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SHORT COMMUNICATION

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Efficient and Rapid Regioselective One-Pot Synthesis of 1,4-Disubstituted 1,2,3-Triazoles from In Situ Generated Potassium Arylethynyltrifluoroborates through Sonogashira Reaction

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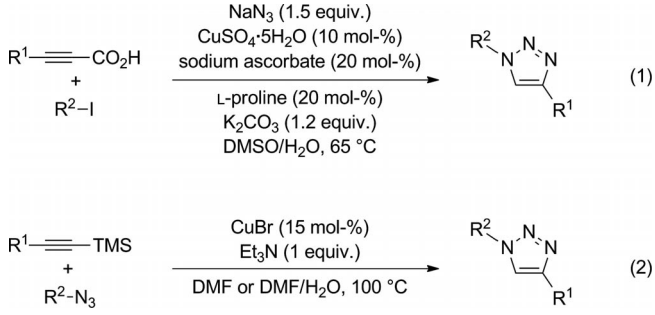
Keywords: Click chemistry / Nitrogen heterocycles / Cross-coupling / Cycloaddition / Regioselectivity

Potassium arylethynyltrifluoroborates, the intermediates generated by the Sonogashira reaction of potassium ethynyltrifluoroborate with various aryl halides, were directly coupled with azides in the presence of a stoichiometric amount of CuI under aqueous conditions, and the desired 1,4-disubstituted 1,2,3-triazoles were isolated in good yields. Both electron-donating and electron-withdrawing substituents on the potassium arylethynyltrifluoroborates gave moderate to excellent yields of the isolated products.

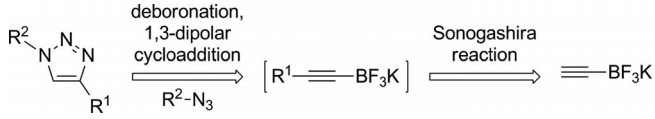
Introduction

1,4-Disubstituted 1,2,3-triazole derivatives, which are obtained from terminal alkynes and azides by 1,3-dipolar cycloaddition, are important small-molecule building blocks for complex compounds, and hence, they find significant application in organic synthesis, pharmaceutical sciences, and the development of functional materials.[1] Since the independent discovery of the Cu-catalyzed Huisgen terminal alkyne–azide 1,3-dipolar cycloaddition by Meldal[2] and Sharpless,[3] numerous papers describing the use of this click chemistry strategy have been published. Further, some methods describing the preparation of azide compounds have been developed.[4] However, terminal alkynes are expensive, have low molecular weights and boiling points, have a short shelf life (storage unstable), and are difficult to handle; these problems hinder the widespread use of terminal alkynes as 1,3-dipolar cycloaddition partners of azides. As a solution, several research groups have attempted the synthesis of 1,4-disubstituted 1,2,3-triazoles from terminal alkynes generated by in situ decarboxylation[4b] and desilylation[5] (Scheme 1).



Scheme 1. Synthesis of 1,4-disubstituted 1,2,3-triazoles from terminal alkynes generated by in situ decarboxylation [Eq. (1)] and desilylation [Eq. (2)].

Herein, we report the preparation of copper arylacetylides from potassium ethynyltrifluoroborate[6] and various aryl halides through the Sonogashira reaction[7] and deboronation of the trifluoroborate salt by using a stoichiometric amount of CuI. The desired 1,4-disubstituted 1,2,3-triazoles were then obtained in good yields through 1,3-dipolar cycloaddition with azides (Scheme 2).



Scheme 2. Synthesis of 1,4-disubstituted 1,2,3-triazoles from terminal alkynes generated by in situ deboronation.

To the best of our knowledge, this is the first report on the one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles

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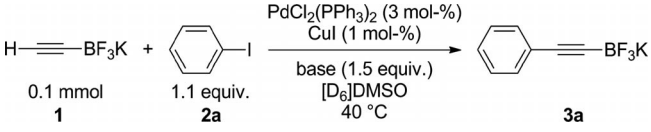
from terminal alkynes generated by in situ deboronation of the potassium trifluoroborate functional group. Furthermore, potassium arylethynyltrifluoroborates are obtained from the corresponding aryl halides by Pd-catalyzed Sonogashira coupling with potassium ethynyltrifluoroborate.

Results and Discussion

We began our study by performing the Sonogashira reaction of potassium ethynyltrifluoroborate (**1**) with iodobenzene (1.1 equiv.) on a 0.1 mmol scale in [D_6]DMSO in an NMR tube, and then directly monitored the progress of the reaction by NMR spectroscopy.[8] The results of these optimization studies are summarized in Table 1. Upon performing the reaction with $PdCl_2$ (3 mol-%), CuI (1 mol-%), and piperidine (1.5 equiv.) as a base in [D_6]DMSO (0.4 mL), coupling product **3a** was obtained in only 15% yield (Table 1, entry 1). The use of $Pd(OAc)_2$, $Pd(PPh_3)_4$, and $PdCl_2(PPh_3)_2$ led to the formation of **3a** in moderate to good yields, that is, 42, 82, and 90% yield, respectively (Table 1, entries 2–4). Although both CuI and CuBr as the catalyst generated **3a** under the same conditions (Table 1, entries 4 and 5), CuI was preferred because it gave a higher yield of the isolated product within a shorter reaction time. The use of other bases such as pyrrolidine, Cs_2CO_3, and Et_3N did not improve the product yield (Table 1, entries 6–8).

Table 1. Survey of Sonogashira reaction conditions.[a]

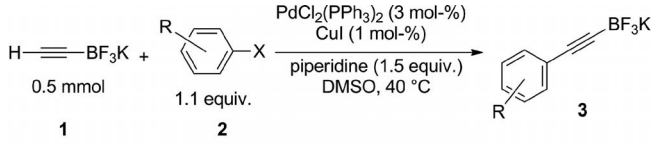


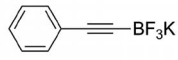
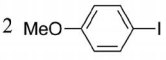
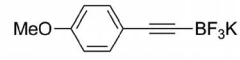
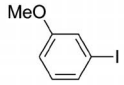
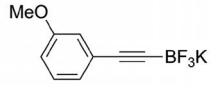
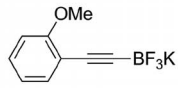
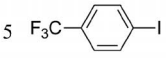
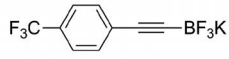
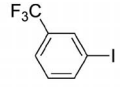
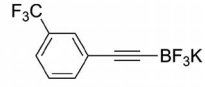
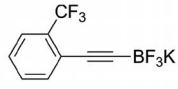
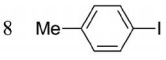
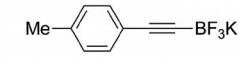
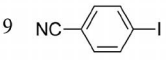
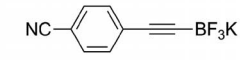
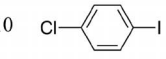
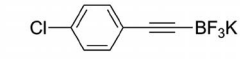
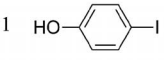
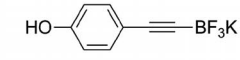
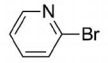
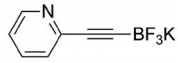
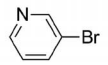
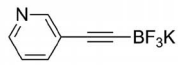
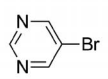
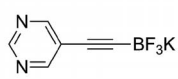
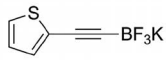
Entry	Pd catalyst	Base	Time [h]	Yield[b] [%]
1	$PdCl_2$	piperidine	4	15
2	$Pd(OAc)_2$	piperidine	5	42
3	$Pd(PPh_3)_4$	piperidine	3	82
4	$PdCl_2(PPh_3)_2$	piperidine	1	90
5[c]	$PdCl_2(PPh_3)_2$	piperidine	2	87
6	$PdCl_2(PPh_3)_2$	pyrrolidine	4	72
7	$PdCl_2(PPh_3)_2$	Et_3N	5	31
8	$PdCl_2(PPh_3)_2$	Cs_2CO_3	12	n.r.[d]

[a] All reactions were performed on a 0.1 mmol scale in [D_6]DMSO (0.4 mL) in an NMR tube and then directly monitored by ^{1}H NMR and ^{19}F NMR spectroscopy. [b] Yield of isolated product. [c] CuBr was used as a catalyst instead of CuI. [d] n.r.: no reaction.

With the optimal conditions in hand, we examined the Sonogashira reaction of various aryl and heteroaryl halides with **1**. All the reactions resulted in complete conversion to the corresponding products (Table 2). For electron-rich and electron-deficient functional groups in the aromatic ring, the reaction times and yields of the isolated products increased in the order *para* > *meta* > *ortho* (Table 2, entries 2–7). 1-Iodo-4-methylbenzene (**2h**) and 4-iodobenzonitrile (**2i**) also delivered products in good to excellent yields (Table 2, entries 8 and 9). As a general trend, electron-de-

Table 2. Preparation of potassium arylethynyltrifluoroborates.[a]



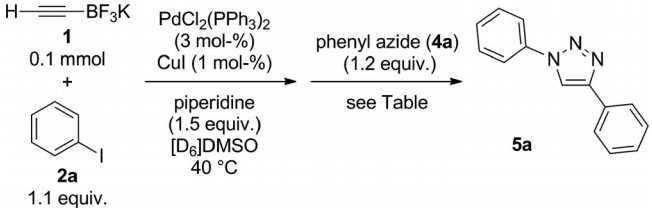
Entry	R^1X		Time [h]	Product		Yield [%]
1		**2a**	1		**3a**	90
2		**2b**	2		**3b**	85
3		**2c**	3		**3c**	79
4		**2d**	4		**3d**	70
5		**2e**	2		**3e**	92
6		**2f**	4		**3f**	76
7		**2g**	5		**3g**	76
8		**2h**	2		**3h**	85
9		**2i**	2		**3i**	94
10		**2j**	2		**3j**	88
11		**2k**	6		**3k**	82
12		**2l**	4		**3l**	79
13		**2m**	5		**3m**	76
14		**2n**	4		**3n**	72
15		**2o**	3		**3o**	65

[a] All reactions were performed on a 0.5 mmol scale in DMSO (2.0 mL) and monitored by ^{1}H NMR spectroscopy in D_2O.

ficient aryl iodides were more reactive than electron-rich iodides. Given that aryl iodides are generally more reactive than the corresponding chlorides, 1-chloro-4-iodobenzene (**2j**) was successfully converted into monoethynyltrifluoroborate product **3j** without affecting the aryl chloride functionality, and it is thus available for further transformations (Table 2, entry 10). Significantly, even a free alcohol group did not interfere with the reaction (Table 2, entry 11). Interestingly, heteroaryl bromides such as pyridyl, pyrimidyl, and thiophenyl bromides **2l**–**o** also readily participated in the reaction, as opposed to the unstable and expensive heteroaryl iodides. To expand the scope of substrates, we examined several functionalized compounds. However, vinyl halides and aryl sulfonates did not react under the standard conditions (data not shown).

After the successful demonstration of the Sonogashira reaction by using potassium ethynyltrifluoroborate, we focused on the use of potassium arylethynyltrifluoroborates for the 1,3-dipolar cycloaddition by using in situ generated **3a** and phenyl azide (**4a**) as the model reaction partners to optimize the reaction. The results are summarized in Table 3. No 1,4-disubstituted 1,2,3-triazole was detected upon performing the reaction in the absence of CuI, and starting material **3a** was recovered completely (Table 3, entry 1). Further, the BF_3K functional group containing the 1,2,3-triazole was not observed. In aqueous [D_6]DMSO, the reaction gave a trace amount of **5a**, as confirmed by ^{1}H NMR spectroscopy (Table 3, entry 2). The conversion yields were proportional to the amount of CuI (Table 3, entries 3–5). An increase in the reaction temperature resulted in satisfactory conversion to desired product **5a** and a reasonable yield of the isolated product (Table 3, entry 6). On the basis of these results, we concluded the optimized set of reaction conditions to be a stoichiometric amount of CuI as the deboronation reagent in aqueous DMSO at 60 °C. Addition of general additives in click chemistry,[9] such as sodium ascorbate and *N*,*N*-dimethylethylenediamine (DMEDA), did not compromise the yield (Table 3, entry 7).

Table 3. Survey of 1,3-dipolar cycloaddition.[a]



Entry	CuI [mol-%]	*T* [°C]	Time [h]	Conversion yield [%]
1	–	40	4	–
2[b]	–	40	4	trace
3[b]	10	40	4	7
4[b]	50	40	4	28
5[b]	100	40	4	79
6[b]	100	60	1	>95 (83)[c]
7[b,d]	100	60	1	>95 (82)[c]

[a] All reactions were performed on a 0.1 mmol scale in [D_6]DMSO (0.4 mL) in an NMR tube and then directly monitored by ^{1}H NMR spectroscopy. [b] H_2O (0.17 mL) was added as a cosolvent. [c] Yield of isolated product is given in parentheses. [d] Sodium ascorbate and DMEDA were used as general additives.

With the optimized conditions for the formation of **5a** in hand, we examined the scope of the 1,3-dipolar cycloaddition with in situ generated copper acetylides and azides for the synthesis of 1,4-disubstituted 1,2,3-triazoles by using a stoichiometric amount of CuI and H_2O at 60 °C. The results for the reactions of general azides with in situ generated potassium arylethynyltrifluoroborates are shown in Table 4. Upon using alkyl azides as coupling partners in the 1,3-dipolar cycloadditions, the products were formed in moderate yields (Table 4, entries 2 and 3). Other in situ generated arylethynyltrifluoroborates from 4-iodoanisole (**2b**), 4-iodobenzonitrile (**2i**), and 5-bromopyrimidine (**2m**) showed almost similar reactivity under the same conditions (Table 4, entries 4–12).

Conclusions

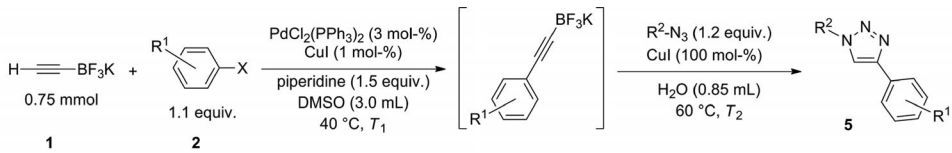
In summary, a versatile and efficient protocol for the direct synthesis of 1,4-disubstituted 1,2,3-triazoles from azides and in situ generated potassium arylethynyltrifluoroborate through Sonogashira coupling of aryl halides with potassium ethynyltrifluoroborate has been developed. This procedure does not require isolation of the potassium arylethynyltrifluoroborate or the aryl acetylene intermediates and would be particularly useful if employing terminal alkynes that are unstable and not commercially available. Further applications with the use of the in situ generated potassium arylethynyltrifluoroborates and copper acetylides are currently under investigation by our group.

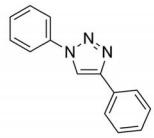
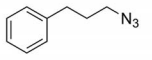
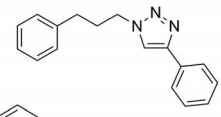
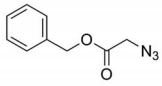
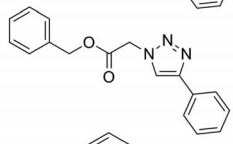
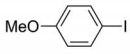
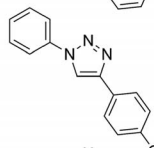
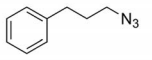
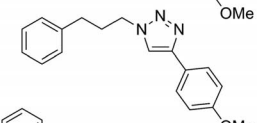
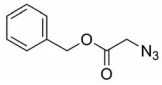
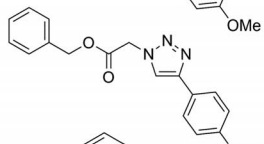
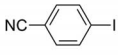
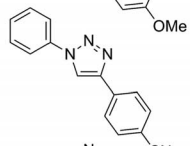
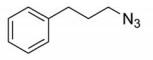
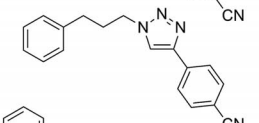
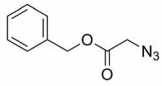
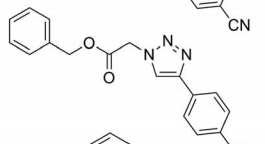
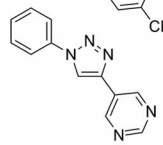
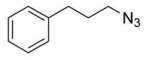
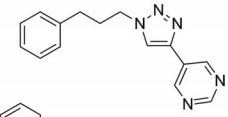
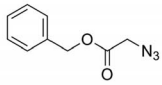
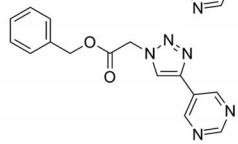
Experimental Section

General Procedure for the Synthesis of Potassium Arylethynyltrifluoroborates: To a solution of potassium ethynyltrifluoroborate (0.5 mmol), $PdCl_2(PPh_3)_2$ (0.015 mmol, 3 mol-%), CuI (0.005 mmol, 1 mol-%), and piperidine (0.75 mmol, 1.5 equiv.) in DMSO (2.0 mL) was added the corresponding aryl halide (0.55 mmol, 1.1 equiv.) under atmospheric conditions. The reaction mixture was stirred in an oil bath at 40 °C. Upon completion of the reaction, the solvent was removed in vacuo at 60–70 °C. The residual product was dissolved in dry acetone (3 × 3 mL), and the insoluble salts were removed by filtration through Celite. The solvent was removed under reduced pressure. The addition of Et_2O led to the precipitation of the product. The product was filtered and dried in vacuo to afford the desired pure product.

General Procedure for the One-Pot Synthesis of 1,4-Disubstituted 1,2,3-Triazoles: To a solution of potassium ethynyltrifluoroborate (0.75 mmol), $PdCl_2(PPh_3)_2$ (0.023 mmol, 3 mol-%), CuI (0.008 mmol, 1 mol-%), and piperidine (1.125 mmol, 1.5 equiv.) in DMSO (3.0 mL) was added the corresponding aryl halide (0.825 mmol, 1.1 equiv.) under atmospheric conditions. The reaction mixture was stirred in an oil bath at 40 °C. Upon completion of the reaction, in situ generated azide (0.90 mmol, 1.2 equiv.) from the corresponding aryl or alkyl halide,[4d,4g] CuI (0.75 mmol, 100 mol-%), and distilled H_2O (0.85 mL) were added. The mixture

Table 4. Synthesis of 1,4-disubstituted 1,2,3-triazoles from in situ generated potassium arylethynyltrifluoroborates.[a]



Entry	R^1-X	R^2-N_3		T_1 [h] T_2 [h]	Product		Yield [%]
1			**4a**	1 3		**5a**	83
2			**4b**	1 3		**5b**	77
3			**4c**	1 3		**5c**	73
4			**4a**	2 3		**5d**	79
5			**4b**	2 3		**5e**	72
6			**4c**	2 3		**5f**	72
7			**4a**	2 3		**5g**	91
8			**4b**	2 3		**5h**	88
9			**4c**	2 3		**5i**	87
10			**4a**	4 3		**5j**	65
11			**4b**	4 3		**5k**	64
12			**4c**	4 3		**5l**	55

[a] All reactions were performed on a 0.75 mmol scale at 40–60 °C in an oil bath.

was stirred at 60 °C. Upon completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 × 3 mL), and the combined organic layer was washed with H_2O (5 mL). Finally, the organic layer was dried with $MgSO_4$. The solvent was removed under reduced pressure. The crude product was purified by silica gel chromatography.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and analytical and spectroscopic data (copies of the ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and ^{11}B NMR spectra) for new compounds.

Acknowledgments

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[8] Monitoring of the reaction by NMR spectroscopy was performed on the basis of the integration of the peaks at $\delta(^1H)$ = 1.89 ppm and $\delta(^{19}F)$ = –132.3 ppm, which are attributable to potassium ethynyltrifluoroborate, and the peak at $\delta(^{19}F)$ = –134.0 ppm, which is attributable to potassium phenylethynyltrifluoroborate.

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