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Preparation of 1-[(3-Trifluoromethyl)phenyl]-3,4-dihydro-2(1*H*)-pyridinone Derivatives from Aza Annulation Reactions of *N*-[(3-Trifluoromethyl)phenyl]-Substituted Enaminones

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Reaction of 3-trifluoromethylaniline with the 1,3-diketones **1a**–**1c** and **5a**–**5d** affords the *N*-[(3-trifluoromethyl)phenyl]-substituted enaminones **2a**–**2c** and **6a**–**6d**. Reaction of **2a** with the acryloyl chloride derivatives **3a**–**3c** gives the 1-[(3-trifluoromethyl)phenyl]-3,4-dihydro-2(1*H*)-pyridinones **4a**, **4c**, **4d**; in a similar manner the 2(1*H*)-pyridinone **4b** is obtained from **2b**. Reaction of **6c**, **6d** with acryloyl chloride affords the 2,5(1*H*,3*H*)-quinolinedione derivatives **7** and **9** together with the acrylamides **8a**, **8b**. The 2(1*H*)-pyridinones **12a**, **12b** and the 3,4-dihydro-2(1*H*)-pyridinone **13** are prepared using routes involving the reaction of **2a** with ethyl propiolate, dimethyl acetylenedicarboxylate, and maleic anhydride.

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Introduction

Phytoene desaturase-inhibiting herbicides (Fig. 1) are a significant class of crop protection chemicals that block the biosynthesis of carotenoids required to protect chlorophyll from photooxidative degradation during photosynthesis.[1–6] With the exception of beflubutamid, all currently registered herbicides from this class contain a 3-(trifluoromethyl)phenyl substituent linked directly (norflurazon, flurochloridone, fluridone, and flurtamone) or by an oxygen atom (diflufenican and picolinafen) to a heterocyclic moiety.[7] We were interested in the preparation of compounds that incorporate the 1-[(3-trifluoromethyl)phenyl]-3,4-dihydro-2(1*H*)-pyridinone structural motif (general structure **4**, Scheme 1) for screening as potential new herbicides with this mode of action.

It was envisaged that cyclization reactions of enaminone[8] derivatives with acryloyl chloride, first reported by Hickmott and Sheppard,[9] could provide a particularly efficient route to compounds of this type. The application of this reaction to the synthesis of 1-phenyl-substituted 2(1*H*)-pyridinones

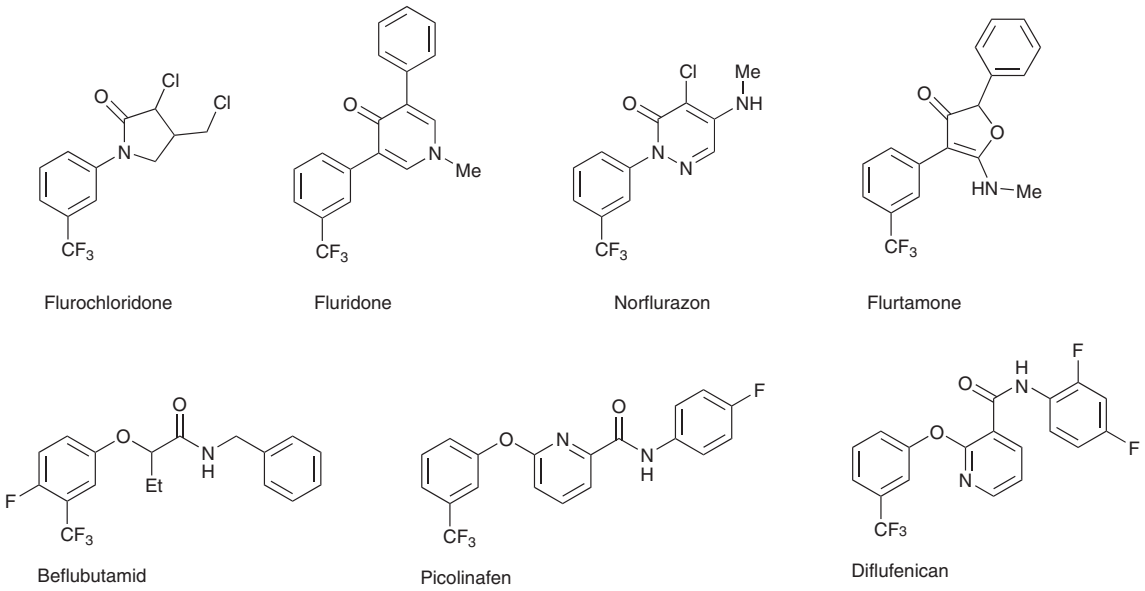

Fig. 1. Phytoene desaturase-inhibiting herbicides.

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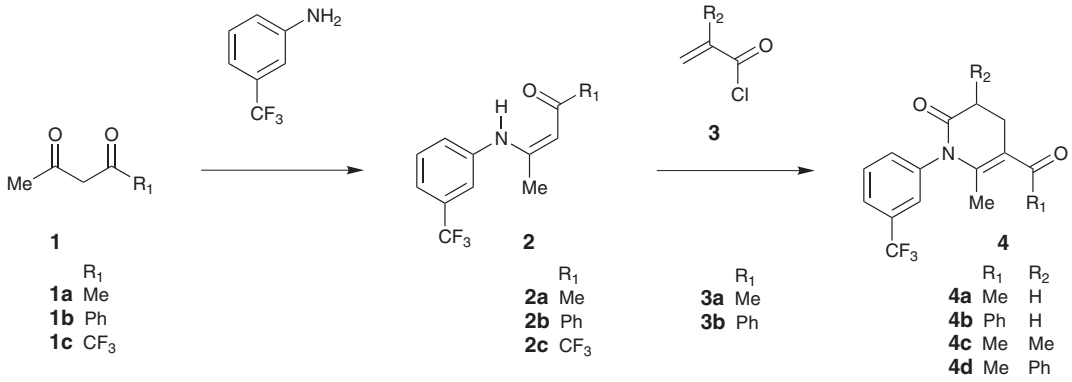
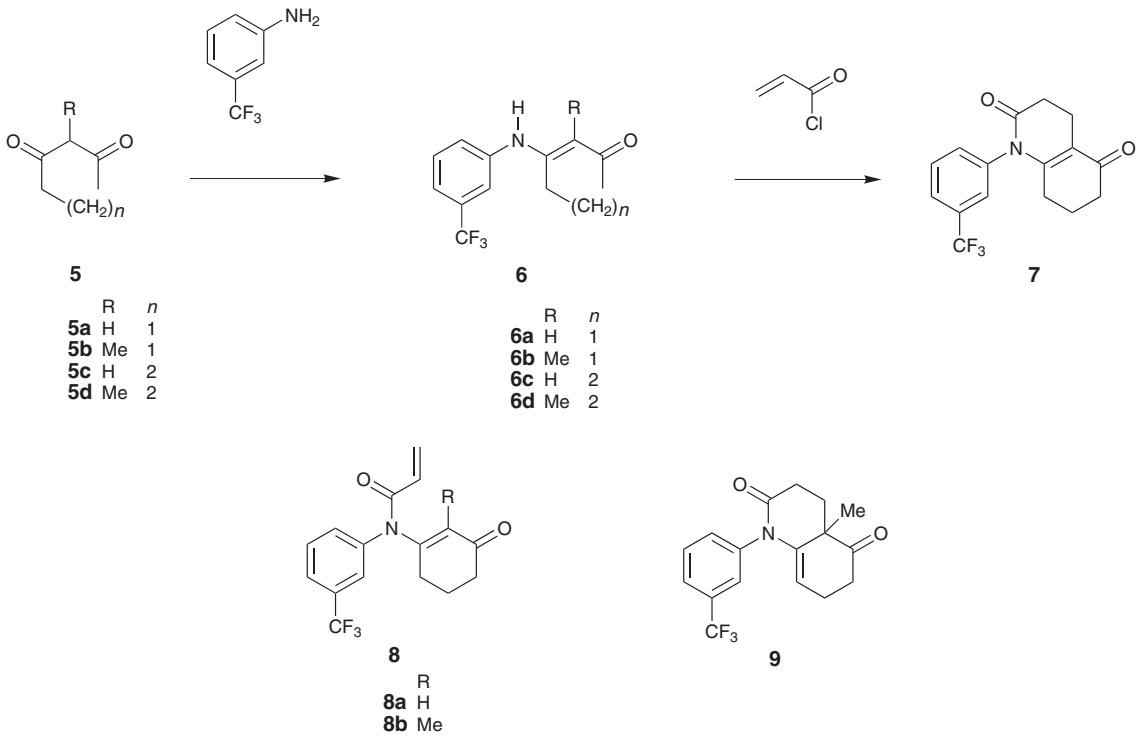


Scheme 1.



Scheme 2.

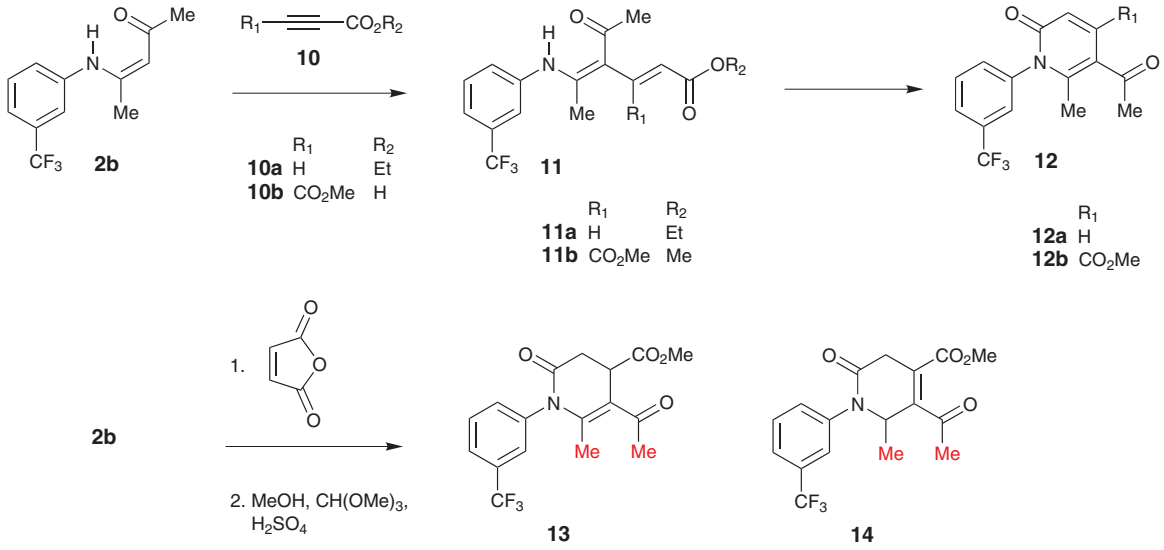
has not been well developed, there being only two reports of the reaction of *N*-phenyl-substituted enaminone derivatives with acryloyl chloride.[10,11] We were also interested to observe whether this aza-annulation strategy could be extended to other alkene- and alkyne-derived electrophiles, and whether this general approach could efficiently deliver 1-[(3-trifluoromethyl)phenyl]-3,4-dihydro-2(1*H*)-pyridinone derivatives as potential starting materials for the preparation and biological assay of yet other more highly elaborated 2(1*H*)-pyridinone derivatives.

Results and Discussion

Preparation of 3-N-*(Phenyl)amino-Substituted Enaminone Derivatives*

The most generally employed method for the preparation of enaminone derivatives entails the direct reaction between an amine and a 1,3-diketone derivative in benzene or toluene solution with azeotropic removal of the water formed.[12] Many of these reactions have been reported to be catalyzed by the addition of acids, but the advantageous use of acid catalysts has been questioned.[12] In our hands, these procedures did not proceed smoothly with weakly nucleophilic 3-trifluoromethylaniline. Other workers have overcome this problem by reacting weakly nucleophilic amines with activated forms of 1,3-diketones, such as vinologous acid halides or vinologous esters.[12] It has been found that heating 3-trifluoromethylaniline and the diketones **1a**–**1c** and **5a**–**5d** at 100–140°C (compared with ref. [13]) under argon provided the *N*-[(3-trifluoromethyl)phenyl]-substituted enaminone derivatives **2a**–**2c** and **6a**–**6d** in good yield (Schemes 1 and 2).

The ^{1}H NMR spectra of compounds **2a**–**2c** showed a broad downfield singlet that was exchangeable with D_2O at δ_H



Scheme 3.

values ranging from 12.56 to 12.7, which is consistent with the presence of intramolecular hydrogen bonding between the NH and carbonyl groups, thereby indicating that these compounds exist predominately in the *Z* configuration. For compounds **2a**, **2b**, and **6c**, the vinyl hydrogen atom of the enaminone moiety, which appears as a singlet between δ_H 5.25 and 5.56, is also observed to exchange on treatment with D_2O, which indicates that these compounds are in equilibrium with imine tautomers. Only one of the two possible regioisomers was isolated from the reaction of 3-trifluoromethylaniline with 1,1,1-trifluoro-2,4-pentanedione (**1b**, Scheme 1). The isolated regioisomer was assigned structure **2c** on the basis of the observation in the ^{13}C NMR spectrum of a downfield quartet at δ_C 177.1 (*J* 33), which is ascribable to the carbonyl of a trifluoroacetyl substituent.

Aza-Annulation Reactions with Acryloyl Chloride Derivatives

Reaction of the enaminones **2a** and **2b** with acryloyl chloride in refluxing benzene for 1 h proceeded smoothly to afford the 3,4-dihydro-2(1*H*)-pyridinone derivatives **4a** and **4b** in good yield. No reaction was observed when the enaminone **2c** was refluxed for 24 h with acryloyl chloride in benzene. The reaction of **2a** with 2-methylacryloyl chloride proceeded slowly to afford, after 24 h, the 2(1*H*)-pyridinone **4c** in 30% yield. By way of contrast the reaction of **2a** with the more reactive and unstable 2-phenylacryloyl chloride, prepared by the base-catalyzed dehydration of 3-hydroxy-2-phenylpropanoic acid,[14] followed by reaction with thionyl chloride, proceeded to completion within 5 h to afford the 2(1*H*)-pyridinone **4d** in good yield.

The reaction of the cyclopentane-1,3-dione-derived enaminones **6a** and **6b** with acryloyl chloride proceeded slowly to give complex mixtures of intractable products, whereas the reactions of **6c** and **6d** with acryloyl chloride proceeded slowly to afford the 2,5(1*H*,3*H*)-quinolinedione derivatives **7** and **9** (in 11 and 29% yield) and the acrylamides **8a** and **8b** (in 35 and 8% yield), respectively, along with other intractable products.

In other experiments, the acrylamide derivatives **8a** and **8b** were recovered unchanged after refluxing in benzene for 24 h with or with out added hydrochloric acid. These results are consistent with the view that acryloyl chloride-mediated aza annulation reactions of enaminone derivatives do not proceed through acrylamide intermediates.[9] Conceptually, these reactions may be viewed as proceeding by the conjugate addition of the enamine to the acryloyl chloride derivative followed by intramolecular *N*-acylation, but other reaction mechanisms can not be discounted.[15]

Other Aza-Annulation Reactions

The preparation of 1-[(3-trifluoromethyl)phenyl]-2(1*H*)-pyridinone derivatives was attempted based upon reaction of **2a** with other alkene and alkyne-derived electrophiles. In the event, no reaction was observed when a benzene solution of **2a** and ethyl acrylate or acrylonitrile was heated at 80 or at 120°C in a sealed tube. The enaminone **2a** did, however, undergo slow reaction with ethyl propiolate when heated for 5 days at 120°C in a sealed tube (Scheme 3).

From the complex mixture of reaction products formed, it was possible to isolate the ester **11a** in 18% yield. In the ^1H NMR spectrum of this compound, a coupling constant of 16 Hz for two doublets at δ_H 7.78 and 5.74, ascribable to H3 and H2, respectively, confirms the *E* configuration of the ethyl acrylate moiety. A broad downfield singlet at δ_H 11.75, exchangeable with D_2O, indicates the presence of intramolecular hydrogen bonding between the NH group and acetyl oxygen atom, and thus supports the assignment of a *Z* configuration to the enamine double bond. Both configurations prevent the cyclization of this ester to the required 2(1*H*)-pyridinone **12a**. When this ester was heated under conditions likely to cause isomerization of these double bonds (refluxing ethanol containing a catalytic amount of sodium ethoxide) a complex mixture of reaction products was obtained. The

2(1*H*)-pyridinone **12a** was isolated from this mixture in 19% yield. Reaction of **2a** with ethyl propiolate at 190°C led directly to the 2(1*H*)-pyridinone **12a** in 25% yield.

The reaction of **2a** with dimethylacetylenedicarboxylate in refluxing toluene proceeded smoothly to afford, in 79% yield, the ester **11b** as an inseparable mixture of two isomers. In the ^{1}H NMR spectrum of this compound, singlets at δ_H 2.03 and 1.87 and at δ 3.77 and 3.86 were assigned to the two methyl and to the two methoxy groups, respectively, of the major isomer, which comprises approx. 90% of the mixture. A broad downfield singlet at δ_H 12.4, exchangeable with D_2O, was assigned to the NH group and indicated a *Z* configuration for the enamine double bond of the major isomer. The configuration of the second double bond in the major isomer was not established. Two singlets at δ_H 2.09 and 2.05, and a further singlet at δ_H 3.80 were assigned to the two methyl groups and to one of the methoxy groups, respectively, of the minor isomer. In view of the low yield of **12a** obtained from the base-induced cyclization of **11a**, we attempted to cyclize **11b** under acidic conditions. Hence, compound **11b** was refluxed in toluene in the presence of *p*-toluenesulfonic acid. A complex mixture of products was obtained, from which the 2(1*H*)-pyridinone **12b** was isolated in 26% yield.

Reaction of **2a** with maleic anhydride in refluxing benzene followed by treatment with methanol in the presence of trimethyl orthoformate and a catalytic amount of sulfuric acid afforded the expected ester **13** (26%) along with the isomeric ester **14** (1%).

Conclusions

The reaction of acyclic enaminones **2a** and **2b** with acryloyl chloride proceeds smoothly to afford 2(1*H*)-pyridinone derivatives in good yield. Our attempts to extend this reaction to enaminones derived from cyclohexane-1,3-dione substrates afforded only poor yields of 2,5(1*H*,3*H*)-quinolinedione derivatives. This annulation reaction failed with the corresponding enaminone substrates derived from cyclopentan-1,3-dione. Moreover, annulation reactions of the prototypical enaminone substrate **2a** with other structurally related electrophiles, such as ethyl propiolate, dimethylacetylenedicarboxylate, and maleic anhydride, afforded only low yields of 1-[(3-trifluoromethyl)phenyl]-2(1*H*)-pyridinone derivatives, further limiting the usefulness of these annulation reactions for the preparation of derivatives of this type. Unfortunately, none of the compounds **4a**–**4d**, **7**, **9**, **12a**, **12b**, **13**, or **14** showed significant activity in herbicide discovery screens.

Experimental

Melting points were determined on a Reichert hot-stage melting point apparatus and are uncorrected. Microanalyses were performed at the Campbell Microanalytical Laboratory, University of Otago. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded with a Bruker AC 200 spectrometer operating at 200 MHz for proton and 50.3 MHz for carbon. All such spectra were recorded in $CDCl_3$ solution at 22°C. The number of protons bonded to each carbon atom was determined by DEPT135 experiments. Assignments of carbon resonances indicated with the same superscript letter may be interchanged.

Infrared spectra (ν_{max}) were recorded on a Perkin Elmer 842 spectrophotometer. Samples were analyzed as either a potassium bromide disc (KBr) or a thin film on NaCl plates (film). High-resolution chemical ionization mass spectra were measured on a Jeol JMS-DX303 mass spectrometer. Radial chromatography was performed on a Harrison Research 7924T Chromatotron using silica plates (Merck No. 7749) of 4 mm thickness.

*Preparation of 4-[(3-Trifluoromethyl)phenyl]aminopent-3-en-2-one **2a** and Related Compounds*

A stirred mixture of 3-trifluoromethylaniline (2.00 g, 12.4 mmol) and pentane-2,4-dione (1.4 g, 14.0 mmol) was heated at 100°C for 4 h under argon. The cooled mixture was extracted with diethyl ether (100 mL). The combined organic extracts were washed in turn with portions (15 mL) of 1 M NaOH, water, brine, 1 M HCl, and saturated $NaHCO_3$ solution, and then dried ($MgSO_4$) and the solvent evaporated to afford, after recrystallization from diethyl ether/light petroleum, the pentenone **2a** (2.35 g, 78%), mp 71–73°C (lit.[16] 62.3–62.8°C). δ_H 12.56 (1H, br s, exchanged with D_2O, NH), 7.51–7.25 (4H, complex m), 5.25 (1H, s, exchanged with D_2O, H3), 2.11 (3H, s, CH_3), 2.03 (3H, s, CH_3).

Reaction of 3-trifluoromethylaniline with benzoylacetone at 100°C for 4 h afforded *2-[(3-trifluoromethyl)phenyl]aminoethenyl phenyl ketone* **2b** in 73% yield, after recrystallization from CH_2Cl_2/diethyl ether, mp 91–93°C (Found: C 67.1, H 4.5, N 4.6%, $[M + H]^{+\bullet}$ 306.1102. $C_{17}H_{14}F_3NO$ requires C 66.9, H 4.6, N 4.6%, $[M + 1]^{+\bullet}$ 306.1100). δ_H 12.7 (1H, br s, exchanged with D_2O, NH), 7.97–7.86 (2H, complex m), 7.55–7.35 (7H, m), 5.98 (1H, br s, exchanged with D_2O), 2.20 (3H, s, CH_3). δ_C 189.2 (C), 161.1 (C), 139.6 (C), 139.4 (C), 131.7 (C, q, *J* 33, C3′), 131.2 (CH), 129.8 (CH), 128.3 (CH), 127.4 (CH), 127.1 (CH), 123.8 (C, q, *J* 272, CF_3), 122.0 (CH, q, *J* 4, C2′^{A}), 121.0 (CH, q, *J* 4, C4′^{A}), 95.3 (CH), 20.4 (CH_3). ν_{max} (KBr)/cm^{-1} 1620, 1600.

Reaction of 3-trifluoromethylaniline with 1,1,1-trifluoropentane-2,4-dione at 100°C for 2 h afforded *1,1,1-trifluoro-4-[(3-trifluoromethyl)-phenyl]aminopent-3-en-2-one* **2c** in 80% yield as a oil that solidified on storage at 0°C, mp 40–42°C (Found: C 48.8, H 2.9, N 4.8%, $[M + Na]^{+\bullet}$ 320.0478. $C_{12}H_9F_6NO$ requires C 48.5, H 3.1, N 4.7%, $[M + Na]^{+\bullet}$ 320.0480). δ_H 12.61 (1H, br s, exchanged with D_2O, NH), 7.61–7.52 (2H, m), 7.44–7.35 (2H, m), 5.60 (1H, s, H3), 2.15 (3H, s, CH_3). δ_C 177.1 (C, q, *J* 33, C=O), 167.7 (C), 137.6 (C), 132.0 (C, q, *J* 33, C3′), 130.2 (CH), 128.4 (CH), 123.9 (CH, q, *J* 3.5, C2′^{A}), 123.4 (C, q, *J* 273, C3′CF_3), 121.9 (CH, q, *J* 3.5, C4′^{A}), 117.4 (C, q, *J* 273, CF_3), 91.5 (CH, C3), 19.9 (CH_3, C5). ν_{max} (KBr)/cm^{-1} 1620, 1590.

Reaction of 3-trifluoromethylaniline with cyclopentane-1,3-dione **5a** at 140°C for 1 h afforded, after recrystallization from benzene, *3-[(3-trifluoromethyl)phenyl]aminocyclopent-2-en-1-one* **6a** in 92% yield, mp 151–152°C (Found: C 59.8, H 4.0, N 5.9%, $[M + H]^{+\bullet}$ 242.0787. $C_{12}H_{10}F_3NO$ requires C 59.8, H 4.2, N 5.8%, $[M + H]^{+\bullet}$ 242.0787). δ_H 7.91 (1H, s, exchanged with D_2O, NH), 7.52–7.32 (4H, m), 5.62 (1H, s, H2), 2.85–2.79 (2H, m, CH_2), 2.51–2.45 (2H, m, CH_2). δ_C 207.0 (C), 174.2 (C), 140.6 (C), 131.7 (C, q, *J* 33, C3′), 129.9 (CH), 124.2 (CH), 123.7 (C, q, *J* 272, CF_3), 121.1 (CH, q, *J* 4, C2′^{A}), 117.8 (CH, q, *J* 4, C4′^{A}), 103.1 (CH), 33.4 (CH_2), 29.0 (CH_2). ν_{max} (KBr)/cm^{-1} 3265, 1645.

Reaction of 3-trifluoromethylaniline with 2-methylcyclopentane-1,3-dione **5b** at 140°C for 2 h afforded, after recrystallization from benzene, *3-[(3-trifluoromethyl)phenyl]amino-2-methylcyclopent-2-en-1-one* **6b** in 67% yield as a colourless solid, mp 155–156°C (Found: C 61.3, H 4.7, N 5.5%, $[M + Na]^{+\bullet}$ 278.0754. $C_{13}H_{12}F_3NO$ requires C 61.2, H 4.7, N 5.5%, $[M + Na]^{+\bullet}$ 278.0763). δ_H 7.55–7.29 (4H, m), 2.86 (1H, br s, exchanged with D_2O, NH), 2.80–2.70 (2H, m, CH_2), 2.50–2.41 (2H, m, CH_2), 1.70 (3H, s, CH_3). δ_C 204.1 (C), 169.7 (C, C3), 140.0 (C), 131.7 (C, q, *J* 33, C3′), 129.8 (CH), 125.6 (CH), 122.9 (C, q, *J* 273, CF_3), 121.1 (CH, q, *J* 4, C2′^{A}), 119.4 (CH, q, *J* 3, C4′^{A}), 112.6 (C), 33.2 (CH_2), 26.3 (CH_2), 7.0 (CH_3). ν_{max} (KBr)/cm^{-1} 3300–2900, 1675, 1630, 1605.

Reaction of 3-trifluoromethylaniline with cyclohexane-1,3-dione **5c** at 120°C for 1 h afforded 3-[(3-trifluoromethyl)phenyl]amino-2-cyclohex-2-en-1-one **6c** in 88% yield, after recrystallization from benzene, mp 157–159°C (lit.[17] 158°C) (Found: $[M + H]^{+\bullet}$ 256.0942.

Calc. for $C_{13}H_{12}F_3NO$ $[M+H]^{+\bullet}$ 256.0949). δ_H 7.47–7.33 (5H, complex m, 1H exchanged with D_2O), 5.56 (1H, s, exchanged with D_2O, H2), 2.56 (2H, t, *J* 6, CH_2), 2.37 (2H, t, *J* 6, CH_2), 2.02 (2H, quintet, *J* 6, H5). δ_C 199.0 (C), 163.5 (C), 139.1 (C), 131.6 (C, q, *J* 33, C3′), 129.7 (CH), 126.8 (CH), 123.6 (C, q, *J* 273, CF_3), 121.7 (CH, q, *J* 3, C2′^{A}), 120.4 (CH, q, *J* 4, C4′^{A}), 99.2 (CH), 36.4 (CH_2), 29.3 (CH_2), 21.6 (CH_2). ν_{max} (KBr)/cm^{-1} 3260, 1605, 1590.

Reaction of 3-trifluoromethylaniline with 2-methylcyclohexane-1,3-dione **5d** at 140°C for 1 h afforded *3-[(trifluoromethyl)phenyl]-amino-2-methylcyclohex-2-en-1-one* **6d** in 48% yield, after recrystallization from benzene, mp 164–165°C (Found: C 62.7, H 5.4, N 5.1%, $[M+H]^{+\bullet}$ 270.1099. $C_{14}H_{14}F_3NO$ requires C 62.5, H 5.2, N 5.2%, $[M+H]^{+\bullet}$ 270.1106). δ_H 7.47 (1H, d, *J* 9, ArH), 7.47 (1H, q, *J* 9, H5′), 7.31 (1H, s, H2′), 7.25 (1H, d, *J* 8, ArH), 6.35 (1H, s, exchanged with D_2O, NH), 2.50 (2H, t, *J* 6, CH_2), 2.42 (2H, t, *J* 6, CH_2), 1.94 (2H, quintet, *J* 6, H5), 1.83 (3H, s, CH_3). δ_C 196.5 (C), 157.5 (C), 139.8 (C), 131.6 (C, q, *J* 33, C3′), 129.7 (CH), 127.1 (CH), 123.7 (C, q, *J* 273, CF_3), 121.3 (CH, q, *J* 4, C2′^{A}), 120.7 (CH, q, *J* 4, C4′^{A}), 109.6 (C), 36.6 (CH_2), 27.4 (CH_2), 21.9 (CH_2), 8.5 (CH_3). ν_{max} (KBr)/cm^{-1} 3260, 1670, 1640, 1605.

Aza-Annulation Reactions with Acryloyl Chloride Derivatives

To a stirred solution of **2a** (500 mg, 2.06 mmol) in dry benzene (40 mL) was added acryloyl chloride (240 mg, 2.67 mmol) using a syringe. The mixture was heated to reflux overnight. The cooled mixture was transferred to a separating funnel using $CHCl_3$ and washed with saturated $NaHCO_3$ solution. The organic phase was dried ($MgSO_4$) and evaporated. The residue was recrystallized from CH_2Cl_2/diethyl ether to afford *5-acetyl-6-methyl-1-[(3-trifluoromethyl)phenyl]-3,4-dihydro-2(1H)-pyridinone* **4a** (380 mg, 62%), mp 116–118°C (Found: C 60.3, H 4.7, N 4.7%, $[M+H]^{+\bullet}$ 298.1046. $C_{15}H_{14}F_3NO_2$ requires C 60.6, H 4.8, N 4.7%, $[M+H]^{+\bullet}$ 298.1055). δ_H 7.66 (1H, d, *J* 7.7, ArH), 7.59 (1H, t, *J* 7.3), 7.39 (1H, s, H5′), 7.33 (1H, d, *J* 7.3, ArH), 2.79–2.70 (4H, m), 2.33 (3H, s, CH_3), 1.95 (3H, s, CH_3). δ_C 198.6 (C), 170.2 (C), 145.5 (C), 138.2 (C), 132.5 (CH), 131.8 (C, q, *J* 33, C3′), 129.8 (CH), 126.0 (CH, q, *J* 4, C2′^{A}), 125.2 (CH, q, *J* 4, C4′^{A}), 123.5 (C, q, *J* 273, CF_3), 117.3 (C), 31.3 (CH_2), 29.6 (CH_3), 22.1 (CH_2), 18.2 (CH_3). ν_{max} (KBr)/cm^{-1} 1700.

In a similar manner the following compounds were prepared.

5-Benzoyl-6-methyl-1-[(3-trifluoromethyl)phenyl]-3,4-dihydro-2(1H)-pyridinone **4b** was obtained in 67% yield, after recrystallization from CH_2Cl_2/diethyl ether, mp 118–120°C (Found: C 67.1, H 4.5, N 3.9%, $[M+Na]^{+\bullet}$ 382.1026. $C_{20}H_{16}F_3NO_2$ requires C 66.9, H 4.5, N 3.9%, $[M+Na]^{+\bullet}$ 382.1025). δ_H 7.84–7.79 (2H, m), 7.69–7.38 (7H, complex m), 2.85–2.70 (4H, complex m), 1.65 (3H, s, CH_3). δ_C 196.9 (C), 170.5 (C), 142.4 (C), 138.4 (C), 138.3 (C), 132.8 (CH), 132.7 (CH), 131.7 (C, q, *J* 33, C3′), 131.4 (CH), 128.8 (CH), 128.7 (CH), 126.1 (CH, q, *J* 4, C2′^{A}), 125.2 (CH, q, *J* 4, C4′^{A}), 123.6 (C, q, *J* 273, CF_3), 117.6 (C), 31.8 (CH_2), 23.7 (CH_2), 18.7 (CH_3). ν_{max} (KBr)/cm^{-1} 1700, 1645.

5-Acetyl-3,6-dimethyl-1-[(3-trifluoromethyl)phenyl]-3,4-dihydro-2(1H)-pyridinone **4c** was obtained as an oil in 30% yield (Found: C 61.4, H 4.9, N 4.5%, $[M+Na]^{+\bullet}$ 334.1028. $C_{16}H_{16}F_3NO_2$ requires C 61.7, H 5.2, N 4.5%, $[M+Na]^{+\bullet}$ 334.1025). δ_H 7.65 (1H, d, *J* 7.6, H4′^{A}), 7.58 (1H, t, *J* 7.7, H5′), 7.38 (1H, br s, H2′), 7.32 (1H, br d, *J* 7.6, H5′^{A}), 2.85–2.50 (3H, complex m, H3 and H4), 2.33 (3H, s, CH_3), 1.95 (3H, s, CH_3), 1.32 (3H, d, *J* 6.5, C3CH_3). δ_C 198.8 (C), 173.4 (C), 145.4 (C), 138.7 (C), 132.7 (C, br s, C5′), 131.9 (C, q, *J* 33, C3′), 129.9 (CH, C6′), 126.0 (CH, br s, C2′^{A}), 125.2 (CH, q, *J* 4, C4′^{A}), 125.6 (C, q, *J* 272, CF_3), 116.9 (C), 35.3 (CH_2), 30.2 (CH_2), 29.8 (CH_3), 18.4 (CH_3), 14.9 (CH_3). ν_{max} (film)/cm^{-1} 1700, 1670, 1600 (br).

5-Acetyl-6-methyl-3-phenyl-1-[(3-trifluoromethyl)phenyl]-3,4-dihydro-2(1H)-pyridinone ***4d***

To a stirred solution of 2-phenylacrylic acid (600 mg, 4.05 mmol) in CH_2Cl_2 (15 mL) was added thionyl chloride (760 mg, 6.39 mmol) using a syringe. The mixture was heated at 40°C for 1.5 h. The solvents were evaporated and the crude 2-phenylacryloyl chloride was dissolved in dry benzene (20 mL). The enaminone **2a** (900 mg, 3.70 mmol) was added, and the reaction mixture was stirred at 50°C for 1 h, and then at 80°C for 4 h. To the cooled mixture was added saturated $NaHCO_3$ solution (20 mL). The mixture was extracted with $CHCl_3$ (3 × 40 mL). The combined $CHCl_3$ extracts were dried ($MgSO_4$) and evaporated. The residue was subjected to radial thin layer chromatography on silica using CH_2Cl_2/light petroleum (1/1) followed by CH_2Cl_2 as the eluent to afford the title compound **4d** (976 mg, 71%) as a gum (Found: $[M+H]^{+\bullet}$ 374.1361. $C_{21}H_{18}F_3NO_2$ requires $[M+H]^{+\bullet}$ 374.1362). δ_H 7.66 (1H, d, *J* 7.5), 7.58 (1H, t, *J* 7.5, H5′), 7.43–7.46 (7H, complex m), 3.93 (1H, dd, *J* 10, 7, H3), 3.12–3.06 (2H, m, H4), 2.31 (3H, s, CH_3), 2.00 (3H, br s, C6CH_3). δ_C 198.5 (C), 171.2 (C), 145.5 (C), 138.6 (C), 137.2 (C), 132.6 (CH), 131.8 (C, q, *J* 33, C3′), 130.0 (CH), 128.8 (CH), 128.1 (CH), 127.6 (CH), 126.0 (CH, q, *J* 4, C2′^{A}), 125.2 (CH, q, *J* 4, C4′^{A}), 123.6 (q, *J* 273, CF_3), 117.4 (C), 46.6 (CH_3), 30.0 (CH_2), 18.5 (CH_3) (the signal arising from C3 was not identified). ν_{max} (film)/cm^{-1} 1755, 1730, 1650.

1-[(3-Trifluoromethyl)phenyl]-4,6,7,8-tetrahydro-2,5(1H,3H)-quinolinedione ***7*** *and*
N-*(3-Oxocyclohex-1-en-1-yl)*-N-*[(3-trifluoromethyl) phenyl]acrylamide* ***8a***

To a stirred solution of **5c** (1.00 g, 3.92 mmol) in benzene (60 mL) was added acryloyl chloride (460 mg, 5.08 mmol). The solution was refluxed for 15 h and then worked up as described for the preparation of **4a**. The crude reaction mixture was subjected to radial thin layer chromatography with CH_2Cl_2 as the eluent to afford the *acrylamide* **8a** (420 mg, 35%) as an oil (Found: $[M+H]^{+\bullet}$ 310.1044. $C_{16}H_{14}F_3NO_2$ requires $[M+H]^{+\bullet}$ 310.1055). δ_H 7.65 (1H, d, *J* 8, H4′^{A}), 7.57 (1H, t, *J* 8, H5′), 7.41 (1H, s, H2′), 7.35 (1H, d, *J* 8, H6′^{A}), 6.44 (1H, dd, *J* 16, 2, H3), 5.97 (1H, dd, *J* 16, 11, H2), 5.67 (1H, dd, *J* 11, 2, H3), 5.37 (1H, s, H2″), 2.80 (2H, t, *J* 6, H4″^{B}), 2.40 (2H, t, *J* 6, H6″), 2.04 (2H, quintet, *J* 6, H5″). δ_C 199.0 (C), 165.5 (C), 162.5 (C), 140.3 (C), 132.6 (C, q, *J* 33, C3′), 131.9 (CH), 130.7 (CH), 130.6 (C), 129.1 (CH), 125.6 (CH, q, *J* 4, C2′^{A}), 125.4 (CH, q, *J* 4, C4′^{A}), 123.2 (q, *J* 273, CF_3), 121.0 (CH), 36.9 (CH_2), 29.3 (CH_2), 22.6 (CH_2). ν_{max} (film)/cm^{-1} 1665, 1595.

Further elution with CH_2Cl_2/MeOH (98/2) afforded the *2,5(1H,3H)-quinolinedione* **7** (130 mg, 11%) as an oil (Found: C 62.1, H 4.5, N 4.5%, $[M+H]^{+\bullet}$ 310.1043. $C_{16}H_{14}F_3NO_2$ requires C 62.1, H 4.6, N 4.5%, $[M+H]^{+\bullet}$ 310.1055). δ_H 7.65 (1H, d, *J* 8, H4′^{A}), 7.57 (1H, t, *J* 8, H5′), 7.41 (1H, s, H2′), 7.33 (1H, d, *J* 8, H6′^{A}), 2.68 (4H, s, 2 × CH_2), 2.37 (2H, t, *J* 6, CH_2), 2.00 (2H, quintet, *J* 6, H7), 1.92 (2H, t, *J* 6, CH_2). δ_C 196.3 (C), 170.7 (C), 154.1 (C), 137.8 (C), 132.5 (CH), 132.0 (C, q, *J* 33, C3′), 130.1 (CH), 125.9 (CH, q, *J* 4, C2′^{A}), 125.6 (CH, q, *J* 4, C4′^{A}), 123.4 (C, q, *J* 272, CF_3), 116.2 (C), 36.1 (CH_2), 31.2 (CH_2), 28.2 (CH_2), 21.9 (CH_2), 17.2 (CH_2).

4a-Methyl-1-[(3-trifluoromethyl)phenyl]-4,4a,6,7-tetrahydro-2,5(1H,3H)-quinolinedione ***9*** *and*
N-*(2-Methyl-3-oxocyclohex-1-en-1-yl)*-N-*[(3-trifluoromethyl)phenyl]acrylamide* ***8b***

To a stirred solution of **5d** (1.00 g, 3.72 mmol) in benzene (60 mL) was added acryloyl chloride (440 mg, 4.86 mmol). The solution was refluxed for 15 h and then worked up as described for the preparation of **4a**. The crude reaction mixture was subjected to radial thin layer chromatography with CH_2Cl_2 as the eluent to afford the *acrylamide* **8b** (260 mg, 22%) as an oil (Found: $[M+H]^{+\bullet}$ 324.1199. $C_{17}H_{16}F_3NO_2$ requires $[M+H]^{+\bullet}$ 324.1211). δ_H 7.41 (1H, t, *J* 8, H5′), 7.29 (1H, *J* 8, H4′^{A}), 6.99 (1H, s, H2′), 6.89 (1H, d, *J* 8, H6′^{A}), 6.58 (1H, dd, *J* 17, 1.5, H3), 6.26 (1H, dd, *J* 17, 10, H2), 6.02 (1H, dd, *J* 10, 1.5, H3), 2.52–2.45 (2H, m), 2.35–2.28 (2H, m), 1.90–1.84 (2H, m), 1.86 (3H, s, CH_3). δ_C 167.7 (C), 163.1 (C), 156.7 (C), 152.0 (C), 132.8 (CH_2), 131.2 (C, q, *J* 33, C3′), 129.4 (CH), 127.5 (CH), 124.3 (C), 124.1 (C, q, *J* 272, CF_3), 122.7 (CH), 119.6 (CH, q, *J* 4, C2′^{A}), 116.4 (CH, q, *J* 4, C4′^{A}), 28.2 (2 × CH_2), 21.3 (CH_2), 9.9 (CH_3).

Further elution with CH_2Cl_2/MeOH (98 : 2) afforded the *2,5(1H,3H)-quinolinedione* **9** (29%) as an oil (Found: $[M+H]^{+\bullet}$ 324.1205. $C_{17}H_{16}F_3NO_2$ requires $[M+H]^{+\bullet}$ 324.1211). δ_H 7.60–7.46 (2H, m, ArH), 7.35–7.20 (2H, m, ArH), 4.58–4.50 (1H, m, H8), 2.73–2.54 (3H, m), 2.42–1.80 (5H, m), 1.42 (3H, s, CH_3). δ_C 211.1 (C), 168.1 (C), 143.4 (C), 139.8 (C), 132.4 (CH), 132.1 (C, q, *J* 33, C3′), 130.2 (CH), 125.8

(CH, q, *J* 4, C2′^{A}), 124.9 (CH, q, *J* 4, C4′^{A}), 120.9 (C, q, *J* 273, CF_3), 107.6 (CH), 45.1 (C), 34.8 (CH_2), 28.7 (CH_2), 27.1 (CH_2), 21.8 (CH_2), 21.7 (CH_3). ν_{max} (film)/cm^{-1} 1715, 1685, 1645.

*(*E,*Z)-Ethyl 4-Acetyl-5-[(3-trifluoromethyl)phenyl]aminohexa-2,4-dienoate* ***11a***

A solution of **2a** (200 mg, 0.822 mmol) and ethyl propiolate (90 mg, 0.917 mmol) in benzene (1 mL) was heated at 120°C in a sealed tube for 4 days. The benzene was evaporated and the residue was subjected to radial thin layer chromatography using CH_2Cl_2/light petroleum (1/1) followed by CH_2Cl_2 as the eluent to afford the ester **11a** (50 mg, 18%) as a colourless oil (Found: C 59.7, H 5.6, N 4.0%, $[M + Na]^{+\bullet}$ 364.1136. $C_{17}H_{18}F_3NO_3$ requires C 59.8, H 5.3, N 4.1%, $[M + Na]^{+\bullet}$ 364.1131). δ_H 11.75 (1H, br s, exchanged with D_2O, NH), 7.78 (1H, d, *J* 16, H3), 7.55–7.52 (2H, m), 7.39–7.29 (2H, m), 5.74 (1H, d, *J* 16, H2), 4.24 (2H, q, *J* 7, OCH_2), 2.38 (3H, s, CH_3), 2.2 (3H, s, CH_3), 1.32 (3H, t, *J* 7, CH_2CH_3). δ_C 197.5, 167.6, 162.5, 142.4, 138.7, 132.0 (q, *J* 33, C3′), 130.0, 128.7, 123.5 (q, *J* 273, CF_3), 123.2 (q, *J* 4, C2′^{A}), 122.3 (q, *J* 3, C4′^{A}), 117.0, 106.7, 60.2, 29.5, 18.6, 14.4. ν_{max} (film)/cm^{-1} 1700.

*5-Acetyl-6-methyl-1-[(3-trifluoromethyl)phenyl]-2(1*H*)-pyridinone* ***12a***

A stirred mixture of **2a** (250 mg, 1.03 mmol) and ethyl propiolate (150 mg, 1.53 mmol) was heated at 190°C for 2.5 h. More ethyl propiolate (50 mg) was added to the mixture and the heating was continued for a further 2.5 h. The crude reaction mixture was subjected to radial thin layer chromatography using CH_2Cl_2/MeOH (97/3) as the eluent to afford the *2(1*H*)-pyridinone* **12a** (75 mg, 25%) as a solid. A sample was recrystallized from MeOH/diethyl ether, mp 158–160°C (Found: C 61.3, H 4.1, N 4.8%, $[M + H]^{+\bullet}$ 296.0904. $C_{15}H_{12}F_3NO_2$ requires C 61.0, H 4.1, N 4.7%, $[M + H]^{+\bullet}$ 296.0893). δ_H 7.84 (1H, d, *J* 10, H3^{A}), 7.78 (1H, d, *J* 7.5, H4′^{B}), 7.69 (1H, t, *J* 7.5, H5′), 7.46 (1H, s, H2′), 7.39 (1H, d, *J* 7.5, H6′^{B}), 6.59 (1H, d, *J* 10, H4^{A}), 2.54 (3H, s, CH_3), 2.30 (3H, s, CH_3). δ_C 196.8 (C), 162.5 (C), 152.6 (C), 140.1 (CH), 138.8 (C), 132.7 (C, q, *J* 33, C3′), 131.5 (CH), 130.7 (CH), 126.2 (CH, q, *J* 4, C2′^{A}), 125.1 (CH, q, *J* 4, C4′^{A}), 123.4 (C, q, *J* 273, CF_3), 117.4 (C), 117.2 (CH), 29.5 (CH_3), 20.1 (CH_3). ν_{max} (KBr)/cm^{-1} 1690, 1650.

The ester **11a** (50 mg, 0.15 mmol) was added to a stirred solution of sodium ethoxide (ca. 20 mg) in ethanol (4 mL). The reaction mixture was refluxed overnight. The ethanol was evaporated and saturated $NaHCO_3$ solution (20 mL) was added to the residue. The mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined $CHCl_3$ extracts were then dried ($MgSO_4$) and evaporated. The residue was subjected to chromatography to afford the *2(1*H*)-pyridinone* **12a** (8 mg, 19%).

Dimethyl 3-Acetyl-4-[(3-trifluoromethyl)phenyl]aminopenta-1,3-diene-1,2-dicarboxylate ***11b***

A stirred solution of **2a** (1.00 g, 4.11 mmol) and dimethylacetylenedicarboxylate (584 mg, 4.11 mmol) in toluene (25 mL) was refluxed for 15 h. The solution was evaporated to dryness and the residue was subjected to radial thin layer chromatography using CH_2Cl_2 and then CH_2Cl_2/MeOH (99/1) as the eluent to afford the *diester* **11b** (1.25 g, 79%) as a yellow liquid (Found: C 56.2, H 4.8, N 3.6%, $[M + Na]^{+\bullet}$ 408.1027. $C_{18}H_{18}F_3NO_5$ requires C 56.2, H 4.8, N 3.7%, $[M + Na]^{+\bullet}$ 408.1029). δ_H 12.4 (1H, br s, exchanged with D_2O, NH), 7.49–7.29 (4H, complex m, ArH), 7.11 (1H, s, H1), 3.86 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 2.03 (3H, s, CH_3), 1.87 (3H, s, CH_3). δ_C 194.5 (C), 167.4 (C), 165.3 (C), 158.6 (C), 142.5 (C), 139.2 (C), 131.6 (C, q, *J* 33, C3′), 131.4 (CH), 129.7 (CH), 128.4 (CH), 123.6 (C, q, *J* 273, CF_3), 122.3 (CH, q, *J* 4, C2′^{A}), 121.9 (CH, q, *J* 4, C4′^{A}), 103.4 (C), 53.0 (CH_3, OCH_3), 52.0 (CH_3, OCH_3), 28.1 (CH_3), 17.5 (CH_3). ν_{max} (film)/cm^{-1} 1775, 1655, 1625.

*Methyl 5-Acetyl-6-methyl-1-[(3-trifluoromethyl)phenyl]-2(1*H*)-pyridinone-4-carboxylate* ***12b***

To a stirred solution of **11b** (1.25 g, 3.24 mmol) in toluene (50 mL) was added *p*-toluenesulfonic acid (75 mg). The reaction mixture was refluxed for 4 h. The solution was evaporated to dryness and to the residue was added saturated $NaHCO_3$ solution (40 mL). The mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined $CHCl_3$ extracts were dried ($MgSO_4$) and evaporated. The residue was subjected to radial thin layer chromatography using CH_2Cl_2 followed by CH_2Cl_2/MeOH (99/1) to afford the *pyridinone* **12b** (379 mg, 33%) as a brown gum (Found: C 57.9, H 4.1, N 4.0%, $[M + Na]^{+\bullet}$ 376.0774. $C_{17}H_{14}F_3NO_4$ requires C 57.8, H 4.0, N 4.0%, $[M + Na]^{+\bullet}$ 376.0767). δ_H 7.78 (1H, d, *J* 7.6, H4′^{A}), 7.70 (1H, t, *J* 7.6, H5′), 7.48 (1H, s, H2′), 7.40 (1H, d, *J* 7.6, H6′), 7.13 (1H, s, H3), 3.92 (3H, s, OCH_3), 2.48 (3H, s, CH_3), 1.93 (3H, s, CH_3). δ_C 201.5 (C), 164.9 (C), 162.0 (C), 143.8 (C), 139.4 (C), 138.2 (C), 132.6 (C, q, *J* 33, C3′), 131.5 (CH), 130.8 (CH), 126.3 (CH, q, *J* 4, C2′^{A}), 125.0 (CH, q, *J* 5, C4′^{A}), 123.3 (C, q, *J* 273, CF_3), 121.0 (CH, C3), 120.2 (C), 53.2 (CH_3, OCH_3), 32.3 (CH_3), 18.9 (CH_3). ν_{max} (film)/cm^{-1} 1730, 1700, 1670.

*Methyl 5-Acetyl-6-methyl-1-[(3-trifluoromethyl)phenyl]-3,4-dihydro-2(1*H*)-pyridinone-4-carboxylate* ***13*** *and Methyl 5-Acetyl-6-methyl-1-[(3-trifluoromethyl)phenyl]-3,6-dihydro-2(1*H*)-pyridinone-4-carboxylate* ***14***

A stirred solution of **2a** (1.00 g, 4.11 mmol) and maleic anhydride (403 mg, 4.11 mmol) in benzene (25 mL) was refluxed for 15 h. The benzene was evaporated and the residue was dissolved in MeOH (40 mL) that had been acidified by the addition of conc. H_2SO_4 (3 drops). Trimethylorthoformate (430 mg, 4.11 mmol) was added and the reaction mixture was refluxed for 1.5 h. The MeOH was evaporated and saturated $NaHCO_3$ solution (30 mL) and $CHCl_3$ (40 mL) were added to the residue. The $CHCl_3$ layer was collected and the aqueous layer was extracted with $CHCl_3$ (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was subjected to radial thin layer chromatography using CH_2Cl_2/light petroleum (1/1) as the eluent to afford the *ester* **14** (19 mg, 1%) as an oil (Found: $[M + Na]^{+\bullet}$ 378.0922. $C_{17}H_{16}F_3NO_4$ requires $[M + Na]^{+\bullet}$ 378.0924). δ_H 7.87 (1H, s, H2′), 7.71 (1H, d, *J* 7.8, H4′^{A}), 7.56 (1H, t, *J* 7.8, H5′), 7.48 (1H, d, *J* 7.8, H6′^{A}), 5.09 (1H, q, *J* 6.5, C6), 3.78 (2H, s, H3), 3.75 (3H, s, OCH_3), 2.52 (3H, s, CH_3CO), 1.37 (3H, d, *J* 6.5, C6CH_3). δ_C 194.9 (C), 169.2 (C), 167.8 (C), 151.7 (C), 136.7 (C), 135.2 (C), 131.7 (C, q, *J* 33, C3′), 129.8 (CH), 125.0 (CH), 123.7 (C, q, *J* 273, CF_3), 122.0 (CH, q, *J* 3, C2′^{A}), 118.7 (CH, q, *J* 3, C4′^{A}), 57.3 (CH_3), 52.6, 30.5, 30.3, 17.3. Further elution with CH_2Cl_2/MeOH (98/2) afforded the *ester* **13** (380 mg, 26%) as an oil (Found: C 57.4, H 4.3, N 3.8%, $[M + H]^{+\bullet}$ 356.1114. $C_{17}H_{16}F_3NO_4$ requires C 57.5, H 4.5, N 3.9%, $[M + 1]^{+\bullet}$ 356.1104). δ_H 7.72 (1H, d, *J* 8, H4′^{A}), 7.65 (1H, t, *J* 8, H5′), 7.55 (1H, s, H2′), 7.51 (1H, d, *J* 8, H6′^{A}), 3.68 (3H, s, OCH_3), 3.66–3.60 (1H, m, H4), 3.65 (3H, s, OCH_3), 3.32 (1H, dd, *J* 17.4, 4.6, H3), 3.14 (1H, dd, *J* 17.4, 4.6, H3), 2.38 (3H, s, CH_3CO), 2.25 (3H, d, *J* 2.2, C6CH_3). δ_C 192.4 (C), 177.6 (C), 171.2 (C), 152.9 (C), 134.6 (C), 132.1 (C, q, *J* 33, C3′), 131.9 (CH), 130.3 (CH), 125.8 (CH, q, *J* 4, C2′^{A}), 125.4 (CH, q, *J* 4, C4′^{A}), 123.4 (C, *J* 272, CF_3), 117.9 (C), 51.7 (CH_3, OCH_3), 43.1 (CH, C4), 33.8 (CH_2, C3), 30.2 (CH_3), 14.6 (CH_3). ν_{max} (film)/cm^{-1} 1735, 1660, 1630, 1600.

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