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Facile and quick synthesis of 1-monosubstituted aryl 1,2,3-triazoles: a copper-free [3+2] cycloaddition

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ABSTRACT

An efficient copper-free synthesis of 1-monosubstituted aryl 1,2,3-triazoles from sodium acetylide and aryl azides was developed, which was found suitable for various aryl azides and completed within 15 min at room temperature with moderate to excellent yields.

1. Introduction

Since the Huisgen 1,3-dipolar cycloaddition of azides and alkynes was developed into the 'click chemistry' at the beginning of this century,[1] the significance of synthesis of 1,2,3-triazoles has increased in medicinal,[2] material,[3] and biological[4] research owing to the unique properties of this heterocycle. Recently, the utilization of 1,2,3-triazoles in catalysts and ligands has also been reported.[5] The fast growing requirements of this heterocycle necessitate the development of effective methods for the preparation of diverse 1,2,3-triazole derivatives. In addition, the procedure is commonly performed in the presence of copper.[6] With consideration on the cytotoxicity of copper residue in particular cases,[7] the processes involving different transition metals (Ru, Ni, Pd, Pt, and Fe) and different ligands (PMDETA, bipyridine derivatives, terpyridine derivatives, and Me_6Tren) have also been examined in recent years.[8] Acetylides, including lithium and magnesium, were used for the preparation of 1,2,3-triazole under the copper-free conditions by Akimova et al. in the 1960s.[9] These methods, however, suffered from several drawbacks: difficulty in preparing the 1-monosubstituted 1,2,3,-triazoles, low yields (<30% for some substrates), and long reaction time (>72 h in most cases). Recently, several metal catalyst-free azide–alkyne cycloadditions were reported to be used in the fields of biology and material science. The reactions employed special kinds of alkyne moieties, such as substituted cyclooctynes,[10] activated alkynes,[11] electron-deficient alkynes,[12] and arynes,[13] in which the reactivity of the alkyne groups was increased,[14] as shown in Fig 1.

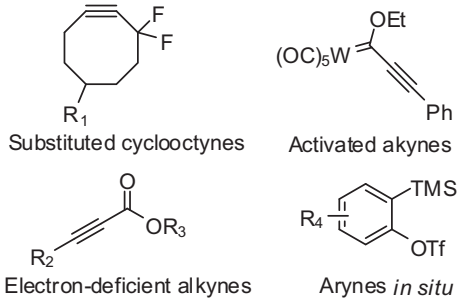

Fig. 1. Reported Alkynes in metal-catalyst free cycloaddition.

Although there are numerous methods for the preparation of 1,4-disubstituted 1,2,3-triazoles, literature concerning the synthesis of 1-monosubstituted aryl 1,2,3-triazoles is relatively rare. One strategy is the decarboxylation of triazoles bearing carboxylic acid substituent, which requires extreme temperature and long reaction time.[15] Another method is the [3+2] cycloaddition of azides to acetylene and its analogs under the conditions of heating and presence of copper catalyst.[16a–d,6j] Recently, we have efficiently synthesized a series of 1-monosubstituted aryl 1,2,3-triazoles utilizing calcium carbide as a source of acetylene.[16b] Thus, for this study, we report on the successful use of commercially available sodium acetylide for the efficient and quick synthesis of 1-monosubstituted aryl 1,2,3-triazoles in the absence of copper catalyst at room temperature.

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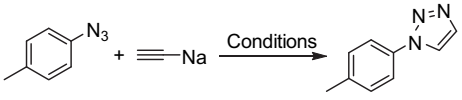
2. Results and discussion

To screen the suitable reaction conditions, 1-azido-4-methylbenzene **1a** was used as model substrate with sodium acetylide. Initially, non-toxic EtOH was employed as solvent at 80°C. Forty percent isolated yield was obtained when CuI and sodium ascorbate catalyst system was used while no product was observed in the absence of catalyst (Table 1, entries 1 and 2). Moderate yields were obtained at both room temperature and 80 °C in the presence of CuI catalyst when DMF was used as solvent (Table 1, entries 3 and 4). Surprisingly, the yield increased to 65% when the reaction was conducted at room temperature without the use of catalyst (Table 1, entry 5). Motivated by this result, we examined other solvents, such as benzene, MeCN, MeCN–H_2O mixture, and DMSO at room temperature in the absence of CuI (Table 1, entries 6–9). DMSO showed more vigorous compared with the others and achieved a significant yield of 70%. Moreover, the system is highly efficient and completed the process within 15 min (Table 1, entry 9). Excellent yield of 81% was achieved when the quantity of sodium acetylide was increased to 6 equiv (Table 1, entry 10). Seemingly, increase in temperature, or use CuI were not necessary (Table 1, entry 11 and 12).

Under the optimized conditions, the substrate scope of the copper-free quick synthesis of 1-monosubstituted aryl 1,2,3-triazoles was investigated and the conditions appeared to be generally similar for a spectrum of aryl azides (Table 2).

Table 1
Optimization of copper-free cycloaddition of **1a** with sodium acetylide[a]



1a **2a**

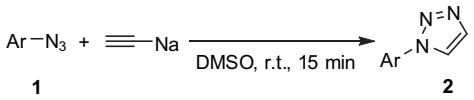
Entry	Solvent	Temp	Catalyst	Time	Yield[b] (%)
1[c]	EtOH	80 °C	—	12 h	0
2	EtOH	80 °C	CuI(20%)	4 h	40
3	DMF	80 °C	CuI(20%)	4 h	50
4	DMF	rt	CuI(20%)	6 h	55
5	DMF	rt	—	6 h	65
6	Toluene	rt	—	8 h	20
7	MeCN	rt	—	8 h	46
8[c]	MeCN/H_2O	rt	—	8 h	0
9	DMSO	rt	—	15 min	70
10[d]	**DMSO**	**rt**	—	**15 min**	**81**
11	DMSO	80 °C	—	15 min	48
12	DMSO	rt	CuI(20%)	15 min	66

The significant of bold value is the optimized conditions.
[a] Unless otherwise noted, the reaction conditions are as follows: 1-azido-4-methylbenzene **1a** (0.3 mmol), sodium acetylide (4 equiv), in solvent (3 mL).
[b] Isolated yield.
[c] Compound **1a** was recovered.
[d] Sodium acetylide (6 equiv) was used.

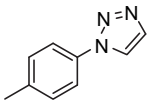
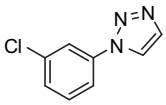
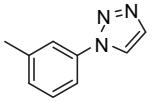
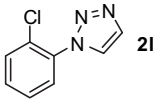
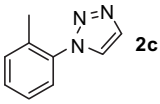
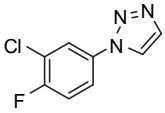
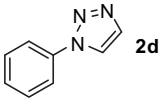
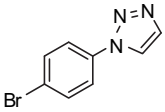
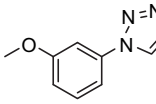
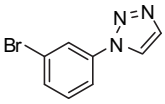
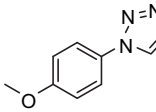
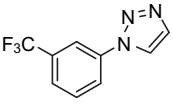
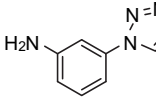
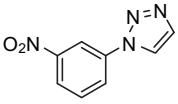
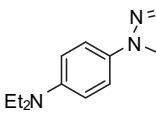
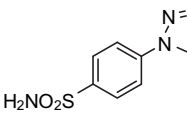
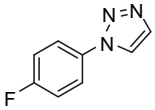
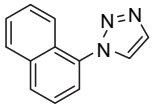
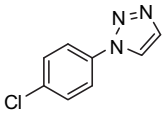
It was observed that aryl azides carrying either an electron donating substituent, such as methyl (Table 2, **2a**–**c**), methoxyl (**2e**–**f**), and amino-group (**2g**–**h**), or an electron withdrawing group including halogens (**2i**–**o**), trifluoromethyl (**2p**), nitryl (**2q**), and sulfonamide (**2r**) could perform efficiently with moderate to excellent yields. Higher yields were obtained when the substrates had a substituent at *meta*-position whether it was electron donating or electron withdrawing (**2b**, **2e**, **2k**). Aryl azides bearing an *ortho*-group could also complete the process within 15 min at room temperature. However, the yield was lower (**2c**, **2l**, **2s**).

Compared to the other acetylides[9] used in copper-free [3+2] cycloaddition, which have been reported, this system is easier to manipulate and showed higher efficiency. The reactions can be completed within 15 min and can produce the 1-monosubstitued 1,2,3-triazoles, which are not as easy to synthesize as the 1,4-disubstituted 1,2,3-triazoles.

Table 2
Copper-free quick synthesis of 1-monosubstituted aryl 1,2,3-triazoles[a,b]



1 **2**

Product **2**	Yield[b](%)	Product **2**	Yield[b](%)
 **2a**	81	 **2k**	93
 **2b**	88	 **2l**	58
 **2c**	55	 **2m**	75
 **2d**	75	 **2n**	75
 **2e**	93	 **2o**	96
 **2f**	90	 **2p**	81
 **2g**	68	 **2q**	73
 **2h**	82	 **2r**	83
 **2i**	72	 **2s**	52
 **2j**	75		

[a] Reaction conditions: azides **1** (0.3 mmol), sodium acetylide (6 equiv), DMSO (3 mL), rt.
[b] Isolated yield.

It is believed that the reactivity of the alkynes group is increased in the copper-free azide–alkyne cycloadditions,[14] although there is minimal information available in literature about the mechanism. In this case, the alkyne group in sodium acetylide is seemingly activated in the system, allowing copper-free azide–alkyne cycloadditions to occur with high efficiency at room temperature. Nevertheless, the exact mechanism remains unknown. Owing to this, further studies on the reaction mechanism are ongoing.

3. Conclusion

We have demonstrated copper-free azide–alkyne cycloadditions, which showed high efficiency and speed; the process was

completed within 15 min at room temperature with moderate to excellent yields. It provides a quick access to 1-monosubstitued aryl 1,2,3-triazoles, which are important kinds of heterocycle compounds for medical, material, and biological research.

4. Experimental

4.1. General

All commercially available reagents and solvent were obtained from the commercial providers and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker AM-500 MHz spectrometer. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00 ppm) for ^{1}H, and $CDCl_3$ (δ 77.0 ppm) for ^{13}C. MS data were measured with a Varian-310 mass spectrometer. High resolution mass spectra were determined using a Finnigan-NAT GC/MS/DS 8430 spectrometer. Flash column chromatography was performed on 300–400 mesh silica gel. Aryl azides were prepared according to procedures in literature.[17]

4.2. General procedure for synthesis of 1-monosubstituted aryl 1,2,3-triazoles 2

DMSO (3 mL) and aryl azide **1** (0.3 mmol) were added to a round-bottomed flask. (*CAUTION*! Aryl azides are poisonous and potentially explosive due to heat, light, and pressure. Any azides synthesized should be stored below 0 °C and in the dark.) The flask was equipped with a rubber septa and sodium acetylide (1.8 mmol, 18 wt % suspension in xylene) was subsequently added to the system via syringe. (*CAUTION*! Sodium acetylide is moisture sensitive and all apparatus should be dried thoroughly before use.) After stirring the mixture for 15 min at room temperature, the reaction was quenched with the addition of 20 mL water. The mixture was extracted with ether (25 mL, three times) and the combined organic layer was washed with water, and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by silica gel column chromatography to derive 1-monosubstituted aryl 1,2,3-triazoles **2** as products.

*4.2.1. 1-p-Tolyl-1H-1,2,3-triazole (**2a**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J=0.9 Hz, 1H), 7.83 (d, J=0.9 Hz, 1H), 7.62 (d, J=8.4 Hz, 1H), 7.32 (d, J=8.6 Hz, 1H), 2.43 (s, 3H).[16b]

*4.2.2. 1-m-Tolyl-1H-1,2,3-triazole (**2b**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.85 (s, 1H), 7.59 (s, 1H), 7.52 (d, J=8.1 Hz, 1H), 7.41 (t, J=7.8, 7.8 Hz, 1H), 7.26 (d, J=6.8 Hz, 1H), 2.46 (s, 3H).[16a]

*4.2.3. 1-o-Tolyl-1H-1,2,3-triazole (**2c**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.76 (s, 1H), 7.44–7.31(m, 4H), 2.21 (s, 3H).[16b]

*4.2.4. 1-Phenyl-1H-1,2,3-triazole (**2d**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J=0.9 Hz, 1H), 7.86 (d, J=0.9 Hz, 1H), 7.76–7.75 (m, 2H), 7.57–7.53 (m, 2H), 7.47–7.44 (m, 1H).[16b]

*4.2.5. 1-(3-Methoxyphenyl)-1H-1,2,3-triazole (**2e**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.84 (s, 1H), 7.43–7.36(m, 2H), 7.27–7.26 (m, 1H), 6.9–6.97 (m, 1H), 3.88 (s, 3H).[6j]

*4.2.6. 1-(4-Methoxyphenyl)-1H-1,2,3-triazole (**2f**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.83 (s, 1H), 7.64 (d, J=9.0 Hz, 2H), 7.03 (d, J=9.0 Hz, 1H), 3.88 (s, 3H).[16a]

*4.2.7. 3-(1H-1,2,3-Triazol-1-yl)aniline (**2g**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J=1.1 Hz, 1H), 7.82 (d, J=1.0 Hz, 1H), 7.29–7.27 (m, 1H), 7.14–7.13 (m, 1H), 7.03–7.01 (m, 1H), 6.74–6.72 (m, 1H), 3.95 (s, 2H).[18a]

*4.2.8. N,N-Diethyl-4-(1H-1,2,3-triazol-1-yl)aniline (**2h**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.78 (s, 1H), 7.50 (d, J=9.0 Hz, 2H), 6.72 (d, J=9.0 Hz, 2H), 3.39 (q, J=7.1, 7.1, 7.0 Hz, 4H), 1.19 (t, J=7.1, 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): 148.0, 133.8, 125.8, 122.3, 121.6, 111.6, 44.5, 12. 4; ESI-MS: m/z (%)=216 (M^+, 100); HRMS calcd for $[M+H]^+$: $C_{12}H_{17}N_4$ 217.2896, found: 217.2898.

*4.2.9. 1-(4-Fluorophenyl)-1H-1,2,3-triazole (**2i**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J=1.0 Hz, 1H), 7.86 (d, J=1.0 Hz, 1H), 7.75–7.71 (m, 2H), 7.25–7.21 (m, 2H).[16b]

*4.2.10. 1-(4-Chlorophenyl)-1H-1,2,3-triazole (**2j**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.86 (s, 1H), 7.71 (d, J=8.8 Hz, 2H), 7.52 (d, J=8.7 Hz, 2H).[16b]

*4.2.11. 1-(3-Chlorophenyl)-1H-1,2,3-triazole (**2k**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J=0.9 Hz, 1H), 7.87 (d, J=0.9 Hz, 1H), 7.81–7.80 (m, 1H), 7.68–7.66 (m, 1H), 7.50–7.47 (m, 1H), 7.45–7.43 (m, 1H).[16a]

*4.2.12. 1-(2-Chlorophenyl)-1H-1,2,3-triazole (**2l**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.87 (s, 1H), 7.63–7.57(m, 2H), 7.48–7.44(m, 2H).[16b]

*4.2.13. 1-(3-Chloro-4-fluorophenyl)-1H-1,2,3-triazole (**2m**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.87–7.87(m, 2H), 7.66–7.33 (m, 1H), 7.34–7.31 (m, 1H).[18b]

*4.2.14. 1-(4-Bromophenyl)-1H-1,2,3-triazole (**2n**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.87 (s, 1H), 7.69–7.64(m, 4H).[16a]

*4.2.15. 1-(3-Bromophenyl)-1H-1,2,3-triazole (**2o**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.96–7.95 (m, 1H), 7.86 (s, 1H), 7.72–7.70 (m, 1H), 7.59 (d, J=8.0 Hz, 1H), 7.43–7.40 (m, 1H).[16a]

*4.2.16. 1-(3-(Trifluoromethyl)phenyl)-1H-1,2,3-triazole (**2p**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 8.05 (s, 1H), 7.99 (d, J=7.6 Hz, 1H), 7.73–7.68 (m, 2H).[18b]

*4.2.17. 1-(3-Nitrophenyl)-1H-1,2,3-triazole (**2q**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62–8.61 (m, 1H), 8.34–8.32 (m, 1H), 8.23–8.21 (m, 1H), 8.13 (d, J=1.1 Hz, 1H), 7.93 (d, J=1.1 Hz, 1H), 7.79–7.76 (m, 1H).[16a]

*4.2.18. 4-(1H-1,2,3-Triazol-1-yl)benzenesulfonamide (**2r**).* ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.14 (d, J=8.5 Hz, 2H), 8.04–8.03 (m, 3H), 7.55 (s, 2H).[16b]

*4.2.19. 1-(Naphthalen-1-yl)-1H-1,2,3-triazole (**2s**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06–8.02 (m, 1H), 7.98–7.96 (m, 3H), 7.62–7.53 (m, 5H).[18c]

Acknowledgements

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References and notes

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