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One-pot synthesis of 4,5-disubstituted 1,2,3-(NH)-triazoles using terminal acetylenes, carbon monoxide, aryl iodides, and sodium azide

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ABSTRACT

A one-pot method for the synthesis of 4,5-disubstituted-1,2,3-(NH)-triazoles via carbonylative Sonogashira reaction/1,3-dipolar cycloaddition of terminal acetylenes, carbon monoxide, aryl iodides, and sodium azide was developed. A series of new 4,5-disubstituted-1,2,3-(NH)-triazoles were prepared readily under mild conditions.

1,2,3-Triazoles are important nitrogen heteroarenes and have been widely used in the pharmaceutical and agricultural industries.[1] Numerous synthesis approaches for this kind of compounds have been developed. Earlier, these compounds were typically prepared by forming a mixture of 1,4-disubstituted- and 1,5-disubstituted-1,2,3-triazoles through thermal cycloaddition of azides and alkynes.[2] Recently, copper(I)-catalyzed Huisgen cycloaddition reaction (CuAAC, often referred to as 'click-chemistry')[3] offered a route to synthesize 1,4-disubstituted-1,2,3-triazoles efficiently. Especially, the Ru-catalyzed reaction of terminal alkynes with alkyl azides was discovered to be an unique way to create 1,5-disubstituted-1,2,3-triazoles.[4] However, these methods lack reactivities toward unsubstituted azides (such as NaN_3 and HN_3) and internal alkynes under mild conditions. It is inconvenient to prepare 4,5-disubstituted 1,2,3-(NH)-triazoles using above-mentioned protocols[5] and only a few other methods for the synthesis of 4,5-disubstituted 1,2,3-(NH)-triazoles were developed.[6] It is very necessary to develop novel ways of synthesizing 4,5-disubstituted 1,2,3-(NH)-triazoles. Recently, we reported a new approach for constructing 4,5-disubstituted 1,2,3-(NH)-triazoles based on Sonogashira coupling reaction.[7] This method is efficient, but its imperfections include the requirements of copper catalyst, ultrasonic, dry solvents, and inert atmosphere. In addition, carbonylative cyclization is an efficient approach for synthesizing heterocycles including indole derivatives,[8] lactones,[9] furan derivatives,[10] quinoline derivatives,[11] and pyrrole derivatives.[12] Based on our previous work and by taking the advantages of one-pot multistep reactions (such as minimizing waste, saving energy, and reducing operating times),[13] we report in this work an efficient, facile, and atom-economic method to produce 4,5-disubstituted 1,2,3-(NH)-triazoles via Pd-catalyzed carbonylative Sonogashira reaction and 1,3-dipolar cycloaddition of terminal acetylenes, carbon monoxide, aryl iodides, and sodium azide.

In order to optimize the reaction conditions, 1-hexyne and iodobenzene were chosen as the test substrates. In this preliminary experiment, 1-hexyne, carbon monoxide, iodobenzene, and sodium azide were added with different catalysts and base Et_3N in DMSO under the balloon pressure of CO. It was found that $PdCl_2(PPh_3)_2$ was more efficient than other catalysts such as $PdCl_2/PPh_3$, Pd/C, $PdCl_2$, and $Pd(dba)_2$ (Table 1, entries 1–4). The yields increased gradually with increasing the time of the second step (Table 1, entries 5–7). When Et_3N was replaced by other bases, the yields decreased (Table 1, entries 8 and 9), and the even trace product was obtained with Na_2CO_3 as base (Table 1, entry 10). Thus, the optimal system for this reaction involves $PdCl_2(PPh_3)_2$ (5 mol %), Et_3N (4 equiv), and 36 h (the time of the second step).

We were encouraged by the above results to examine the reactions with a broad range of substrates to determine the suitability and scope of substrates.[14,15] Various aryl iodides were investigated via reacting with 1-hexyne, CO, and sodium azide.

The reaction conditions and results are summarized in Table 2. Several electron-rich aryl iodides were suitable substrates for the reaction, producing 4,5-disubstituted-1,2,3-(NH)-triazoles in good

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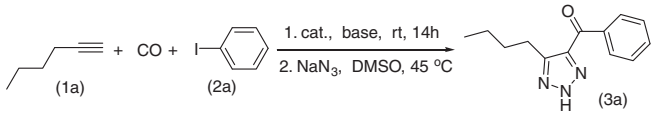
Table 1
Effects of bases and catalysts[a]



(1a) (2a) (3a)

Entry	Catalyst (mol %)	Base	Time[b] (h)	Yield[c] (%)
1	$PdCl_2$ (5)/PPh_3 (10)	Et_3N	36	78
2	Pd/C (5)	Et_3N	36	Trace
3	$PdCl_2$ (5)	Et_3N	36	Trace
4	$Pd(dba)_2$ (5)	Et_3N	36	Trace
5	$PdCl_2(PPh_3)_2$ (5)	Et_3N	12	74
6	$PdCl_2(PPh_3)_2$ (5)	Et_3N	24	78
7	$PdCl_2(PPh_3)_2$ (5)	Et_3N	36	82
8	$PdCl_2(PPh_3)_2$ (5)	Pyridine	36	36
9	$PdCl_2(PPh_3)_2$ (5)	*tert*-Butylamine	36	60
10	$PdCl_2(PPh_3)_2$ (5)	Na_2CO_3	36	Trace

[a] The reaction was carried out with iodobenzene (0.3 mmol) and base (4 equiv, 1.2 mmol) in the presence of catalyst under stirring for 10 min and then 1-hexyne (0.45 mmol) was added. The mixture was stirred at room temperature for 14 h under a balloon pressure of CO, then NaN_3 (1.8 equiv, 0.54 mmol) and 1 mL DMSO were added to the mixture and the reaction continued at 45 °C.
[b] The time of the second step.
[c] Isolated yields after column chromatography.

to excellent yields (74–90%) as given in entries 2–6 (Table 2). When electron-deficient aryl iodides were employed, the yields were somewhat lower (Table 2, entries 7 and 8). Iodobenzenes containing substituents at the 2-position gave poorer results, probably because of the steric influence (Table 2, entries 4 and 6). When the procedure was applied to α-iodonaphthalene and β-iodonaphthalene, the corresponding 4,5-disubstituted-1,2,3-(NH)-triazoles were obtained in good yield (82% and 80%, respectively, Table 2, entries 9 and 10). The above results indicated that this reaction was associated with the electronic properties and steric effect of aryl iodides.

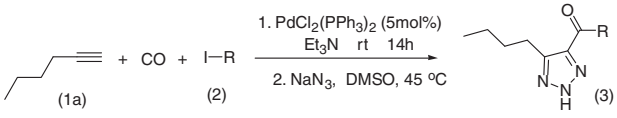
The substrate scope of terminal acetylenes was further investigated. The results indicated that the reaction system can tolerate a variety of terminal acetylenes. As shown in Table 3, 3,3-dimethyl-1-butyne can react with various aryl iodides, and the yields were consistent with those from 1-hexyne (Table 3, entries 1–5), indicating that the branch chain of aliphatic terminal acetylene did not affect the yields. In addition, the aliphatic terminal acetylenes with longer chain can produce better yields (Table 3, entries 6–12). Aromatic acetylenes containing electron-donating, electron-withdrawing substituents, and heteroatom-containing were also examined and they can readily afford the corresponding 4,5-disutituted 1,2,3-trizoles under milder conditions (room temperature, 1 h) in 60–90% yields (Table 3, entries 13–18). So, the reaction conditions are compatible with a variety of terminal acetylenes. The longer chain aliphatic terminal acetylenes can promote the process and the electronic properties of aromatic acetylenes do not affect the yields.

The proposed mechanism for the involved reactions was shown in Scheme 1. Firstly, the aryl palladium iodide species (**I**) was obtained through the oxidative addition of aryl iodide to Pd(0), then, the alkyne would react with the electron-deficient acylpalladium (**II**) derived from the insertion of CO to (**I**).[16] The carbonylative coupling reaction product (**IV**) was obtained through (**IIIA**). Alternatively, insertion of an arylalkyne to the acylpalladium species giving **(IIIB)** followed by β-hydrogen elimination might be a plausible pathway.[17] Subsequent 1,3-dipolar cycloaddition reaction of alkynyl ketones with sodium azide would lead to the formation of the sodium salt of triazoles (**V**). The desired 4,5-disubstituted 1,2,3-(NH)-triazoles (**VI**) was obtained through acidating the sodium salt of triazoles.[7]

Interestingly, when the aryl iodides containing nitro group reacted with terminal acetylenes and NaN_3 under CO atmosphere, the carboxide-free 4,5-disubstituted-1,2,3-(NH)-triazoles were obtained in 32–55% yields (Scheme 2), which could be attributed to Sonogashira coupling of aryl iodides with terminal acetylenes. Because of the strong electrophilic property of nitro group, the carbonylative sonogashira reactions do not happen.[18]

In conclusion, an efficient reaction for the synthesis of 4,5-disubstituted-1,2,3-(NH)-triazoles directly from terminal acetylenes, carbon monoxide, aryl iodides, and sodium azide was

Table 2
Substrate scope of aryl iodides[a]

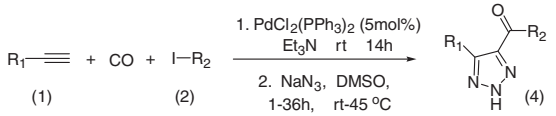


(1a) (2) (3)

Entry	R	Product	Yield[b] (%)
1	Phenyl	**3a**	82
2	3,4-$(CH_3)_2C_6H_3$	**3b**	90
3	4-$CH_3C_6H_4$	**3c**	88
4	2-$CH_3C_6H_4$	**3d**	80
5	4-$CH_3OC_6H_4$	**3e**	86
6	2- $CH_3OC_6H_4$	**3f**	74
7	4-ClC_6H_4	**3g**	49
8	4-BrC_6H_4	**3h**	54
9	α-Naphthyl	**3i**	82
10	β-Naphthyl	**3j**	80

[a] The reaction was carried out with aryl iodides (0.3 mmol) and Et_3N (4 equiv, 1.2 mmol) in the presence of $PdCl_2(PPh_3)_2$ under stirring for 10 min and then 1-hexyne (0.45 mmol) was added. The mixture was stirred at room temperature for 14 h under a balloon pressure of CO, then NaN_3 (1.8 equiv, 0.54 mmol) and 1 mL DMSO were added to the mixture and the reaction continued at 45 °C for 36 h.
[b] Isolated yields after column chromatography.

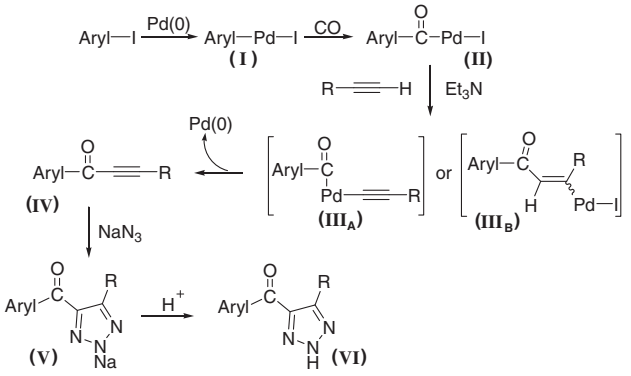
Table 3
Substrate scope of terminal acetylenes[a]



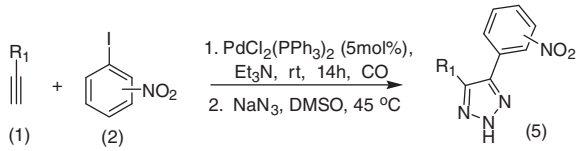
(1) (2) (4)

Entry	R_1	R_2	Time[b] (h)	Product	Yield[c] (%)
1	*t*-C_4H_9	3,4-$(CH_3)_2C_6H_3$	36	**4a**	93
2	*t*-C_4H_9	4-$CH_3OC_6H_4$	36	**4b**	85
3	*t*-C_4H_9	2-$CH_3OC_6H_4$	36	**4c**	74
4	*t*-C_4H_9	4-$CH_3C_6H_4$	36	**4d**	91
5	*t*-C_4H_9	4-$C_2H_5OC_6H_4$	36	**4e**	82
6	*n*-C_8H_{17}	Phenyl	36	**4f**	83
7	*n*-C_8H_{17}	3,4-$(CH_3)_2C_6H_3$	36	**4g**	95
8	*n*-C_8H_{17}	4-$CH_3OC_6H_4$	36	**4h**	89
9	*n*-C_8H_{17}	2-$CH_3OC_6H_4$	36	**4i**	81
10	*n*-C_8H_{17}	4-$CH_3C_6H_4$	36	**4j**	98
11	*n*-C_8H_{17}	4-$C_2H_5OC_6H_4$	36	**4k**	86
12	*n*-C_8H_{17}	α-Naphthyl	36	**4l**	90
13	Phenyl	4-$CH_3C_6H_4$	1	**4m**	75[d]
14	Phenyl	2-$CH_3C_6H_4$	1	**4n**	60[d]
15	Phenyl	4-$CH_3OC_6H_4$	1	**4o**	77[d]
16	4-FC_6H_4	4-$CH_3OC_6H_4$	1	**4p**	90[d]
17	Thiophen-3-yl	4-$CH_3OC_6H_4$	1	**4q**	65[d]
18	4-*n*-$C_5H_{11}OC_6H_4$	4-$CH_3OC_6H_4$	1	**4r**	88[d]

[a] The reaction was carried out with aryl iodides (0.3 mmol) and Et_3N (4 equiv, 1.2 mmol) in the presence of $PdCl_2(PPh_3)_2$ under stirring for 10 min and then terminal acetylenes (0.45 mmol) were added. The mixture was stirred at room temperature for 14 h under a balloon pressure of CO, then NaN_3 (1.8 equiv, 0.54 mmol) and 1 mL DMSO were added to the mixture and the reaction continued at 45 °C for 1–36 h.
[b] The time of the second step.
[c] Isolated yields after column chromatography.
[d] The reaction temperature is room temperature.



Scheme 1. Possible mechanism to synthesize 4,5-disubstituted 1,2,3-(NH)-triazoles.



5a: R_1 = *n*-C_4H_9, 4-NO_2PhI, yield 53%
5b: R_1 = *n*-C_4H_9, 2-NO_2PhI, yield 32%
5c: R_1 = *n*-C_8H_{17}, 4-NO_2PhI, yield 55%

Scheme 2. Synthesis of carboxide-free 4,5-disutituted 1,2,3-trizoles.

developed based on carbonylative Sonogashira reaction in one pot. The procedure is suitable to many substrates. Different 4,5-disubstituted-N-unsubstituted 1,2,3-triazoles can be produced using cheap and easily available starting materials. The developed method is atom economic and performed easily, making it possibly acceptable for industrial-scale production.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.053.

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14. Typical procedure for the preparation of 4,5-disubstituted-1,2,3-(NH)-triazoles (synthesis of **3a**): A round-bottom sidearm flask (10 mL) containing $PdCl_2(PPh_3)_2$ (0.015 mmol) was subjected to the Schlenk-line procedures of evacuation and purging of CO for three cycles. Iodobenzene and 4 equiv Et_3N (1.2 mmol) were successively added, and the mixture was stirred at room temperature for 10 min, then 1-hexyne (0.45 mmol) was added, continuously stirred at room temperature for 14 h. Then NaN_3 (35.1 mg, 0.54 mmol) and 1 mL DMSO were added to the mixture and the reaction continued at 45 °C for 36 h. Following, to the reaction mixture was added water (2 mL), 20% HCl solution (1 mL) and extracted with ether (3 × 10 mL). The combined organic phases were washed with brine (2 × 5 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was subjected to flash column chromatography with hexanes/EtOAc (5/1) as eluent to obtain the desired **3a** (56.33 mg, 82% yield). All products gave satisfactory spectroscopic and analytical data.
15. Spectroscopic data for representative examples: *(5-butyl-2H-1,2,3-triazol-4-yl)(3,4-dimethylphenyl)methanone (***3b**, Table 2, *entry 2)*: mp: 71–73 °C. IR (cm^{-1}):3166.68, 2959.12, 1646.18, 1472.08, 1325.62, 1258.03, 1118.52. ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 6.0 Hz, 2H), 7.25 (t, J = 8.0 Hz, 1H), 3.06 (t, J = 7.8 Hz, 2H), 2.32 (d, J = 4.8 Hz, 6H), 1.64–1.78 (m, 2H), 1.31–1.40 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.64, 147.40, 142.74, 142.08, 136.68, 135.17, 131.29, 129.56, 128.24, 30.62, 24.34, 22.35, 20.01, 19.71, 13.64. MS *m/z*: 257 (M^+, 30%), 242 (100), 228 (11), 214 (16), 200 (55), 133 (45), 122 (46), 105 (48), 77 (48), 41 (51). Anal. Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.05; H, 7.46; N, 16.38. *(5-Butyl-2H-1,2,3-triazol-4-yl)(4-methoxyphenyl)methanone* (**3e**, Table 2, *entry 5*): IR (cm^{-1}): 3171.25, 2931.41, 1598.72, 1467.64, 1260.70, 1151.33, 921.09. ^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H), 3.08 (t, J = 7.8 Hz, 2H), 1.70 (t, J = 7.4 Hz, 2H), 1.34–1.39 (m, 2H), 0.87–0.91 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.35, 163.65, 147.38, 142.17, 132.87, 130.10, 113.59, 55.44, 30.63, 24.39, 22.37, 13.66. MS *m/z*: 259 (M^+, 21%), 216 (55), 186 (41), 135 (100). Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found: C, 64.87; H, 6.67; N, 16.23. See Supplementary data for spectral data of all other compounds.
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