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Multi-Component Reaction for the Preparation of 1,5-Disubstituted 1,2,3-Triazoles by In-Situ Generation of Azides and Nickel-Catalyzed Azide-Alkyne Cycloaddition.

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Abstract

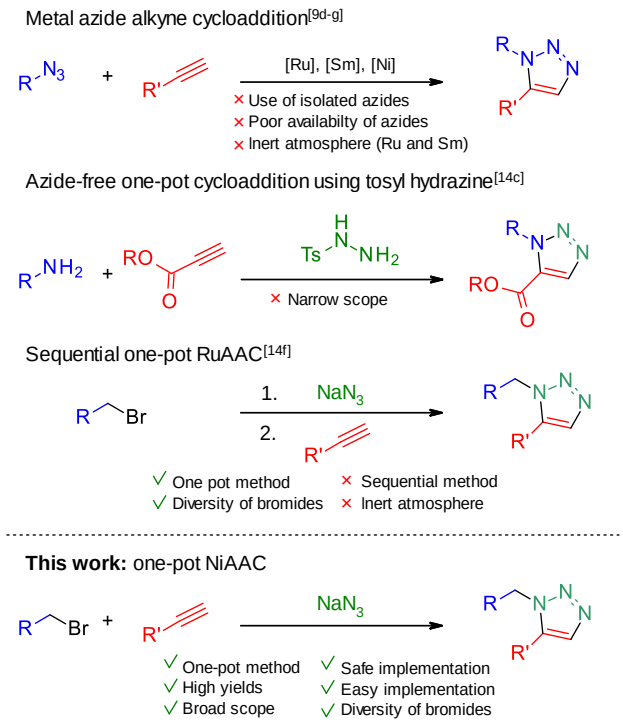
An efficient one-pot procedure combining bromide conversion into azide followed by NiAAC for the preparation of 1,5-disubstituted 1,2,3-triazoles has been developed. This procedure prevents the use of isolated azides, which are insufficiently commercially available and could be potentially unstable and difficult to handle. Moreover, this one-pot method tolerates a broad range of functional moieties including ester, carbamate or alcohol. Diverse 1,5-disubstituted 1,2,3-triazoles can be obtained from functionalized aryl and alkyl alkynes and bromides with modest to excellent yields and regioselectivities. This procedure will enable the synthesis of libraries of functionalizable 1,5-disubstituted 1,2,3-triazoles particularly helpful for diverse applications such as medicinal chemistry and chemical biology purposes.

click chemistry ; molecular diversity ; multicomponent reactions ; regioselectivity ; synthetic methods

Introduction

Spearhead of the heterocycles generated by click chemistry, 1,2,3-triazoles are broadly found in several domains such as materials science,[1] organometallic science[2] but also chemical biology[3] and medicinal chemistry[4]. This considerable importance is due to the favorable properties linked to this heteroaromatic ring but also thanks to the easiness of access of the 1,4-disubstituted 1,2,3-triazoles by copper-catalyzed azide-alkyne cycloaddition (CuAAC).[5] This methodology is indeed powerful with excellent regioselectivity, high yield and is easy to implement. Noteworthy, the 1,5-disubstituted 1,2,3-triazoles are less represented. As there is a high interest for 1,5-disubstituted regioisomers in drug discovery as disulfide bond surrogate[6] or cis-peptide bond mimetic[7] or enzyme modulator[8], it is valuable to facilitate the access of this scaffold. Several teams have worked on this purpose and to date there are few methods to synthesize 1,5–disubstituted 1,2,3-triazoles, which are for most of them with very limited scope. The main methodologies use azide-alkyne cycloadditions either mediated by metal acetylide or metal catalysts.[9] The alkynes can also be replaced by nitroolefins with the use of metallic additives to afford 1,5–disubstituted 1,2,3-triazoles substituted by aryl groups.[10] Moreover, in a lesser extent, other functional moieties have also been used for playing the role of dipolarophile in 1,5-disubstituted 1,2,3-triazole synthesis.[11] An alternative method based on a cascade Michael addition was also described for the construction of 1,5-disubstituted 1,2,3-triazoles.[12] Regrettably, most of these methodologies have scope constraints. Besides, most of them require the handling of isolated organic azides, which are not often commercially available and are known to be unstable, especially those of low molecular weight.[13]

In order to bypass these drawbacks, only few methods, most of them being multicomponent, have been developed.[14] These methodologies have the advantage to be safer by preventing the manipulation of organic azides. However, they suffer from a very limited substrate scope, often requesting high temperatures, strict inert atmosphere conditions or an inconvenient sequential pattern, all of which have confined their use. In order to provide an extensive procedure that circumvent all these drawbacks and that afford functionalized 1,5-disubsituted 1,2,3-triazoles suitable for diverse applications, we investigated the feasibility to implement an efficient and safe one-pot, two-step method. This procedure would allow the in situ bromides conversion by nucleophilic substitution with sodium azide into azides, which react consecutively with alkynes by NiAAC (Scheme 1).



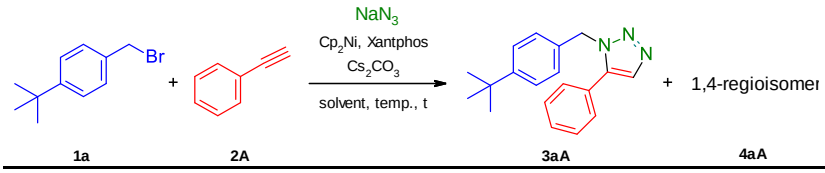
Scheme 1. Strategies for the synthesis of 1,5-disubstituted 1,2,3-triazoles.

Results and discussion

First we performed the screening of different reaction conditions on the model substrates 4-tert-butylbenzyl bromide **1a** and phenylacetylene **2A** (Table 1). Reaction conditions close to the recently published NiAAC ones[9g] were applied with the combination of bromide **1a** (1.0 equiv), sodium azide (1.0 equiv), alkyne **2A** (1.2 equiv) in presence of nickelocene (Cp_2Ni) precatalyst (20 mol%), bidentate Xantphos ligand (20 mol%) and Cs_2CO_3 (1.0 equiv) at room temperature for 2 h in water. Under these conditions, the bromide **1a** was converted into azide but the cycloaddition was not observed (entry 1). To facilitate the triazole formation, several conditions were screened. First, dimethylformamide, often used as a solvent for azide formation from bromide and shown to be efficient for the NiAAC, was evaluated (entry 2). Pleasantly, this solvent allowed the triazole formation with good yield (71 %) contrary to other solvents such as dichloromethane, ethanol and tetrahydrofuran (entries 2-5). In order to improve the reaction conversion into triazole, the reaction vessel was slightly heated at 50°C under microwave irradiation for 1 h (entry 6). This heating condition was beneficial for the regioselectivity (from 88:12 to 93:7) without compromising the yield (entries 2 vs 6). Higher temperature (80 °C or 100 °C) resulted to a lower yield and a poorer regioselectivity (entries 7 and 8), probably due to the catalyst degradation. Increasing reaction time to 4 h improved yield (86 %, entry 9) but slightly decreased the regioselectivity (from 93:7 to 92:8). In the attempt to improve the yield of the 1,5-disubsituted 1,2,3-triazole **3aA**, the bromide **1a** and the sodium azide were defined as excess reagents (1.2 equiv and 1.5 equiv respectively) (entries 10). Appealingly, after 4 h under microwave irradiation at 50°C, the calculated yield fo triazole **3aA** was excellent (89 %) with no secondary products and

excellent regioselectivity (92:8). To investigate the mechanism of this multicomponent method, 4-tert-butylbenzyl bromide **1a** was submitted to sodium azide at room temperature for 2 h in DMF with or without the Cp_2Ni/Xantphos catalytic system. For both conditions, 4-tert-butylbenzyl azide was formed in quantitative yield. Thus, the nickelocene precatalyst in association with its Xantphos ligand has no influence on the SN2 event and only has positive effect for the azide-alkyne cycloaddition and its regioisomerism.

Table 1. Condition screening[a].



Entry	Solvent	Temp (°C)	Time (h)	*c*Yield (%)[c]	Ratio **3aA/4aA**[d]
1	H_2O	rt	2	–[e]	–[e]
2	DMF	rt	2	71	88:12
3	EtOH	rt	2	–[e]	–[e]
4	DCM	rt	2	–[e]	–[e]
5	THF	rt	2	–[e]	–[e]
6	DMF	50 °C (MW)	1	73	93:7
7	DMF	80 °C (MW)	1	49	64:36
8	DMF	100 °C (MW)	1	–[e]	–[e]
9	DMF	50 °C (MW)	4	86	92:8
10[b]	DMF	50 °C (MW)	4	89	92:8

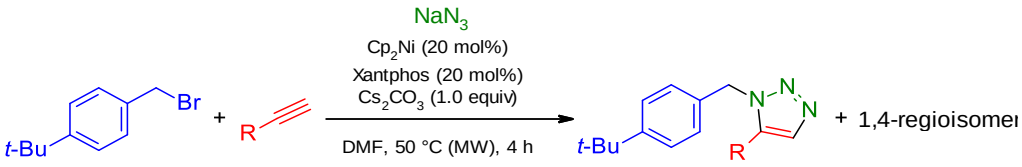
[a]Reaction conditions: Run on a 0.5 mmol scale of alkyne **2A** (1.2 equiv), bromide **1a** (1.0 equiv), NaN_3 (1.0 equiv), solvent (2 mL), Cp_2Ni (20 mol%), Xantphos (20 mol%), Cs_2CO_3 (1.0 equiv). [b]Run on a 0.5 mmol scale of alkyne **2A** (1.0 equiv), bromide **1a** (1.2 equiv), NaN_3 (1.5 equiv), solvent (2 mL), Cp_2Ni (20 mol%), Xantphos (20 mol%), Cs_2CO_3 (1.0 equiv). [c]Calculated yield of **3aA** determined by LCMS analysis from the crude product. [d]Determined by LCMS analysis from the crude product. [e]No triazole formation. Cp, cyclopentadienyl; *c*Yield, calculated yield; DCM, dichloromethane; DMF, dimethylformamide; MW, microwave irradiation; temp, temperature; rt, room temperature.

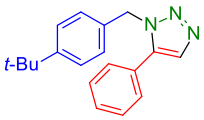
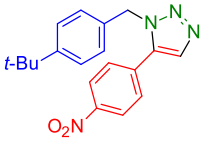
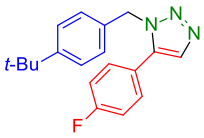
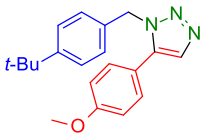
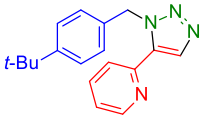
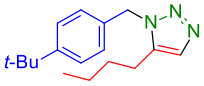
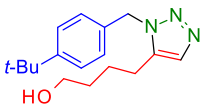
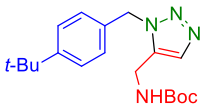
After determining the optimized conditions for this one-pot procedure, we explored the scope with various alkynes and bromides. The integrity of the 1,5-disubstituted 1,2,3-triazole template was validated by NMR NOESY and HSQC experiments to corroborate the distinctive ^{13}C chemical shift of the triazole CH at ~133 ppm.[14]

The evaluation of substrate scope with various aromatic (**2A**–**2E**) and aliphatic alkynes (**2F**–**2H**) in reaction with bromide **1a** is summarized in Table 2. Except for alkynes **2D** and **2E**, the attempts to separate and isolate the two regioisomers **3** and **4** were not fruitful either by classical flash column chromatography, or by C-18 reversed-phase flash column chromatography with the use of classical or pentafluorophenyl columns. However, because of the high regioselectivity rates associated with this methodology (from 66:34 to >99:1), flash chromatography was still performed to afford **3** in mixture with **4** in order to evaluate the efficiency of this one-pot multicomponent procedure. Modest to excellent calculated yields ranging from 27% to 84% were obtained. Besides, in order to isolate and characterize properly the 1,5-regioisomers **3**, the reaction crude mixtures were also purified by semi-preparative supercritical fluid chromatography (SFC) and comparable isolated yields (24% to 72%) were obtained.

The regioselectivity of the reactions was determined by supercritical fluid chromatography (SFC) analysis of the crude reaction mixtures obtained after the work-up of the reactions carried out with alkynes **2A**–**2E** and **2H**, or according to the ^{1}H-NMR spectra for reactions carried out with alkynes **2F** and **2G,** whose separation of the two regioisomers by SFC was not optimal. Modest to excellent regioselectivities were obtained. Considering the regioselectivity obtained with the *p*-nitrophenylacetylene **2B** (ratio 66:34) compared to the phenylacetylene **2A** (ratio 89:11) and then the *p*-fluorophenylacetylene **2C** (ratio 91:9) and the *p*-methoxyphenylacetylene **2D** (ratio >99:1), a positive mesomeric effect on the phenyl ring seems to induce a positive contribution to the regioselectivity without having an effect on the yield. Noteworthy, heteroaryl and alkyl chains are accepted for this procedure (**2E**–**2H**). Interestingly, the scope was widened by hydroxyl and carbamate moieties, which were compatible with this process.

Table 2. Substrate scope with various alkynes[a].



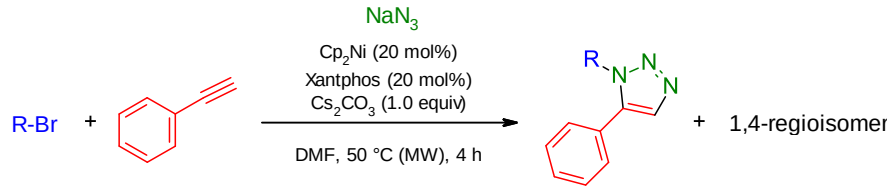
	**3aA** 72 (64) 89:11		**3aB** 24 (37) 66:34		**3aC** 34 (84) 91:9		**3aD** 76[b] >99:1
	**3aE** 73[b] 92:8		**3aF** 36 (27) 86:14[c]		**3aG** 56 (70) 89:11[c]		**3aH** 34 (34) 67:33

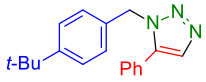
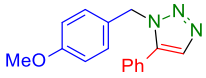
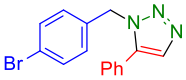
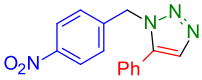
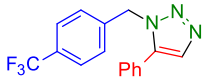
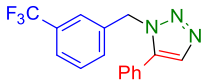
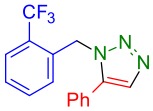
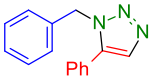
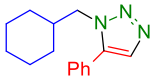
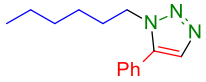
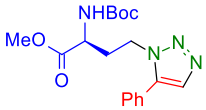
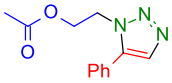
[a]Reaction conditions: Run on a 0.3-0.6 mmol scale of alkyne **2** with **1a** (1.2 equiv), NaN_3 (1.5 equiv), Cp_2Ni (20 mol%), Xantphos (20 mol%), Cs_2CO_3 (1.0 equiv), DMF (2.0 mL), 50 °C (MW), 4 h. Isolated yields of **3** obtained after SFC purification; **3**/**4** ratio determined from the crude product by SFC analysis

unless noted otherwise; in brackets: calculated yields of **3** obtained after flash column chromatography purification (in mixture with **4**); [b]Isolated yield of **3** obtained after flash column chromatography purification; [c]Determined by ^{1}H-NMR. Boc, tert-butoxycarbonyl; Cp, cyclopentadienyl; t-Bu, tert-butyl.

The substrate scope was also examined with various bromides (Table 3). Aromatic benzyl bromide possessing either electron-donating (**1a** and **1b**) or electron-withdrawing (**1c**–**1g**) groups are tolerated and afforded the 1,5-regioisomers (**3aA**–**3gA**) with modest to high yields both after flash chromatography purification (calculated yield: 64% – 79%) and after semi-preparative SFC purification (isolated yield: 31% – 84%). The ortho isomer **3gA** was obtained with the lowest yield in the series, probably due to steric effect. Besides, regioisomerism of the phenyl substitution (**1e**–**1g**) has only minor impact on the yield and does not influence the regioselectivity. Strikingly, high to excellent regioselectivities from 85:15 to 97:3 ratios were also obtained. Interestingly, the scope of this one-pot procedure could be efficiently enlarged with non-saturated bromide (**1i**–**1l**). Noteworthy, functional groups such as carbamate-protected amine and ester are well tolerated with these reaction conditions (**1k**–**1l**) providing the related 1,5-disubstituted 1,2,3-triazoles with high to excellent yields and regioselectivities.

Table 3. Substrate scope with various alkynes[a].



	**3aA** 72 (64) 89:11		**3bA** 67 (69) 85:15		**3cA** 68 (64) 85:15		**3dA** 68[b] 97:3
	**3eA** 84 (73) 93:7		**3fA** 73 (79) 95:5		**3gA** 31 (64) 94:6		**3hA** 89 (25) 93:7
	**3iA** 46 (65) 91:9		**3jA** 45 (67) 94:6		**3kA** 64 (90) 96:4		**3lA** 34 (34) 81:19

[a]Reaction conditions: Run on a 0.49 mmol scale of alkyne **2A** with **1** (1.2 equiv), NaN_3 (1.5 equiv), Cp_2Ni (20 mol%), Xantphos (20 mol%), Cs_2CO_3 (1.0 equiv), DMF (2.0 mL), 50 °C (MW), 4 h. Isolated yields of **3** obtained after SFC purification; **3**/**4** ratio determined from the crude product by SFC analysis unless noted otherwise; in brackets: calculated yields of **3** obtained after flash column chromatography purification (in mixture with **4**); [b]Isolated yield of **3** obtained after flash column chromatography. Boc, tert-butoxycarbonyl; Cp, cyclopentadienyl; Me, methyl; Ph, phenyl; t-Bu, tert-butyl.

Briefly, we succeeded in providing a procedure to efficiently access diverse 1,5-disubstitued 1,2,3-triazoles in a fast and simple manner. Remarkably, one of the advantages of this one-pot reaction is the in situ generation of azides from bromides, which are commercially available with a large diversity. Thus, this one-pot method prevents the sequential and time-consuming synthesis and isolation of azides, which could be unstable and are rarely commercially available. It makes this procedure very convenient, especially when sensitive low-molecular weight azides are required. A diverse range of functional moieties including N-protected amines, hydroxyls and esters are tolerated by these reaction conditions. This method will enable the synthesis of libraries of functionalizable 1,5-regioisomers especially useful for drug discovery and chemical biology purposes.

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