A facile and convenient way to functionalized trifluoromethylated spirocyclic[indole-3,4-pyrano[2,3-*c*]pyrazole] derivatives

Xiaoqing Liu, Xiaoling Xu, Xu Wang, Wenxin Yang, Qun Qian, Min Zhang, Liping Song, Hongmei Deng, Min Shao

PII: S0040-4039(13)01005-8
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.06.038
Reference: TETL 43091

To appear in: *Tetrahedron Letters*

Received Date: 8 April 2013
Revised Date: 6 June 2013
Accepted Date: 11 June 2013

Please cite this article as: Liu, X., Xu, X., Wang, X., Yang, W., Qian, Q., Zhang, M., Song, L., Deng, H., Shao, M., A facile and convenient way to functionalized trifluoromethylated spirocyclic[indole-3,4-pyrano[2,3-*c*]pyrazole] derivatives, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.06.038

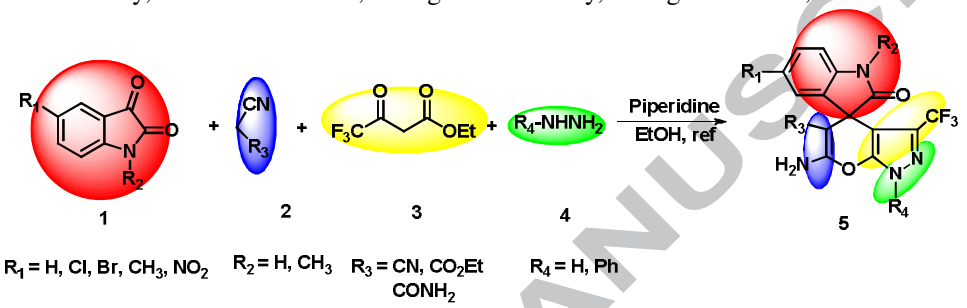
Graphical Abstract

A Facile and convenient way to functionalized trifluoromethylated spirocyclic[indole-3,4-pyrano[2,3-*c*]pyrazole derivatives

Leave this area blank for abstract info.

Xiaoqing Liu[a], Xiaoling Xu[a], Xu Wang[a], Wenxin Yang[a], Qun Qian[a], Min Zhang[a], Liping Song[a,b,*], Hongmei Deng[c], Min Shao[c]

Department of Chemistry, School of Science, Shanghai University, Shanghai 200444, China



Tetrahedron Letters
journal homepage: www.elsevier.com

A facile and convenient way to functionalized trifluoromethylated spirocyclic[indole-3,4-pyrano[2,3-*c*]pyrazole] derivatives

Xiaoqing Liu[a], Xiaoling Xu[a], Xu Wang[a], Wenxin Yang[a], Qun Qian[a], Min Zhang[a], Liping Song[a,b]*, Hongmei Deng[c], Min Shao[c]

[a] *Department of Chemistry, School of Science, Shanghai University, No. 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] *Laboratory for Microstructures, Shanghai University*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
combinatorial synthesis
spirooxindole, multi-component reaction
X-ray crystallographic analysis
synthesis

ABSTRACT

An efficient and consecutive one-pot, two-step, four-component reaction for synthesis of trifluoromethylated spirocyclic[indole-3,4-pyrano[2,3-*c*]pyrazole] derivatives by reaction of isatin, malononitrile, ethyl cyanoacetate or cyanoacetamide, ethyl 4,4,4-trifluoroacetoacetate and hydrazine in the presence of a catalytic amount of piperidine in good yields was described. The structures of new compounds were determined by spectroscopic methods, microanalysis and X-ray diffraction analysis. In addition, a possible mechanism of the reaction was proposed herein.

* Corresponding author. Tel.: +86-21-6613-4846; fax: +86-21-6613-4594; e-mail: lpsong@shu.edu.cn

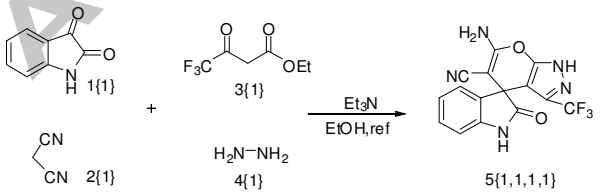
Indole and indoline fragments are a class of important structural motif central to a large number of natural biologically active compounds.[1] Compounds bearing the 2-oxindole nucleus moiety exhibit different pharmacological activities[2] and C-3 spiroindoline derivatives dramatically enhance biological activity.[3] Therefore, searching for efficient methods for the preparation of those compounds has aroused great interest in organic synthesis, and developments in the synthesis of diversely structured spirocyclic derivatives have made a tremendous progress, such as Heck reactions,[4] cyclopropane expansions,[5] Diels-Alder reactions[6] and [3+2] cycloadditions.[7]

Multicomponent reactions (MCRs) have attracted much attention for the construction of bioactive heterocyclic compounds by virtue of their convergence, productivity, facile execution, and generally high yields of products.[8] In recent years, literatures showed a series of simple and convenient methods for synthesis of spirocyclic compound via multicomponent condensation reactions in good to excellent yields catalyzed by $InCl_3$,[9] K_2CO_3,[10] quaternary cationics,[11] β-CD,[12] sodium stearate,[13] L-proline[14] etc. Other effective synthetic methods were microwave irradiation[15] and the use of electrogenerated base.[16] It is widely recognized that the introduction of fluorine to organic molecules can often significantly improve their physical, chemical and boilogical properties.[17] However, to the best of our knowledge, tremendous progress has been achieved in the synthesis of spirocyclic compounds, while the preparation of trifluoromethylated spirooxindole derivatives has been considerably less studied.

As part of our ongoing research programs directed at the development of efficient methodologies for the preparation of the fluorine-containing heterocyclic compounds and our continued work on the synthesis of fluorine-containing heterocyclic compounds via MCRs based on the trifluoromethyl-1,3-dicarbonyl compounds, a versatile fluorine-containing building-block,[18] herein, we investigated a facile and convenient way to functionalized trifluoromethylated spirocyclic[indole-3,4-pyrano[2,3-*c*]pyrazole] derivatives.

Initially, we carried out the one-pot, two-step, four-component reaction of isatin **1{1}**, malononitrile **2{1}**, ethyl 4,4,4-trifluoroacetoacetate **3{1}** and hydrazine **4{1}** as a model reaction. A stirring solution of **3{1}** (1.5 mmol) and **4{1}** (1.5 mmol) in ethanol (10 mL) was refluxed at 78 ^oC for 30 mins. Then **1{1}** (1.5 mmol), **2{1}** (1.5 mmol) and a catalytic amount of Et_3N (25 mol%, 0.375 mmol) were added. The resulting mixture was continued to stir at 78 ^oC for 6h. TLC analysis showed that the reaction was completed. General workup afforded the major pure product **5{1,1,1,1}** in 70% yield as a white solid (Scheme 1).

Scheme 1. Model Reaction



Based on the above results, a series of commercially available bases and solvents were investigated in order to find the optimal condition for the envisaged one-pot, two-step, four-component reaction for synthesis of trifluoromethylated spirooxindole derivatives (Table 1). It was found that pyridine catalyzed this reaction with moderate yield (Table 1, entry 2) and other common bases, such as Et_3N, DABCO, DMAP, Morpholine and DBU, gave a little bit higher yields (Table 1, entries 1, 3-6). Among those bases examined, piperidine was identified as the optimal catalyst, which afforded the product **5{1,1,1,1}** in 93% yield (Table 1, entry 7). Next, we screened the effect of catalyst loading, the solvent factors and the reaction time. We observed that the reaction in protic solvents could generally give a higher yield than that in aprotic solvents (Table 1, entries 7-11). Also higher amounts of catalyst and prolonged reaction time did not further improve the yield obviously (Table 1, entries 12-14). Consequently, the best result was obtained by using 25 mol % of piperidine as the catalyst and ethanol as the solvent (Table 1, entry 7).

Table 1. Optimization of the reaction conditions[a]

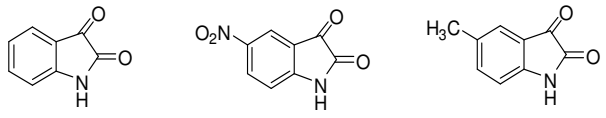
Entry	Base/equiv.	Solvent	Time/h	Yield of **5{1,1,1,1}** [b] (%)
1	Et_3N/0.25	EtOH	6	70
2	Pyridine/0.25	EtOH	6	50
3	DABCO/0.25	EtOH	6	71
4	Morpholine /0.25	EtOH	6	70
5	DBU/0.25	EtOH	6	87
6	DMAP/0.25	EtOH	6	65
7	Piperidine/0.25	EtOH	6	93
8	Piperidine/0.25	MeOH	6	83
9	Piperidine/0.25	DME	6	50
10	Piperidine/0.25	CH_2Cl_2	24	35
11	Piperidine/0.25	CH_3CN	24	40
12	Piperidine/0.5	EtOH	6	91
13	Piperidine/1	EtOH	6	91
14	Piperidine/0.25	EtOH	12	90

[a] Reaction conditions: **1{1}** (1.5 mmol), **2{1}** (1.5 mmol), **3{1}** (1.5 mmol), **4{1}** (1.5 mmol), solvent: 10.0 mL EtOH, refluxing.
[b] Isolated yield.

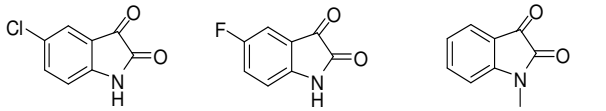
Figure 1. Diversity of Reagents

groups on isatins. The protocol was also effective with isatins bearing N-methyl group (Table 2, entries 11-12) or N-phenyl group (Table 2, entries 13-14).

isatins 1

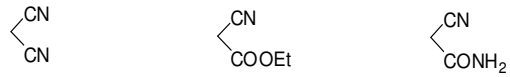


{1} {2} {3}



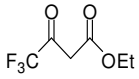
{4} {5} {6}

malononitrile or ethyl cyanoacetate or cyanoacetamide 2



{1} {2} {3}

Ethyl 4,4,4-trifluoroacetoacetate 3



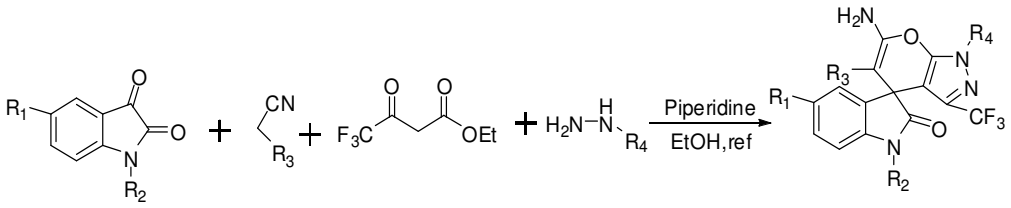
{1}

hydrazines 4

{1} {2}

To investigate the scope and limitation of this process, six isatins **1{1-6}**, three acetonitrile derivatives **2{1-3}**, ethyl 4,4,4-trifluoroacetoacetate **3{1}** and two hydrazines **4{1-2}** were chosen for the library validation (Figure 1). The corresponding trifluoromethylated spirocyclic [indole-3,4-pyrano[2,3-*c*]pyrazole] derivatives **5{(1-6),(1-2),1,(1-2)}** were obtained in excellent yields. The reaction facilitated various isatins bearing either electron-withdrawing substituents, such as fluoro, chloro and nitro (Table 2, entries 3-4,7-10), or electron-donating substituents such as alkyl (Table 2, entries 5-6). Gratifyingly, it was found that nearly all of the corresponding products were obtained in excellent yields, regardless the effect of substituted

Table 2. Synthesis of trifluoromethylated spirocyclic[indole-3,4-pyrano[2,3,-*c*] pyrazole] derivatives by using malononitrile or ethyl cyanoacetate [a, 20,21]



1{1-6} 2{1-2} 3{1} 4{1-2} 5{(1-6),(1-2),1,(1-2)}

Entry	Product **5**	Time/h	M.p.[b]	Yield/ %[c]
1	5{1,1,1,1}	6	>222 °C	93
2	5{1,2,1,1}	8	>210 °C	90
3	5{2,1,1,1}	7	>236 °C	90
4	5{2,2,1,1}	9	>190 °C	87
5	5{3,1,1,1}	4	>246 °C	96
6	5{3,2,1,1}	7	>214 °C	91
7	5{4,1,1,1}	6	>255 °C	93
8	5{4,2,1,1}	9	>220 °C	90
9	5{5,1,1,1}	6	>244 °C	94
10	5{5,2,1,1}	9	>212 °C	90
11	5{6,1,1,1}	7	>240 °C	95
12	5{6,2,1,1}	10	>210 °C	93
13	5{1,1,1,2}	7	>227 °C	94
14	5{1,2,1,2}	10	>202 °C	91

[a] Reaction conditions: **1{(1-6)}** (1.5 mmol), **2{(1-2)}** (1.5 mmol), **3{1}** (1.5 mmol), **4{(1-2)}** (1.5 mmol), solvent: 10.0 mL EtOH, refluxing.
[b] Decomposed.
[c] Isolated yield.

It should be noted that the reaction with ethyl cyanoacetate afforded a lower yield than that with malonanitrile, which was probably due to the lower reactivity of ethyl cyanoacetate, resulting in the requirement of prolonged reaction time. To our surprise, in the case of cyanoacetamide instead of malononitrile or ethyl cyanoacetate, we could not obtain the corresponding products bearing carbamoyl group **5{(1-6),3,1,1}**. As a result, products bearing ethoxycarbonyl group **5{(1-6),2,1,1}** were obtained in moderate yields (Table 3, Scheme 2) and a yellow precipitate was formed, which showed no fluorine signal in ^{19}F NMR. Apparently, the envisaged products were ethanolyzed under the present reaction conditions.

Scheme 2. Unexpected reaction results by using cyanoacetamide as the starting materials

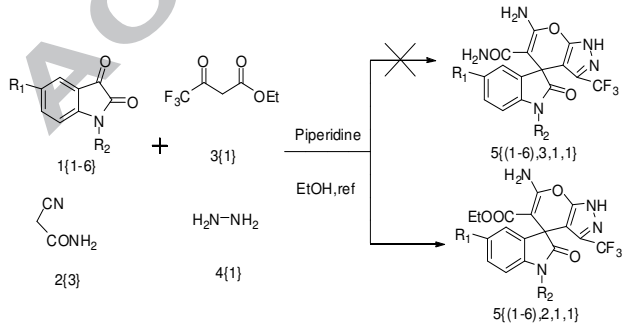


Table 3. Reaction results by using cyanoacetamide as the starting materials[a]

Entry	Product	Time/h	Yield (%)
1	5{1,2,1,1}	5	50
2	5{2,2,1,1}	6	48
3	5{3,2,1,1}	5	53
4	5{4,2,1,1}	6	51
5	5{5,2,1,1}	6	52
6	5{6,2,1,1}	12	50

[a] Reaction conditions: **1{1-6}** (1.5 mmol), **2{3}** (1.5 mmol), **3{1}** (1.5 mmol), **4{1}** (1.5 mmol), solvent: 10.0 mL EtOH, refluxing

The structure of all products **5{(1-6),(1-2),1,(1-2)}** was fully characterized by IR, ^{1}H, ^{19}F, ^{13}C NMR spectroscopies, MS and elemental analysis or HRMS. It should be noted that, in some cases, the CF_3 signals in ^{19}F NMR displayed a major peak and a minor peak respectively, indicating the tautomeric structures of trifluoromethylated pyrazole ring in solvent. Thus, with all the information at hand, we were hard to deduce which of the tautomeric structures (A or B) the resulting compounds correspond (Scheme 3). To unambiguously establish the regioselectivity of the products obtained by one-pot, two-step, four-component reaction, the structure of **5{5,2,1,1}** was further confirmed by X-ray diffraction analysis (Figure 2).[19] The fine crystal suitable for XRD analysis was obtained from acetone. As shown in Figure 2, the tautomeric structure of **5{5,2,1,1}** was 2H isomers in solid state.

Scheme 3. Two isomers formation of products

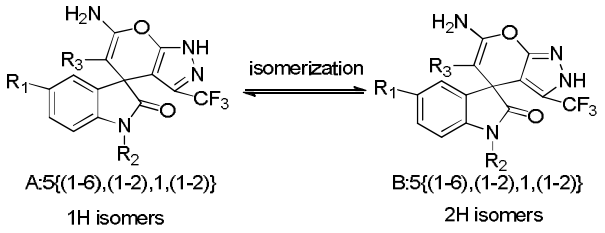
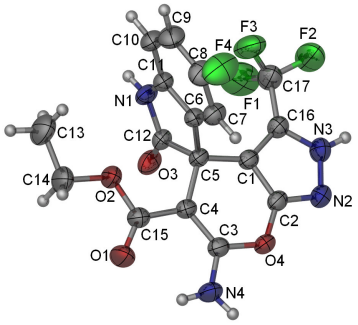


Figure 2. X-Ray crystal structure of **5**{5,2,1,1}



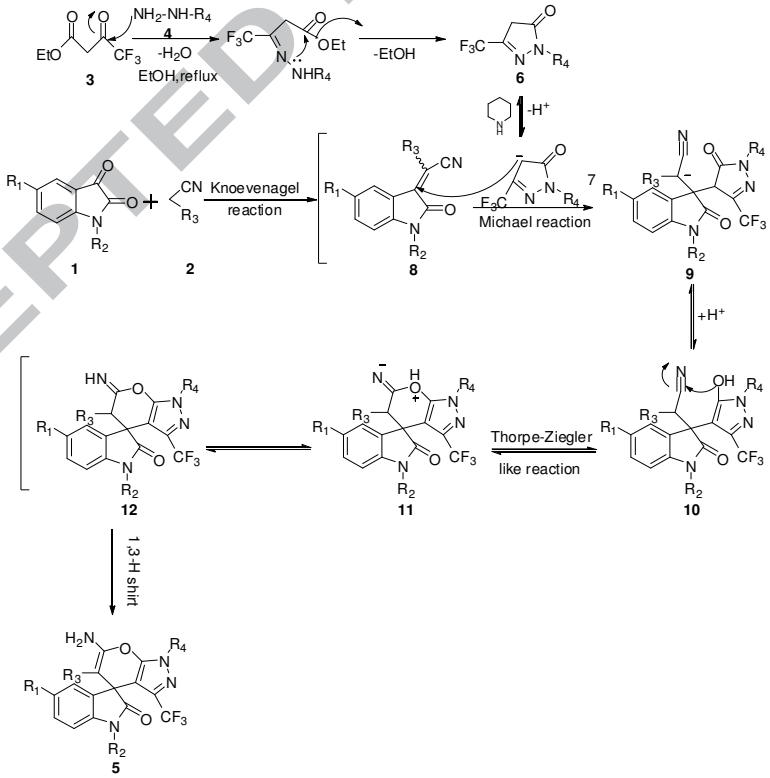
Based on the above results, a plausible mechanism for theformation of **5** was illustrated in Scheme 4. In the first step, a condensation of hydrazine **4** with ethyl 4,4,4-trifluoroacetoacetate **3** was proposed to give the intermediate **6**. In the second step, Isatins **1** condensed with malononitrile derivatives to give unsaturated nitriles **8** via Knoevenagel condensation reaction in the presence of a catalytic amount of piperidine. Under the present reaction conditions, the resulting intermediate **6** reacted with intermediate **8** by Michael addition reaction to afford the intermediate **9**, which then underwent the intra-molecular cyclization via Thorpe-Ziegler like reaction to afford the final product **5**.

In conclusion, we have showed that the one-pot, two-step, four-component reaction provides a facile and convenient way to functionalized trifluoromethylated spirocyclic[indole-3,4-pyran o[2,3-*c*]pyrazole] derivatives from readily available starting materials in the presence of a catalytic amount of piperidine. Excellent chemical yields have been achieved and the reaction may be considered as a useful synthetic method of fluorine-containing heterocyclic compounds with potential biological activity.

Acknowledgments

The authors thank the National Natural Science Foundation of China (NNSFC) (Nos. 21072128, 21272153), the Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry for financial support.

Scheme 4. Plausible Mechanism for the Formation of **5**



References and notes

1. Sundberg, R. J. The Chemistry of Indoles; Academic: New York, **1996**.
2. Rahman, A.; Qureshi, M. M.; Muzaffar, A.; De Silva, K. T. D. *Heterocycles*. **1988**, *27*, 725-732.
3. (a) Da, S.; J. F. M.; Garden, S. J.; Pinto, A. C. The chemistry of isatins: a review from 1975 to 1999. *J. Braz. Chem. Soc.* **2001**, *12*, 273 –324; (b) Abdel, A. H.; Keshk, E. M.; Hanna, M. A.; El-Bady, S. M. *Bioorg. Med. Chem.* **2004** , *12*, 2483 –2488.
4. (a) Overman, L. E.; Rosen, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4596–4599; (b) Dounay, A. B.; Overman, L. E. *Chem. Rev*. **2003**, *103*, 2945–2963; (c) Kamisaki, H.; Yasui, Y.; Takemoto, Y. *Tetrahedron Lett.* **2009**, *39*, 4596–4599; (d) Overman, L. E.; Rosen, M. D. *Tetrahedron*. **2010**, *66*, 6514–6525; (e) Kamisaki, H.; Nanjo, T.;Tsukano, C.;Takemoto, Y. *Chem.Eur. J.* **2011**, *17*, 626–633.
5. (a) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed*. **1999**, *38*, 3186–3189; (b) Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, *124*, 14826–14847; (c) Meyers, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 694–696; (d) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505–11515.
6. (a) Hojo, D.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 5820–5822; (b) Jia, Z. J.; Jiang, H.; Li, J.; Gschwend, B.; Li, Q.; Yin, X.; Grouleff, J.; Chen, Y. C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 5053–5061.
7. (a) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135–3137; (b) Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396–12397; (c) Voituriez, A.; Pinto, N.; Neel, M.; Retailleau, P.; Marinetti, A. *Chem.; Eur. J.* **2010**, *16*, 12541–12544; (d) Selvakumar, K.; Vaithiyanathana, V.; Shanmugam, P. *Chem. Commun.* **2010**, *46*, 2826–2828; (e) Antonchick, A. P.; Reimers, C. G.; Catarinella, M.; Schuramnn, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. *Nat. Chem.* **2010**, *2*, 735–740; (f) Liu, T. L.; Xue, Z. Y; Tao, H. Y.; Wang, C. J. *Org. Biomol. Chem.* **2011**, *9*, 1980–1986.
8. (a) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210; (b) Suresh Babu, A. R.; Raghunathan, R. *Tetrahedron Lett.* **2006**, *47*, 9221–9225.
9. Gnanamani, S.; Ganesan, S.; Paramasivan, T. P. *Tetrahedron.* **2007**, *63*, 2057–2063.
10. Liu, Y.; Zhong, D.; Ren, Z. J.; Cao, W. G.; Chen, J.; Dong, H. M.; Qing, G. *J. Fluorine Chem.*, **2009**, *3*, 154-156.
11. (a) Zhu, S. L.; Ji, S. J.; Zhang, Y. *Tetrahedron.* **2007**. *63*. 9365–9372; (b) Gao, S. J.; Cai, T. T.; Chi T.; Yao, C. F. *Tetrahedron.* **2008**, *64*, 9143–9149; (c) Akbar, M; Naser, F.; Mohammad, A. B. F. *Synth. Commun.* **2011**, *41*, 441–450.
12. Regati, S.; Boga, S.; Bandaru, M.; Vutukuri, P. R.; Yadavalli, V. D.; Kakulapati, R. *R. C. J. Chem.* **2009**, *81*, 1704–1707 .
13. Wang, L. M.; Jiao, N.; Qiu, J.; Yu, J. J; Liu, J. Q.; Guo, F. L.; Liu, Y. *Tetrahedron* . **2010**, *66*, 339–343
14. Li, Y. L.; Chen, H.; Shi, C. L.; Shi, D. Q.; Ji, S. J. *J. Comb. Chem.* **2010**, *12*, 231–237
15. (a) Anshu, D.; Anuj, K. J. ; Dharmendra, S. B. *Synth. Commun.* **2011**, *41*, 2905–2919; (b) Minoo, D; Zeinab, N. T.; Mahboobeh, B.; Ayoob, B. *Ultrason. Sonochem.* **2011**, *18*, 1153–1159; (c) Zou, Y.; Hu, Y.; Liu, H.; Shi, D. Q. *ACS. Comb. Sci.* **2012**, *14*, 38– 43.
16. Fotouhi, L.; Heravi, M. M.; Fatehi, A.; Bakhtiari, K. *Tetrahedron Lett.* **2007**, *48*, 5379–5381.
17. (a) Bank. R. E. Organofluorine Chemistry: Principles and Commercial Application, Plenum and Elsevier, New York, **1994**; (b) Filler. R. E., Organic Chemistry in Medicinal Chemistry and Biochemical Applications, Plenum and Elsevier, Amsterdam, **1993**; (c) Iwai, N.; Sakai, R.; Tsuchida, S.; Kitazume , M.; Kitazume, T. *J. Fluorine Chem.* **2009**, *130*, 434–437.
18. (a) Liu, J. N.; Li, J.; Zhang, L.; Song, L. P.; Zhang, M.; Cao, W. G.; Zhu, S. Z.; Dong, H. M.; Shao, M. *Tetrahedron Letters.* **2012**, *53*, 2469–2472; (b) Wang, W.; Li, J.; Zhang, L.; Song, L. P.; Zhang, M.; Cao, W. G; Zhu, S. Z. *Synthesis.* **2012**, *44(11)*, 1686-1692; (c) Yi, H.; Song, L. P.; Wang, W.; Liu, J. N.; Zhu, S. Z.; Deng, H. M.; Shao, M. *Chem. Commun.* **2010**, *46*, 6941–6943; (d) Wang, P. Y.; Song, L. P.; Yi, H.; Zhang, M.; Deng, H. M.; Shao, M. *Tetrahedron Lett*. **2010**, *51*, 3975–3977; (e) Song, L. P.; Li, X. F.; Xing, C. H.; Li, D. M.; Zhu, S. Z.; Deng, H. M.; Shao, M. *Synlett.* **2010**, *5*, 830–834; (f) Dai, B. F.; Song, L. P.; Wang, P. Y.; Yi, H.; Jin, G. F.; Zhu, S. Z.; Shao, M. *Synlett* **2009**, *11*, 1842–1846; (g) Song, S. D.; Song, L. P.; Dai, B. F.; Yi, H.; Jin, G. F.; Zhu, S. Z.; Shao, M. *Tetrahedron*. **2008**, *64*, 5728–5735; (h) Li, D. M.; Song, L. P.; Li, X. F.; Xing, C. H.; Peng, W. M.; Zhu, S. Z. *Eur. J. Org. Chem.* **2007**, *21*, 3520–3525; (i) Li, D. M.; Song, L. P.; Song, S. D.; Zhu, S. Z. *J. Fluorine Chem*. **2007**, *128* , 952–957; (j) Li, X. F.; Song, L. P.; Xing, C. H.; Zhao, J. W.; Zhu, S. Z. *Tetrahedron*. **2006**, *62*, 2255–2263.
19. CCDC 922624 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Centre via www.ccdc.ac.uk/data_request/cif.
20. Typical experimental procedure for synthesis of **5{1,1,1,1}**: To a mixture of ethyl 4,4,4-trifluoroacetoacetate **3** (276.0mg, 1.5mmol) and 85% hydrazine hydrate **4** (88.4 mg,1.5 mmol,) was refluxed in 10ml EtOH for 30min. Then isatin **1** (220.5 mg, 1.5 mmol), malononitrile **2** (99 mg, 1.5 mmol) and piperdine (21.3 mg, 25 mol %, 0.25 mmol) were added. The mixture was continuously stirred at 78 ℃ for 6h. After the completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure and the residue was chromatographed on a silica column using petroleum ether-ethyl acetate (1/1, v/v) as eluent to afford the final product **5{1,1,1,1}**, 484.1mg, 93% yield.
21. Spectroscopic data for products **5{1,1,1,1}**: compound **5{1,1,1,1}**, white solid, yield: 93%. M. p.: >222 ^{o}C (decomposed). IR (KBr) v: 3470, 3313, 3177, 3095, 2205, 1717, 1646, 1620, 1498, 1402, 1334, 1146, 1014, 928, 754, 699 cm^{-1}. ^{1}H NMR (500 MHz, acetone-d_6): δ 2.09 (s, 6H, CH_3, solvent), 6.67 (s, 2H, NH_2), 6.99 (d, J = 7.0 Hz , 1H, Ar-H), 7.03 (dt, J_1 = 7.5 Hz, J_2 = 0.5 Hz, 1 H, Ar-H), 7.20 (d, J = 7.0 Hz, 1H, Ar-H), 7.28 (dt, J_1 = 7.5 Hz, J_2 = 1.0 Hz□1H, Ar-H), 9.64 (s, 1H, NH), 13.12 (br, s, 1H, NH). ^{13}C NMR (100 MHz, acetone-d_6): δ 30.95 (acetone-C), 48.55, 59.72, 99.41, 111.02, 111.07, 117.98, 120.70 (q, $^{1}J_{C-F}$ = 267.0 Hz), 123.88, 126.00, 130.84, 142.77, 142.89, 162.42, 178.30, 207.06 (acetone-C). ^{19}F NMR (470 MHz, acetone-d_6): δ -61.81 (s, 3F). ESI-MS: 348 $[M+H]^+$. Anal. Calcd for $C_{18}H_{14}F_3N_5O_3$: C, 53.34; H, 3.48; N,17.28. Found: C, 52.95; H, 3.62; N, 17.20. (Recrystallized from acetone. The product contains a molecular of acetone).