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Synthesis of isomerically pure 3-(5-trifluoromethyl-1,2,3-triazol-4-yl)cinnamic acid derivatives via the reaction of 4-aryl-6-trifluoromethyl-2-pyrones with sodium azide

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ABSTRACT

Treatment of 4-aryl-6-trifluoromethyl-2-pyrones with sodium azide in DMSO afforded the corresponding (*Z*)-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)cinnamic acids in good yields. Similarly, 4-aryl-3-carbethoxy-6-trifluoromethyl-2-pyrones smoothly reacted with sodium azide in acetonitrile to produce (*E*)-2-ethoxycarbonyl-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)cinnamic acids in high yields, whereas their reactions in ethanol, accompanied by a configurational change, gave the thermodynamically more stable (*Z*)-2-ethoxycarbonyl-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)cinnamic acids.

1. Introduction

Vicinal triazoles are an important class of heterocyclic compounds[1] mainly because of their pharmacological properties including antiviral,[2a] antifungal,[2b] anticoccidial,[2c] antimicrobial,[2d] and other types of biological activities.[2e,f] Trifluoromethyl-substituted vicinal triazoles have also drawn considerable attention because they often show unique biological and physiological activities.[3] Since inorganic azides are not good reagents in the Huisgen 1,3-dipolar cycloaddition, most of the developed methods for the preparation of CF_3-triazoles lead to N-substituted 1,2,3-triazoles **I** and **II** (Fig. 1). These compounds are primarily prepared by the [3+2] cycloaddition reactions of organic azides to CF_3-containing acetylenes[4] and by the reaction of azides with trifluoromethyl-substituted β-diketones and β-ketoesters or β-alkoxyenones and enaminones derived from them.[5] The latter reaction was assumed to proceed through a cycloaddition of the azide with the alkene moiety of carbonyl compounds, followed by the elimination of water, alcohol or secondary amine.

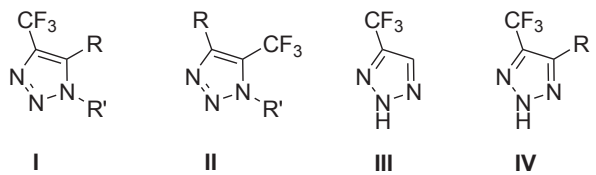

Fig. 1. Vicinal CF_3-triazoles **I**–**IV**.

However, N-unsubstituted 4-trifluoromethyl-1,2,3-triazoles **III** and **IV** are a small and poorly explored group of compounds, probably owing to the limited number of methods available for their preparation. The parent 4-CF_3-1,2,3-triazole **III** has been synthesized by the cycloaddition of trimethylsilyl azide with 3,3,3-trifluoropropyne.[6a] Alternatively, this compound can be obtained from the reactions of trifluoroacetonitrile with (diazomethyl)trimethylsilane,[6b] 1,2,3-triazole-4-carboxylic acid with SF_4,[6c] and 1,1-dihydroperfluoropropyl sulfone with trimethylsilyl azide.[6d] N-Unsubstituted 4-CF_3-5-R-1,2,3-triazoles **IV** can be synthesized from 2-(trifluoromethyl)chromones[7a] and β-chloro-β-perfluoroalkyl substituted acroleins[7b] with sodium azide, by the oxidation of 1,1,1,5,5,5-hexafluoro-4-(trifluoromethyl)pentane-2,3-dione dihydrazone,[7c] by the N-debenzylation of the corresponding 1,2,3-triazole derivative,[3e] and by the cycloaddition of 3-diazomethylcephem with trifluoroacetonitrile.[7d] Apart from these approaches towards the synthesis of triazoles **IV**, a simple procedure for the preparation of CF_3-triazoles bearing a cinnamic acid

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moiety at the 5-position from 4-aryl-6-trifluoromethyl-2-pyrones and sodium azide has been developed by us recently.[8] This reaction is the first example of conversion of the α-pyrone system to 1,2,3-triazoles and deserves further investigations in order to expand the scope of its possible applications.

Within the framework of our project on the synthetic exploitation of the ring-opening of 2-pyrones, incorporating the pharmaceutically relevant trifluoromethyl group at the 6-position,[3] we now report on the use of readily available 4-aryl-6-trifluoromethyl-2-pyrones and 4-aryl-3-carbethoxy-6-trifluoromethyl-2-pyrones[9] as valuable building blocks for the construction of novel derivatives of cinnamic acid bearing a trifluoromethylated triazole ring. Moreover, in this paper we describe the preparation of (*Z*)- and (*E*)-2-ethoxycarbonyl-3-(5-trifluoromethyl-1,2,3-triazol-4-yl) cinnamic acids in isomerically pure forms in various solvents.

2. Results and discussion

Although much attention has been paid to the chemistry of α-pyrones, mainly due to their use as excellent substrates for the preparation of a variety of complex heterocyclic compounds,[10] their reactions with azides have not been described in the literature. However, it is known that the activation of 2-pyrones by the introduction of the electron-withdrawing CF_3 group at the 6-position makes this heterocyclic system more electrophilic and enables a diverse range of productive chemistry, with or without ring-opening. Although several papers have appeared regarding the preparation of 6-CF_3-2-pyrones in the recent literature, the synthetic utility of these compounds has not been extensively explored.[9] From this point of view, we envisaged that the reaction of 4-aryl-6-trifluoromethyl-2-pyrones **1a**–**d** and ethyl 4-aryl-6-(trifluoromethyl)-2-oxo-2*H*-pyran-3-carboxylates **4a**–**d**, prepared from commercial 1-aryl-4,4,4-trifluorobutane-1,3-diones, PCl_5 and sodium diethyl malonate,[9a,b] with sodium azide would produce the corresponding cinnamic acid derivatives bearing the N-unsubstituted triazole ring.

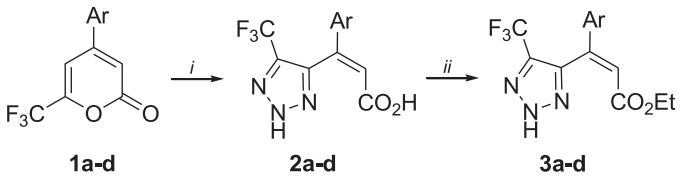
In our initial studies, we optimized the reaction conditions by using 4-(4-chlorophenyl)-6-trifluoromethyl-2-pyrone (**1b**); the progress of the reaction was monitored by TLC, and the results are summarized in Table 1. As observed from Table 1 (entries 1–5), such solvents as ethanol, acetic acid, dioxane, diglyme and acetonitrile cannot be used for the reaction with NaN_3 due to low rate and unfavourable equilibrium of the addition of azide anion to the pyrone double bond. While very low conversion was achieved in EtOH and EtOH/AcOH, no conversion at all was observed for other solvents except for diglyme, in which a complex mixture was obtained. Only DMF and DMSO promoted the [3+2] cycloaddition of sodium azide with **1b** to a large extent (entries 6–14). The elevated temperatures (100–120 °C, entries 6, 7, 11–14) were most suitable for the formation of **2b** in the presence of an excess of NaN_3. At both 3.0 and 1.1 equiv of NaN_3, almost the same product yields were observed (entries 11–14) and the amount of azide was reduced to improve overall reaction efficiency. The use of harsher reaction conditions for the synthesis increased the content of side products. These experiments suggested that dissolving both NaN_3 and the substrate in the reaction medium was important for improving the reaction.

Table 1
Optimization of the model reaction with 2-pyrone **1b**

Entry	Solvent	NaN_3, equiv.	Temp, °C	Time, h	Yield, %
1	EtOH/AcOH (1:1)	1.5	Reflux	72	24
2	EtOH	1.5	Reflux	8	24
3	Dioxane	1.1	Reflux	12	NR[a]
4	Diglyme	1.1	130	12	Mixture
5	MeCN	2.0	Reflux	8	NR
6	DMF	1.1	120	0.25	69
7	DMSO	1.1	100	1.5	75
8	DMSO	3.0	rt	50	84
9	DMSO	3.0	50	21	41
10	DMSO	3.0	70	2.5	65
11	DMSO	3.0	100	1	90
12	DMSO	1.5	100	1	88
13	DMSO	1.5	120	0.5	87
14	*DMSO*	*1.1*	*120*	*0.5*	*86*

[a] NR=no reaction.

Thus, the optimum reaction conditions were 1.1 equiv of NaN_3 in DMSO at 120 °C for 0.5 h. Under these conditions, 2-pyrones **1a**–**d** gave the corresponding β-(triazolyl)cinnamic acids **2a**–**d** in good yields (58–86%) and complete *Z*-stereoselectivity. The products were isolated as colourless solids following an aqueous hydrochloric acid work-up and recrystallization from toluene. Conversion of acids **2a**–**d** to the esters **3a**–**d** was effected with 96% H_2SO_4 in ethanol for 2.5 h in excellent yields (Scheme 1). Thus, the reactions of 2-pyrones **1** with sodium azide lead to the successful synthesis of β-(1,2,3-triazol-4-yl)cinnamic acids containing a CF_3 group in the triazole ring, a previously unknown group of cinnamic acid derivatives.



1a-d **2a-d** **3a-d**

Ar	Acid **2**	Yield, %	Mp, °C	Ester **3**	Yield, %	Mp, °C
Ph	**a**	58	72–73	**a**	85	147–150
4-ClC_6H_4	**b**	86	108–110	**b**	92	113–114
4-FC_6H_4	**c**	78	184–186	**c**	85	119–121
2-$C_{10}H_7$	**d**	70	187–189	**d**	89	155–157

Scheme 1. Synthesis of triazoles **2** and **3**. Reagents and conditions: (i) NaN_3, DMSO, 120 °C, 0.5–1 h; (ii) concd H_2SO_4, ethanol, reflux, 2.5 h.

The structures of CF_3-triazoles **2** and **3** were confirmed from ^1H, ^{19}F, and ^{13}C NMR, IR spectra, elemental analysis, and X-ray diffraction studies. In the ^1H NMR spectra of compounds **2a**–**d** in

DMSO-d_6 the vinyl proton appeared as a singlet in the range of δ 6.8–7.0 ppm; two broad signals due to the labile protons at about δ 12.7 (CO_2H) and 16.0 ppm (NH) were observed. In the ^{19}F NMR spectra of these products the CF_3 group appeared as a singlet at δ −59.6 ppm. In the ^{13}C NMR spectra of **2a**,**b** two characteristic quartets at δ 121.2 (CF_3, $^1J_{C,F}$=268.0 Hz) and 134.3 (C-5, $^2J_{C,F}$=38.0 Hz) were observed confirming the CF_3-triazole structure. It should be noted that compounds **2a**–**d** were isolated in an isomerically pure form and their *Z*-geometry was supported unambiguously by X-ray diffraction analysis of **2b**. According to this they exist in the 2*H*-triazole form in the solid state; the benzene moiety has a more planar conformation (dihedral angle 27°) and the triazole moiety is twisted against the double bond plane (dihedral angle 90°).[8]

Ethyl 4-aryl-6-trifluoromethyl-2-oxo-2*H*-pyran-3-carboxylates **4a**–**d** due to the presence on the pyrone ring of another activating electron-withdrawing substituent (CO_2Et), reacted with NaN_3 under milder conditions leading to the formation of cinnamic acid derivatives **5a**–**d**. To optimize the reaction conditions, we investigated the preparation of (*Z*)-3-(4-chlorophenyl)-2-ethoxycarbonyl-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylic acid (**5b**) from pyrone **4b** as a model compound (the progress of the reaction was monitored by TLC, eluent—ethyl acetate/hexane (1:2); configuration discussion see below). Among the different solvents (DMSO, DMF, EtOH) tested, ethanol appeared to give the best results; the rate and yield are substantially increased at reflux temperature (Table 2, entries 3 and 4). Large amounts of the unidentified side products were observed in DMSO and DMF, which accounted for the reduced yields (entries 1 and 2).

Table 2
Optimization of the model reaction with 2-pyrone **4b**

Entry	Solvent	NaN_3, equiv	Temp, °C	Time, h	Yield, %
1	DMSO	1.1	80	0.5	27
2	DMF	1.1	80	0.33	20
3	EtOH	1.5	25	25	53
4	*EtOH*	*1.1*	*Reflux*	*4.5*	*79*

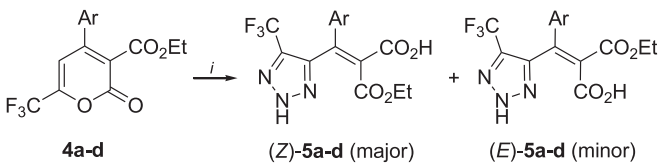
The optimum conditions for the transformation of pyrone **4b** into triazole **5b** were applied for the preparation of triazoles **5a**, **5c** and **5d** (1.1 equiv of NaN_3, 90% EtOH, reflux, 4.5–5.5 h). Compounds **5a**–**d** were obtained as a mixture of isomeric alkenes (*Z*)-**5a**–**d** and (*E*)-**5a**–**d** in 67–81% yield (Scheme 2). Their ratio was easily determined by ^1H NMR analysis; in all cases examined, the dominant product was the *Z*-isomer (75–96%). Only the major *Z*-isomer of **5** could be isolated in a pure form by recrystallization of the mixture from toluene in 58–63% yield. These monoesters owing to the various possible transformations of the different carboxylic functionalities appear as a suitable class of building blocks useful for the synthesis of biologically active compounds.

Previously, a mixture of (*E*)- and (*Z*)-benzylidene malonic acid monoethyl esters was prepared from ethyl potassium malonate and benzaldehyde.[11] Some limitation in the use of monoethyl malonate is apparent because the decarboxylation often occurs spontaneously during the reaction. Recently reported synthesis of arylidene malonates with two different geminal carboxylate functions rely on the Knoevenagel condensation of ethyl *tert*-butyl malonate with different aromatic aldehydes[12] and dialkyl malonates with benzaldehydes followed by a controlled saponification of the resulting dialkyl arylidene malonates with 1 equiv of alkali.[13]

Interestingly, we found a remarkable solvent effect in alkene stereochemistry, when acetonitrile was used as solvent for the reaction of sodium azide with 2-pyrones **4a**–**d**. We investigated the transformation of pyrone **4b** in acetonitrile under various conditions and found that it reacts smoothly with sodium azide (2 equiv) at reflux for 3.5 h (Table 3). In contrast to the above conditions in ethanol, when acetonitrile was employed the stereoselectivity obtained was the opposite and the (*E*)-**5b** isomer was the only product (Scheme 3). The reaction was carried out by simply pouring a substrate solution directly over excess, dry NaN_3, and stirring the two-phase system vigorously at reflux temperature for 3.5 h. The sodium salt of acid (*E*)-**5b**, which is virtually insoluble in acetonitrile, was filtered, washed with dry acetonitrile and acidified with an aqueous HCl to give analytically pure product (*E*)-**5b** (no signals due to the *Z*-isomer were found in the ^1H NMR spectra).

Table 3
Optimization of the model reaction with 2-pyrone **4b** in acetonitrile

Entry	NaN_3, equiv	Time, h	Yield of (*E*)-**5b**, %
1	1.1	20 min	46
2	1.1	2	77
3	1.1	3.5	80
4	1.1	4.5	70
5	1.1	16	52
6	*2*	*3.5*	*89*
7	2	4	83
8	3	3.5	79



4a-d (*Z*)-**5a-d** (major) (*E*)-**5a-d** (minor)

Triazole **5**	Time, h	Yield, %	*Z*/*E* ratio	Mp, °C (*Z*-**5**)
a	4.5	74	85:15	202–203
b	4.5	79	75:25	185–187
c	4.5	81	87:13	201–202
d	5.5	67	96:4	194–197

Scheme 2. Synthesis of triazoles (*Z*)-**5**. Reagents and conditions: (i) NaN_3, 90% ethanol, reflux, 5 h.

With optimized reaction conditions established, the substrate scope was studied (all reactions were run using at least a 2-fold excess of sodium azide). The electronic nature of the aryl substituents in pyrones **4** has no significant effect on the yield of the reaction. With 2-pyrones **4a**–**e** bearing neutral, moderately electron-rich, or electron-poor aryl substituents, the reactions were found to be highly stereoselective affording (*E*)-triazoles **5a**–**e** in excellent yield (79–91%). However, in the case of derivative **4f**, with a 2-thienyl group as aryl substituent, a 70:30 mixture of *Z*- and *E*-isomers **5f**, was obtained in 50% yield. Clearly the electron-withdrawing CF_3 group enhances the electrophilicity of the substrate and encourages conjugate addition at the initial stage. At the same time, the reaction of pyrone **4g** bearing the $(CF_2)_2H$ group with sodium azide in acetonitrile at reflux gives the corresponding alkene (*E*)-**5g** in only 30% yield, indicating the importance of the steric accessibility at the 6-position of the pyrone ring (Scheme 3). Thus, from these results, the reaction seems to be an interesting synthetic method, which allows to prepare the thermodynamically less stable derivatives of cinnamic acid (*E*)-**5** from a given 2-pyrone due to a low solubility of this geometric isomer in acetonitrile. It should be noted that the less reactive pyrones **1** did not react with NaN_3 under these conditions.

It was also found that monoesters **5** are convenient precursors of diesters **6** because of their ability to undergo easy esterification. Thus, when alkenes (*E*)-**5** were refluxed in ethanol with addition of concd H_2SO_4 for 5 h, the desired compounds **6a**,**b**,**d** were isolated in

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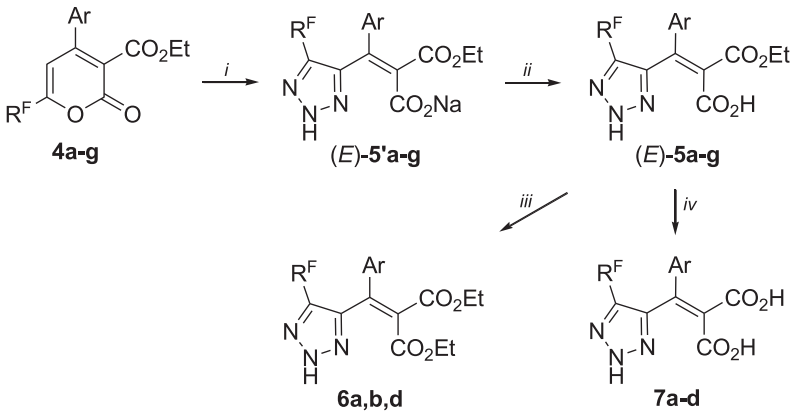


R^F	Ar	5	Yield, %	Mp, °C	6	Yield, %	7	Yield, %
CF_3	Ph	**a**	80	143–145	**a**	91	**a**	92
CF_3	4-ClC_6H_4	**b**	89	167–168	**b**	90	**b**	97
CF_3	4-FC_6H_4	**c**	81	156–157	**c**	–	**c**	92
CF_3	2-$C_{10}H_7$	**d**	79	148–149	**d**	83	**d**	95
CF_3	4-MeC_6H_4	**e**	91	199–201	–	–	–	–
CF_3	2-C_4H_3S	**f**	50[a]	204–207	–	–	–	–
$(CF_2)_2H$	4-BrC_6H_4	**g**	30	159–161	–	–	–	–

[a] Mixture of (*Z*)- and (*E*)-isomers (70:30).

Scheme 3. Synthesis of triazoles (*E*)-**5**, **6** and **7**. Reagents and conditions: (i) NaN_3, MeCN, reflux, 3.5 h; (ii) 5 M HCl, ~20 °C; (iii) concd H_2SO_4, ethanol, reflux, 5 h; (iv) 1 N NaOH, ~20 °C, overnight.

high yields. On the other hand, treatment of (*E*)-**5** with an aqueous 1 N NaOH solution at room temperature gave diacids **7a**–**d**, novel methylidene malonic acid derivatives, in nearly quantitative yields (Scheme 3).

The stereochemistry of the tetrasubstituted alkenes **5** merits some comment. To establish the geometry of alkenes **5**, we carried out a 2D NOESY experiment for (*E*)-**5b**, prepared in MeCN, which demonstrates the spatial proximity of CO_2Et group to aromatic protons. In this case, a strong one cross-peak for CH_2O with H-2, H-6 (Ar) and two cross-peaks for Me with H-2, H-6, and H-3, H-5 (Ar) show that these protons are sited close to each other, thus establishing the trans configuration of the CO_2Et group and triazolyl moiety relative to the double bond. Note that none of these cross-peaks were found in the NOESY spectrum of alkene (*Z*)-**5b**, all in accord with such configuration assignment. Because of the similar shielding effects of the ester and carboxylic acid groups as well as the aryl and triazolyl moieties the geometric isomers **5** are distinguishable by ^1H NMR spectroscopy due to only a small difference between the chemical shifts of the CH_2O group and the *ortho*-aryl protons. In the ^1H NMR spectra of (*E*)- and (*Z*)-alkenes **5a**–**d** the methylene protons appeared as quartets at δ 4.05–4.10 and 4.01–4.05 ppm, whereas the *ortho*-aryl protons appeared at δ 7.13–7.20 and 7.20–7.29 ppm, respectively. Thus, in the *E*-isomer the CO_2Et protons resonated downfield and the *ortho* aromatic protons resonated upfield in comparison to *Z*-isomer (Fig. 2).

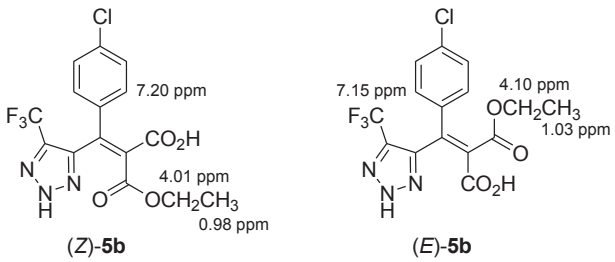
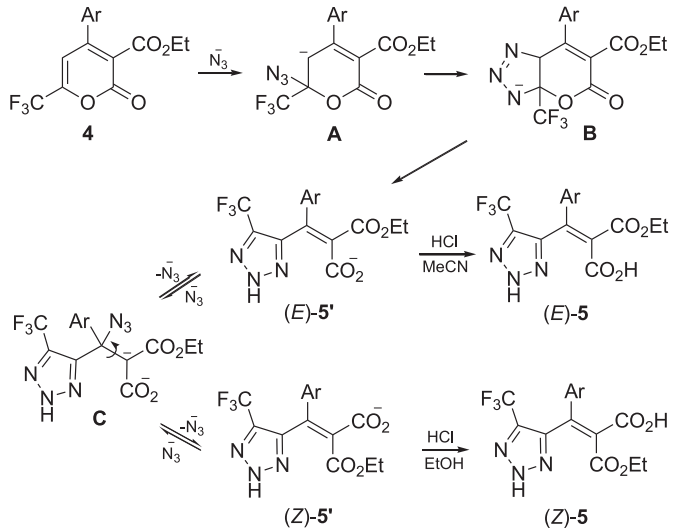


Fig. 2. Diagnostic ^1H NMR signals (DMSO-d_6) of compounds (*Z*)- and (*E*)-**5b**.

Monoesters **5** can be regarded as representatives of polarized alkenes with a highly electrophilic β-C atom, which allows them to react in solution with sodium azide. This is confirmed by the data on the isomerization of pure *Z*-**5b** and *E*-**5b** in the presence of 1 equiv of sodium azide. Thus, the sodium salt of *Z*-isomer **5b** was found to isomerize in refluxing acetonitrile in the presence of NaN_3 for 4 h to give a 9:1 mixture of *E*- and *Z*-isomers, respectively. When *E*-isomer **5b** as sodium salt was treated with NaN_3 in refluxing 90% ethanol for 5 h a 1:1 mixture of *E*- and *Z*-isomers **5b** was obtained. It should be noted that when the neutral form or sodium salt was used in the absence of NaN_3 or in the presence of NaOAc the isomerization process occurs only to a very small degree (2–3%). The proportions of *E*- and *Z*-isomers were determined by integration of the CO_2Et protons in the ^1H NMR spectra.

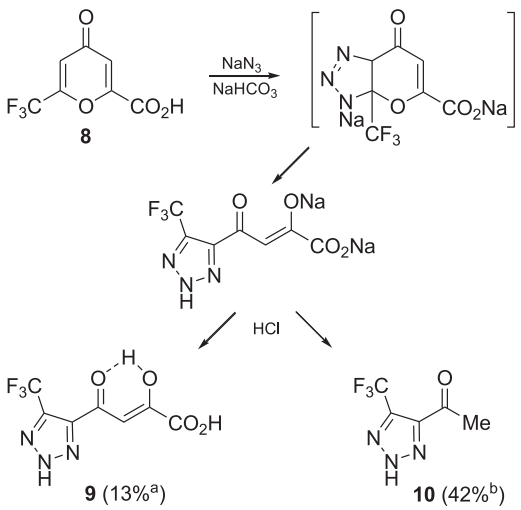
Based on these results and in accord with the previously reported mechanism,[14] a plausible pathway leading to compounds **5** via intermediates **A**–**C** is outlined in Scheme 4. The first stage of the reaction most likely involves Michael addition of azide ion on the C-6 atom. Subsequent cyclization of an incipient β-azido α-carbanion **A** would lead to intermediate **B**. Ring-opening in **B** affords insoluble in acetonitrile sodium salts (*E*)-**5′**, which can be separated and after acidification results in the formation of *E*-isomers **5**. Soluble in ethanol salts (*E*)-**5′** through an addition–elimination process of azide anion can yield the thermodynamically more stable (due to steric reasons) sodium salts (*Z*)-**5′** leading to *Z*-isomers **5** after addition of hydrochloric acid. Thus, the control of the double bond geometry was realized. This result may imply that the stereochemistry of alkenes **5** is controlled by solubility of salts **5′** in organic solvents and in a less degree steric effects. Thus, starting from 2-pyrones **4** the two methods yield isomeric products and are thus complimentary. It should be noted that ethyl 6-methyl-2-oxo-4-phenyl-2*H*-pyran-3-carboxylate and dehydroacetic acid as

representatives of non-fluorinated α-pyrones did not form the corresponding triazoles even in DMSO at 120 °C.



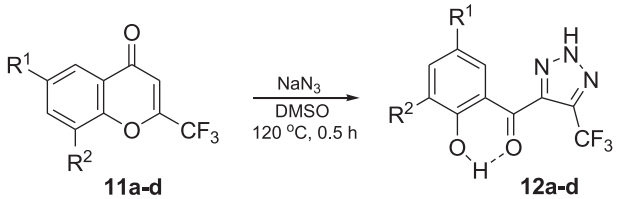
Scheme 4. Possible mechanism for the formation of products **5**.

Next, we were interested in the reactivity of γ-pyrones, carrying the CF_3 group on the 6-position.[15] We envisaged that 6-(trifluoromethyl)comanic acid **8** could be converted into previously unknown tricarbonyl derivative **9** by its reaction with sodium azide. In fact, we found that when 4-pyrone **8** was heated in DMSO with NaN_3 at 120 °C for 3.5 h, the desired product **9** was obtained, albeit in only 13% yield, and presumably arises via ring-opening of the initially formed fused intermediate. The ^{1}H NMR spectrum of **9** in DMSO showed two sets of signals, which were consistent with the enol and keto forms with the former predominating (94%). A similar reaction, when performed in 90% ethanol at reflux for 40 h, provided 4-acetyl-5-(trifluoromethyl)-1,2,3-triazole (**10**) in 42% yield as the product of a ketonic cleavage (Scheme 5). Note that 6-(trifluoromethyl)comanic acid ethyl ester did not give positive results under the above experimental conditions. In this case, the reaction in DMSO gave a complex multicomponent mixture, from which no individual compounds could be isolated; in ethanol only triazole **10** was obtained in a low yield. Thus, the differences in behaviour between the derivatives of 6-CF_3-2-pyrones and those of 6-CF_3-4-pyrones are remarkable. This reaction did not work for comanic and 6-methylcomanic acids.



Scheme 5. Synthesis of compounds **9** and **10** ([a]DMSO, 120 °C, 3.5 h; [b]90% EtOH, reflux, 40 h).

Finally, we investigated the reactivity of 2-(trifluoromethyl) chromones **11a**–**d** towards sodium azide as an entry into trifluoromethylated salicyloyltriazoles. Previously, we reported that 2-CF_3-chromones **11a**,**b** having electron-withdrawing substituents react with sodium azide in AcOH/EtOH (1:1) at 80 °C for 4–10 h to produce 5-salicyloyl-4-trifluoromethyl-1,2,3-triazoles **12a**,**b**, while chromones **11c**,**d** with electron-donating groups on the benzene ring did not give the corresponding triazoles **12c**,**d** after longer reaction time. The latter were prepared from the more reactive in acidic medium but less accessible chromone-4-imines.[7a] It was felt that the direct formation of triazoles **12c**,**d** by treatment of **11c**,**d** with NaN_3 in DMSO might be possible. Indeed, we found that at 120 °C for 0.5 h not only the expected **12a**,**b** but also the target compounds **12c**,**d** can be obtained in excellent yields (Scheme 6). In the case of unsubstituted chromone and 2-methylchromone, this reaction failed presumably due to a low electrophilicity of the C-2 atom. These facts, along with the similar results obtained in the series of α- and γ-pyrones, suggest an important electronic effect of the CF_3 group in pyrones and chromones on the course of the annulation reaction with sodium azide.



11	R^1	R^2	12	Yield, %	Mp, °C (lit.[7a])
a	Cl	H	**a**	95	146–148 (148–149)
b	Br	Br	**b**	96	169–171 (175–176)
c	H	H	**c**	92	149–151 (150–151)
d	Me	H	**d**	85	122–124 (125–126)

Scheme 6. Synthesis of compounds **12a**–**d**.

3. Conclusion

In conclusion, we have shown that the reaction of sodium azide with α- and γ-pyrones and chromones, activated by the trifluoromethyl group provides a convenient and short approach to the synthesis of a variety of cinnamic acid derivatives bearing the triazole ring. Both (*E*)- and (*Z*)-2-ethoxycarbonyl-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)cinnamic acids could be obtained by varying the nature of the solvent. The products obtained constitute an important structural subunit of a variety of biologically active compounds and could be serve as useful substrates in the construction of more complex heterocyclic systems.

4. Experimental

4.1. General

NMR spectra were recorded on Bruker DRX-400 and Bruker Avance II spectrometers (^{1}H—400 MHz, ^{19}F—376 MHz and ^{13}C—100 MHz) in DMSO-d_6 and $CDCl_3$ with TMS, $CFCl_3$ and C_6F_6 (δ=−162.9 ppm) as internal standards. IR spectra were recorded on a Perkin–Elmer Spectrum BX-II and Nicolet 6700 instruments (KBr pellets, FTIR mode, ZnSe crystal). Elemental analyses were performed at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. All solvents

used were dried and distilled per standard procedures. Melting points were determined on a Stuart SMP30 apparatus. The starting 4-aryl-6-(trifluoromethyl)-2*H*-pyran-2-ones **1** and ethyl 4-aryl-2-oxo-(6-trifluoromethyl)-2*H*-pyran-3-carboxylates **4**,[9a,b] as well as 6-(trifluoromethyl)comanic acid[15c] were prepared according to described procedures.

4.2. General procedure for the synthesis of compounds 2a–d

A solution of 4-aryl-6-(trifluoromethyl)-2*H*-pyran-2-one **1** (0.72 mmol) and NaN_3 (52 mg, 0.79 mmol) in 2 mL of DMSO was heated at 120 °C until completion of the reaction (TLC, ethyl acetate/hexane, 1:2). The reaction mixture was then cooled to ~20 °C and acidified with an aqueous 5 M HCl solution. The viscous liquid product was separated by decantation and crystallized from toluene to give triazoles (*Z*)-**2a**–**d** as colourless (**2a**–**c**) or slightly brown (**2d**) solids.

*4.2.1. (Z)-3-Phenyl-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylic acid (**2a**).* Yield 58% (40 min), mp 72–73 °C (hydrate), 126–128 °C (anhydrous). IR (ATR): 1710, 1697, 1637, 1525, 1300, 1199, 1160, 1132, 1072 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.80 (s, 1H, =CH), 7.31 (dd, J=7.8, 1.5 Hz, 2H, Ph), 7.38–7.47 (m, 3H, Ph), 11.80–13.70 (br s, 1H, OH), 15.50–16.50 (br s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6) δ −59.6 (s, CF_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 121.2 (q, $^1J_{C,F}$=268.0 Hz, CF_3), 123.8, 126.8, 129.0, 130.2, 134.3 (q, $^2J_{C,F}$=39.0 Hz), 136.8, 138.5–141.0 (br s, 2C), 165.5. Anal. Calcd for $C_{12}H_8F_3N_3O_2 \cdot H_2O$: C, 47.85; H, 3.35; N, 13.95. Found: C, 48.05; H, 3.26; N, 13.60.

*4.2.2. (Z)-3-(4-Chlorophenyl)-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylic acid (**2b**).* Yield 86% (30 min), mp 108–110 °C (hydrate), 184–186 °C (anhydrous). IR (ATR): 1705, 1692, 1626, 1585, 1526, 1491, 1297, 1194, 1160, 1133, 1095, 1070 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.83 (s, 1H, =CH), 7.34 (d, J=8.7 Hz, 2H, Ar), 7.48 (d, J=8.7 Hz, 2H, Ar), 12.30–13.20 (br s, 1H, OH), 15.70–16.50 (br s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6) δ −59.6 (s, CF_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 121.2 (q, $^1J_{C,F}$=268.0 Hz, CF_3), 124.6, 128.7, 129.1, 134.4 (q, $^2J_{C,F}$=37.7 Hz), 135.0, 135.7, 138.0–139.4 (br s, 2C), 165.5. Anal. Calcd for $C_{12}H_7ClF_3N_3O_2 \cdot H_2O$: C, 42.94; H, 2.70; N, 12.52. Found: C, 43.12; H, 2.68; N, 12.56.

*4.2.3. (Z)-3-(4-Fluorophenyl)-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylic acid (**2c**).* Yield 78% (30 min), mp 184–186 °C. IR (ATR): 1716, 1685, 1635, 1605, 1579, 1509, 1433, 1396, 1336, 1274, 1228, 1205, 1169, 1159, 1132, 1081, 1024 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.79 (s, 1H, =CH), 7.25 (t, J=8.3 Hz, 2H, Ar), 7.37 (dd, J=8.3, 5.4 Hz, 2H, Ar), 12.00–13.30 (br s, 1H, OH), 15.50–16.50 (br s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6) δ −111.1 (br s, F), −59.6 (s, CF_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 116.0 (d, $^2J_{C,F}$=21.9 Hz, C-3, C-5), 121.2 (q, $^1J_{C,F}$=268.1 Hz, CF_3), 123.9, 129.3 (d, $^3J_{C,F}$=8.4 Hz, C-2, C-6), 133.3, 133.5–135.4 (br s), 136.6–140.6 (br s, 2C), 163.1 (d, $^1J_{C,F}$=248.8 Hz, C-4), 165.5. Anal. Calcd for $C_{12}H_7F_4N_3O_2$: C, 47.85; H, 2.34; N, 13.95. Found: C, 47.46; H, 2.38; N, 13.75.

*4.2.4. (Z)-3-(2-Naphthyl)-3-(5-trifluoromethyl-1,2,3-triazol-4-yl) acrylic acid (**2d**).* Yield 64% (1 h), mp 187–189 °C (toluene/petroleum ether 2:1, bp 40–70 °C). IR (ATR): 1705, 1683, 1653, 1624, 1585, 1576, 1558, 1540, 1521, 1507, 1490, 1473, 1457, 1437, 1411, 1327, 1303, 1285, 1237, 1211, 1184, 1165, 1138, 1118, 1074, 1012, 988 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.97 (s, 1H, =CH), 7.50–7.62 (m, 2H, H-6, H-7), 7.66 (d, J=8.9 Hz, 1H, H-3), 7.69 (s, 1H, H-1), 7.90–8.00 (m, 3H, H-4, H-5, H-8), 11.90–13.90 (br s, 1H, OH), 15.50–16.50 (br s, 1H, NH); ^{19}F NMR (471 MHz, DMSO-d_6) δ −59.6 (s, CF_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 121.2 (q, $^1J_{C,F}$=268.0 Hz, CF_3), 123.5, 124.2, 126.9, 127.4, 127.5, 127.6, 128.70, 128.74, 132.6, 133.4, 134.2, 135.5–137.4 (br s), 137.6–141.6 (br s, 2C), 165.6. Anal. Calcd for $C_{16}H_{10}F_3N_3O_2 \cdot 0.5H_2O$: C, 56.15; H, 3.24; N, 12.28. Found: C, 56.08; H, 2.97; N, 12.40.

4.3. General procedure for the synthesis of compounds 3a–d

A solution of β-(1,2,3-triazol-4-yl)acrylic acid **2** (1.2 mmol) and 0.5 mL 96% H_2SO_4 in 3 mL of ethanol was refluxed for 2.5 h. The reaction mixture was then diluted with water and the product was filtered and recrystallized from heptane to give esters **3a**–**d** as colourless solids.

*4.3.1. (Z)-Ethyl 3-phenyl-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylate (**3a**).* Yield 85%, mp 147–150 °C. IR (ATR): 3211, 1701, 1631, 1521, 1454, 1370, 1347, 1292, 1242, 1193, 1136, 1069, 1024, 990 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, J=7.1 Hz, 3H, Me), 4.13 (q, J=7.1 Hz, 2H, CH_2O), 6.68 (s, 1H, =CH), 7.29 (d, J=7.1 Hz, 2H, Ph), 7.33–7.43 (m, 3H, Ph), 12.40–12.80 (br s, 1H, NH); ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.6 (s, CF_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.0, 61.3, 120.8 (q, $^1J_{C,F}$=269.1 Hz, CF_3), 122.8, 127.4, 129.0, 130.6, 136.8 (q, $^2J_{C,F}$=39.1 Hz), 137.2, 141.2, 143.0, 165.7. Anal. Calcd for $C_{14}H_{12}F_3N_3O_2$: C, 54.02; H, 3.89; N, 13.50. Found: C, 54.13; H, 3.63; N, 13.71.

*4.3.2. (Z)-Ethyl 3-(4-chlorophenyl)-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylate (**3b**).* Yield 92%, mp 113–114 °C. IR (ATR): 3225, 1694, 1628, 1589, 1518, 1492, 1448, 1370, 1342, 1293, 1237, 1192, 1155, 1129, 1094, 1070, 1027, 1011, 991 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J=7.1 Hz, 3H, Me), 4.13 (q, J=7.1 Hz, 2H, CH_2O), 6.66 (s, 1H, =CH), 7.23 (d, J=8.7 Hz, 2H, Ar), 7.34 (d, J=8.7 Hz, 2H, Ar); ^1H NMR (400 MHz, DMSO-d_6) δ 1.07 (t, J=7.1 Hz, 3H, Me), 4.01 (q, J=7.1 Hz, 2H, CH_2O), 6.92 (br s, 1H, =CH), 7.38 (d, J=8.7 Hz, 2H, Ar), 7.49 (d, J=8.4 Hz, 2H, Ar), 16.10–16.30 (br s, 1H, NH); ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.6 (s, CF_3); ^{19}F NMR (376 MHz, DMSO-d_6) δ −59.3 (br s, CF_3), −59.4 (br s, CF_3). Anal. Calcd for $C_{14}H_{11}ClF_3N_3O_2$: C, 48.64; H, 3.21; N, 12.15. Found: C, 48.65; H, 3.11; N, 12.16.

*4.3.3. (Z)-Ethyl 3-(4-fluorophenyl)-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylate (**3c**).* Yield 85%, mp 119–121 °C. IR (ATR): 3206, 1698, 1631, 1600, 1508, 1452, 1371, 1346, 1292, 1279, 1248, 1176, 1137, 1069, 1025, 991 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J=7.1 Hz, 3H, Me), 4.13 (q, J=7.1 Hz, 2H, CH_2O), 6.62 (s, 1H, =CH), 7.05 (t, J=8.6 Hz, 2H, Ar), 7.28 (dd, J=8.9, 5.2 Hz, 2H, Ar), 10.00–13.50 (br s, 1H, NH); ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.7 (br s, F), −60.6 (s, CF_3). Anal. Calcd for $C_{14}H_{11}F_4N_3O_2$: C, 51.07; H, 3.37; N, 12.76. Found: C, 50.97; H, 3.12; N, 12.73.

*4.3.4. (Z)-Ethyl 3-(2-naphthyl)-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylate (**3d**).* Yield 89%, mp 155–157 °C. IR (ATR): 3191, 1688, 1620, 1514, 1447, 1371, 1290, 1203, 1181, 1157, 1126, 1067, 1027, 990 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J=7.1 Hz, 3H, Me), 4.14 (q, J=7.1 Hz, 2H, CH_2O), 6.81 (s, 1H, =CH), 7.46–7.56 (m, 3H, H-3, H-6, H-7), 7.58 (s, 1H, H-1), 7.76 (d, J=7.8 Hz, 1H, H-5/8), 7.83 (d, J=7.6 Hz, 1H, H-8/5), 7.84 (d, J=8.7 Hz, 1H, H-4), 11.70–13.10 (br s, 1H, NH); ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.6 (s, CF_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.0, 61.4, 120.8 (q, $^1J_{C,F}$=269.1 Hz, CF_3), 122.7, 123.5, 127.0, 127.7, 127.8, 128.4, 128.9, 129.0, 133.0, 134.2, 134.3, 136.9 (q, $^2J_{C,F}$=39.1 Hz), 141.1, 142.9, 165.9. Anal. Calcd for $C_{18}H_{14}F_3N_3O_2$: C, 59.83; H, 3.91; N, 11.63. Found: C, 59.87; H, 3.73; N, 11.63.

4.4. General procedure for the synthesis of compounds (Z)-5a–d

A solution of ethyl 4-aryl-2-oxo-(6-trifluoromethyl)-2*H*-pyran-3-carboxylate **4** (0.6 mmol) and NaN_3 (43 mg, 0.66 mmol) in 2 mL of 90% ethanol was refluxed for 4.5–5.5 h (TLC, ethyl acetate/hexane, 1:2). The reaction mixture was then acidified with an aqueous 5 M

HCl solution and the product formed was crystallized from toluene to give pure *Z*-triazoles **5a**–**d** as colourless solids. The mother liquor was then diluted with light petroleum (bp 40–70 °C) affording a mixture of *Z*- and *E*-isomers.

*4.4.1. (Z)-2-Ethoxycarbonyl-3-phenyl-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylic acid (Z-**5a**).* Overall yield 74%: 61% as a pure *Z*-isomer, mp 202–203 °C, and 13% as a mixture of *E*- and *Z*-isomers (85:15). IR (ATR): 1728, 1702, 1640, 1516, 1446, 1410, 1369, 1291, 1263, 1223, 1144, 1100, 1068 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.05 (t, J=7.1 Hz, 3H, Me), 4.02 (q, J=7.1 Hz, 2H, CH_2O), 7.20 (dd, J=7.6, 1.7 Hz, 2H, Ph), 7.33–7.42 (m, 3H, Ph), 12.40–14.10 (br s, 1H, OH), 15.50–16.30 (br s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6) δ −59.3 (s, CF_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 13.4, 61.1, 120.8 (q, $^1J_{C,F}$=268.4 Hz, CF_3), 128.0, 128.6, 129.9, 132.2, 134.2 (q, $^2J_{C,F}$=41.4 Hz), 136.4, 138.2, 163.3, 165.8. Anal. Calcd for $C_{15}H_{12}F_3N_3O_4$: C, 50.71; H, 3.40; N, 11.83. Found: C, 50.70; H, 3.27; N, 11.87.

*4.4.2. (Z)-3-(4-Chlorophenyl)-2-ethoxycarbonyl-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylic acid (Z-**5b**).* Overall yield 79%: 45% a pure *Z*-isomer, mp 185–187 °C, and 34% as a mixture of *E*- and *Z*-isomers (59:41). IR (ATR): 3202, 1733, 1697, 1637, 1591, 1484, 1444, 1400, 1374, 1321, 1298, 1280, 1237, 1204, 1170, 1140, 1117, 1089, 1078, 1022, 1010 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.98 (t, J=7.1 Hz, 3H, Me), 4.01 (q, J=7.1 Hz, 2H, CH_2O), 7.20 (d, J=8.5 Hz, 2H, Ar), 7.50 (d, J=8.5 Hz, 2H, Ar), 13.40–14.20 (br s, 1H, OH), 16.00–16.60 (br s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6) δ −59.2 (s, CF_3). Anal. Calcd for $C_{15}H_{11}ClF_3N_3O_4 \cdot 0.33H_2O$: C, 45.53; H, 2.97; N, 10.62. Found: C, 45.38; H, 2.75; N, 10.51.

*4.4.3. (Z)-2-Ethoxycarbonyl-3-(4-fluorophenyl)-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylic acid (Z-**5c**).* Overall yield 81%: 62% as a pure *Z*-isomer, mp 201–202 °C, and 19% as a mixture of *E*- and *Z*-isomers (57:43). IR (ATR): 1724, 1715, 1604, 1579, 1510, 1478, 1369, 1325, 1300, 1250, 1226, 1206, 1165, 1148, 1102, 1074, 1019 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.98 (t, J=7.1 Hz, 3H, Me), 4.01 (q, J=7.1 Hz, 2H, CH_2O), 7.22–7.30 (m, 4H, Ar), 12.90–14.40 (br s, 1H, OH), 15.60–16.80 (br s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6) δ −110.8 (br s, F), −59.0 (s, CF_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.4, 61.2, 115.8 (d, $^2J_{C,F}$=22.1 Hz, C-3, C-5), 120.8 (q, $^1J_{C,F}$=268.5 Hz, CF_3), 130.5 (d, $^3J_{C,F}$=8.9 Hz, C-2, C-6), 132.3, 132.8, 134.3 (q, $^2J_{C,F}$=38.5 Hz), 137.2, 162.8 (d, $^1J_{C,F}$=248.5 Hz, C-4), 163.3, 165.7. Anal. Calcd for $C_{15}H_{11}F_4N_3O_4$: C, 48.27; H, 2.97; N, 11.26. Found: C, 48.01; H, 2.93; N, 11.48.

*4.4.4. (Z)-2-Ethoxycarbonyl-3-(2-naphthyl)-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylic acid (Z-**5d**).* Overall yield 67%: 58% as a pure *Z*-isomer, mp 194–197 °C, and 9% (crystallized from $CHCl_3$/CCl_4) as a mixture of *E*- and *Z*-isomers (27:73). IR (ATR): 1707, 1578, 1476, 1370, 1299, 1260, 1233, 1152, 1102, 1075, 1018 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.07 (t, J=7.1 Hz, 3H, Me), 4.05 (q, J=7.1 Hz, 2H, CH_2O), 7.29 (d, J=8.3 Hz, 1H, H-3), 7.47–7.57 (m, 2H, H-6, H-7), 7.72 (s, 1H, H-1), 7.82–7.92 (m, 3H, H-4, H-5, H-8), 12.30–14.30 (br s, 1H, OH), 15.70–16.70 (br s, 1H, NH). Anal. Calcd for $C_{19}H_{14}F_3N_3O_4$: C, 56.30; H, 3.48; N, 10.37. Found: C, 56.22; H, 3.53; N, 10.40.

4.5. General procedure for the synthesis of compounds (*E*)-5a–g

A solution of ethyl 4-aryl-2-oxo-(6-trifluoromethyl)-2*H*-pyran-3-carboxylate **4** (0.3 mmol) and NaN_3 (39 mg, 0.6 mmol) in 2 mL of dry acetonitrile was refluxed with a drying tube until completion of the reaction (TLC, ethyl acetate/hexane, 1:2). The precipitate formed (sodium salt) was filtered, washed with a small amount of dry acetonitrile and acidified with an aqueous 5 M HCl solution to give the product (*E*)-**5** as a colourless oil, which solidified eventually as a colourless solid.

*4.5.1. (E)-2-Ethoxycarbonyl-3-phenyl-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylic acid (E-**5a**).* Yield 80% (4 h), mp 143–145 °C. IR (ATR): 1727, 1702, 1638, 1448, 1409, 1290, 1263, 1223, 1141, 1099, 1066 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.03 (t, J=7.1 Hz, 3H, Me), 4.06 (q, J=7.1 Hz, 2H, CH_2O), 7.13 (dd, J=7.9, 1.6 Hz, 2H, Ph), 7.30–7.44 (m, 3H, Ph), 12.00–14.00 (br s, 1H, OH), 15.60–16.10 (br s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6) δ −59.2 (s, CF_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 13.5, 61.4, 120.9 (q, $^1J_{C,F}$=268.3 Hz, CF_3), 127.9, 128.7, 130.0, 132.3, 134.1 (q, $^2J_{C,F}$=38.4 Hz), 136.6, 139.0, 164.2, 165.1. Anal. Calcd for $C_{15}H_{12}F_3N_3O_4$: C, 50.71; H, 3.40; N, 11.83. Found: C, 50.65; H, 3.35; N, 11.79. *Sodium (E)-2-ethoxycarbonyl-3-phenyl-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylate (E-**5′a**)*: ^1H NMR (500 MHz, DMSO-d_6) δ 0.91 (t, J=7.1 Hz, 3H, Me), 3.87 (q, J=7.1 Hz, 2H, CH_2O), 7.00 (dd, J=7.5, 1.9 Hz, 2H, Ph), 7.18–7.24 (m, 3H, Ph); ^{13}C NMR (101 MHz, DMSO-d_6) δ 13.7, 59.7, 123.8 (q, $^1J_{C,F}$=267.1 Hz, CF_3), 127.4, 127.5, 128.2, 131.9 (q, $^2J_{C,F}$=34.4 Hz), 133.7, 136.9, 140.8, 141.5, 168.0, 168.3.

*4.5.2. (E)-3-(4-Chlorophenyl)-2-ethoxycarbonyl-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylic acid (E-**5b**).* Yield 89% (3.5 h), mp 167–168 °C. IR (ATR): 3207, 3006, 2932, 1704, 1631, 1591, 1493, 1438, 1402, 1368, 1315, 1278, 1227, 1187, 1169, 1151, 1105, 1093, 1074, 1009, 992 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.03 (t, J=7.1 Hz, 3H, Me), 4.10 (q, J=7.1 Hz, 2H, CH_2O), 7.15 (d, J=8.6 Hz, 2H, Ar), 7.50 (d, J=8.6 Hz, 2H, Ar), 13.00–14.30 (br s, 1H, OH), 15.90–16.70 (br s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6+CCl_4) δ −59.2 (s, CF_3); ^{13}C NMR (101 MHz, DMSO-d_6+CCl_4) δ 13.4, 61.1, 120.6 (q, $^1J_{C,F}$=268.5 Hz, CF_3), 128.4, 129.4, 132.6, 134.7, 132.9–136.6 (br s), 135.3, 136.4–139.8 (br s, 2C), 140.3–143.8 (br s, 2C), 163.7, 164.5. Anal. Calcd for $C_{15}H_{11}ClF_3N_3O_4$: C, 46.23; H, 2.84; N, 10.78. Found: C, 45.97; H, 2.52; N, 10.74. *Sodium (E)-3-(4-chlorophenyl)-2-ethoxycarbonyl-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylate (E-**5′b**)*: IR (ATR): 1689, 1605, 1577, 1487, 1398, 1386, 1327, 1288 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.96 (t, J=7.1 Hz, 3H, Me), 3.93 (q, J=7.1 Hz, 2H, CH_2O), 7.01 (d, J=8.5 Hz, 2H, Ar), 7.33 (d, J=8.5 Hz, 2H, Ar).

*4.5.3. (E)-2-Ethoxycarbonyl-3-(4-fluorophenyl)-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylic acid (E-**5c**).* Yield 81% (2.5 h), mp 156–157 °C. IR (ATR): 3191, 1703, 1685, 1603, 1506, 1451, 1391, 1375, 1281 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.02 (t, J=7.1 Hz, 3H, Me), 4.09 (q, J=7.1 Hz, 2H, CH_2O), 7.18 (dd, J=8.7, 5.4 Hz, 2H, Ar), 7.26 (t, J=8.8 Hz, 2H, Ar), 12.90–14.10 (br s, 1H, OH), 15.90–16.50 (br s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6) δ −111.2 (br s, F), −59.3 (s, CF_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.4, 61.3, 115.8 (d, $^2J_{C,F}$=22.1 Hz, C-3, C-5), 120.8 (q, $^1J_{C,F}$=268.4 Hz, CF_3), 130.3 (d, $^3J_{C,F}$=8.8 Hz, C-2, C-6), 132.3, 132.9, 134.1 (q, $^2J_{C,F}$=38.1 Hz), 137.8, 139.4–142.0 (br s), 162.7 (d, $^1J_{C,F}$=248.3 Hz, C-4), 164.0, 164.9. Anal. Calcd for $C_{15}H_{11}F_4N_3O_4 \cdot 0.5H_2O$: C, 47.13; H, 3.16; N, 10.99. Found: C, 47.38; H, 2.86; N, 10.87. *Sodium (E)-2-ethoxycarbonyl-3-(4-fluorophenyl)-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylate (E-**5′c**)*: ^1H NMR (400 MHz, DMSO-d_6) δ 0.94 (t, J=7.1 Hz, 3H, Me), 3.88 (q, J=7.1 Hz, 2H, CH_2O), 6.96–7.06 (m, 4H, Ar); ^{19}F NMR (376 MHz, DMSO-d_6) δ −55.0 (s, CF_3), −116.3 (m, F).

*4.5.4. (E)-2-Ethoxycarbonyl-3-(2-naphthyl)-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylic acid (E-**5d**).* Yield 79% (4 h), mp 148–149 °C. IR (ATR): 3193, 1702, 1683, 1515, 1446, 1387, 1373, 1296, 1281, 1222, 1169, 1149, 1097, 1070, 994 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.98 (t, J=7.1 Hz, 3H, Me), 4.05 (q, J=7.1 Hz, 2H, CH_2O), 7.20 (dd, J=8.5, 1.7 Hz, 1H, H-3), 7.48–7.57 (m, 2H, H-6, H-7), 7.68 (s, 1H, H-1), 7.83–7.89 (m, 3H, H-4, H-5, H-8), 11.00–14.00 (br s, 1H, OH), 15.70–16.20 (br s, 1H, NH). Anal. Calcd for $C_{19}H_{14}F_3N_3O_4$: C, 56.30; H, 3.48; N, 10.37. Found: C, 56.14; H, 3.44; N, 10.38. *Sodium*

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*(E)-2-ethoxycarbonyl-3-(2-naphthyl)-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylate (E-**5′d**)*: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, J=7.1 Hz, 3H, Me), 3.85 (q, J=7.1 Hz, 2H, CH_2O), 7.12 (dd, J=8.5, 1.6 Hz, 1H, H-3), 7.42–7.46 (m, 2H, H-6, H-7), 7.49 (s, 1H, H-1), 7.71 (d, J=8.6 Hz, 1H, H-4), 7.73–7.77 (m, 1H, H-5/8), 7.80–7.84 (m, 1H, H-8/5); ^{19}F NMR (376 MHz, DMSO-d_6) δ −55.0 (s, CF_3).

*4.5.5. (E)-2-Ethoxycarbonyl-3-p-tolyl-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylic acid (E-**5e**).* Yield 91% (6 h), mp 199–201 °C. IR (ATR): 3241, 1717, 1673, 1623, 1605, 1526, 1508, 1450, 1408, 1374, 1314, 1300, 1245, 1223 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, J=7.1 Hz, 3H, Me), 2.31 (s, 3H, Me), 4.09 (q, J=7.1 Hz, 2H, CH_2O), 7.01 (d, J=8.0 Hz, 2H, Ar), 7.21 (d, J=8.0 Hz, 2H, Ar), 12.90–13.90 (br s, 1H, OH), 15.90–16.60 (br s, 1H, NH). Anal. Calcd for $C_{16}H_{14}F_3N_3O_4$: C, 52.04; H, 3.82; N, 11.38. Found: C, 51.80; H, 3.96; N, 11.34.

*4.5.6. 2-Ethoxycarbonyl-3-(2-thienyl)-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylic acid (**5f**).* Yield 50% (5 h, Z/E=70:30), pale yellow solid, mp 204–207 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (*Z*): 1.22 (t, J=7.1 Hz, 3H, Me), 4.27 (q, J=7.1 Hz, 2H, CH_2O), 6.98 (dd, J=3.8, 1.1 Hz, 1H, H-3), 7.13 (dd, J=5.1, 3.8 Hz, 1H, H-4), 7.85 (dd, J=5.1, 1.1 Hz, 1H, H-5), 13.00–14.00 (br s, 1H, OH), 15.90–16.40 (br s, 1H, NH); (*E*): 0.98 (t, J=7.1 Hz, 3H, Me), 3.98 (q, J=7.1 Hz, 2H, CH_2O), 7.12 (dd, J=3.8, 1.1 Hz, 1H, H-3), 7.14 (dd, J=5.1, 3.8 Hz, 1H, H-4), 7.85 (dd, J=5.1, 1.1 Hz, 1H, H-5), 13.00–14.00 (br s, 1H, OH), 15.90–16.40 (br s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6) δ (*Z*): −59.59 (s, CF_3); (*E*): −59.64 (s, CF_3). Anal. Calcd for $C_{13}H_{10}F_3N_3O_4S\cdot 0.5H_2O$: C, 42.17; H, 2.99; N, 11.35. Found: C, 42.29; H, 2.84; N, 11.34.

*4.5.7. (E)-3-(4-Bromophenyl)-2-ethoxycarbonyl-3-(5-(1,1,2,2-tetrafluoroethyl)-1,2,3-triazol-4-yl)acrylic acid (E-**5g**).* Yield 30% (5 h), mp 159–161 °C. IR (ATR): 3318, 1698, 1631, 1586, 1487, 1411, 1393, 1370, 1302, 1266, 1227, 1211, 1183, 1143, 1106, 1091, 1074, 1011, 990 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.03 (t, J=7.1 Hz, 3H, Me), 4.08 (q, J=7.1 Hz, 2H, CH_2O), 6.72 (t, $^2J_{H,F}$=52.2 Hz, 1H, CF_2H), 7.05 (d, J=8.3 Hz, 2H, Ar), 7.61 (d, J=8.3 Hz, 2H, Ar), 12.90–13.90 (s, 1H, OH), 15.80–16.40 (s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6) δ −137.0 (s, CF_2), −111.3 (s, CF_2H). Anal. Calcd for $C_{16}H_{12}BrF_4N_3O_4$: C, 41.22; H, 2.59; N, 9.01. Found: C, 40.92; H, 2.51; N, 8.84.

4.6. General procedure for the synthesis of compounds 6a–d

A solution of corresponding (*E*)-3-aryl-2-(ethoxycarbonyl)-3-(5-trifluoromethyl-1,2,3-triazol-4-yl)acrylic acid (*Z*)-**5** (0.3 mmol) and 0.3 mL 96% H_2SO_4 in 2 mL of ethanol was refluxed for 5 h. The reaction mixture was then diluted with water and the product was extracted with $CHCl_3$ (3×2 mL). The extract was dried with Na_2SO_4, filtered and then evaporated. The resulting diester was purified by flash-chromatography on silica gel using $CHCl_3$/EtOH gradient system.

*4.6.1. Diethyl phenyl(5-trifluoromethyl-1,2,3-triazol-4-yl)methylenemalonate (**6a**).* Yield 90%, colourless viscous liquid. IR (ATR): 3213, 2987, 2941, 1729, 1626, 1517, 1494, 1446, 1393, 1372, 1327, 1294, 1251, 1221, 1198, 1162, 1141, 1095, 1071, 1004, 989 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, J=7.1 Hz, 3H, Me), 1.14 (t, J=7.1 Hz, 3H, Me), 4.129 (q, J=7.1 Hz, 2H, CH_2O), 4.132 (q, J=7.1 Hz, 2H, CH_2O), 7.19–7.25 (m, 2H, Ph), 7.31–7.40 (m, 3H, Ph); ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.2 (s, CF_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.7, 13.8, 62.1, 62.2, 120.5 (q, $^1J_{C,F}$=269.3 Hz, CF_3), 128.4, 128.7, 130.2, 131.5, 136.6 (q, $^2J_{C,F}$=39.2 Hz), 136.7, 142.0, 142.6, 163.9, 165.4. Anal. Calcd for $C_{17}H_{16}F_3N_3O_4\cdot 0.66H_2O$: C, 51.64; H, 4.42; N, 10.63. Found: C, 51.53; H, 4.22; N, 10.39.

*4.6.2. Diethyl (4-chlorophenyl)(5-trifluoromethyl-1,2,3-triazol-4-yl) methylenemalonate (**6b**).* Yield 91%, colourless viscous liquid. IR (ATR): 3212, 2987, 2941, 1729, 1593, 1517, 1491, 1447, 1400, 1372, 1324, 1294, 1253, 1143, 1090, 1071, 1013, 990 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, J=7.1 Hz, 3H, Me), 1.14 (t, J=7.1 Hz, 3H, Me), 4.14 (q, J=7.1 Hz, 2H, CH_2O), 4.17 (q, J=7.1 Hz, 2H, CH_2O), 7.17 (d, J=8.6 Hz, 2H, Ar), 7.32 (d, J=8.6 Hz, 2H, Ar), 7.80–11.20 (br s, 1H, NH); ^{19}F NMR (471 MHz, $CDCl_3$) δ −61.4 (s, CF_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 13.8, 62.3, 62.4, 120.5 (q, $^1J_{C,F}$=269.2 Hz, CF_3), 129.0, 129.8, 131.9, 135.1, 136.5, 136.7 (q, $^2J_{C,F}$=39.4 Hz), 140.8, 142.6, 163.8, 165.1. Anal. Calcd for $C_{17}H_{15}ClF_3N_3O_4$: C, 48.87; H, 3.62; N, 10.06. Found: C, 48.70; H, 3.62; N, 9.99.

*4.6.3. Diethyl (2-naphthyl)(5-trifluoromethyl-1,2,3-triazol-4-yl) methylenemalonate (**6d**).* Yield 83%, light yellow viscous liquid. IR (ATR): 3205, 2986, 2938, 1712, 1597, 1516, 1469, 1446, 1371, 1293, 1237, 1138, 1089, 1066, 1004, 988 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J=7.1 Hz, 3H, Me), 1.14 (t, J=7.1 Hz, 3H, Me), 4.12 (q, J=7.1 Hz, 2H, CH_2O), 4.14 (q, J=7.1 Hz, 2H, CH_2O), 7.28 (dd, J=8.6, 1.8 Hz, 1H, H-3), 7.46–7.55 (m, 2H, H-6, H-7), 7.73 (d, J=1.1 Hz, 1H, H-1), 7.75–7.83 (m, 3H, H-4, H-5, H-8), 8.10–11.50 (br s, 1H, NH); ^{19}F NMR (471 MHz, $CDCl_3$) δ −61.4 (s, CF_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 13.8, 62.1, 62.2, 120.6 (q, $^1J_{C,F}$=269.2 Hz, CF_3), 125.2, 127.0, 127.6, 127.9, 128.5, 128.6, 128.7, 131.7, 132.9, 133.9, 134.1, 136.8 (q, $^2J_{C,F}$=39.3 Hz), 141.9, 142.7, 163.9, 165.5. Anal. Calcd for $C_{21}H_{18}F_3N_3O_4\cdot 0.25H_2O$: C, 57.60; H, 4.26; N, 9.60. Found: C, 57.48; H, 4.07; N, 9.58.

4.7. General procedure for the synthesis of compounds 7a–d

A solution of acid **5** (0.3 mmol) in 2 mL of an aqueous 1 N NaOH was allowed to stand during overnight at room temperature. The reaction mixture was then diluted with 1 mL of concd HCl to give the target product **8** as a colourless solid.

*4.7.1. Phenyl(5-trifluoromethyl-1,2,3-triazol-4-yl)methylenemalonic acid (**7a**).* Yield 92%, mp 214–216 °C (with decarboxylation). IR (ATR): 3398, 1716, 1687, 1645, 1586, 1497, 1447, 1410, 1320, 1273, 1247, 1228, 1210, 1165, 1141, 1103, 1069, 1017 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 (m, 2H, Ph), 7.31–7.50 (m, 3H, Ph), 13.38 (br s, 2H, OH), 16.08 (br s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6) δ −58.9 (s, CF_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 120.9 (q, $^1J_{C,F}$=268.3 Hz, CF_3), 127.9, 128.6, 129.7, 132.7–135.1 (br s), 133.6, 135.7–138.5 (br s), 136.7, 141.7–144.7 (br s), 164.5, 166.4. Anal. Calcd for $C_{13}H_8F_3N_3O_4\cdot 0.5H_2O$: C, 46.44; H, 2.70; N, 12.50. Found: C, 46.56; H, 2.84; N, 12.44.

*4.7.2. (4-Chlorophenyl)(5-trifluoromethyl-1,2,3-triazol-4-yl)methylenemalonic acid (**7b**).* Yield 97%, mp 203–204 °C (with decarboxylation). IR (ATR): 3404, 1715, 1689, 1648, 1589, 1493, 1405, 1325, 1279, 1228, 1210, 1170, 1146, 1104, 1092, 1071, 1018 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 (d, J=8.5 Hz, 2H, Ar), 7.38 (d, J=8.4 Hz, 2H, Ar), 13.18 (br s, 2H, 2OH), 15.87 (s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6+CCl_4) δ −59.1 (s, CF_3); ^{13}C NMR (101 MHz, DMSO-d_6+CCl_4) δ 120.7 (q, $^1J_{C,F}$=268.6 Hz, CF_3), 128.4, 129.6, 134.0, 134.5, 132.8–137.9 (br s, 2C), 135.6, 140.3–144.2 (br s, 3C), 164.2, 166.0. Anal. Calcd for $C_{13}H_7ClF_3N_3O_4\cdot 0.5H_2O$: C, 42.12; H, 2.18; N, 11.34. Found: C, 42.04; H, 2.09; N, 11.24.

*4.7.3. (4-Fluorophenyl)(5-trifluoromethyl-1,2,3-triazol-4-yl)methylenemalonic acid (**7c**).* Yield 92%, mp 216–217 °C (with decarboxylation). IR (ATR): 3406, 1714, 1684, 1645, 1604, 1584, 1511, 1405, 1324, 1276, 1243, 1228, 1210, 1164, 1140, 1101, 1070, 1017 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.31 (m, 4H, Ar), 13.46 (br s, 2H, 2OH), 16.13 (br s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6) δ −111.3 (br s, F), −59.0 (s, CF_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 115.8 (d, $^2J_{C,F}$=21.7 Hz, C-3, C-5); 120.9 (q, $^1J_{C,F}$=268.2 Hz, CF_3), 130.4 (d, $^3J_{C,F}$=8.8 Hz, C-2, C-6), 133.0–135.5 (br s), 133.2, 133.8, 135.6–136.2 (br s), 142.2–144.4 (br s), 162.7 (d, $^1J_{C,F}$=247.9 Hz, C-4),

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164.5, 166.4. Anal. Calcd for $C_{13}H_7F_4N_3O_4 \cdot 0.25H_2O$: C, 44.65; H, 2.16; N, 12.02. Found: C, 44.68; H, 2.35; N, 11.92.

*4.7.4. (Naphthalen-2-yl)(5-trifluoromethyl-1,2,3-triazol-4-yl)methylenemalonic acid (**7d**).* Yield 95%, mp 205–207 °C (with decarboxylation). IR (ATR): 3401, 1724, 1684, 1576, 1505, 1428, 1394, 1325, 1292, 1274, 1252, 1234, 1186, 1164, 1127, 1103, 1070, 1021 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.28 (dd, J=8.6, 1.7 Hz, 1H, H-3), 7.45–7.60 (m, 2H, H-6, H-7), 7.72 (s, 1H, H-1), 7.82–7.91 (m, 3H, H-4, H-5, H-8), 13.13 (br s, 2H, 2OH), 15.90 (s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6+CCl_4) δ −59.1 (s, CF_3); ^{13}C NMR (101 MHz, DMSO-d_6+CCl_4) δ 120.7 (q, $^1J_{C,F}$=268.3 Hz), 125.0, 126.4, 126.9, 127.4, 127.6, 127.8, 128.2, 132.2, 132.9, 133.4–135.3 (br s), 133.8, 134.4, 136.4–138.6 (br s), 142.0–143.8 (br s), 164.3, 166.3. Anal. Calcd for $C_{17}H_{10}F_3N_3O_4 \cdot H_2O$: C, 51.65; H, 3.06; N, 10.63. Found: C, 51.76; H, 3.24; N, 10.63.

4.8. Compounds 9 and 10

*4.8.1. 2,4-Dioxo-4-(5-trifluoromethyl-1,2,3-triazol-4-yl)butanoic acid (**9**).* To a solution of 6-(trifluoromethyl)comanic acid **8** (0.1 g, 0.48 mmol) in DMSO (1 mL), $NaHCO_3$ (40 mg, 0.48 mmol) was added. After completion of CO_2 evolution, NaN_3 (34 mg, 0.52 mmol) was added and the reaction mixture was heated at 120 °C for 3.5 h, then cooled to room temperature and acidified with an aqueous 5 M HCl solution to give the product **9** as a colourless solid. Yield 0.016 g (13%), mp 192–194 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 4.45 (s, 2H, CH_2, keto), 7.11 (s, 1H, =CH, enol), 11.7–14.7 (br s, OH), 15.6–16.6 (br s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6) δ −60.8 (s, CF_3, keto), −60.3 (s, CF_3, enol). We were unable to isolate this compound in an analytically pure state.

*4.8.2. 1-(5-Trifluoromethyl-1,2,3-triazol-4-yl)ethanone (**10**).* To a solution of 6-(trifluoromethyl)comanic acid **8** (0.1 g, 0.48 mmol) in 90% ethanol (1.5 mL), $NaHCO_3$ (40 mg, 0.48 mmol) was added. After completion of CO_2 evolution, NaN_3 (63 mg, 0.97 mmol) was added and the reaction mixture was refluxed for 40 h, then cooled to room temperature and saturated with gaseous HCl. The solvent was then evaporated and the product was separated by hot extraction with toluene. The most amount of toluene was then evaporated to give the product **10** as a colourless solid. Yield 0.036 g (42%), mp 125–127 °C. The product contains a small amount of toluene (ca. 3%), which is difficult to remove because of its sublimation at elevated temperatures. It can be recrystallized for elemental analysis with a high loss from a small amount of water. IR (ATR): 3124, 3009, 2926, 2871, 2828, 2748, 1684, 1516, 1445, 1366, 1330, 1309, 1193, 1157, 1047, 986, 962, 859 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.61 (s, 3H, Me), 15.5–17.5 (br s, 1H, NH); ^{19}F NMR (471 MHz, DMSO-d_6) δ −60.5 (s, CF_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 30.0, 120.6 (q, $^1J_{C,F}$=268.8 Hz, CF_3), 136.1 (q, $^2J_{C,F}$=39.7 Hz), 142.9, 190.8. Anal. Calcd for $C_5H_4F_3N_3O$: C, 33.53; H, 2.25; N, 23.46. Found: C, 33.78; H, 2.25; N, 23.32.

4.9. General procedure for the synthesis of compounds 12a–d

A solution of chromone **11** (0.25 mmol) and NaN_3 (18 mg, 0.28 mmol) in DMSO (1 mL) was heated at 120 °C for 30 min. The reaction mixture was then cooled to room temperature and acidified with an aqueous HCl solution (1:1) to give the product **12** as yellow solid in an excellent yield (Scheme 6). All properties of 4-salicyloyl-5-trifluoromethyl-1,2,3-triazoles **12** were in good agreement with the literature data.[7a]

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Supplementary data

2D NOESY experiments for (*E*)-**5b** and (*Z*)-**5b**; copies of ^1H, ^{19}F, and ^{13}C NMR spectra. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.09.093.

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