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Concise synthesis of ω-fluoroalkylated ketoesters. A building block for the synthesis of six-, seven-, and eight-membered fluoroalkyl substituted 1,2-diaza-3-one heterocycles

Wen Wan [a], Jie Hou [a], Haizhen Jiang [a], Yangli Wang [a], Shizheng Zhu [b,*], Hongmei Deng [c], Jian Hao [a,b,*]

[a] Department of Chemistry, Shanghai University, 99 Shangda Road, Shanghai 200444, China
[b] Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China
[c] Instrumental Analysis & Research Center, Shanghai University, 99 Shangda Road, Shanghai 200444, China

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ABSTRACT

A concise and general synthetic route toward the small and medium-sized fluoroalkyl substituted 1,2-diaza-3-one heterocyclic ring skeletons via a sequential reaction of condensation and ring-closure reaction of ω-fluoroalkylated ketoesters **4** with hydrazines **5** catalyzed by 10–20 mol % TsOH has been developed. A practical preparation of biologically interested ω-fluoroalkylated ketoesters **4**, which were subsequently subjected as a fluorine-containing building block to the synthesis of 1,2-diaza-3-one heterocycles has been optimized. Trifluoromethyl substituted seven- and eight-membered 1,2-diazapinone **8**, 1,2-diazocinone **10** were also obtained via this sequential reaction of δ- (or ε-) trifluoromethyl ketoesters with hydrazine hydrates in acidic condition. In contrast, the sequential reaction of ω-fluoroalkylated δ- or ε-ketoesters with aryl hydrazines under the same conditions did not result in the formation of diazepinones and diazocinones, and instead, the reaction provided a direct access to the biologically important 2-fluoroalkyl-indole-3-carboxylate derivatives via a Fisher indole synthesis.

1. Introduction

Small and medium-sized nitrogen-containing heterocyclic skeletons, such as 1,2-diaza-3-one heterocyclic frameworks have recently drawn much attention due to their potential applications either as the key intermediates in the synthesis of more complex structures or as core structures for the synthesis of pharmaceutically important molecules.[1]

Many 1,2-diaza-3-one heterocycles have been found to have potent anticonvulsant, antituberculosis, antitumor, and herbicidal activities.[2] It's quite interesting that the electronic substituent effects on the bioactivity changes at certain positions of such heterocycles have been observed. For instance, the bioactivities of pyridazinone and its 4,5-dihydro derivatives were found to be quite sensitive to the electronic effects of substituent group at specific 2- or 6-position.[3] To the best of our knowledge, however, the structures of fluoroalkyl substituted analogies, especially 6-fluoroalkyl substituted pyridazinones, and their expected potential bioactivities are still far from understanding. Moreover, the method for the preparation of biologically equal important various ω-fluoroalkyl ketoesters is also less well-investigated. The development of a reliable and efficient method for such preparation and further investigation into their synthetic applications is still remaining as a challenge.

In general, a sequential condensation and ring-closure reaction of ketoesters or ketocarboxylic acids with hydrazines is one of the practical processes toward the construction of nonfluoroalkyl substituted 1,2-diaza-3-one heterocyclic ring system.[4] Other methods, such as oxidation followed by ring-expansion reaction of *N*-amino-lactam,[5] and intramolecular cyclization of hydrazides of *vic*-acetylenylbenzoic[6] have also been reported to produce corresponding pyridazinones and diazepinones.

Our approach toward the construction of fluoroalkyl substituted 1,2-diaza-3-one heterocycles with different ring sizes is based on the development and optimization of a practical preparation of ω-fluoroalkyl substituted ketoesters. As a fluorine-containing building block, ω-fluoroalkyl substituted ketoesters can be then subjected to a sequential process of condensation and ring-closure reaction with various hydrazines under catalysis of 10–20 mol % TsOH, and lead to the formation of 1,2-diaza-3-one heterocycles. Interestingly, such sequential reaction of ω-fluoroalkylated δ- or ε-ketoesters with aryl hydrazines under the same acidic conditions cannot provide the formation of diazepinones and diazocinones, and instead, the reaction provides us a possibility to directly access to the biologically interested 2-fluoroalkyl-indole-3-carboxylate derivatives via a Fisher indole synthesis.

* Corresponding authors. Tel./fax: +86 21 66133380.
E-mail address: jhao@staff.shu.edu.cn (J. Hao).

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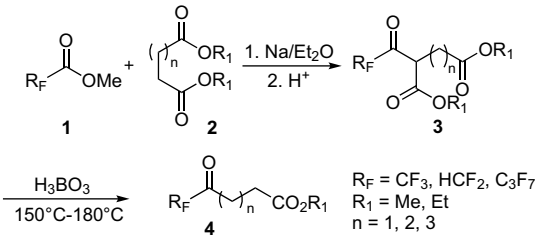
2. Results and discussion

As for the key fluorine-containing building block for the synthesis of 1,2-diaza-3-one heterocycles, fluoroalkylated ketoesters were prepared in moderate yields through a condensation of fluorinated methyl acetate **1** with various α,ω-diesters **2**, such as dimethyl succinate, followed by decarboxylation with H_3BO_3,[7] as outlined in Scheme 1. $NaOCH_3$, NaH, *t*-BuOK, or metal sodium was, respectively, employed as a base in a model reaction of *Claisen* condensation of methyl trifluoroacetate with dimethyl succinate in dry ether to produce trifluoromethylated ketodiester **3a** (n=1). It was found that commonly used $NaOCH_3$, NaH, or *t*-BuOK was not an ideal base for this condensation reaction, reaction treated with these bases resulted either a lower yield (less than 50%) with longer reaction time (more than 24 h) or more complicated mixture. Treatment of dimethyl succinate with metal sodium, however, produced 75% isolated yield of **3a** within 12 h. Nevertheless, the yield could not be further improved remarkably even when the reaction time was prolonged over 72 h. It's quite certain that small amount of alcohol (methanol or ethanol), which was existed in diester as an impurity reacted with metal sodium and produced corresponding $NaOCH_3$ or NaOEt in situ, respectively, such in situ generated base accelerated the condensation reaction. The subsequential decarboxylation of **3a** in the presence of boric acid (1.1 equiv) at 150–180 °C yielded, after a quick aqueous work-up, the desired trifluoromethyl substituted γ-ketoester **4a** in 76% yield. The overall yield of two steps was 57% and was higher than that was reported in literature. After optimization of reaction conditions, the scope of this sequential process was then successfully extended to the synthesis of other fluoroalkyl substituted ω-ketoesters, such as 4-difluoromethyl-γ-ketoester **4c**, 4-heptafluoropropanyl γ-ketoester **4d**, 5-trifluoromethyl-δ-ketoester **4e**, and 6-trifluoromethyl-ε-ketoester **4f**, under the similar conditions described above (Table 1). This sequential reaction generally undergoes smoothly even in 100-g scale in laboratory and provides reasonable overall yield. However, in the case of using difluoroacetate as a starting material, the base could directly affect the difluoromethyl group, and result partial decomposition of either difluoroacetate or condensation product **3c**. As a result, the overall yield for difluoromethyl ketoester **4c** was only 34%. As for the parafluoroalkyl ketoester **4d** (Table 1, entry 4), decomposition was observed at the stage of decarboxylation at high temperature, though a high yield of condensation reaction was obtained at first step. The reason for this decomposition is not clear yet.



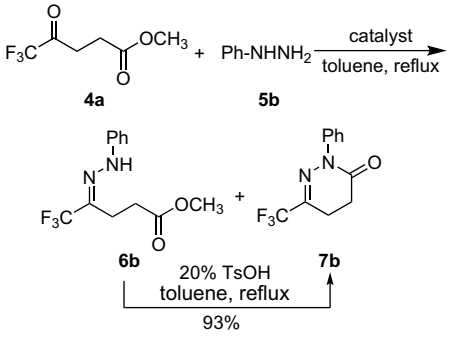
Scheme 1. Optimized route toward ω-fluoroalkylated ketoesters **4**.

The condensation of fluoroalkyl substituted ketoester **4** with hydrazine followed by ring-closure reaction is a simple and typical route toward 1,2-diaza-3-one compounds.[8] This sequential process, however, is sensitive and chemoselectively controlled by either the ratio of ketoester **4** and hydrazine or the percentage of acidic catalyst that is added to catalyze this reaction. A variety of catalysts including Lewis acids, *Bronsted* acid, and acidic buffer (pH=5.0, entry 12, Table 2) were employed in a model reaction of **4a** with phenyl hydrazine (1:1 mole ratio) to examine their effects on the proportion of desired products of corresponding hydrazone and 4,5-dihydro-6-trifluoromethyl pyridazinone (Table 2). High conversions of substrates were successfully realized when the condensations were carried out in refluxed toluene under the catalysis of *Bronsted* acids. In particular, an almost quantitative yield of the desired 4,5-dihydropyridazinone was obtained when the amount of catalyst of TsOH, or CF_3COOH, was increased from 10 to 20 mol % (entries 8 and 10, Table 2), the reaction time was significantly shortened from 36 h to 12 h. In the case of using concentrated H_2SO_4 as a catalyst (either 10 or 20 mol %), reaction could yield the desired 4,5-dihydropyridazinone products in high yield (entry 11, Table 2), however, the partial carbonization of substrates was also clearly observed. In the case of using Lewis acids as catalysts, for instance $Ti(OEt)_4$, $AlCl_3$, CuI_2, $ZnBr_2$, reaction generally resulted lower yield of 4,5-dihydropyridazinone but higher yield of hydrazone even with longer reaction time (48 h). $TiCl_4$ (10%) could not promote such condensation reaction. The optimization study of this sequential process revealed an interesting result that the ratio of product **6b** and **7b** was also dominated by the molar ratio of the starting materials of ketoester **4** and hydrazine **5**; 1:1 molar ratio of **4a** and phenyl hydrazine **5b** could result the *N*-phenyl-4,5-dihydro-6-trifluoromethyl-pyridazinones **7b** as a major product under the catalysis of 10% TsOH, while 1:2 molar ratio of same substrates could efficiently terminate the reaction at first step and prevent the subsequential ring-closure reaction to the formation of dihydropyridazinone product **7b**. In addition, the hydrazone **6b** could

Table 1
The overall yields of ω-fluoroalkylated ketoesters **4**

Entry	Compd.	n	R_F	R_1	Overall yield (%)
1	**4a**	1	CF_3	Me	57
2	**4b**	1	CF_3	Et	65
3	**4c**	1	CF_2H	Et	34
4	**4d**	1	C_3F_7	Et	17
5	**4e**	2	CF_3	Me	55
6	**4f**	3	CF_3	Me	50

Table 2
Catalyst effects on the condensation and ring-closure reaction of phenyl hydrazine with trifluoromethyl γ-ketoester **4a**

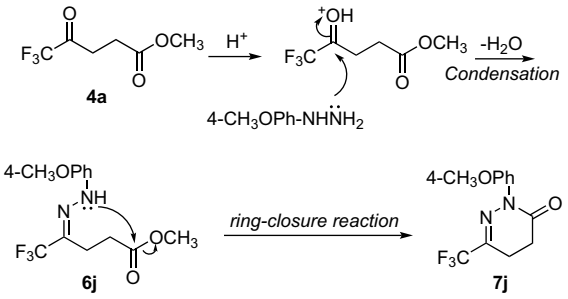


Entry	Catalyst	mol %	Yield (**6b**)	Yield (**7b**)
1	$TiCl_4$	10	—	—
2	$Ti(OEt)_4$	10	97%	1%
3	CuI_2	10	87%	10%
4	$ZnBr_2$	10	94%	1%
5	$AlCl_3$	10	73%	20%
6	TsOH	5	80%	15%
7	TsOH	10	40%	55%
8	TsOH	20	0	98%
9	CF_3COOH	10	1%	95%
10	CF_3COOH	20	0	99%
11	H_2SO_4	10	2%	90%
12	HOAc/NaOAc	10	25%	67%

All reactions were carried out on a 1 mmol scale and giving isolated yields.

be readily converted to **7b** with 100% conversion and 93% isolated yield under the catalysis of 20% TsOH.[9]

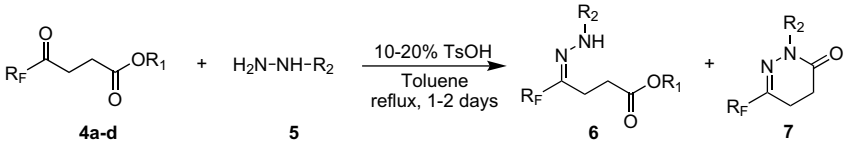
For better understanding the mechanism of this sequential process, the reaction of 4-methoxyphenyl hydrazine **5j** with trifluoromethyl-γ-ketoester **4j** was selectively monitored by ^{19}F NMR and ^{1}H NMR. The formation of hydrazone intermediate **6j** was clearly observed during the course of ^{19}F NMR study. The first condensation step of this sequential process was relatively slower than the second ring-closure step. Once hydrazone **6j** was formed, the following ring-closure reaction toward dihydropyridazinone product would be formed in a shorter period. This phenomenon was also observed in all other examined cases. The plausible mechanistic interpretation of formation of **7** is explained by the condensation of hydrazine with ketone and ring-closure reaction of hydrazone, as shown in Scheme 2.



Scheme 2. Plausible reaction pathway from ketoester to dihydropyridazinones.

With optimization of reaction conditions, we applied this protocol to a range of hydrazine substrates, including aryl hydrazines, alkyl hydrazines, and acetyl hydrazines (Table 3). To ensure a good performance with a wide range of both ketoester **4** and hydrazine **5** substrates, which results the formations of dihydropyridazinones **7**, 20 mol% TsOH as catalyst and 1:1 molar ratio of ω-fluoroalkyl ketoester **4** and hydrazine **5** were finally determined as a standard condition. Moreover, 10 mol% of TsOH catalyst with 1:2 ratio of fluoroalkylated γ-ketoesters (n=1) and hydrazines could be an effective condition to improve the yield of hydrazone product **6** if the hydrazone **6** is demanded to be a dominated product. Results from substituent effects on the ring-closure reaction in Table 3 indicated that the electron rich hydrazine, such as 4-methoxyphenyl hydrazine **5j**, provided higher yield of dihydropyridazinone product **7j** (entry 10 of Table 3), reaction process was difficult to be terminated at first step. Whereas, reaction process with electron deficient hydrazine, for instance NO_2 substituted hydrazine **5f** (entry 6, Table 3), could either be selectively terminated at first step and form the hydrazone **6** as a major product or directly form the final dihydropyridazinone **7** as a major product depending on the different molar ratio of ketoester **4** and hydrazine **5**. Furthermore, no cyclized product could be detected by ^{19}F NMR in reaction of dinitro substituted hydrazines (**7g** and **7h**, entries 7 and 8, Table 3) even under the catalysis of stoichiometric TsOH. Only hydrazone products **6g**, **6h** were obtained. It was also found that treatment of acetohydrazide **5k** (entry 11, Table 3) with **4a** mainly afforded *N*-deprotected 6-trifluoromethyl dihydropyridazinone **7a** due to the hydrolysis of acetyl group under the acetic condition. With the intent of expanding the spectrum of this sequential reaction to accommodate more diverse substituents, the heptafluoropropyl and difluoromethyl substituted γ-ketoester were also investigated (entries 12 and 13, Table 3). The reaction conditions were proved to be compatible with hydrazines in good yields. In general, the hydrazone product **6** could be isolated if it was clearly detected during the reaction. Subsequential ring-closure reaction was successfully implemented for the transformation from hydrazone **6** to dihydropyridazinone **7**. The base promoted ring-closure reaction, for instance by using NaH, could partially result the formation of

Table 3
Synthesis of hydrazones **6** and pyridazinones **7**[a]



Entry	R_F	R_1	R_2	Ratio of **4** and **5**[b]	Product (s)	Yield (%)	
						6	**7**
1	CF_3	Me	H (**5a**)	1:1	**6a** and **7a**	Trace[c]	83
2	CF_3	Me	Ph (**5b**)	1:1	**6b** and **7b**	Trace[c]	92
				1:2		70	20
3	CF_3	Me	4-Cl-Ph (**5c**)	1:1	**6c** and **7c**	0	80
				1:2		67	25
4	CF_3	Me	4-F-Ph (**5d**)	1:1	**6d** and **7d**	Trace[c]	85
5	CF_3	Me	PhCO (**5e**)	1:1	**6e**	82	—[d]
6	CF_3	Me	4-NO_2-Ph (**5f**)	1:1	**6f** and **7f**	15	80[e]
				1:2		85	10
7	CF_3	Me	2,4-NO_2-Ph (**5g**)	1:1	**6g**	15	—[d]
				1:2		81	—[d]
8	CF_3	Et	2,4-NO_2-Ph (**5h**)	1:1	**6h**	30	—[d]
				1:2		85	—[d]
9	CF_3	Et	4-CH_3-Ph (**5i**)	1:1	**6i** and **7i**	Trace[c]	77
10	CF_3	Me	4-CH_3O-Ph (**5j**)	1:1	**6j** and **7j**	Trace[c]	94
11	CF_3	Me	CH_3CO (**5k**)	1:1	**6k** and **7k**	Trace[c]	76
12	C_3F_7	Et	H (**5l**)	1:1	**6l** and **7l**	Trace[c]	72
13	CF_2H	Et	H (**5m**)	1:1	**6m** and **7m**	Trace[c]	82

[a] All reactions were carried out on a 5 mmol scale and giving isolated yields.
[b] The reaction was conducted at molar ratio of 1:1 (**4**:**5**) catalyzed by 20% TsOH or at molar ratio of 1:2 (**4**:**5**) catalyzed by 10% TsOH, respectively.
[c] Trace product was detected by ^{19}F NMR.
[d] Dihydropyridazinone was not detected.
[e] The yield of **7j** could be further improved to 93% if 25% TsOH was employed.

product **7**,[10] however, reaction was generally complicated even in lower temperature (lower than −60 °C), the isolated yield of product **7** was commonly less than 20%.

The assignment of configuration of **7j** (CCDC 704552) was unambiguously confirmed by X-ray crystallographic analysis (Fig. 1). In the diagram of crystal structure of **7j**, the molecules are linked firstly into centrosymmetric dimmers, and then into infinite chains. The dipole–dipole and van der Waals interaction may be effective in this molecular packing.

Taking into account the good results obtained from the previous condensation and ring-closure reaction, other ω-fluoroalkyl ketoester possessing longer carbon chain, for instance, trifluoromethyl δ-ketoester **4e** and trifluoromethyl ε-ketoester **4f** were also envisaged. Similar condensation and ring-closure reaction of **4e** or **4f** with hydrazine were also experimented toward the synthesis of 1,2-diazaone derivatives. With previously optimized condition, reaction of ω-trifluoromethyl ketoester (**4e**, n=2) with hydrazine hydrate **5a** was successfully carried out in refluxed toluene and produced the desired trifluoromethylated dihydrodiazepinone **8** in 85% yield (Scheme 3). However, the reaction of ω-trifluoromethyl ketoester (**4f**, n=3) with hydrazine hydrate **5a** under same condition was stopped at the first step and formed hydrazone **9** in 92% yield when 10% TsOH was applied. The trace amount of desired 1,2-diazocinone **10** was only detected by ^{19}F NMR in this case. 1,2-Diazocinone **10** could only be obtained stepwise if the catalytic amount of TsOH is employed in the condensation step, the ring-closure reaction of hydrazone **9** to form 1,2-diazocinone **10** required the existence of stoichmetric TsOH, and could be accomplished in 45% yield. In addition, ring-closure reaction promoted by base, such as NaH, could not produce desired 1,2-diazocinone **10** in good yield (less than 10% isolated yield) even in low reaction temperature, and instead, reaction was complicated. It's worth to be mentioned that reaction of **4e** or **4f** with aryl hydrazines catalyzed by stoichiometric TsOH could not yield desired diazepinone or diazocinone derivatives, instead, 2-trifluoromethyl indole-3-propanoate **11a** or 2-trifluoromethyl indole-3-butanoate **11b** was obtained in 72% or 78%, respectively, through a Fischer indole synthesis (Scheme 3). Catalytic amount of TsOH, for instance 10%, could also stop the reaction at condensation step and form the corresponding hydrazone product. In such circumstance, trace amount of indole product could only be detected by ^{19}F NMR.[11]

It should be pointed out that indole ring could only be formed in the cases of using **4e** and **4f** (n=2, 3) with *N*-aryl hydrazines catalyzed by stoichiometric TsOH. This phenomenon of indole formation was not clearly observed in the condensation of fluoroalkylated γ-ketoesters **4a**–**4d** (n=1) with *N*-aryl hydrazines even under the catalysis of 100% TsOH. Ring-closure reaction to form six-membered dihydropyridazinone **7** became a dominative process in this sequential reaction.

One application of 4,5-dihydro-6-trifluoromethyl-pyridazinone **7a** was successfully subjected to the synthesis of pharmaceutically

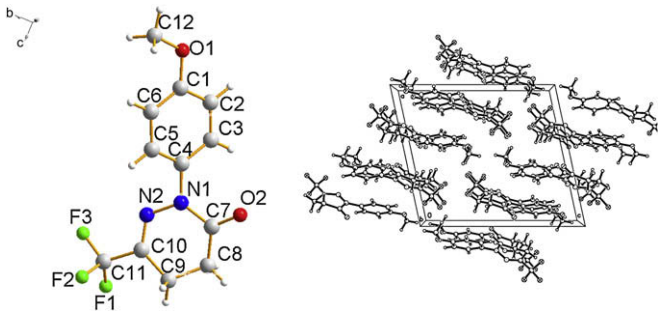
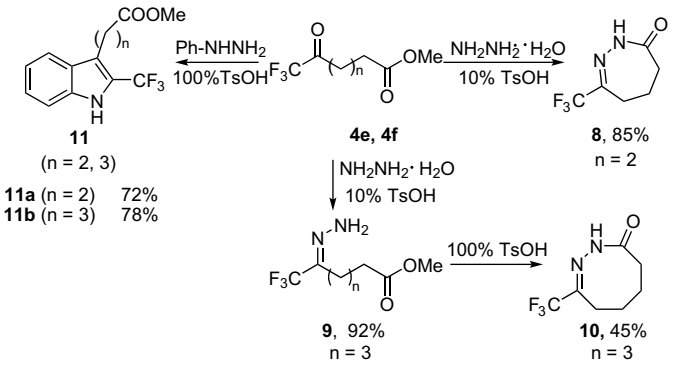
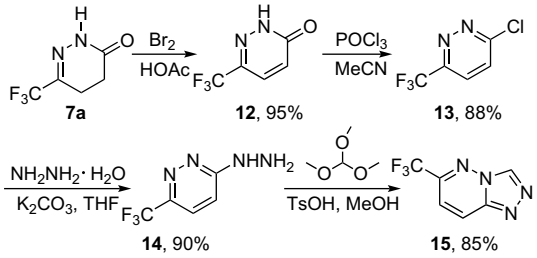


Figure 1. ORTEP diagram of **7j** and its packing diagram.



Scheme 3. The methods for the synthesis of fluoroalkylated 1,2-diazaones and indoles.

interested trifluoromethylated triazolopyridazine derivative **15** (Scheme 4). Triazolopyridazine derivatives play an important role in pharmaceuticals and have received much attention in related fields for long time.[12] Fluoroalkylated analogs are also expected to have the potential biological significance and unique chemical properties. The synthetic route toward 6-trifluoromethyl substituted triazolopyridazine **15** was fulfilled starting from 4,5-dihydro-6-trifluoromethyl pyridazinones **7a** according to the procedures in literatures. Compound **7a** was initially oxidized and formed 6-fluoroalkyl pyridazinones **12** in 95% yield in the presence of Br_2/AcOH.[13] The subsequential chlorination of hydroxyl group in **12** by $POCl_3$ in MeCN resulted the formation of **13** in 88% yield.[14] Substitution of Cl atom in **13** and followed by the cyclization of **14** resulted the formation of 6-trifluoromethyl substituted triazolopyridazine **15** (Scheme 4).[15] Bioactivity assay for 6-trifluoromethyl triazolopyridazine **15** is currently in progress.



Scheme 4. A transformation of 4,5-dihydro-6-trifluoromethyl pyridazinone **7a** to triazolopyridazine **15**.

3. Conclusions

A concise and general synthetic route toward the small and medium-sized fluoroalkyl substituted 1,2-diaza-3-one heterocyclic ring skeletons via a sequential reaction of condensation and ring-closure reaction of ω-fluoroalkylated ketoesters **4** with hydrazines **5** catalyzed by 10%–20 mol % TsOH has been successfully developed. A practical preparation of ω-fluoroalkylated ketoesters **4**, which are recognized as an important fluorinated building blocks has been optimized. Initial application of ω-fluoroalkylated ketoesters **4** was also succeeded in the synthesis of 2-trifluoromethyl-indole-3-carboxylate via a Fischer indole synthesis.

4. Experimental section

4.1. General

Reactions were conducted in an appropriate round bottom three-necked flask equipped with magnetic stirring bar and

condenser under nitrogen protection. Thin layer chromatography (TLC) was performed on a silica gel. All melting points were taken on WRS-1 digital melting point apparatus made by Shanghai physical instrument factory (SPOIF), China, and were uncorrected. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker AV-500 spectrometer. Chemical shifts for ^{1}H NMR spectra are reported in parts per million downfield from TMS, chemical shifts for ^{13}C NMR spectra are reported in parts per million relative to internal chloroform (δ 77.2 ppm for ^{13}C), and chemical shifts for ^{19}F NMR spectra are reported in parts per million downfield from internal fluorotrichloromethane ($CFCl_3$). Coupling constants (J) are given in hertz (Hz). The terms m, s, d, t, q refer to multiplet, singlet, doublet, triplet, quartet; br refers to a broad signal. Infrared spectra (IR) were recorded on AVATAR 370 FT-IR spectrometer, absorbance frequencies are given at maximum of intensity in cm^{-1}. Elemental analyses were performed with Elemental Vario EL III instrument. High resolution mass spectra were obtained on a CONCEPT 1H spectrometer, using EI at 70 eV. Single-crystal XRD was performed with graphite-monochromatic Mo K_α radiation (λ=0.71073 Å) on a Bruker Smart ApexII CCD diffractometer at T=273(2) K. The structures were solved by direct method with SHELXS-97 program and refined by full matrix least-squares on F2 with SHELXL-97 program. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were located and included at their calculated position.

The syntheses of some main products are shown below.

4.2. Procedure for the synthesis of ω-fluoroalkylated ketoesters (4)

To a 250 mL three-necked round bottom flask equipped with condenser and magnetic stir bar was added dry ether (80 mL), sodium wire (0.5 mol), and methyl (or ethyl) 2,2,2-trifluoroacetate (0.5 mol) at 0 °C under nitrogen atmosphere and stirred for 10 min. A solution of dimethyl succinate (1 mol) in ether (200 mL) was added dropwisely to the reaction mixture, keeping the temperature at 0–5 °C. The reaction continued until all the sodium wire had dissolved. After the solution was refluxed for 36 h, the ether and excess of dimethyl succinate were then distilled off in vacuo to leave a black tarry residue of sodio-derivative. The free ketoester was liberated by treatment with sulfuric acid (100 mL, 5 N) and was extracted with ether (3×100 mL). Distillation of the dried extracts (over anhydrous $MgSO_4$) gave crude dimethyl trifluoroacetosuccinate, bp 90–120 °C/5 mmHg. This crude material was used without purification in further hydrolysis experiments. Dimethyl trifluoroacetosuccinate (0.5 mol) and boric acid (0.55 mol) in flask were heated to 150 °C (oil bath, magnetic stirring, *Claisen* condenser connected with a gas collected device). As the temperature was raised to 180 °C, the rate of CO_2 evolution increased and the reaction mixture became a clear, light yellow appearance after 3 h. The contents of the flask were cooled to room temperature, poured onto ice water (350 mL), and extracted with ether (3×100 mL). After the combined organic layers were dried over anhydrous $MgSO_4$, the solvent was removed in vacuo and the residue was distilled through a 10 mm Vigreux apparatus. A main fraction was collected.

4.2.1. Methyl 5,5,5-trifluoro-4-oxopentanoate (**4a**)

Compound **4a** was obtained as a colorless liquid in 57% yield (65 °C/10 mmHg); ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 3.73 (s, 3H, $-OCH_3$), 3.06 (t, 2H, J=6.5 Hz, $-CH_2-$), 2.74 (t, 2H, J=6.5 Hz, $-CH_2-$); ^{13}C NMR ($CDCl_3$, 125 MHz, ppm) δ 190.3 (q, J=35.0 Hz), 172.0, 115.6 (q, J=290.0 Hz), 52.3, 31.6, 26.8; ^{19}F NMR ($CDCl_3$, 470 MHz, ppm) δ −68.26 (s, 3F); IR (KBr): ν 2960, 1741, 1442, 1207, 1147, 1072.

4.2.2. Ethyl 5,5,5-trifluoro-4-oxopentanoate (**4b**)

Compound **4b** was obtained as a colorless liquid in 65% yield (72 °C/10 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 4.16 (q, 2H, J=7.0 Hz, $-OCH_2-$), 3.04 (t, 2H, J=6.0 Hz, $-CH_2-$), 2.71 (t, 2H, J=6.0 Hz, $-CH_2-$), 1.27 (t, 3H, J=7.0 Hz, $-CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 190.1 (q, J=35.0 Hz), 171.2, 115.5 (q, J=290.0 Hz), 61.1, 31.4, 26.8, 13.9; ^{19}F NMR ($CDCl_3$, 470 MHz, ppm) δ −74.98 (s, 3F); IR (KBr) ν 2961, 1747, 1445, 1216, 1141, 1086, 914.

4.2.3. Ethyl 5,5-difluoro-4-oxopentanoate (**4c**)

Compound **4c** was obtained as a colorless liquid in 34% yield by reduced pressure distillation (71 °C/10 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 5.78 (t, 1H, J=53.5 Hz, $-CF_2H-$), 4.13 (q, 2H, J=7.0 Hz, $-OCH_2-$), 2.96 (t, 2H, J=6.5 Hz, $-CH_2-$), 2.66 (t, 2H, J=6.5 Hz, $-CH_2-$), 1.25 (t, 3H, J=7.0 Hz, $-CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5 (t, J=25.0 Hz), 172.0, 109.8 (t, J=250.0 Hz), 61.1, 31.2, 27.2, 14.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ −127.85 (d, 2F, J=51.7 Hz); IR (KBr) ν 2968, 1742, 1445, 1198, 1119, 998.

4.2.4. Ethyl 5,5,6,6,7,7,7-heptafluoro-4-oxoheptanoate (**4d**)

Compound **4d** was obtained as a colorless liquid in 17% yield by reduced pressure distillation (78 °C/10 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 4.16 (q, 2H, J=7.5 Hz, $-OCH_2-$), 2.69 (t, 2H, J=6.0 Hz, $-CH_2-$), 2.63 (t, 2H, J=6.0 Hz, $-CH_2-$), 1.27 (t, 3H, J=7.5 Hz, $-CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5 (t, J=26.3 Hz), 172.0, 121.5–114.1 (q, t, J=286.3 Hz, J_F=33.8 Hz), 111.3–109.6 (t, t, J=263.8, 32.5 Hz), 109.3–105.5 (t, t, q, J=267.5, 35, 33.8 Hz), 66.0, 35.3, 32.2, 13.4; ^{19}F NMR ($CDCl_3$, 470 MHz, ppm) δ −80.85 (t, 3F, J=9.4 Hz), −119.55 (q, 2F, J=9.4 Hz), −127.13 (s, 2F); IR (KBr) ν 2987, 1811, 1716, 1410, 1378, 1349, 1232,1021.

4.2.5. Methyl 6,6,6-trifluoro-5-oxohexanoate (**4e**)

Compound **4e** was obtained as a colorless liquid in 55% yield by reduced pressure distillation (80 °C/10 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 3.69 (s, 3H, $-OCH_3$), 2.84 (t, 2H, J=7.0 Hz, $-CH_2-$), 2.41 (t, 2H, J=7.0 Hz, $-CH_2-$), 2.04–1.98 (m, 2H, $-CH_2-$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.9 (q, J=35.0 Hz), 172.9, 115.4 (q, J=291.3 Hz), 51.6, 35.3, 32.2, 17.5; ^{19}F NMR ($CDCl_3$, 470 MHz, ppm) δ −79.31 (s, 3F); IR (KBr) ν 2958, 1764, 1736, 1441, 1209, 1172.

4.2.6. Methyl 7,7,7-trifluoro-6-oxoheptanoate (**4f**)

Compound **4f** was obtained as a colorless liquid in 50% yield by reduced pressure distillation (83 °C/10 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 3.68 (s, 3H, $-OCH_3$), 2.75 (t, 2H, J=6.5 Hz, $-CH_2-$), 2.36 (t, 2H, J=7.0 Hz, $-CH_2-$), 1.74–1.65 (m, 4H, $-CH_2-$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.1 (q, J=35.0 Hz), 173.4, 115.5 (q, J=291.3 Hz), 51.6, 36.0, 33.5, 24.4, 23.9; ^{19}F NMR ($CDCl_3$, 470 MHz, ppm) δ −79.35 (s, 3F); IR (KBr) ν 2942, 1768, 1741, 1445, 1210, 1186.

4.3. General procedure for the synthesis of 6, 7, 8, 9, and 10

To a 100 mL three-necked round bottom flask equipped with condenser and magnetic stir bar was added phenyl hydrazine, methyl 5,5,5-trifluoro-4-oxopentanoate, TsOH, and toluene (50 mL) under nitrogen atmosphere, stirred in reflux for 24 h. Once the reaction was completed, the precipitation was removed via filtration, the residue was then carefully washed with ethyl acetate for three times, the solvent was removed by rotary evaporator. The residue was then purified by column chromatography product.

4.3.1. 6-(Trifluoromethyl)-4,5-dihydropyridazin-3(2H)-one (**7a**)

Compound **7a** was obtained as a pale colorless solid in 83% yield by column chromatography (6:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 75–77 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.76 (s, 1H, –NH), 2.78 (t, 2H, J=8.5 Hz, $-CH_2-$), 2.64 (t, 2H, J=8.5 Hz, $-CH_2-$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 140.6 (q,

J=36.3 Hz), 120.3 (q, J=272.5 Hz), 25.3, 19.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ −71.29 (s, 3F); IR (KBr) ν 3285, 1703, 1652, 1212, 1133.

4.3.2. Methyl 5,5,5-trifluoro-4-(2-phenylhydrazono)-pentanoate (**6b**)

Compound **6b** was obtained as a brick red liquid in 70% yield by column chromatography (8:1 petroleum ether/ethyl acetate) on neutral aluminum oxide; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.29 (s, 1H, –NH), 7.29 (t, 2H, J=7.5 Hz, –ArH), 7.16 (d, 2H, J=7.5 Hz, –ArH), 6.94 (t, 1H, J=7.5 Hz, –ArH), 3.73 (s, 3H, –OCH_3), 2.74 (t, 2H, J=7.0 Hz, –CH_2–), 2.69 (t, 2H, J=7.0 Hz, –CH_2–); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 144.1, 131.0 (q, J=32.5 Hz), 129.4, 122.3 (q, J=271.3 Hz), 121.7, 113.8, 52.7, 30.9, 19.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ −68.26 (s, 3F); IR (KBr) ν 3316, 3023, 1723, 1602, 1526, 1497, 754, 696. MS (ESI): m/z 275.09 $[M+H]^+$; HRMS [M+1] calcd for $C_{12}H_{13}F_3N_2O_2$: 274.0929; found 274.0785.

4.3.3. 2-Phenyl-6-(trifluoromethyl)-4,5-dihydropyridazin-3(2H)-one (**7b**)

Compound **7b** was obtained as a chocolate brown solid in 92% yield by column chromatography (8:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 83–85 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.46–7.40 (m, 4H, –ArH), 7.31 (t, 1H, J=7.0 Hz, –ArH), 2.88 (t, 2H, J=7.0 Hz, –CH_2–), 2.81 (t, 2H, J=7.0 Hz, –CH_2–); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 141.0 (q, J=36.3 Hz), 140.1, 128.8, 127.4, 124.9, 120.4 (q, J=272.5 Hz), 26.9, 20.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ −70.95 (s, 3F); IR (KBr) ν 3067, 2923,1709, 1596, 1494, 1393, 765, 693. Anal. Calcd for $C_{11}H_9F_3N_2O$ (242.2): C, 54.55; H, 3.75; N, 11.57. Found: C, 54.28; H, 3.88; N, 11.29.

4.3.4. Methyl 4-(2-(4-chlorophenyl)hydrazono)-5,5,5-trifluoro-pentanoate (**6c**)

Compound **6c** was obtained as a red-brown solid in 67% yield by column chromatography (10:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 92–93 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.17 (s, 1H, –NH), 8.18 (d, 2H, J=9.0 Hz, –ArH), 7.22 (d, 2H, J=9.0 Hz, –ArH), 3.77 (s, 3H, –OCH_3), 2.79 (t, 2H, J=2.5 Hz, –CH_2–), 2.76 (t, 2H, J=2.5 Hz, –CH_2–); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 143.9, 130.9 (q, J=32.5 Hz), 129.3, 122.2 (q, J=272.5 Hz), 121.5, 113.6, 52.6, 30.8, 18.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −69.06 (s, 3F); IR (KBr) ν 3326, 3031, 1738, 1590, 1527, 1109, 847.

4.3.5. 2-(4-Chlorophenyl)-6-(trifluoromethyl)-4,5-dihydro-pyridazin-3(2H)-one (**7c**)

Compound **7c** was obtained as a pale yellow solid in 80% yield by column chromatography (6:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 88–92 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.42 (d, 2H, J=9.0 Hz, –ArH), 7.37 (d, 2H, J=9.0 Hz, –ArH), 2.87 (t, 2H, J=7.0 Hz, –CH_2–), 2.80 (t, 2H, J=7.0 Hz, –CH_2–); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.1, 141.3 (q, J=36.3 Hz), 138.5, 132.6, 128.7, 125.9, 120.2 (q, J=271.3 Hz), 26.7, 20.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ −71.00 (s, 3F); IR (KBr) ν 3097, 2963, 1907, 1709, 1655, 1590, 1489, 1457, 1205, 1126, 833. Anal. Calcd for $C_{11}H_8ClF_3N_2O$ (276.64): C, 47.76; H, 2.91; N, 10.13. Found: C, 47.74; H, 2.99; N, 10.34. (EI): m/z 276 $[M]^+$.

4.3.6. 2-(4-Fluorophenyl)-6-(trifluoromethyl)-4,5-dihydro-pyridazin-3(2H)-one (**7d**)

Compound **7d** was obtained as a pale colorless solid in 85% yield by column chromatography (8:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 105–107 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.44–7.41 (m, 2H, –ArH), 7.10 (t, 2H, J=8.5 Hz, –ArH), 2.87 (t, 2H, J=8.0 Hz, –CH_2–), 2.79 (t, 2H, J=8.0 Hz, –CH_2–); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 161.4 (d, J=245.0 Hz), 141.2 (q, J=36.3 Hz), 136.1 (d, J=2.5 Hz), 126.8 (d, J=8.8 Hz), 120.3 (q, J=271.3 Hz), 115.6 (d, J=22.5 Hz), 26.8, 20.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ −70.99 (s, 3F), −114.21 to 114.25 (m, 1F); IR (KBr) ν 3026, 2917, 1706, 1651, 1599, 1506, 1204, 1120, 842. Anal. Calcd for $C_{11}H_8F_4N_2O$ (260.19): C, 50.78; H, 3.10; N, 10.77. Found: C, 50.59; H, 3.15; N, 10.69.

4.3.7. Methyl 4-(2-benzoylhydrazono)-5,5,5-trifluoropentanoate (**6e**)

Compound **6e** was obtained as a colorless solid in 82% yield by column chromatography (6:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 102–105 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 11.28 (s, 1H, –NH), 8.01 (d, 2H, J=5.5 Hz, –ArH), 7.56 (t, 1H, J=7.5 Hz, –ArH), 7.47 (t, 2H, J=7.5 Hz, –ArH), 3.72 (s, 3H, –OCH_3), 2.83 (t, 2H, J=4.0 Hz, –CH_2–), 2.80 (t, 2H, J=4.0 Hz, –CH_2–); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 166.1, 132.6, 132.5, 128.5 (q, J=31.3 Hz), 127.8, 127.0, 121.2 (q, J=273.8 Hz,), 53.1, 30.6, 25.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ −69.21 (s, 3F); IR (KBr) ν 3325, 3087, 2962, 1734, 1666, 1123, 728, 697. Anal. Calcd for $C_{13}H_{13}F_3N_2O_3$ (302.25): C, 51.66; H, 4.34; N, 9.27. Found: C, 51.43; H, 4.33; N, 9.01. MS (ESI): m/z 303.0 $[M+H]^+$; HRMS [M+1] calcd for $C_{13}H_{13}F_3N_2O_3$: 302.0878; found 302.0887.

4.3.8. Methyl 5,5,5-trifluoro-4-(2-(4-nitrophenyl)hydrazono)-pentanoate (**6f**)

Compound **6f** was obtained as a red-brown solid in 85% yield by column chromatography (10:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 92–93 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.17 (s, 1H, –NH), 8.17 (d, 2H, J=7.5 Hz, –ArH), 7.21 (d, 2H, J=7.5 Hz, –ArH), 3.76 (s, 3H, –OCH_3), 2.80 (t, 2H, J=6.0 Hz, –CH_2–), 2.76 (t, 2H, J=6.0 Hz, –CH_2–); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 149.3, 141.6, 135.5 (q, J=33.8 Hz), 125.8, 121.6 (q, J=272.5 Hz), 113.0, 52.9, 30.8, 19.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −68.89 (s, 3F); IR (KBr) ν 3308, 3041, 1733, 1594, 1533, 1110, 851.

4.3.9. 2-(4-Nitrophenyl)-6-(trifluoromethyl)-4,5-dihydro-pyridazin-3(2H)-one (**7f**)

Compound **7f** was obtained as a red-brown solid in 80% yield by column chromatography (8:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 96–99 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.27 (d, 2H, J=7.0 Hz, –ArH), 7.78 (d, 2H, J=7.0 Hz, –ArH), 2.94 (t, 2H, J=7.5 Hz, –CH_2–), 2.88 (t, 2H, J=7.5 Hz, –CH_2–); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 145.6, 145.1, 142.8 (q, J=36.3 Hz), 125.9, 124.1, 120.1 (q, J=272.5 Hz), 27.2, 20.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ −71.10 (s, 3F); IR (KBr) ν 3051, 2924, 1713, 1594, 1519, 1132, 854. Anal. Calcd for $C_{11}H_8F_3N_3O_3$ (287.19): C, 46.00; H, 2.81; N, 14.63. Found: C, 45.94; H, 2.79; N, 14.43.

4.3.10. Methyl 4-(2-(2,4-dinitrophenyl)hydrazono)-5,5,5-trifluoro-pentanoate (**6g**)

Compound **6g** was obtained as a yellow solid in 81% yield by column chromatography (6:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 99–101 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 11.78 (s, 1H, –NH), 9.10 (s, 1H, –ArH), 8.40 (d, 1H, J=9.5 Hz, –ArH), 8.04 (d, 1H, J=9.5 Hz, –ArH), 3.75 (s, 3H, –OCH_3), 2.94 (t, 2H, J=7.0 Hz, –CH_2–), 2.86 (t, 2H, J=7.0 Hz, –CH_2–); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 144.4, 142.0 (q, J=32.5 Hz), 139.7, 131.3, 130.0, 122.8, 120.9 (q, J=273.8 Hz,), 117.2, 52.4, 29.5, 20.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ −68.75 (s, 3F); IR (KBr) ν 3314, 3108, 2957,1734, 1616, 1597, 1547, 1435, 1334, 837. Anal. Calcd for $C_{12}H_{11}F_3N_4O_6$ (364.23): C, 39.57; H, 3.04; N, 15.38. Found: C, 39.51; H, 3.03; N, 15.26.

4.3.11. Ethyl 4-(2-(2,4-dinitrophenyl)hydrazono)-5,5,5-trifluoro-pentanoate (**6h**)

Compound **6h** was obtained as a brilliant yellow solid in 85% yield by column chromatography (8:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp: 101–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 11.97 (s, 1H, –NH), 9.13 (s, 1H, –ArH), 8.41 (d, 1H, J=9.5 Hz, –ArH), 7.97 (d, 1H, J=9.5 Hz, –ArH), 4.19 (q, 2H, J=7.5 Hz, –OCH_2–), 2.97 (t, 2H, J=6.5 Hz, –CH_2–), 2.78 (t, 2H,

J=6.5 Hz, –CH_2–), 1.29 (t, 3H, J=7.5 Hz, –CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 144.4, 142.1 (q, J=33.8 Hz), 139.8, 131.4, 130.0, 122.9, 120.9 (q, J=273.8 Hz,), 117.2, 61.6, 29.8, 20.7, 14.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ −68.55 (s, 3F); IR (KBr) ν 3323, 3118, 2943, 1738, 1617,1593, 1567, 1425, 835.

4.3.12. 2-p-Tolyl-6-(trifluoromethyl)-4,5-dihydropyridazin-3(2H)-one (**7i**)

Compound **7i** was obtained as a pale red solid in 77% yield by column chromatography (6:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 89–90 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.31 (d, 2H, J=8.5 Hz, –ArH), 7.22 (d, 2H, J=8.5 Hz, –ArH), 2.86 (t, 2H, J=8.5 Hz, –CH_2–), 2.79 (t, 2H, J=8.5 Hz, –CH_2–), 2.36 (s, 3H, –CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 140.7 (q, J=36.3 Hz), 137.6, 137.5, 129.4, 124.9, 120.3 (q, J=272.5 Hz), 27.0, 21.1, 20.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −70.93 (s, 3F); IR (KBr) ν 3010, 2918, 1714, 1650, 1511, 1426, 1131, 818. Anal. Calcd for $C_{12}H_{11}F_3N_2O$ (256.22): C, 56.25; H, 4.33; N, 10.93. Found: C, 56.08; H, 4.47; N, 10.75.

4.3.13. 2-(4-Methoxyphenyl)-6-(trifluoromethyl)-4,5-dihydropyridazin-3(2H)-one (**7j**)

Compound **7j** was obtained as a colorless solid in 94% yield by column chromatography (4:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 92–94 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.33 (d, 2H, J=6.5 Hz, –ArH), 6.93 (d, 2H, J=6.5 Hz, –ArH), 3.82 (s, 3H, –OCH_3), 2.87 (t, 2H, J=8.0 Hz, –CH_2–), 2.80 (t, 2H, J=8.0 Hz, –CH_2–); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 158.7, 140.7 (q, J=36.3 Hz), 133.1, 126.5, 120.3 (q, J=271.3 Hz), 114.1, 55.5, 26.9, 20.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −70.92 (s, 3F); IR (KBr) ν 3007, 2963, 1705, 1606, 1508, 1198, 1120, 834. Anal. Calcd for $C_{12}H_{11}F_3N_2O_2$ (272.08): C, 52.94; H, 4.07; N, 10.29. Found: C, 52.67; H, 4.05; N, 10.10.

4.3.14. 6-(1,1,2,2,3,3-Hexafluoropropyl)-4,5-dihydropyridazin-3(2H)-one (**7l**)

Compound **7l** was obtained as a chocolate brown solid in 72% yield by column chromatography (8:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 105–107 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ: 8.99 (s, 1H, –NH), 2.78 (t, 2H, J=8.0 Hz, –CH_2–), 2.62 (t, 2H, J=8.0 Hz, –CH_2–); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 154.3 (t, J=25.0 Hz), 121.5–111.4 (q, t, J=286.3, 33.8 Hz), 113.5–110.4 (t, t, J=257.5, 32.5 Hz), 109.3–106.7 (t, t, q, J=267.5, 32.5 Hz, J=33.8 Hz), 26.9, 19.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ −80.12 (t, 3F, J=9.4 Hz), −109.96 (q, 2F, J=9.4 Hz), −125.24 (s, 2F); IR (KBr) ν 2995, 1813, 1381, 1359, 1228, 1022.

4.3.15. 6-(Difluoromethyl)-4,5-dihydropyridazin-3(2H)-one (**7m**)

Compound **7m** was obtained as a pale colorless solid in 82% yield by column chromatography (4:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 71–73 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.81 (s, 1H, –NH), 6.13 (t, 1H, J=53.5 Hz, –CF_2H–), 2.72 (t, 2H, J=8.0 Hz, –CH_2–), 2.60 (t, 2H, J=8.0 Hz, –CH_2–); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 146.3 (t, J=31.3 Hz), 113.5 (t, J=235.0 Hz), 25.4, 17.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −119.38 (d, 2F, J=51.7 Hz); IR (KBr) ν 2978, 1714, 1648, 1202, 1143.

4.3.16. 7-(Trifluoromethyl)-5,6-dihydro-2H-1,2-diazepin-3(4H)-one (**8**)

Compound **8** was obtained as a pale colorless solid in 85% yield by column chromatography (8:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 102–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.61 (s, 1H, –NH), 2.70 (t, 2H, J=7.2 Hz, –CH_2–), 2.62 (t, 2H, J=6.8 Hz, –CH_2–), 2.22–2.15 (m, 2H, –CH_2–); ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.7, 150.7 (q, J=33.8 Hz), 120.8 (q, J=273.7 Hz), 35.3, 27.6, 22.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ −71.55 (s, 3F); IR (KBr) ν 3258, 1712, 1645, 1237, 1131.

4.3.17. Methyl 7,7,7-trifluoro-6-hydrazonoheptanoate (**9**)

Compound **9** was obtained as a pale yellow solid in 92% yield by column chromatography (2:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 92–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.93 (s, 2H, –NH_2), 3.67 (s, 3H, –OCH_3), 2.39–2.31 (m, 4H, –CH_2–), 1.71 (t, 2H, J=7.0 Hz, –CH_2–), 1.60 (t, 2H, J=6.5 Hz, –CH_2–); ^{13}C NMR (400 MHz, $CDCl_3$) δ 173.8, 136.8 (q, J=32.5 Hz), 115.1 (q, J=271.3 Hz), 51.5, 33.2, 24.7, 23.4, 23.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ −69.60 (s, 3F); IR (KBr) ν 3258, 1712, 1645, 1237, 1131.

4.3.18. 8-(Trifluoromethyl)-4,5,6,7-tetrahydro-1,2-diazocin-3(2H)-one (**10**)

Compound **10** was obtained as a yellow solid in 45% yield by column chromatography (4:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 103–105 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.36 (s, 1H, –NH), 2.44 (t, 2H, J=7.5 Hz, –CH_2–), 2.34 (q, 4H, J=7.0 Hz, –CH_2–), 1.60–1.54 (m, 2H, –CH_2–); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 140.6 (q, J=36.3 Hz), 126.1 (q, J=281.3 Hz), 33.5, 29.3, 25.0, 24.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ −70.68 (s, 3F); IR (KBr) ν 3275, 1706, 1658, 1217, 1129.

4.4. General procedure for the synthesis of indoles (11)

To a 100 mL three-necked round bottom flask equipped with condenser and magnetic stir bar was added phenyl hydrazine (2.7 mmol), methyl 6,6,6-trifluoro-5-oxohexanoate (2.7 mmol), TsOH (0.27 mmol), and toluene (50 mL) under nitrogen atmosphere, the solution was heated to 90 °C and stirred for 24 h. Once the reaction was completed, the precipitation was removed via filtration, the residue was then carefully washed with ethyl acetate for three times, the solvent was removed by rotary evaporator. The residue was then purified by column chromatography product **11**.

4.4.1. Methyl 3-(2-(trifluoromethyl)-1H-indol-3-yl)-propanoate (**11a**)

Compound **11a** was obtained as a pale yellow solid in 72% yield by column chromatography (6:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 151–154 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.38 (s, 1H, –NH), 7.68 (d, 1H, J=8.0 Hz, –ArH), 7.41 (d, 1H, J=8.0 Hz, –ArH), 7.33 (t, 1H, J=7.5 Hz, –ArH), 7.20 (t, 1H, J=8.0 Hz, –ArH), 3.68 (s, 3H, –OCH_3), 3.26–3.22 (m, 2H, –CH_2–), 2.67 (t, 2H, J=8.0 Hz, –CH_2–); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 135.5, 127.0, 124.9, 122.2 (q, J=266.3 Hz), 121.9 (q, J=36.3 Hz), 120.7, 120.0, 116.4 (q, J=2.5 Hz), 112.0, 51.9, 35.4, 19.5; ^{19}F NMR ($CDCl_3$, 470 MHz, ppm) δ −58.44 (s, 3F); IR (KBr) ν 3363, 3031, 1718, 1592, 1570, 1115, 742. Anal. Calcd for $C_{13}H_{12}F_3NO_2$ (271.24): C, 57.57; H, 4.46; N, 5.16. Found: C, 57.34; H, 4.70; N, 5.07.

4.4.2. Methyl 4-(2-(trifluoromethyl)-1H-indol-3-yl)butanoate (**11b**)

Compound **11b** was obtained as a yellow solid in 68% yield by column chromatography (6:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 156–159 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.43 (s, 1H, –NH), 7.68–7.67 (m, 1H, –ArH), 7.39–7.37 (m, 1H, –ArH), 7.32–7.29 (m, 1H, –ArH), 7.20–7.16 (m, 1H, –ArH), 3.67 (s, 3H, –CH_3), 2.96–2.93 (m, 2H, –CH_2–), 2.93–2.40 (m, 2H, –CH_2–), 2.06–2.00 (m, 2H, –CH_2–); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 135.5, 127.4, 124.9, 122.2 (q, J=266.3 Hz), 121.8 (q, J=24.0 Hz), 120.6, 120.4, 117.7 (q, J=2.5 Hz), 111.9, 51.7, 33.6, 25.9, 23.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.15 (s, 3F); IR (KBr) ν 3341, 2953, 1720, 1585, 1544, 1123, 751.

4.4.3. 6-(Trifluoromethyl)pyridazin-3(2H)-one (**12**)

To a 100 mL three-necked round bottom flask equipped with condenser and magnetic stir bar was added 6-(trifluoromethyl)-4,5-dihydropyridazin-3(2*H*)-one (0.5 g, 3 mmol), and bromine

(0.53 g, 3.3 mmol) in glacial acetic acid (50 mL) under nitrogen atmosphere. Then the solution was heated to 80 °C and refluxed for 1 h. Once the reaction was completed, the ice water (100 mL) was added and extract with ethyl acetate (80 mL). Washed with saturated sodium bicarbonate (150 mL) until pH=7. The solvent was removed by rotary evaporator. The residue was white powder, yield in 95% yield by column chromatography (4:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 80–81 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.13 (s, 1H, –NH), 7.54 (d, 1H, J=10.0 Hz, –CH=), 7.14 (d, 1H, J=10.0 Hz, –CH=); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 137.4 (q, J=37.5 Hz), 113.4, 129.5, 120.5 (q, J=271.3 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −67.41 (s, 3F); IR (KBr) ν 3134, 3079, 2978, 1707, 1346, 848.

4.4.4. 3-Chloro-6-(trifluoromethyl)pyridazine (**13**)

To a 100 mL three-necked round bottom flask equipped with condenser and magnetic stir bar was added 6-(trifluoromethyl) pyridazin-3(2*H*)-one (0.5 g, 3 mmol), and phosphoryl trichloride (1.84 g, 12 mmol), cyanide as solvent. Then the solution was heated to 130 °C and refluxed for 8 h. TLC traced. Once the reaction was completed, excessive phosphoryl trichloride and cyanide were removed by rotary evaporator. The ice water (50 mL) was added into system and washed with saturated sodium bicarbonate (aq, 100 mL) until pH=7 and extract with ethyl acetate. The solvent was removed by rotary evaporator. The residue was red-brown powder, yield 88% by column chromatography (10:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 92–96 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.92 (d, 1H, J=9.0 Hz, –CH=), 7.85 (d, 1H, J=9.0 Hz, –CH=); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 151.0 (q, J=35.0 Hz), 129.6, 126.2 (d, J=1.3 Hz), 121.1 (q, J=272.5 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −66.86 (s, 3F); IR (KBr) ν 3063, 2962, 2011, 1571, 868.

4.4.5. 3-Hydrazinyl-6-(trifluoromethyl)pyridazine (**14**)

To a 100 mL three-necked round bottom flask equipped with condenser and magnetic stir bar was added 3-chloro-6-(trifluoromethyl)pyridazine (0.5 g, 2.7 mmol) with hydrazine hydrate(85%) (0.32 g, 5.5 mmol), potassium carbonate (20 mol %), THF as solvent. Then the solution was heated to 130 °C and refluxed for 8 h, TLC traced. Once the reaction was completed, THF removed by rotary evaporator. The product was chocolate brown solid, yield 90% by column chromatography (1:4 methanol/ethyl acetate) on neutral aluminum oxide: mp 102–104 °C; ^{1}H NMR (500 MHz, DMSO, ppm) δ 8.82 (s, 1H, –NH), 7.71 (d, 1H, J=8.5 Hz, –CH=), 7.16 (d, 1H, J=8.5 Hz, –CH=), 4.53 (s, 2H, –NH_2); ^{13}C NMR (125 MHz, DMSO) δ 164.2, 141.8 (q, J=32.5 Hz), 125.2, 123.0 (q, J=271.3 Hz), 111.8; ^{19}F NMR (470 MHz, DMSO) δ −66.19 (s, 3F); IR (KBr) ν 3455, 1607, 1354, 1184, 1135, 852, 588. MS (ESI): m/z 179.0 $[M+H]^+$; HRMS [M+1] calcd for: $C_5H_5F_3N_4$: 178.0466; found 178.0455.

4.4.6. 6-(Trifluoromethyl)-7H-pyrazolo[4,3]pyridazine (**15**)

To a 100 mL three-necked round bottom flask equipped with condenser and magnetic stir bar was added 3-hydrazinyl-6-(trifluoromethyl)pyridazine (0.5 g, 2.8 mmol) with trimethoxymethane (0.89 g, 8.4 mmol), 5 mol % TsOH, methanol as solvent. Then the solution was heated to 80 °C and refluxed for 36 h, TLC traced. Once the reaction was completed, the system was washed by ethyl acetate (80 mL) then filtered. The filtrate was collected then removed solvent by rotary evaporator. The product was yellow solid, yield 85% by column chromatography (6:1 petroleum ether/ethyl acetate) on neutral aluminum oxide: mp 112–113 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.31 (s, 1H, –CH=N–), 8.44 (d, 1H, J=9.5 Hz, –*CH*=), 7.49 (d, 1H, J=9.5 Hz, –CH=); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7 (q, J=37.5 Hz), 142.9, 139.2, 127.2, 120.0 (q, J=273.8 Hz), 116.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −67.25 (s, 3F); IR (KBr) ν 3095, 3065, 3043, 2986, 1543, 1387, 1199, 1153, 840. Anal. Calcd for $C_6H_3F_3N_4$ (188.11): C, 38.31; H, 1.61; N, 29.78. Found: C, 38.28; H, 1.628; N, 29.49. MS (ESI): m/z 189.2 $[M+H]^+$; HRMS [M+1] calcd for $C_6H_3F_3N_4$: 188.0310; found 188.0303.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.03.029.

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