Tetrahedron 69 (2013) 2352–2356

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Novel synthesis of 1,4,5-trisubstituted 1,2,3-triazoles via a one-pot three-component reaction of boronic acids, azide, and active methylene ketones

Jian Zhang, Guanyi Jin, Senhan Xiao, Jingjing Wu, Song Cao *

Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China

ARTICLE INFO

Article history:
Received 20 October 2012
Received in revised form 13 December 2012
Accepted 21 December 2012
Available online 11 January 2013

Keywords:
Boronic acids
Azides
Multicomponent reactions
Cyclization
1,4,5-Trisubstituted 1,2,3-triazoles

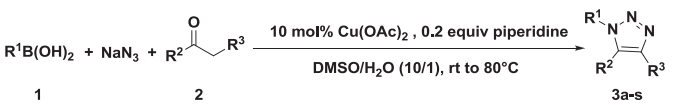
ABSTRACT

A series of 1-aryl-5-trifluoromethyl (or difluoromethyl)−1,4,5-trisubstituted 1,2,3-triazoles were synthesized in high yield by a novel one-pot three-component reaction of arylboronic acids, sodium azide, and active methylene ketones, such as ethyl 4,4-difluoroacetoacetate or ethyl 4,4,4-trifluoroacetoacetate in the presence of $Cu(OAc)_2$ and piperidine using a DMSO/H_2O (10/1) mixture as solvent.

1. Introduction

1,4-Disubstituted 1,2,3-triazole derivatives have been found widespread applications in a variety of areas including agrochemicals, polymers, dyes, and pharmaceuticals.[1] The most common method for the construction of 1,4-disubstituted 1,2,3-triazole framework is the Cu(I)-catalyzed 1,3-dipolar cycloaddition of terminal alkynes with azides.[2] Recently, the synthesis and applications of 1,4,5-trisubstituted 1,2,3-triazoles have received much attention.[3] However, only a limited number of methods are available for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles compared to their 1,4-disubstituted 1,2,3-triazoles analogues.[4] Furthermore, some methods at present used for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles always involve the preparation and isolation of toxic and unstable organic azide or the use of expensive metal catalysts.[5] Therefore, there remains a need for more efficient and simpler methods for the synthesis of structurally diverse 1,4,5-trisubstituted 1,2,3-triazoles.

-In recent years, the introduction of trifluoromethyl and difluoromethyl group (−CF_3 and −CF_2H) into biologically active compounds has attracted much interest due to its special physical and chemical properties, such as high electronegativity, increased lipophilicity, and improved bioavailability.[6] Up till now, the method of the introduction of CF_3 or CF_2H to 1,2,3-triazole ring is very scarce.[7] In addition, the utility of organoboronic acids in synthetically valuable organic transformations has flourished,[8] particularly through the development of Suzuki−Miyaura cross-coupling reactions and allylboration.[9] Nowadays, more and more structurally diverse boronic acids can be easily prepared from the corresponding aryl halides or purchased commercially.[10] Recently, we reported a general and efficient method for the construction of difluoromethyl-containing 1,4-disubstituted 1,2,3-triazoles.[11] In continuation of our interest in the synthesis of new trifluoromethyl and difluoromethyl containing 1,2,3-triazoles, herein we reported a facile and practical method for the synthesis of CF_3 or CF_2H-containing 1-aryl-1,4,5-trisubstituted 1,2,3-triazole derivatives via a one-pot three-component reaction of boronic acids, sodium azide, and active methylene ketones, such as ethyl 4,4-difluoroacetoacetate or ethyl 4,4,4-trifluoroacetoacetate in the presence of $Cu(OAc)_2$ and piperidine by using the mixed solvent dimethylsulfoxide/water (10/1) (Scheme 1).



Scheme 1. Synthesis of 1-aryl-1,4,5-trisubstituted 1,2,3-triazole via a one-pot three-component reaction starting from boronic acids.

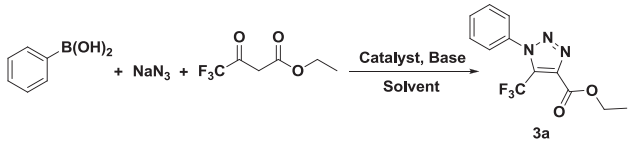
2. Results and discussion

In our previous paper, we developed a novel method for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles by a one-pot, three-

* Corresponding author. E-mail address: scao@ecust.edu.cn (S. Cao).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.12.086

component cycloaddition of primary alcohols, sodium azide, and active methylene ketones in the presence of *N*-(*p*-toluenesulfonyl) imidazole, tetrabutylammonium iodide, and triethylamine in DMF/DMSO.[12] However, when primary alcohol was replaced by phenol to undergo the reaction, the expected 1-phenyl-1,4,5-trisubstituted 1,2,3-triazole was not detected. It indicated that the scope of this method limited to the preparation of 1-alkyl-1,4,5-trisubstituted 1,2,3-triazoles. Furthermore, the reaction also did not proceed when ethyl 4,4-difluoroacetoacetate or ethyl 4,4,4-trifluoroacetoacetate was used as substrates, and the desired CF_3 or CF_2H-bearing 1,4,5-trisubstituted 1,2,3-triazoles could not be obtained. In 2011, Wang et al. have synthesized two trifluoromethyl-containing 1,4,5-trisubstituted 1,2,3-triazoles by treatment of phenyl azide with ethyl 4,4,4-trifluoroacetoacetate or 4,4,4-trifluoro-1-phenylbutane-1,3-dione, respectively.[5b] However, drawback of this method is that the starting materials, various aryl azides, which are unstable and toxic, should be prepared and isolated in advance one by one. The review of literature indicates that aryl azides could be efficiently prepared in high yields by a $CuSO_4$-catalyzed cross-coupling reaction between sodium azide and various arylboronic acids in methanol.[13] In order to avoid the isolation of unstable, hazardous, and potentially-explosive aryl azides, we tried to prepare 1-aryl-1,4,5-trisubstituted 1,2,3-triazoles via a one-pot reaction of boronic acids, sodium azide, and active methylene ketones. Initially, phenylboronic acid, sodium azide, and ethyl trifluoroacetoacetate were used as model substrates to examine the compatibility among the catalyst, substrate, and solvent (Scheme 2).



Scheme 2. Model reaction for the synthesis of **3a**.

According to literature, methanol can be used as solvent for the reaction of sodium azides and boronic acids.[13a,b] Therefore, our initial model experiment was carried out in methanol, however, only intermediate phenyl azide was obtained, the desired cyclization product **3a** wasn't observed (Table 1, entry 1). When toluene, THF, DMF, and DMSO were used as solvents, no cyclization products were isolated (Table 1, entries 2–5). Finally, to our delight, this novel one-pot three-component reaction could be greatly improved by the addition of a small amount of water in DMSO and DMF, and **3a** was obtained as the only major product (Table 1, entries 7–8).

Next, we have studied the influence of catalyst on the model reaction. In the absence of the catalyst, the reaction hardly proceeded and no cyclization product **3a** was observed (Table 1, entry 9). Liu and Guo have successfully synthesized aryl azides by the reaction of sodium azides with boronic acids in the presence of $CuSO_4$,[13a] but only moderate yield of **3a** was obtained when we used $CuSO_4$ as catalyst in our novel three-component reaction (Table 1, entry 13). It implied that $CuSO_4$ is not compatible with the novel reaction system. Thus, several different metal salts were screened in our model reaction (entries 10–18). It was found that $Cu(OAc)_2$ exhibited high catalytic activity (entry 8). The copper powder and copper (I) salts also had good catalytic effect on the reaction. The nickel and palladium catalyst showed no catalytic activity for the reaction.

The effect of base was also examined in the presence of $Cu(OAc)_2$ (Table 1, entries 20–25). Among the various bases tested (DEA: diethylamine, DABCO: 1,4-diazabicyclo-[2.2.2]octane, DMA: dimethylamine, TEA: triethylamine), piperidine promoted the reaction much more efficiently and 0.2 equiv of piperidine is enough to make the reaction proceed smoothly (entry 8). Other base, such as TEA could also improve the reaction but 1 equiv of TEA was needed (entry 25). In addition, only moderate yield of **3a** was obtained when DEA was used as the base (entry 22). To our surprise, inorganic base, such as KOH, which was used in our previous paper, has no effect on the reaction (entry 20). It indicated that the mechanism might be involved in the formation of enamine rather than enolate.[5b]

Table 1
Optimization of reaction conditions for the synthesis of **3a**[a]

Entry	Solvent[b]	Catalyst (10 mol %)	Base (0.2 equiv)	Time/h	Yield of **3a** (%)[d]
1	MeOH	$Cu(OAc)_2$	Piperidine	24	0
2	Toluene	$Cu(OAc)_2$	Piperidine	48	0
3	THF	$Cu(OAc)_2$	Piperidine	48	0
4	DMF[c]	$Cu(OAc)_2$	Piperidine	24	0
5	DMSO[c]	$Cu(OAc)_2$	Piperidine	48	0
6	MeOH/H_2O (10:1)	$Cu(OAc)_2$	Piperidine	24	0
7	DMF/H_2O (10:1)	$Cu(OAc)_2$	Piperidine	24	72
8	DMSO/H_2O (10:1)	$Cu(OAc)_2$	Piperidine	24	94
9	DMSO/H_2O (10:1)	None	Piperidine	48	0
10	DMSO/H_2O (10:1)	Cu (powder)	Piperidine	24	82
11	DMSO/H_2O (10:1)	CuI	Piperidine	24	60
12	DMSO/H_2O (10:1)	CuBr	Piperidine	24	56
13	DMSO/H_2O (10:1)	$CuSO_4$	Piperidine	24	73
15	DMSO/H_2O (10:1)	$Cu(OTf)_2$	Piperidine	24	24
16	DMSO/H_2O (10:1)	Cu_2O	Piperidine	24	69
17	DMSO/H_2O (10:1)	$Ni(acac)_2$	Piperidine	48	0
18	DMSO/H_2O (10:1)	$Pd(PPh)_4$	Piperidine	48	0
19	DMSO/H_2O (10:1)	$Cu(OAc)_2$	None	48	0
20	DMSO/H_2O (10:1)	$Cu(OAc)_2$	KOH[e]	48	0
21	DMSO/H_2O (10:1)	$Cu(OAc)_2$	K_2CO_3[e]	24	28
22	DMSO/H_2O (10:1)	$Cu(OAc)_2$	DEA	24	45
23	DMSO/H_2O (10:1)	$Cu(OAc)_2$	DABCO[e]	24	45
24	DMSO/H_2O (10:1)	$Cu(OAc)_2$	DMA	24	66
25	DMSO/H_2O (10:1)	$Cu(OAc)_2$	TEA[e]	24	82

[a] Reaction condition: phenylboronic acid (2 mmol), sodium azide (4 mmol), catalyst (0.2 mmol), solvent, room temperature, 2 h. Then, ethyl trifluoroacetoacetate (2 mmol), base (0.4 mmol) were added to the solution. Reaction was continued for 22 h at 80 °C.
[b] All organic solvents were dried. The 10 mL DMSO (or DMF, THF, MeOH, toluene) and 1 mL H_2O was used as the mixed solvent.
[c] Both dry or 'wet' DMF and DMSO were used.
[d] Yields were based on GC analysis.
[e] Base (1 equiv) was used.

Under these optimized reaction conditions, the generality and scope of this new one-pot three-component protocol was explored. A range of structurally diverse arylboronic acids and several active methylene ketones, such as ethyl 4,4-difluoroacetoacetate, ethyl acetoacetate, acetylacetone, and 3-oxo-3-phenylpropanenitrile were examined (Table 2). In all cases, the three-component reaction proceeded smoothly to give the corresponding fully substituted 1,2,3-triazoles in good to high yields, and no regioisomers were observed. The presence of electron-withdrawing or electron-donating substituents on the aromatic ring of boronic acids makes no differences to the yields of reaction (for example, entries 5 and 6). Much to our delight, no matter whether the substrate is $CF_3COCH_2CO_2Et$, $HCF_2COCH_2CO_2Et$ or $CH_3COCH_2CO_2Et$, the reaction proceeded satisfactorily, and the final cyclization products were obtained in high yields (for example, entries 1, 8, and 15).

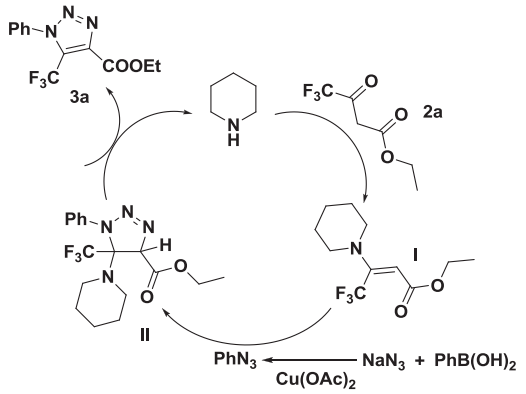
Based on the above results and literature, we tentatively suggest a plausible mechanism analogous to that proposed for organocatalytic enamide–azide cycloaddition reaction by Wang et al. (Scheme 3).[5b] First, small organic catalyst, piperidine, reacts with active methylene ketone, such as ethyl trifluoroacetoacetate **2a** to produce the key intermediate enamine **I**. Subsequently, dipolar

Table 2
One-pot three-component synthesis of 5-aryl-1,4,5-trisubstituted 1,2,3-triazoles[a]

Entry	R^1	R^2	R^3	Product	Yield[b] (%)
1	C_6H_5	CF_3	CO_2Et	**3a**	90
2	*p*-FC_6H_4	CF_3	CO_2Et	**3b**	86
3	*p*-$CH_3C_6H_4$	CF_3	CO_2Et	**3c**	84
4	3-Thiophen	CF_3	CO_2Et	**3d**	79
5	*p*-$CH_3OC_6H_4$	CF_3	CO_2Et	**3e**	80
6	*m*-$NO_2C_6H_4$	CF_3	CO_2Et	**3f**	81
7	*m*-$NH_2C_6H_4$	CF_3	CO_2Et	**3g**	77
8	C_6H_5	CF_2H	CO_2Et	**3h**	84
9	*p*-FC_6H_4	CF_2H	CO_2Et	**3i**	80
10	*p*-$CH_3C_6H_4$	CF_2H	CO_2Et	**3j**	81
11	*p*-$CH_3OC_6H_4$	CF_2H	CO_2Et	**3k**	82
12	*m*-$NH_2C_6H_4$	CF_2H	CO_2Et	**3l**	75
13	3-Thiophen	CF_2H	CO_2Et	**3m**	78
14	C_6H_5	CH_3	COMe	**3n**	87
15	C_6H_5	CH_3	CO_2Et	**3o**	92
16	*p*-$CH_3OC_6H_4$	CH_3	COMe	**3p**	88
17	C_6H_5	C_6H_5	CN	**3q**	86
18	*p*-FC_6H_4	C_6H_5	CN	**3r**	83
19	*p*-$CH_3OC_6H_4$	C_6H_5	CN	**3s**	82

[a] Reaction condition: arylboronic acid (2 mmol), sodium azide (4 mmol), $Cu(OAc)_2$ (0.2 mmol), DMSO/H_2O (10 mL/1 mL), room temperature, 2 h. Then, active methylene ketones (2 mmol), base (0.4 mmol) were added to the solution, reaction was continued for 22 h at 80 °C.
[b] Isolated yield.

cycloaddition of enamine **I** with the aromatic azide, which is obtained by the reaction of phenylboronic acid with sodium azide in the presence of $Cu(OAc)_2$, to afford triazoline intermediate **II**. Finally, elimination of triazoline provides the desired product **3a** and regenerates the piperidine, closing the catalytic cycle.



Scheme 3. Proposed reaction mechanism.

In summary, we reported a novel approach for the synthesis of CF_2H or CF_3 containing 1-aryl-1,4,5-trisubstituted 1,2,3-triazoles by a one-pot three-component reaction of arylboronic acids, sodium azide, and active methylene ketones in the presence of $Cu(OAc)_2$ and piperidine using a DMSO/H_2O (10/1) mixture as solvent. The outstanding advantage of this method is that it avoids the isolation of the unstable and hazardous aryl azides. It provides a new and practical one-step route to synthesize the structural diversity of 1-aryl-1,4,5-trisubstituted 1,2,3-triazoles from easily commercially available boronic acids.

3. Experimental section

3.1. General

All reagents were of analytic grade, obtained from commercial suppliers, and used without further purification. Melting points were measured in an open capillary with a Büchi melting point B-540 apparatus. ^1H NMR and ^{13}C NMR spectroscopic data were recorded with a Bruker AM-400 spectrometer using TMS as an internal standard. The ^{19}F NMR spectroscopic data were recorded with a Bruker AM-400 spectrometer, and the ^{19}F NMR were measured with external CF_3CO_2H as the standard. Chemical shifts are given in the δ scale in parts per million (ppm). High-resolution mass spectra (ESI) were recorded with a MicroMass LCTTM spectrometer. Column chromatography was carried out with Merck silica gel 60 (230–400 mesh).

3.2. General procedure for compounds 3a–s

To a stirred solution of **1** (2 mmol) in 10 mL DMSO and 1 mL H_2O, sodium azide (0.26 g, 4 mmol), $Cu(OAc)_2$ (0.04 g, 0.2 mmol) were added successively. The mixture was stirred for 0.5–4 h at room temperature (TLC). Then, **2** (2 mmol), piperidine (0.03 g, 0.4 mmol) were added to the solution. Reaction was continued for 2–20 h (TLC), and quenched with H_2O (20 mL). The resulting suspension was filtered and the filtrate was diluted with CH_2Cl_2, washed successively with H_2O and brine, dried over anhydrous $MgSO_4$, concentrated under reduced pressure to leave the crude product. The resultant crude residue was purified by chromatography on silica gel (petroleum ether/EtOAc=5:1) to afford the product **3**.

*3.2.1. Ethyl 1-phenyl-5-(trifluoromethyl)-1H-1,2,3-triazole-4-carboxylate (**3a**).*[5b] Colorless oil, ^1H NMR: δ 7.60–7.44 (m, 5H), 4.47 (q, J=7.1 Hz, 2H), 1.41 (t, J=7.2 Hz, 3H); ^{13}C NMR: δ 159.0, 139.4, 135.5, 131.2, 129.5 (q, $^2J_{CF}$=42.0 Hz), 129.4, 125.7, 118.8 (q, $^1J_{CF}$=271.2 Hz), 62.3, 14.0; ^{19}F NMR: δ −55.6 (s, 3F); GC–MS: m/z=285, 189, 165, 77.

*3.2.2. Ethyl 1-(4-fluorophenyl)-5-(trifluoromethyl)-1H-1,2,3-triazole-4-carboxylate (**3b**).* Colorless oil, ^1H NMR: δ 7.50–7.25 (m, 4H), 4.50 (q, J=7.0 Hz, 2H), 1.44 (t, J=7.0 Hz, 3H); ^{13}C NMR: δ 163.9 (d, $^{1'}J_{CF}$=252.9 Hz), 158.9, 139.5, 131.5 (d, $^{4'}J_{CF}$=2.7 Hz), 129.6 (q, $^2J_{CF}$=42.1 Hz), 127.9 (d, $^{3'}J_{CF}$=9.2 Hz), 118.8 (q, $^1J_{CF}$=271.2 Hz), 116.7 (d, $^{2'}J_{CF}$=23.6 Hz), 62.4, 14.0; ^{19}F NMR: δ −55.6 (s, 3F), −108.0 (m, 1F); HRMS (ESI): calcd for $C_{12}H_9F_4N_3O_2Na$ $(M+Na)^+$ 326.0529, found: 326.0522.

*3.2.3. Ethyl 1-(p-tolyl)-5-(trifluoromethyl)-1H-1,2,3-triazole-4-carboxylate (**3c**).* White solid, mp: 48.1–48.4 °C, ^1H NMR: δ 7.38–7.33 (m, 4H), 4.50 (q, J=7.1 Hz, 2H), 2.47 (s, 3H), 1.45 (t, J=7.1 Hz, 3H); ^{13}C NMR: δ 159.1, 141.7, 139.3, 133.0, 130.1, 129.7, 118.9 (q, $^1J_{CF}$=271.3 Hz), 114.8, 62.3, 21.3, 14.0; ^{19}F NMR: δ −55.7 (s, 3F); HRMS (ESI): calcd for $C_{13}H_{12}F_3N_3O_2Na$ $(M+Na)^+$ 322.0779, found: 322.0764.

*3.2.4. Ethyl 1-(thiophen-3-yl)-5-(trifluoromethyl)-1H-1,2,3-triazole-4-carboxylate (**3d**).* Colorless oil, ^1H NMR: δ 7.66–7.24 (m, 3H), 4.49 (q, J=7.1 Hz, 2H), 1.43 (t, J=7.1 Hz, 3H); ^{13}C NMR: δ 159.0, 139.3, 132.5, 129.4 (q, $^2J_{CF}$=42.7 Hz), 127.0, 124.2, 122.8, 118.8 (q, $^1J_{CF}$=271.3 Hz), 62.4, 14.0; ^{19}F NMR: δ −56.2 (s, 3F); HRMS (ESI): calcd for $C_{10}H_8F_3N_3O_2S$ $(M+Na)^+$ 314.0187, found: 314.0190.

*3.2.5. Ethyl 1-(4-methoxyphenyl)-5-(trifluoromethyl)-1H-1,2,3-triazole-4-carboxylate (**3e**).*[7a] White solid, mp: 82.3–82.8 °C, ^1H NMR: δ 7.39 (d, J=8.3 Hz, 2H), 7.05 (d, J=8.2 Hz, 2H), 4.51 (q, J=7.0 Hz, 2H), 3.90 (s, 3H), 1.45 (t, J=6.8 Hz, 3H); ^{13}C NMR: δ 161.5, 159.1, 139.5, 129.6, 128.2, 127.1, 118.9 (q, J=271.2 Hz), 114.6, 62.3, 55.7, 14.0; ^{19}F NMR: δ −55.8 (s, 3F). GC–MS: m/z=315, 219, 200, 107.

*3.2.6. Ethyl 1-(3-nitrophenyl)-5-(trifluoromethyl)-1H-1,2,3-triazole-4-carboxylate (**3f**).* White solid, mp: 70.7–71.1 °C, ^1H NMR: δ 8.53–7.86 (m, 4H), 4.52 (q, J=7.0 Hz, 2H), 1.46 (t, J=7.0 Hz, 3H); ^{13}C NMR: δ 158.6, 148.5, 140.3, 136.2, 131.6, 130.9, 129.8, 126.0, 121.3, 118.7 (q, J=271.6 Hz), 62.6, 14.0; ^{19}F NMR: δ −55.2 (s, 3F); HRMS

(ESI): calcd for $C_{12}H_9F_3N_4O_4Na$ $(M+Na)^+$ 353.0474, found: 353.0460.

*3.2.7. Ethyl 1-(3-aminophenyl)-5-(trifluoromethyl)-1H-1,2,3-triazole-4-carboxylate (**3g**).* Colorless oil, ^1H NMR: δ 7.32 (t, J=8.0 Hz, 1H), 6.91–6.77 (m, 3H), 4.51 (q, J=7.2 Hz, 2H), 3.83 (b, 2H), 1.46 (t, J=7.1 Hz, 3H); ^{13}C NMR: δ 159.2, 147.6, 139.3, 136.3, 130.1, 129.4 (q, J=42.0 Hz), 118.8 (q, J=271.1 Hz), 117.3, 115.2, 111.7, 62.3, 14.0; ^{19}F NMR: δ −55.8 (s, 3F); HRMS (ESI): calcd for $C_{12}H_{11}F_3N_4O_2Na$ $(M+Na)^+$ 323.0732, found: 323.0717.

*3.2.8. Ethyl 5-(difluoromethyl)-1-phenyl-1H-1,2,3-triazole-4-carboxylate (**3h**).* Colorless oil, ^1H NMR: δ 7.57–7.54 (m,5H), 7.51 (t, J=52.5 Hz, 1H), 4.49 (q, J=7.1 Hz, 2H), 1.44 (t, J=7.1 Hz, 3H); ^{13}C NMR: δ 160.3, 139.0 (t, $^3J_{CF}$=4.6 Hz), 135.9, 133.5 (t, $^2J_{CF}$=25.4 Hz), 130.8, 129.4, 125.5, 106.7 (t, $^1J_{CF}$=238.9 Hz), 62.2, 14.2; ^{19}F NMR: δ −113.4 (d, J=52.7 Hz, 2F); HRMS (ESI): calcd for $C_{12}H_{11}F_2N_3O_2Na$ $(M+Na)^+$ 290.0717, found: 290.0717.

*3.2.9. Ethyl 5-(difluoromethyl)-1-(4-fluorophenyl)-1H-1,2,3-triazole-4-carboxylate (**3i**).* Colorless oil, ^1H NMR: δ 7.60–7.57 (m, 2H), 7.54 (t, J=52.5 Hz, 1H), 7.28–7.24 (m, 2H), 4.52 (q, J=7.1 Hz, 2H), 1.48 (t, J=7.1 Hz, 3H); ^{13}C NMR: δ 163.7 (d, $^{1'}J_{CF}$=252.1 Hz), 160.3, 139.0 (t, $^3J_{CF}$=4.7 Hz), 133.7 (t, $^2J_{CF}$=25.2 Hz), 131.9 (d, $^{4'}J_{CF}$=3.2 Hz), 127.7 (d, $^{3'}J_{CF}$=9.1 Hz), 116.5 (d, $^{2'}J_{CF}$=23.4 Hz), 106.7 (t, $^1J_{CF}$=238.9 Hz), 62.3, 14.2; ^{19}F NMR: δ −108.9 (m, 1F), −113.3 (d, J=52.6 Hz, 2F); HRMS (ESI): calcd for $C_{12}H_{10}F_3N_3O_2Na$ $(M+Na)^+$ 308.0623, found: 308.0622.

*3.2.10. Ethyl 5-(difluoromethyl)-1-(p-tolyl)-1H-1,2,3-triazole-4-carboxylate (**3j**).* White solid, mp: 70.7–71.2 °C, ^1H NMR: δ 7.52 (t, J=52.5 Hz, 1H), 7.47–7.35 (m, 4H), 4.52 (q, J=7.1 Hz, 2H), 2.47 (s, 3H), 1.48 (t, J=7.1 Hz, 3H); ^{13}C NMR: δ 160.4, 141.2, 138.9 (t, $^3J_{CF}$=4.6 Hz), 133.5 (t, $^2J_{CF}$=25.2 Hz), 133.4, 129.9, 125.3, 106.7 (t, $^1J_{CF}$=238.8 Hz), 62.2, 21.3, 14.2; ^{19}F NMR: δ −113.5 (d, J=52.6 Hz, 2F); HRMS (ESI): calcd for $C_{13}H_{13}F_2N_3O_2Na$ $(M+Na)^+$ 304.0874, found: 304.0862.

*3.2.11. Ethyl 5-(difluoromethyl)-1-(4-methoxyphenyl)-1H-1,2,3-triazole-4-carboxylate (**3k**).* White solid, mp: 95.9–96.3 °C, ^1H NMR: δ 7.52 (t, J=52.5 Hz, 1H), 7.51–7.05 (m, 4H), 4.53 (q, J=7.1 Hz, 2H), 3.91 (s, 3H), 1.49 (t, J=7.1 Hz, 3H); ^{13}C NMR: δ 161.2, 160.4, 138.8 (t, $^3J_{CF}$=4.6 Hz), 133.5 (t, $^2J_{CF}$=25.3 Hz), 128.7, 126.9, 114.4, 106.8 (t, $^1J_{CF}$=238.6 Hz), 62.1, 55.6, 14.2; ^{19}F NMR: δ −113.6 (d, J=52.2 Hz, 2F); HRMS (ESI): calcd for $C_{13}H_{13}F_2N_3O_3Na$ $(M+Na)^+$ 320.0823, found: 320.0810.

*3.2.12. Ethyl 1-(3-aminophenyl)-5-(difluoromethyl)-1H-1,2,3-triazole-4-carboxylate (**3l**).* White solid, mp: 97.9–98.1 °C, ^1H NMR: δ 7.45 (t, J=52.5 Hz, 1H), 7.30–6.80 (m, 4H), 4.49 (q, J=7.1 Hz, 2H), 3.93 (b, 2H), 1.45 (t, J=7.1 Hz, 3H); ^{13}C NMR: δ 160.3, 147.4, 138.8, 136.5, 133.3 (t, $^2J_{CF}$=25.9 Hz), 129.9, 117.2, 115.1, 111.7, 106.7 (t, $^1J_{CF}$=239.0 Hz), 62.2, 14.2; ^{19}F NMR: δ −113.7 (d, J=52.3 Hz, 2F); HRMS (ESI): calcd for $C_{12}H_{12}F_2N_4O_2Na$ $(M+Na)^+$ 305.0826, found: 305.0821.

*3.2.13. Ethyl 5-(difluoromethyl)-1-(thiophen-3-yl)-1H-1,2,3-triazole-4-carboxylate (**3m**).* White solid, mp: 47.3–47.6 °C, ^1H NMR: δ 7.72–7.71 (m, 1H), 7.57 (t, J=52.4 Hz, 1H), 7.49–7.47 (m, 1H), 7.39–7.38 (m, 1H), 4.49 (q, J=7.1 Hz, 2H), 1.45 (t, J=7.2 Hz, 3H); ^{13}C NMR: δ 160.3, 138.8 (t, $^3J_{CF}$=4.6 Hz), 133.3, 132.9 (t, $^2J_{CF}$=25.3 Hz), 126.6, 124.0, 121.5, 106.7 (t, $^1J_{CF}$=238.6 Hz), 62.2, 14.2; ^{19}F NMR: δ −114.4 (d, J=52.1 Hz, 2F); HRMS (ESI): calcd for $C_{10}H_9F_2N_3O_2SNa$ $(M+Na)^+$ 296.0281, found: 296.0270.

*3.2.14. 1-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)ethanone (**3n**).*[5b] White solid, mp: 101.5–101.8 °C, ^1H NMR: δ 7.60–7.45 (m, 5H), 2.77 (s, 3H), 2.60 (s, 3H); ^{13}C NMR: δ 194.4, 137.4, 135.4, 130.1, 129.7, 125.3, 27.8, 10.1; GC–MS: m/z=201, 158, 130, 77.

*3.2.15. Ethyl 5-methyl-1-phenyl-1H-1,2,3-triazole-4-carboxylate (**3o**).*[5b] White solid, mp: 60.4–60.8, ^1H NMR: δ 7.54–7.41 (m, 5H), 4.42 (q, J=7.1 Hz, 2H), 2.55 (s, 3H), 1.41 (t, J=7.1 Hz, 3H); ^{13}C NMR: δ 161.7, 138.8, 136.7, 135.4, 130.1, 129.7, 125.3, 61.0, 14.4, 10.0; GC–MS: m/z=231, 158, 130, 77.

*3.2.16. 1-(1-(4-Methoxyphenyl)-5-methyl-1H-1,2,3-triazol-4-yl) ethanone (**3p**).*[4a] White solid, mp: 113.4–113.7 °C, ^1H NMR: δ 7.36–7.04 (m, 4H), 3.88 (s, 3H), 2.74 (s, 3H), 2.55 (s, 3H); ^{13}C NMR: δ 194.4, 160.7, 143.5, 137.6, 128.1, 126.7, 114.8, 55.7, 27.8, 10.1; GC–MS: m/z=231, 188, 146, 107.

*3.2.17. 1,5-Diphenyl-1H-1,2,3-triazole-4-carbonitrile (**3q**).*[5b] White solid, mp: 160.4–161.2 °C, ^1H NMR: δ 7.54–7.44 (m, 6H), 7.37–7.35 (m, 4H); ^{13}C NMR: δ 143.1, 135.3, 131.1, 130.3, 129.8, 129.4, 129.0, 125.2, 123.3, 120.6, 112.1; GC–MS: m/z=246, 218, 190, 77.

*3.2.18. 1-(4-Fluorophenyl)-5-phenyl-1H-1,2,3-triazole-4-carbonitrile (**3r**).* White solid, mp: 162.5–162.9 °C, ^1H NMR: δ 7.55–7.45 (m, 3H), 7.38–7.35 (m, 4H), 7.20–7.16 (m, 2H); ^{13}C NMR: δ 163.2 (d, $^1J_{CF}$=252.1 Hz), 143.2, 131.4 (d, $^4J_{CF}$=3.4 Hz), 131.3, 129.5, 128.9, 127.2 (d, $^3J_{CF}$=9.0 Hz), 123.1, 120.6, 116.9 (d, $^2J_{CF}$=23.4 Hz), 112.0; ^{19}F NMR: δ −109.0 (m, 1F); HRMS (ESI): calcd for $C_{15}H_9FN_4$ $(M+H)^+$ 265.0889, found: 265.0887.

*3.2.19. 1-(4-Methoxyphenyl)-5-phenyl-1H-1,2,3-triazole-4-carbonitrile (**3s**).*[5b] White solid, mp: 144.5–144.9 °C, ^1H NMR: δ 7.48–7.34 (m, 5H), 7.25 (d, J=8.29 Hz, 2H), 6.95 (d, J=8.30 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR: δ 160.8, 143.0, 131.0, 129.4, 128.9, 128.1, 126.6, 123.4, 120.2, 114.9, 112.3, 55.7; GC–MS: m/z=276, 248, 233, 205, 115, 77.

Acknowledgements

We are grateful for financial supports from the National Natural Science Foundation of China (Grant No. 21072057, 21272070), the Key Project in the National Science & Technology Pillar Program of China in the twelfth five-year plan period (2011BAE06B01-15), the National Basic Research Program of China (973 Program, 2010CB126101), and the National High Technology Research and Development Program of China (863 Program, 2011AA10A204).

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.12.086.

References and notes

1. (a) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302–1315; (b) Calderone, V.; Fiamingo, F. L.; Amato, G.; Giorgi, I.; Livi, O.; Martelli, A.; Martinotti, E. *Eur. J. Med. Chem.* **2008**, *43*, 2618–2626; (c) Kalesh, K. A.; Liu, K.; Yao, S. Q. *Org. Biomol. Chem.* **2009**, *7*, 5129–5136; (d) Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E. *J. Med. Chem.* **2000**, *43*, 953–970; (e) Bock, V. D.; Perciaccante, R.; Jansen, T. P.; Hiemstra, H.; Maarseveen, J. H. *Org. Lett.* **2006**, *8*, 919–922; (f) Dondoni, A. *Chem.—Asian J.* **2007**, *2*, 700–708; (g) Agalave, S. G.; Maujan, S. R.; Pore, V. S. *Chem.—Asian J.* **2011**, *6*, 2696–2718.
2. (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021; (b) Bock, V. D.; Hiemstra, H.; Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51–68; (c) Pachón, L. D.; Maarseveen, J. H.; Rothenberg, G. *Adv. Synth. Catal.* **2005**, *347*, 811–815; (d) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. *Eur. J. Org. Chem.* **2010**, 1875–1884.
3. (a) Romeiro, G. A.; Pereira, L. O. R.; Souza, M. C. B. V.; Ferreira, V. F.; Cunha, A. C. *Tetrahedron Lett.* **1997**, *38*, 5103–5106; (b) Campos, V. R.; Abreu, P. A.; Castro, H. C.; Rodrigues, C. R.; Jordão, A. K.; Ferreira, V. F.; Souza, M. C. B. V.; Santos, F. da C.; Moura, L. A.; Domingos, T. S.; Carvalho, C.; Sanchez, E. F.; Fuly, A. L.; Cunha, A. C. *Bioorg. Med. Chem.* **2009**, *17*, 7429–7434; (c) Ackermann, L.; Potukuchi, H.

K. *Org. Biomol. Chem.* **2010**, *8*, 4503–4513; (d) Zhou, Y.; Lecourt, T.; Micouin, L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2607–2610.
4. (a) Kamalraj, V. R.; Senthil, S.; Kannan, P. *J. Mol. Struct.* **2008**, *892*, 210–215; (b) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081–3084; (c) Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8018–8021; (d) Krasiński, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett.* **2004**, *6*, 1237–1240; (e) Reddy, M. N.; Swamy, K. C. K. *Eur. J. Org. Chem.* **2012**, 2013–2022; (f) Stazi, F.; Cancogni, D.; Turco, L.; Westerduin, P.; Bacchi, S. *Tetrahedron Lett.* **2010**, *51*, 5385–5387.
5. (a) Cottrell, I. F.; Hands, D.; Houghton, P. G.; Humphrey, G. R.; Wright, S. H. B. *J. Heterocycl. Chem.* **1991**, *28*, 301–304; (b) Danence, L. J. T.; Gao, Y.; Li, M.; Huang, Y.; Wang, J. *Chem.—Eur. J.* **2011**, *17*, 3584–3587; (c) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333–2336; (d) He, T.; Wang, M.; Li, P.; Wang, L. *Chin. J. Chem.* **2012**, *30*, 979–984; (e) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923–8930; (f) Ackermann, L.; Vicente, R. *Org. Lett.* **2009**, *11*, 4922–4925; (g) Wang, L.; Peng, S.; Danence, L. J. T.; Gao, Y.; Wang, J. *Chem.—Eur. J.* **2012**, *18*, 6088–6093.
6. (a) Prakash, G. K. S.; Hu, J. B. *Acc. Chem. Res.* **2007**, *40*, 921–930; (b) Roy, S.; Gregg, B. T.; Gribble, G. W.; Le, V. D.; Roy, S. *Tetrahedron* **2011**, *67*, 2161–2195; (c) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475–4521; (d) Ma, J. A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975–996; (e) Chu, L.; Qing, F. L. *Org. Lett.* **2012**, *14*, 2106–2109; (f) Zhang, X. G.; Dai, H. X.; Wasa, M.; Yu, J. Q. *J. Am. Chem. Soc.* **2012**, *134*, 11948–11951; (g) Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 12462–12465; (h) Ye, Y.; Lee, S. H.; Sanford, M. S. *Org. Lett.* **2011**, *13*, 5464–5467; (i) Fujikawa, K.; Fujioka, Y.; Kobayashi, A.; Amii, H. *Org. Lett.* **2011**, *13*, 5560–5563; (j) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 5524–5527.
7. (a) Peng, W.; Zhu, S. *Tetrahedron* **2003**, *59*, 4395–4404; (b) Rozin, Y. A.; Leban, J.; Dehaen, W.; Nenajdenko, V. G.; Muzalevskiy, V. M.; Eltsov, O. S.; Bakulev, V. A. *Tetrahedron* **2012**, *68*, 614–618; (c) Hiramatsu, T.; Guo, Y.; Hosoya, T. *Org. Biomol. Chem.* **2007**, *5*, 2916–2919; (d) Lermontov, S. A.; Shkavrov, S. V.; Pushin, A. N. *J. Fluorine Chem.* **2000**, *105*, 141–147; (e) Bonnamour, J.; Legros, J.; Crousse, B.; Bonnet-Delpon, D. *Tetrahedron Lett.* **2007**, *48*, 8360–8362; (f) Wu, Y. M.; Deng, J.; Fang, X.; Chen, Q. Y. *J. Fluorine Chem.* **2004**, *125*, 1415–1423; (g) Deng, J.; Wu, Y. M.; Chen, Q. Y. *Synthesis* **2005**, *16*, 2730–2738; (h) Wu, Y. M.; Deng, J.; Li, Y.; Chen, Q. Y. *Synthesis* **2005**, *8*, 1314–1318; (i) Zhang, C. P.; Wang, Z. L.; Chen, Q. Y.; Zhang, C. T.; Gu, Y. C.; Xiao, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 1896–1900.
8. (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211; (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2008**, *64*, 3047–3101; (c) Tang, Z. Y.; Hu, Q. S. *J. Am. Chem. Soc.* **2004**, *126*, 3058–3059; (d) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168; (e) Zhang, J.; Wu, J.; Xiong, Y.; Cao, S. *Chem. Commun.* **2012**, 8553–8555.
9. (a) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6723–6737; (b) Miyaura, N. *Synlett* **2009**, 2039–2050; (c) Leadbeater, N. E. *Chem. Commun.* **2005**, 2881–2902; (d) Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710.
10. (a) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394–5397; (b) Molander, G. A.; Cavalcanti, L. N.; Canturk, B.; Pan, P. S.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 7364–7369; (c) Laza, C.; Duñach, E.; Serein-Spirau, F.; Moreau, J. J. E.; Vellutini, L. *New J. Chem.* **2002**, *26*, 373–375; (d) Sleveland, D.; Bjørsvik, H. R. *Org. Process Res. Dev.* **2012**, *16*, 1121–1130.
11. Zhang, J.; Wu, J. J.; Shen, L.; Jin, G. Y.; Cao, S. *Adv. Synth. Catal.* **2011**, *353*, 580–584.
12. Jin, G.; Zhang, J.; Fu, D.; Wu, J.; Cao, S. *Eur. J. Org. Chem.* **2012**, 5446–5449.
13. (a) Tao, C. Z.; Cui, X.; Li, J.; Liu, A. X.; Liu, L.; Guo, Q. X. *Tetrahedron Lett.* **2007**, *48*, 3525–3529; (b) Grimes, K. D.; Gupte, A.; Aldrich, C. C. *Synthesis* **2010**, 1441–1448; (c) Mohammeda, S.; Padala, A. K.; Dar, B. A.; Singh, B.; Sreedhar, B.; Vishwakarma, R. A.; Bharate, S. B. *Tetrahedron* **2012**, *68*, 8156–8162; (d) Kaboudin, B.; Abedia, Y.; Yokomatsu, T. *Org. Biomol. Chem.* **2012**, *10*, 4543–4548.