_2O$: C, 60.81; H, 5.10; N, 9.45. Found: C, 61.20; H, 5.11; N, 9.47.

4.1.8. 6-(Difluoromethyl)-5-ethyl-2-phenyl-3-(2-propynyl)-4(3*H*)-pyrimidinone (1v). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 3H, J=7.4 Hz), 2.40 (t, 1H, J=2.4 Hz), 2.77 (q, 2H, J=7.4 Hz), 4.60 (d, 2H, J=2.4 Hz), 6.56 (t, 1H, J=54.2 Hz), 7.50–7.60 (3H), 7.70–7.80 (2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 18.9, 73.8, 78.1, 114.3 (t), 128.6, 128.7, 129.3, 131.3, 134.0, 150.1 (t), 158.5, 162.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −116.8 (d); IR ($CDCl_3$) 3300, 1660. Anal. Calcd for $C_{16}H_{14}F_2N_2O$: C, 66.66; H, 4.89; N, 9.72. Found: C, 66.54; H, 4.95; N, 9.67.

4.1.9. 6-(Difluoromethyl)-5-methoxy-2-phenyl-3-(2-propynyl)-4(3*H*)-pyrimidinone (1y). Mp 131–133°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.38 (t, 1H, J=2.5 Hz), 4.10 (s, 3H), 4.60 (d, 2H, J=2.5 Hz), 6.79 (t, 1H, J=54 Hz), 7.50–7.60 (3H), 7.65–7.75 (2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.2, 60.7, 73.4, 77.3, 109.5 (t), 128.2, 128.7, 130.8, 133.4, 141.6 (t), 143.2, 155.3, 158.4; IR ($CDCl_3$) 3300, 1670. Anal. Calcd for $C_{15}H_{12}F_2N_2O_2$: C, 62.07; H, 4.17; N, 9.65. Found: C, 61.91; H, 3.86; N, 9.53.

4.1.10. 2-Chloropyridine-4-(*N*-prop-2-ynyl)carboxamidine (7l). *Method B2, Step 1*. To a stirred suspension of 2-chloro-4-cyanopyridine[19] (5.77 g, 41.7 mmol) in methanol (50 mL) was added 25% by weight sodium methoxide in methanol (0.81 g, 3.8 mmol). The mixture was stirred for 18 h and propargylamine hydrochloride (4.35 g, 47.5 mmol) was added. The mixture was stirred for 4 h and evaporated under reduced pressure to remove methanol. The residue was partitioned between ether (150 mL) and 5% aqueous HCl (2×75 mL). The combined aqueous layers were carefully basified to pH ~12 by addition of 50% aq NaOH and extracted with ethyl acetate (2×90 mL). The combined ethyl acetate extracts were dried over $MgSO_4$ and concentrated under reduced pressure with the water bath at (40°C to afford crude **7l** (8.34 g, 107%) as an amber oil which solidified on standing. The crude product was used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.32 (1H, t, J=2.5 Hz), 4.08 (2H, d, J=2.5 Hz), 5.50–5.90 (2H), 7.48 (d, 1H, J=7.5 Hz), 7.60 (s, 1H), 8.38 (d, 1H, J=7.5 Hz).

4.1.11. 2,6-Dichloropyridine-4-(*N*-2-propynyl)carboxamidine (7m). To a stirred suspension of 2,6-dichloropyridine-4-carbonitrile (66.44 g, 0.38 mol) in methanol (800 mL) was added 25% by sodium methoxide in methanol by weight (28.30 g, 38.4 mmol). The mixture was stirred at room temperature for 2 h and solid propargylamine hydrochloride (42.28 g, 0.46 mol) was added. The mixture was stirred for 3 h and evaporated to dryness under reduced pressure (bath temp <40°C). The solid residue was treated with cold 10% aqueous NaOH (1 L) and extracted with ethyl acetate (2×800 mL). The combined organic extracts were washed with 10% aqueous NaOH (200 mL), dried over $MgSO_4$ and evaporated to dryness under reduced pressure to afford crude **7m** (89.18 g, 103%) as a yellow solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.32 (t, 1H, J=2.5 Hz), 4.08 (d, 1H, J=2.5 Hz), 4.90–5.70 (2H), 7.57 (s, 2H).

The following crude amidine intermediates were prepared under similar conditions.

4.1.12. 3-Chloro-*N*-prop-2-ynylbenzamidine (7d). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.28 (t, 1H, J=2.5 Hz), 4.08 (d, 2H, J=2.5 Hz), 5.0–5.6 (2H), 7.20–7.55 (3H), 7.61 (s, 1H).

4.1.13. 3-Fluoro-*N*-prop-2-ynylbenzamidine (7e). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (t, 1H, J=2.5 Hz), 4.09 (d, 2H, J=2.5 Hz), 5.30–5.70 (2H), 7.05–7.20 (1H), 7.30–7.50 (3H).

4.1.14. 3,5-Dichloro-*N*-prop-2-ynylbenzamidine (7f). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (t, 1H, J=2.5 Hz), 4.07 (d, 2H, J=2.5 Hz), 7.50–7.65 (2H), 7.38 (br s, 1H), 7.50 (br s, 2H).

4.1.15. 3,5-Difluoro-*N*-prop-2-ynylbenzamidine (7g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (t, 1H, J=2.5 Hz), 4.08 (d, 2H, J=2.5 Hz), 5.15–5.50 (2H), 6.80–6.95 (1H), 7.10–7.30 (2H).

4.1.16. Pyridine-2-(*N*-prop-2-ynyl)carboxamidine (7h). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.31 (t, 1H, J=2.5 Hz), 4.12 (d, 2H, J=2.5 Hz), 5.80–6.40 (2H), 7.35 (dd, 1H, J=6.5, 8.0 Hz), 7.75 (t, 1H, J=6.5 Hz), 8.22 (d, 1H, J=8.0 Hz), 8.54 (d, 1H, J=6.5 Hz).

4.1.17. Pyridine-3-(*N*-prop-2-ynyl)carboxamidine (7i). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.32 (t, 1H, J=2.5 Hz), 4.11 (d, 2H, J=2.5 Hz), 5.00–5.60 (2H), 7.30 (dd, 1H, J=5.5, 7.5 Hz), 7.98 (br d, 1H, J=5.5 Hz), 8.62 (br d, 1H, J=7.5 Hz), 8.84 (br s, 1H).

4.1.18. 5-Bromopyridine pyridine-3-(*N*-prop-2-ynyl)carboxamidine (7j). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.31 (d, 1H, J=2.5 Hz), 3.90–4.20 (2H), 4.12 (d, 2H, J=2.5 Hz), 8.20 (br s, 1H), 8.75 (s, 1H), 8.80 (s, 1H).

4.1.19. Pyridine-4-(*N*-prop-2-ynyl)carboxamidine (7k). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.32 (t, 1H, J=2.5 Hz), 4.05 (d, 2H, J=2.5 Hz), 5.96 (s, 2H), 7.50 (d, 2H, J=7.5 Hz), 8.55 (d, 2H, J=7.5 Hz).

4.1.20. 2-(2-Chloro-4-pyridyl)-3-(prop-2-ynyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1s). *Method B2, Step 2*. A mixture of crude **7l** (8.34 g, (41.7 mmol), ethyl trifluoroacetoacetate (10.24 g, 55.6 mmol) and dichloromethane (20 mL) was placed in a 60°C oil bath and the mixture was heated at reflux for 2 d. The mixture was cooled, diluted with ether (150 mL), washed with 5% aqueous HCl (2×50 mL) and 5% aqueous NaOH (2×50 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure left a yellow solid (8.37 g). The crude product was recrystallized from methanol (30 mL) to afford **1s** (6.31 g, 48%) as a white solid. Mp 125–126°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54 (t, 1H, J=2.2 Hz), 4.64 (d, 2H, J=2.2 Hz), 6.93 (s, 1H), 7.65 (dd, 1H, J=5.0, 1.4 Hz), 7.74 (d, 1H, J=1.4 Hz), 8.63 (d, 1H, J=5.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.9, 75.2, 76.8, 113.2, 120.4 (q), 121.2, 123.6, 143.2, 151.0, 151.4 (q), 152.9, 158.9, 160.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.1; IR ($CDCl_3$) 3300, 1690. Anal. Calcd for $C_{13}H_7ClF_3N_3O$: C, 49.78; H, 2.25; N, 13.40. Found: C, 49.89; H, 2.05; N, 13.34.

The following pyrimidinones were prepared in a similar fashion.

4.1.21. 2-(3,5-Difluorophenyl)-5-ethyl-3-(prop-2-ynyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1d). Mp 88–90°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (t, 3H, J=7.5 Hz), 2.48 (d, 1H, J=2.5 Hz), 2.77 (q, 2H, J=7.5 Hz), 4.62 (d, 2H, J=2.4 Hz), 6.98–7.15 (m, 1H), 7.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8, 19.3, 37.0, 74.1, 76.9, 106.7 (m), 111.8 (d), 121.3 (q), 130.0, 135.7 (m), 145.7 (q), 154.3, 161.5, 164.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.8, −107.2; IR ($CDCl_3$) 3300, 1650; Anal. Calcd for $C_{16}H_{11}F_5N_2O$: C, 56.15; H, 3.24; N, 8.18. Found: C, 56.21; H, 3.13; N, 8.09.

4.1.22. 5-Ethyl-2-(3-pyridyl)-3-(prop-2-ynyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1e). Mp 116–118°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 3H, J=7.4 Hz), 2.44 (t, 1H, J=2.4 Hz), 2.78 (br q, 2H, J=7.4 Hz), 4.64 (d, 2H, J=2.4 Hz), 7.50 (dd, 1H, J=4.9, 7.9 Hz), 8.10 (m, 1H), 8.82 (dd, 1H, J=4.9, 1.5 Hz), 9.02 (d, 1H, J=2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 19.5, 37.1, 74.2, 77.1, 121.4 (q),

123.5, 129.7, 129.9, 135.9, 145.5 (q), 149.0, 152.0, 155.3, 161.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.5; IR ($CDCl_3$) 3300, 1670. Anal. Calcd for $C_{15}H_{12}F_3N_3O$: C, 58.63; H, 3.94; N, 13.68. Found: C, 58.38; H, 3.99; N, 13.40.

4.1.23. 2-(5-Bromo-3-pyridyl)-5-ethyl-3-(prop-2-ynyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1f). Mp 123–125°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (t, 3H, *J*=7.5 Hz), 2.52 (t, 2H, *J*=2.5 Hz), 2.78 (q, 2H, *J*=7.5 Hz), 4.65 (d, 2H, *J*=7.5 Hz), 8.28 (t, 1H, *J*=2 Hz), 8.91 (d, 1H, *J*=2 Hz), 8.96 (d, 1H, *J*=2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 19.5, 36.9, 74.5, 76.7, 120.7, 121.3 (q), 130.4, 130.7, 138.5, 146.2 (q), 146.9, 153.1, 153.8, 161.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.3; IR ($CDCl_3$) 3300, 1710. Anal. Calcd for $C_{15}H_{11}BrF_3N_3O$: C, 46.65; H, 2.87; N, 10.88. Found: C, 46.43; H, 2.78; N, 10.58.

4.1.24. 5-Ethyl-2-(4-pyridyl)-3-(prop-2-ynyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1g). Mp 114–116°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (t, 3H, *J*=7.5 Hz), 2.48 (t, 1H, *J*=2.5 Hz), 2.80 (q, 2H, *J*=7.5 Hz), 4.63 (d, 2H, *J*=2.4 Hz), 7.69 (d, 2H, *J*=3.0 Hz), 8.86 (d, 2H, *J*=3.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8, 19.4, 36.9, 74.2, 76.8, 121.3 (q), 122.2, 130.2, 140.4, 145.8, 150.5, 155.3, 161.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.4; IR ($CDCl_3$) 3300, 1670. Anal. Calcd for $C_{15}H_{12}F_3N_3O$: C, 58.63; H, 3.94; N, 13.68. Found: C, 58.58; H, 3.99; N, 13.60.

4.1.25. 2-(2-Chloro-4-pyridyl)-5-ethyl-3-(prop-2-ynyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1h). Mp 82–84°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, 3H, *J*=7.4 Hz), 2.51 (t, 1H, *J*=2.4 Hz), 2.77 (q, 2H, *J*=7.4 Hz), 4.62 (d, 2H, *J*=2.4 Hz), 7.63 (dd, 1H, *J*=5.0, 1.3 Hz), 7.72 (s, 1H), 8.61 (d, 1H, *J*=5.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 19.9, 37.3, 74.9, 77.7, 121.3, 121.6 (q), 123.8, 131.2, 143.6, 146.2 (q), 150.9, 152.9, 154.4, 161.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.5; IR ($CDCl_3$) 3295, 1670. Anal. Calcd for $C_{15}H_{11}ClF_3N_3O$: C, 52.72; H, 3.24; N, 12.30. Found: C, 52.55; H, 3.16; N, 12.10.

4.1.26. 2-(2,6-Dichloro-4-pyridyl)-5-ethyl-3-(prop-2-ynyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1i). Mp 129–131°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24 (t, 3H, *J*=7.5 Hz), 2.53 (t, 1H, *J*=2.5 Hz), 2.78 (q, 2H, *J*=7.5 Hz), 4.63 (d, 2H, *J*=2.5 Hz), 7.68 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7, 19.4, 36.7, 74.7, 76.2, 121.1 (q), 121.8, 131.3, 145.0, 145.6 (q), 151.5, 152.9, 161.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.3; IR ($CDCl_3$) 3300, 1670. Anal. Calcd for $C_{15}H_{10}Cl_2F_3N_3O$: C, 47.90; H, 2.68; N, 11.17. Found: C, 48.16; H, 2.66; N, 10.92.

4.1.27. 2,3-Diphenyl-5-methyl-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1l). Mp 146–147°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (q, 3H, *J*=2.1 Hz), 7.05–7.40 (10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.0, 121.5 (q), 123.6, 127.9, 128.3, 128.9, 129.0, 129.1, 129.9, 133.8, 136.8, 146.5 (q), 157.1, 163.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.8; IR ($CDCl_3$) 1670, 1540; MS (EI) *m/z* 330, 329, 301. Anal. Calcd for $C_{18}H_{13}F_3N_2O$: C, 65.45; H, 3.97; N, 8.48. Found: C, 65.38; H, 3.85; N, 8.43.

4.1.28. 2-(2-Chloro-4-pyridyl)-5-methyl-3-(prop-2-ynyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1m). Mp 96–98°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.35 (br s, 3H), 2.47 (t, 1H, *J*=2.5 Hz), 4.60 (d, 2H, *J*=2.5 Hz), 7.60 (dd, 1H, *J*=5.0, 1.4 Hz), 7.70 (d, 1H, *J*=1.4 Hz), 8.62 (d, 1H, *J*=5.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.1, 36.8, 74.4, 76.4, 119.1, 121.0 (q), 123.2, 125.1, 142.9, 145.9 (q), 150.2, 152.1, 153.7, 161.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.9; IR ($CDCl_3$ 3300, 1665, 1530. Anal. Calcd for $C_{14}H_9ClF_3N_3O$: C, 51.31; H, 2.77; N, 12.82. Found: C, 51.28; H, 2.75; N, 12.89.

4.1.29. 2-(2,6-Dichloro-4-pyridyl)-5-methyl-3-(prop-2-ynyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1n). Mp 131–134°C. ^{1}H NMR (200 MHz,) δ 2.35 (br s, 3H), 2.55 (t, 1H, *J*=2.5 Hz), 4.60 (d, 2H, *J*=2.5 Hz), 7.65 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.1, 36.8, 74.8, 76.3, 121.0 (q), 121.8, 125.8, 145.0, 146.3 (q), 151.4, 152.7, 161.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.9; IR ($CDCl_3$) 3300, 1675. Anal. Calcd for $C_{14}H_8Cl_2F_3N_3O$: C, 46.43; H, 2.23; N, 11.60. Found: C, 46.20; H, 2.03; N, 11.49.

4.1.30. 5-Methyl-2,3-tetramethylene-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1o). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (m, 2H), 2.00 (m, 2H), 2.22 (q, 3H, *J*=2.1 Hz), 3.00 (t, 2H, *J*=6.9 Hz), 3.97 (t, 3H, *J*=6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.9, 18.2, 21.1, 29.9, 43.0, 121.2 (q), 120.2, 145.4 (q), 157.0, 162.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.9; IR ($CDCl_3$) 1650, 1540; MS(EI) *m/z* 232, 217, 203, 192. Anal. Calcd for $C_{10}H_{11}F_3N_2O$: C, 51.73; H, 4.78; N, 12.06. Found: C, 51.85; H, 4.74; N, 12.03.

4.1.31. 2-(3-Fluorophenyl)-3-(prop-2-ynyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1p). Mp 71–74°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.43 (t, 1H, *J*=2.5 Hz), 4.61 (d, 2H, *J*=2.5 Hz), 6.90 (s, 1H), 7.25–7.4 (m, 1H), 7.45–7.6 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.9, 74.0, 76.8, 111.7, 115.7 (m), 118.2 (m), 120.2 (q), 123.9, 130.8, 134.5, 151.1 (q), 160.5, 160.8 (m), 164.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.8, −110.8; IR ($CDCl_3$) 3300, 1685. Anal. Calcd for $C_{14}H_8F_4N_2O$: C, 56.77; H, 2.72; N, 9.46. Found: C, 56.80, H, H, 3.00; N, 9.32.

4.1.32. 2-(3,5-Dichlorophenyl)-3-(prop-2-ynyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1q). Mp 149–152°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.49 (t, 1H, *J*=2.4 Hz), 4.62 (d, 2H, *J*=2.4 Hz), 6.91 (s, 1H), 7.59 (t, 1H, *J*=1.9 Hz), 7.66 (d, 2H, *J*=1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.2, 74.8, 77.0, 112.7, 120.5 (q), 127.1, 132.0, 135.6, 136.3, 151.5 (q), 160.0, 160.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.8; IR ($CDCl_3$) 3300, 1690. Anal. Calcd for $C_{14}H_7Cl_2F_3N_2O$: C, 48.44; H, 2.03; N, 8.07. Found: C, 48.19; H, 2.25; N, 7.98.

4.1.33. 2-(5-Bromo-3-pyridyl)-3-(prop-2-ynyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1r). Mp 119–121°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51 (t, 1H, *J*=2.4 Hz), 4.65 (d, *J*=2.4 Hz), 6.93 (s, 1H), 8.28 (dd, 1H, *J*=2.1, 1.8 Hz), 8.91 (d, 1H, *J*=2.1 Hz), 8.96 (d, 1H, *J*=1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.5, 74.7, 76.3, 112.3, 119.9 (q), 120.6, 130.2, 138.3, 146.5, 150.9 (q), 153.3, 158.2, 160.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.8; IR ($CDCl_3$) 3300, 1680. Anal. Calcd for $C_{13}H_7BrF_3N_3O$: C, 43.60; H, 1.97; N, 11.73. Found: C, 43.37; H, 1.90; N, 11.54.

4.1.34. 2-(2,6-Dichloro-4-pyridyl)-3-(prop-2-ynyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1t). Mp 149–152°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (t, 1H, J=2.4 Hz), 4.55 (d, 2H, J=2.4 Hz), 6.84 (s, 1H), 7.59 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.9, 75.5, 76.6, 113.5, 120.3 (q), 122.1, 145.1, 151.4 (q), 152.0, 157.8, 160.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.9; IR ($CDCl_3$) 3300, 1700. Anal. Calcd for $C_{13}H_6Cl_2F_3N_3O$: C, 44.85; H, 1.74; N, 12.07. Found: C, 44.56; H, 1.61; N, 11.87.

4.1.35. 2-(2-Chloro-4-pyridyl)-5-methoxy-3-(prop-2-ynyl)-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1u). Mp 126–128°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.52 (t, 1H, J=2.5 Hz), 4.17 (s, 3H), 4.61 (d, 2H, J=2.5 Hz), 7.60 (dd, 1H, J=5.0, 1.4 Hz), 7.68 (d, 1H, J=1.4 Hz), 8.60 (d, 1H, J=5.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.8, 60.7, 74.7, 76.1, 120.4 (q), 120.9, 123.3, 137.1 (q), 142.9, 144.5, 150.0, 150.1, 152.1, 157.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.7; IR ($CDCl_3$) 3300, 1680, 1585. Anal. Calcd for $C_{14}H_9ClF_3N_3O_2$: C, 48.93; H, 2.64; N, 12.23. Found: C, 48.94; H, 2.53; N, 12.25.

4.1.36. 6-(Difluoromethyl)-5-ethyl-2-(3-fluorophenyl)-3-(2-propynyl)-4(3*H*)-pyrimidinone (1w). Mp 90–92°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, 3H, J=7.4 Hz), 2.42 (t, 1H, J=2.4 Hz), 2.77 (tq, 2H, J=1.5, 7.4 Hz), 4.62 (d, 2H, J=2.4 Hz), 6.56 (t, 1H, J=54.0 Hz), 7.27 (m, 1H), 7.44 (m, 1H), 7.50–7.60 (3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.0, 18.2, 36.7, 77.2, 113.1 (t), 115.4 (m), 117.7 (m), 123.8, 128.4, 130.4, 135.0, 149.1 (t), 156.5, 160.5, 161.6, 163.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −111.1, −116.9 (d); IR ($CDCl_3$) 3300, 1660. Anal. Calcd for $C_{16}H_{13}F_3N_2O$: C, 62.74; H, 4.28; N, 9.15. Found: C, 62.60; H, 4.19; N, 8.85.

4.1.37. 2-(2,6-Dichloro-4-pyridyl)-6-(difluoromethyl)-3-(2-propynyl)-4(3*H*)-pyrimidinone (1x). Mp 129–131°C. ^{1}H NMR (200 MHz, $CDCl_3$); (2.52 (t, 1H, J=2.5 Hz), 4.61 (d, 2H, J=2.5 Hz), 6.39 (t, 1H, J=54 Hz), 6.88 (s, 1H), 7.64 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.2, 63.5, 74.8, 111.1, 112.4, 121.7, 145.1, 151.7, 155.5 (t), 156.8, 160.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −122.8 (d); IR ($CDCl_3$) 3300, 1685, 1520; MS (EI) m/z 330, 294. Anal. Calcd for $C_{13}H_7Cl_2F_2N3O$: C, 47.30; H, 2.14; Cl, 21.48; F, 11.51; N, 12.73; O, 4.85.

4.1.38. 2-(2,6-Dichloro-4-pyridyl)-6-(difluoromethyl)-5-methoxy-2-phenyl-3-(2-propynyl)-4(3*H*)-pyrimidinone (1z). Mp 149–152°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.53 (t, 1H, J=2.5 Hz), 4.18 (s, 3H), 4.59 (d, 2H, J=2.5 Hz), 6.81 (t, 1H, J=54 Hz), 7.65 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.6, 60.8, 74.8, 76.3, 108.8 (t), 121.9, 141.0 (t), 144.3, 145.2, 149.9, 151.4, 157.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −122.1 (d); IR ($CDCl_3$ 3300, 1675. Anal. Calcd for $C_{14}H_9Cl_2F_2N_3O_2$: C, 46.69; H, 2.52; Cl, 19.69; F, 10.55; N, 11.67. Found: C, 46.52, H, 2.67; N, 11.51.

4.1.39. Ethyl 2-(trifluoroacetyl)butanoate (4a). *Method C*. Sodium hydride (60% in oil, 46.11 g, 1.15 mol) was washed with hexanes (3×80 mL) and suspended in toluene (200 mL). A mixture of ethyl trifluoroacetate (80 mL, 0.67 mol) and ethanol (0.5 mL) was added dropwise over 10 min to the stirred mixture. The mixture was heated to 80°C and a solution of ethyl butanoate (**14a**, 60 mL, 0.45 mol) in toluene (50 mL) was added dropwise over 0.5 h. The mixture was heated at reflux for 3 h, cooled and poured into 18% aqueous HCl (300 mL). The layers were separated and the aqueous layer was extracted with ether (300 mL). The combined organic layers were washed with 5% aqueous HCl (100 mL) and brine (100 mL), and dried over $MgSO_4$. Removal of the solvent on a rotary evaporator left crude **4a** (79.91 g) as a brown oil. This product was combined with crude **4a** (83.27 g) from a second run at the same scale distilled through a short Vigreaux column at 60 mm Hg to afford **4a** (84.88 g, 44%) as a straw colored liquid boiling from 60–85°C. The purity was estimated to be 85% by GC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (3H, t, J=7.4 Hz), 1.28 (3H, t, J=7.2 Hz), 2.02 (2H, m), 3.77 (1H, t, J=7.2 Hz), 4.22 (2H, q, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7, 14.3, 21.6, 54.9, 62.5, 115.5 (q), 167.5, 187.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.7 (major), −84.4 (minor).

4.1.40. Ethyl 2-methoxy-2-(trifluoroacetyl)acetate (4f). Reaction of sodium hydride (60% in oil, 40.21 g, 1.0 mol), ethyl trifluoroacetate (72 mL, 0.60 mol) and ethyl methoxyacetate (**14f**, 47 mL, 0.40 mol) as described above afforded crude **4f** (66.46 g). Distillation at 20 mm Hg through a Vigreaux column afforded **4f** (45.77 g, 53%). ^{1}H NMR ($CDCl_3$) δ 1.32 (3H, t, J=7 Hz), 3.50 (3H, s), 4.07 (1H, s), 4.33 (2H, q, J=7 Hz).

4.1.41. Ethyl 2-(difluoroacetyl)acetate (4i). Reaction of sodium hydride (40.14 g, 1.0 mol), ethyl difluoroacetate (45.0 mL, 0.45 mol) and ethyl acetate (37.5 mL, 0.38 mol) following the procedure described above afforded a mixture of crude **4i** and toluene (78.43 g). The crude product was distilled through a short Vigreaux column at 10 mm Hg to afford **4i** (15.67 g, 25%) boiling 55–80°C. ^{1}H NMR was comparable to that in the literature.[21]

4.1.42. Ethyl 2-(difluoroacetyl)-2-methoxyacetate (4j). Reaction of sodium hydride (40.34 g, 1.0 mol), ethyl difluoroacetate (40.0 mL, 0.40 mol) and ethyl methoxyacetate (**14f**, 47.0 mL, 0.40 mol) following the procedure described above afforded crude **4j** (26.97 g). The crude product was distilled through a short Vigreaux column at 10 mm Hg to afford **4j** (5.57 g, 34%) boiling 85–95°C. ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, t, J=7.1 Hz), 3.59 (1H, s), 3.67 (3H, s), 4.23 (2H, q, J=7.1 Hz), 6.65 (1H, t, J=53.7 Hz); MS (EI) 196, 168, 150, 122.

4.1.43. Ethyl 2-(trifluoroacetyl)butanoate (4a). *Method D*. To a stirred solution of butanoyl chloride (**15a**, 50 mL, 0.48 mol) in methylene chloride (300 mL) was added trifluoroacetic anhydride (70.1 mL, 0.50 mol). The mixture was cooled to ca. 10°C in an ice bath and pyridine (80 mL, 0.99 mol) that had been dried over NaOH pellets was added dropwise such that the temperature did not rise above 12°C. The mixture was stirred for an additional 15 min in the ice bath and at room temperature for 3 h. The mixture was recooled to below 0°C and ice cold absolute ethanol (80 mL) was added dropwise such that the temperature did not rise above 0°C. The mixture was allowed to stir overnight at room temperature, washed with 10% aqueous HCl (3×), water (1×) and saturated aqueous sodium bicarbonate (3×), and dried over $MgSO_4$. The solvent was removed under reduced pressure with a room temperature

water bath to afford of crude **4a** (63.15 g, 62%) which had a similar ^{1}H NMR to the distilled sample produced by Method C.

4.1.44. Ethyl 2-(difluoroacetyl)butanoate (4h). Reaction of difluoroacetic anhydride[22] (10.03 g, 57.5 mmol), butanoyl chloride (**15a**, 6.0 mL, 57.8 mmol), pyridine (9.3 mL, 115.4 mmol) and ethanol (12 mL, 200 mmol) as described above afforded crude **4h** (5.74 g, 51%). This material was used in subsequent reactions without further purification. ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, t, J=7.5 Hz), 1.28 (3H, t, J=7.1 Hz), 1.99 (2H, m), 3.76 (1H, t, J=6.9 Hz), 4.22 (2H, q, J=7.1 Hz), 5.90 (1H, t, J=53.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 14.5, 21.2, 54.7, 62.2, 109.8 (t), 168.6, 195.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ −128.4.

4.1.45. 5-Ethyl-3-methoxymethyl-2-phenyl-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (1ae). To a stirred solution of **5a** (3.62 g, 13.5 mmol) in chloroform (100 mL) and dimethoxymethane (100 mL) was added powdered phosphorus pentoxide (37.88 g, 267 mmol). The mixture was stirred vigorously overnight and quenched by cautious addition of 5% aqueous NaOH (100 mL). The mixture was allowed to cool to room temperature and extracted with ethyl acetate (2×150 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford an off-white solid (4.06 g). This material was purified by flash chromatography on silica gel (50 g), eluting with 0, 25, 50 and 75% ether in hexanes (200 mL of each) to afford **1ae** (2.76 g, 65%) as a white solid, mp 85–87°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (t, 3H, J=7.5 Hz), 2.75 (q, 2H, J=7.5 Hz), 4.51 (s, 3H), 5.20 (s, 2H), 7.45–7.55 (3H), 7.60–7.70 (2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.0, 19.4, 58.2, 76.5, 121.5 (q), 128.5, 129.0, 130.9, 133.4, 146.2 (q), 148.5, 159.0, 163.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.8; IR ($CDCl_3$) 1665. Anal. Calcd for $C_{15}H_{15}F_3N_2O_2$: C, 57.69; H, 4.84; N, 8.97. Found: C, 57.66; H, 4.81; N, 8.94.

4.1.46. 4-methyl-2-phenylimidazole (11) and 4-methyl-2-phenyl-3-(prop-2-ynyl)imidazole (13). Ethyl benzimidate hydrochloride (1.86 g, 10.0 mmol) was suspended in acetonitrile (6 mL) and powdered sodium bicarbonate (0.84 g, 10.0 mmol) was added. The mixture was stirred for 0.5 h and propargylamine (0.69 mL, 10.0 mmol) was added. The mixture was heated at reflux for 16 h, cooled, diluted with ethyl acetate (150 mL), washed with water (50 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure left a yellow solid (1.32 g) which was purified by flash chromatography on a silica gel column (30 g) eluted with 10, 25, 50, 75 and 100% ether in hexanes (100 mL of each). Concentration of the ether eluate, which contained a single spot on TLC, afforded an off-white solid (1.10 g), which contained a mixture of the two products. This solid was triturated twice with 1:1 ether/hexanes (20 mL) to afford **11** (0.89 g, 56%) as an off-white solid, identical by TLC and ^{1}H NMR to a commercially obtained sample. ^{1}H NMR (300 MHz, $CDCl_3$) 2.29 (s, 3H), 6.79 (s, 1H), 7.29 (m, 1H), 7.39 (m, 2H), 7.91 (m, 2H). The mother liquors were concentrated to afford **13** (0.11 g, 6%) as a waxy solid. Mp 79–81°C (lit 88°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.45 (t, 1H, J=2.4 Hz), 4.60 (d, 2H, J=2.4 Hz), 6.88 (s, 1H), 7.42 (m, 3H), 7.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.6, 34.3, 73.6, 78.0, 125.0, 126.4, 128.6, 128.7, 128.8, 130.6, 147.4; IR ($CDCl_3$) 3300; MS (EI) *m/z* 196, 181, 157. HRMS (EI) Calcd for $C_{13}H_{12}N_2$ 196.0996. Found 196.0997.

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