Copper(I)-Mediated Synthesis of Trisubstituted 1,2,3-Triazoles

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Abstract: A copper-catalysed coupling of bromo-alkynes and organic azides is described. This coupling results in the formation of bromo-containing trisubstituted 1,2,3-triazole derivatives in high yield and a regioselective manner.

Key words: 1,4,5-trisubstituted-1,2,3-triazole, click reaction, [3+2] dipolar cycloaddition, Cu-catalysis, glycopeptide

1,2,3-Triazoles are versatile compounds, which are applied for strongly varying purposes including anti-corrosive agents, dyes, agrochemicals and photographic materials.[1] Although the 1,2,3-triazole structural moiety does not occur in nature, it features in diverse biologically active substances displaying anti-HIV[2] and anti-microbial[3] behaviour as well as selective β_3-adrenergic receptor agonism.[4] After the synthesis of 1,2,3-triazoles had been studied intensively for many years,[5] recently a new and powerful method was developed. The groups of Meldal and Sharpless independently discovered that Cu(I) salts efficiently catalyse the [3+2] cycloaddition between organic azides and acetylenes ('click reactions') giving the corresponding 1,4-disubstituted-1,2,3-triazoles regioselectively in generally high yields.[6] Most of these procedures, however, lead to disubstituted triazoles, while methods for the synthesis of trisubstituted triazoles are less well studied. The latter methods are frequently hampered by a lack of regioselectivity or by a restriction in choice of functional groups.[7] Chen et al. recently published a method for the preparation of 5-iodo-1,4-disubstituted-1,2,3-triazoles from acetylenes and azides using a combination of stoichiometric amounts of CuI and ICl The methodology was applicable to a variety of substrates with yields averaging around 70%.[8] Although this represents a one-pot procedure to this compound class, equimolar quantities of copper salts are required.

Prompted by this report, we wish to disclose our own results in this area, focusing on the synthesis of trisubstituted 1,2,3-triazoles from organic azides and bromoacetylenes, mediated by a catalytic amount of a Cu(I)/Cu(II) mixture.

Given the fact that the acetylene proton plays an essential role in the proposed mechanism for the Cu(I)-catalysed 'click reaction', we were intrigued by the question if bromo-substituted acetylenes would also undergo [3+2] cycloaddition under similar conditions. Bromoacetylenes[9] are stable compounds, readily prepared in quantitative yields from acetylenes upon the action of NBS and catalytic $AgNO_3$ and would afford versatile trisubstituted triazoles in one step. Thus, we selected *p*-nitrobenzylazide (**1**) and methyl bromopropiolate (**2**) for model studies, the results of which are summarised in Table 1. In the first experiment (entry 3), a 1:1 mixture of **1** and **2** in THF was subjected to 10 mol% of CuI. It was intriguing to find that a reaction took place and a 4:1 mixture of bromo- and iodo-substituted 1,4-disubstituted triazole[10] was formed. More promising than that, the low yield (32%) of this reaction could easily be raised to 78% upon heating to 55 °C (entry 4).[11] Encouraged by these results and the finding that Cu-catalysis plays an essential role in this mechanism (entries 1 and 2), we investigated the influence of other Cu salts (e.g., CuCN, $Cu(OAc)_2$, CuBr, CuCl) and solvents (e.g., CH_2Cl_2, DMF, MeCN, Et_2O and toluene). In most cases, however, only small amounts of the desired compound could be isolated. Much to our satisfaction though, upon the combined action of CuI and $Cu(OAc)_2$, the conversion could be greatly improved to 66% at room temperature (entry 6) and was driven to completion upon prolonging the reaction time or heating to 50 °C (entries 7 and 9).

In cases where CuI was used, a small amount of the corresponding 5-iodotriazole **4** was also formed. To circumvent the formation of iodide **4** a CuBr/$Cu(OAc)_2$ couple was used, which provided solely the 5-bromo-1,4-disubstituted triazole **3**, albeit that the reaction proceeded significantly slower (entry 10). In general, elevating the temperature (entries 7 and 8) and increasing the amount of catalyst (entries 11 and 12) independently accelerated the reaction rate.

We also investigated the possibility of synthesising 5-iodotriazoles starting from the corresponding iodo-acetylenes using the CuI/$Cu(OAc)_2$ couple, unfortunately the iodoacetylenes appeared too unstable to survive the reaction conditions so that in some cases no reaction occurred.

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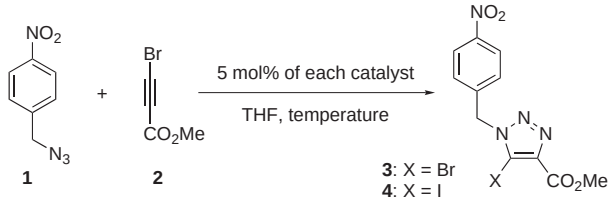
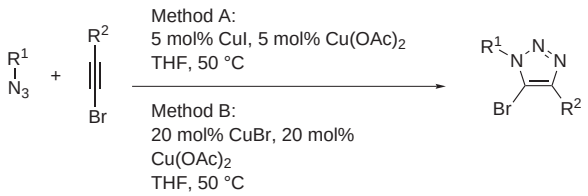
Table 1 Optimisation of the [3+2] Cycloaddition Conditions



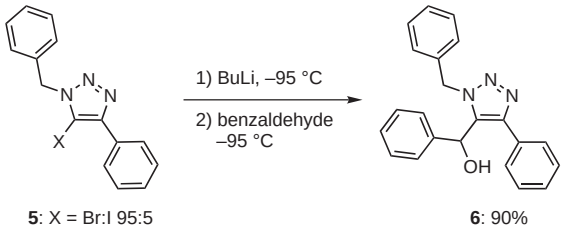
Entry	Catalyst	Temp	Time (h)	Conversion[a]	Yield (%)[d]	**3**:**4**
1	–	r.t.	22	Trace		100:0
2	–	55 °C	22	12%		100[b]:0
3	CuI	r.t.	22	32%[e]		80:20
4	CuI	55 °C	22	78%[e]		84[b]:16
5	$Cu(OAc)_2$	r.t.	40	trace		n.d.
6	$CuI/Cu(OAc)_2$	r.t.	16	66%		95:5
7	$CuI/Cu(OAc)_2$	50 °C	16	>99%	99%	94:6
8	$CuI/Cu(OAc)_2$	reflux	16	>99%	95%	93[b]:7
9	$CuI/Cu(OAc)_2$	r.t.	40	97%	93%	95:5
10	$CuBr/Cu(OAc)_2$	r.t.	40	29%		100:0
11	$CuBr/Cu(OAc)_2$	r.t.	40	56%		100:0
12	$CuBr/Cu(OAc)_2$	50 °C	16	>99%	97%[c]	100:0

[a] Conversion determined by ^1H NMR.
[b] Small amounts of the regioisomer were also detected.
[c] The amount of 20 mol% of both catalysts was used.
[d] Isolated yields.
[e] The amount of 10 mol% of catalyst was used.



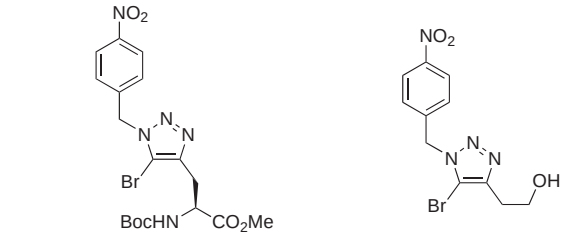
Scheme 1 Optimised cycloaddition conditions

The optimal conditions that we eventually selected are shown in Scheme 1. Using Method A, the reactions generally proceeded faster, but with the formation of small amounts of the 5-iodotriazole by-products. This may not be an issue in the case that the halide substituent is directly reacted further to introduce other substituents such as in palladium-catalyzed cross-coupling reactions as reported by Chen et al.[12] Alternatively, both halides can be exchanged by lithium, using BuLi at low temperature and subsequently reacted with an appropriate electrophile such as benzaldehyde to give the corresponding adduct **6** (Scheme 2). In connection with the previously mentioned Pd-catalysed functionalisation, this example underlines the versatility of these 5-halo-1,4-disubstituted-1,2,3-triazoles. In cases where a mixture of halide substituents is not desired, Method B can be applied which leads solely to the bromo-substituted triazoles.

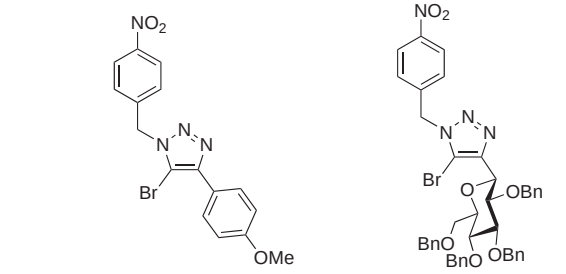


Scheme 2 Example of halogen–metal exchange

Having selected these two methods, an array of triazole products was prepared. Figure 1 shows the products of the reaction of *p*-nitrobenzylazide (**1**) with different acetylenes. It becomes clear that the reaction tolerates different acetylenes including electron-donating, electron-withdrawing and sterically demanding ones as in the case of products **10a** and **10b**. The yields are generally high for both conditions, with a clear difference in reaction rate.



Method A: **7a**: 88%[a,b] (16 h) **8a**: 85%[b] (16 h)
Method B: **7b**: 85% (76 h) **8b**: 92% (75 h)

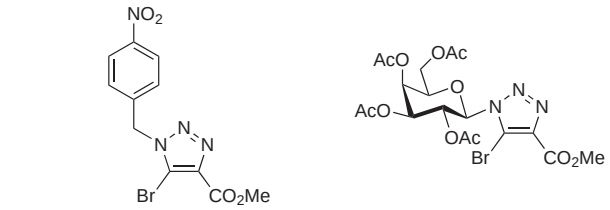


Method A: **9a**: 85%[c,d] (50 h) **10a**: 63% (16 h)[b]
Method B: **9b**: 83% (124 h) **10b**: 99% (69 h)

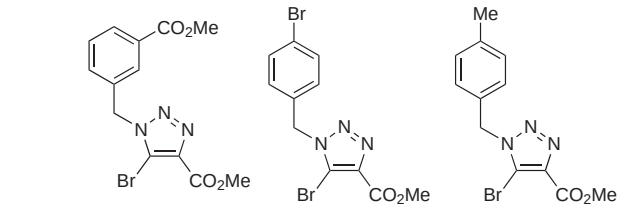
[a] Reactions performed at r.t.
[b] Isolated as a 95:5 Br:I mixture.
[c] Isolated as a 84:16 Br:I mixture.
[d] Reactions were carried out with 20 mol% of each catalyst.

Figure 1 Variation of the bromoacetylene

The products of the coupling of methyl bromopropiolate (**2**) with a selection of organic azides are displayed in Figure 2.



Method A: **11a**: 99%[a] (16 h) **12a**: 83%[a] (16 h)
Method B: **11b**: 97% (16 h) **12b**: 99% (140 h)



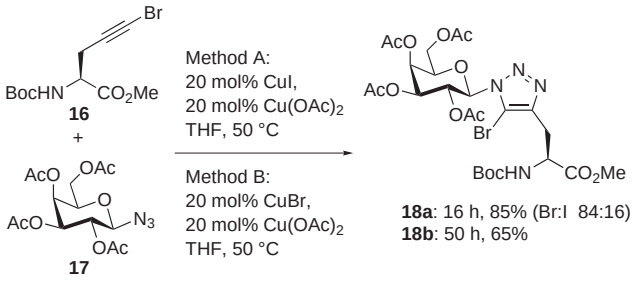
Method A: **13a**: 81%[a,b] (16 h) **14a**: 80%[a,b] (40 h) **15a**: 81%[a,b] (40 h)
Method B: **13b**: 99% (164 h)

[a] Isolated as a 95:5 Br:I mixture.
[b] Reactions were performed at r.t.

Figure 2 Variation of the azide

The reaction allows a variety of different azides, including sterically demanding ones resulting in the monosaccharide-substituted triazoles **12a** and **12b**. Furthermore, several substituted benzylic azides were also successfully used, leading to triazoles **11**, **13**–**15**. Again, it is clear that Method B proceeds considerably slower than Method A. However, by elongating the reaction times, the CuBr-mediated reactions can generally be driven to completion.

We recently reported a method for the synthesis of stable triazole-linked glycopeptides[13] using 'click chemistry' to couple acetylene-containing amino acids to azido-functionalised monosaccharides and vice versa. Halide-containing derivatives of these glycopeptides can be synthesised using the aforementioned conditions, exemplified in Scheme 3. Thus, the bromo-substituted propargylglycine derivative **16** was coupled to azidogalactoside **17**, resulting in fair yields of the glycosidic amino acid derivative **18** using both methods.



Scheme 3 Synthesis of a 5-bromotriazole-linked glyco-amino acid

This new procedure provides, in addition to the Chen method, an efficient and straightforward pathway into the synthesis of trisubstituted 1,2,3-triazoles starting from bromo-alkynes. In contrast to the method of Chen, only catalytic amounts of catalyst are required. Furthermore, the use of hazardous and strongly corrosive ICl is avoided.

To the best of our knowledge, these are the first examples where isolable disubstituted acetylenes participate in a Cu-mediated [3+2] cycloaddition. At present, the exact mechanism remains unclear to us. One possibility is that only Cu(I) species are involved. In this case the mechanism would proceed via Cu–Br exchange, followed by cycloaddition and subsequent reaction of the Cu(I)–triazole complex with 'Br^+'. Other possibilities include an oxidative addition–reductive elimination cycle, in which initial oxidative addition of the bromoalkyne to Cu(I) leads to a Cu(III) species, which is then followed by cycloaddition to a Cu(III)–triazole complex, and subsequent reductive elimination to the corresponding halo-triazole.

In conclusion, we have shown that the Cu-catalysed reaction between bromoalkynes and organic azides proceeds readily to form the corresponding 5-bromo-1,2,3-triazole derivatives in high yield and a regioselective manner. This procedure therefore offers facile access to a variety of halide-containing trisubstituted triazoles. The halogen substituent offers multiple pathways for further metal-mediated derivatisation. Further studies into the scope and applications of this method, as well as the exact mechanism, are currently under investigation.

^{1}H- and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Varian Inova 400 (400 MHz) or a Bruker DMX300 (300 MHz) spectrometer. The chemical shifts (δ) are given in ppm downfield from tetramethylsilane. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. IR spectra were recorded on an ATI Mattson, Genesis series FTIR spectrometer. Low-resolution mass spectra were recorded on a Thermo Finnigan LCQ, high-resolution spectra were recorded on a Fisons (VG) 7070. Commercially available reagents were used as received.

General Procedure for Method A

To a solution of the bromoacetylene (1 equiv) and the azide derivative (1 equiv) in dry THF (0.5 M) was added CuI (5 mol%) and $Cu(OAc)_2$ (5 mol%) The reaction was stirred at 50 °C. The solution was concentrated, H_2O was added and the product was extracted with CH_2Cl_2 (2 ×). The combined organic layers were washed with aq $NaHCO_3$, aq NaCl, dried over $MgSO_4$, and evaporated in vacuo. The product was purified by flash chromatography using EtOAc–heptane mixtures.

General Procedure for Method B

To a solution of the bromoacetylene (1 equiv) and the azide derivative (1 equiv) in dry THF (0.5 M) was added CuBr (20 mol%) and $Cu(OAc)_2$ (20 mol%) The reaction was stirred at 50 °C. The solution was concentrated, H_2O was added and the product was extracted with CH_2Cl_2 (2 ×). The combined organic layers were washed with aq $NaHCO_3$, aq NaCl, dried over $MgSO_4$, and evaporated in vacuo. The product was purified by flash chromatography using EtOAc–heptane mixtures.

Data of Representative Products

Bromotriazole 3

White solid, 204 mg (0.60 mmol, 97%). R_f = 0.38 (EtOAc–heptane, 1:1). IR (film): ν = 2954, 1722, 1519, 1342 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26–8.23 (m, 2 H), 7.46–7.44 (m, 2 H), 5.73 (s, 2 H), 3.99 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1, 148.4, 140.0, 138.2, 128.9, 124.5, 116.6, 52.7, 52.3. HRMS (CI): *m/z* calcd for $C_{11}H_9BrN_4O_4$ $[M + H]^+$: 340.9885; found: 340.9887.

Bromotriazole 8b

White solid, 111 mg (0.34 mmol, 92%). R_f = 0.22 (EtOAc–heptane, 2:1). IR (film): ν = 3357, 2848, 1611, 1538, 1517 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24–8.22 (d, *J* = 8.4 Hz, 2 H), 7.44–7.42 (d, *J* = 8.4 Hz, 2 H), 5.65 (s, 2 H), 4.01 (q, *J* = 6.0 Hz, 2 H), 2.90 (t, *J* = 6.0 Hz, 2 H), 2.48 (t, *J* = 6.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.2, 145.4, 140.9, 128.8, 124.4, 110.2, 61.0, 52.1, 28.3. HRMS (CI): *m/z* calcd for $C_{11}H_{11}Br^{81}N_4O_3$ [M]: 327.9994; found: 327.9993. HRMS (CI): *m/z* calcd for $C_{11}H_{11}Br^{79}N_4O_3$ $[M^+]$: 326.0014; found: 326.0001.

Bromotriazole 18b

Colorless oil, 89 mg (0.13 mmol, 65%). R_f = 0.54 (EtOAc–heptane, 2:1). IR (film): ν = 2971, 1748, 1368 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.01 (t, *J* = 10.0 Hz, 1 H), 5.78 (d, *J* = 9.2 Hz, 1 H), 5.58 (d, *J* = 8.0 Hz, 1 H), 5.56 (d, *J* = 3.2 Hz, 1 H), 5.25 (dd, *J* = 3.2, 10.0 Hz, 1 H), 4.69–4.64 (m, 1 H), 4.26–4.14 (m, 3 H), 3.75 (s, 3 H), 2.22 (s, 3 H), 2.06 (s, 3 H), 2.03 (s, 3 H), 1.98 (s, 3 H), 1.44 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 170.1, 170.0, 168.8, 155.3, 143.2, 111.2, 86.0, 79.8, 73.9, 71.1, 66.9, 66.7, 61.3, 52.6, 52.5, 28.4, 27.4, 20.7, 20.6, 20.2. HRMS (FAB): *m/z* calcd for $C_{25}H_{36}BrN_4O_{13}$: 679.1462 $[M + H]^+$; found: 679.1469.

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References

(1) For reviews see: (a) Fan, W.-Q.; Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry II*, Vol. 4; Katritzky, A. R.; Rees, C. W.; Scriven, C. W. V., Eds.; Elsevier: Oxford, **1996**, 1–126. (b) Dehne, H. In *Methoden der organischen Chemie (Houben–Weyl)*, Vol. E8d; Schaumann, E., Ed.; Thieme: Stuttgart, **1994**, 305–405. (c) Abu-Orabi, S. T.; Alfah, M. A. I.; Jibril Mari'I, F. M.; Ali, A. A.-S. *J. Heterocycl. Chem.* **1989**, *26*, 1461.

(2) Alvarez, R.; Velazquez, S.; San-Felix, A.; Aquaro, S.; Clercq, E. D.; Perno, C. F.; Karlesson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185.

(3) Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenco, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953.

(4) Brockunier, L. L.; Parmee, E. R.; Ok, H. O.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F.; Deng, L.; Feeney, W. P.; Forest, M. J.; Hom, G. J.; MacIntyre, D. E.; Tota, L.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2111.

(5) (a) Huisgen, R.; Szeimies, G.; Mobius, L. *Chem. Ber.* **1967**, *100*, 2494. (b) For a recent review on synthesis of 1,2,3-triazoles, see: Tome, A. C. In *Science of Synthesis*, Vol. 13; Thieme: Stuttgart, **2004**, 415–601.

(6) (a) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.

(7) For a selection of recent entries into trisubstituted triazole synthesis, see: (a) Holzer, W.; Ruso, K. *J. Heterocycl. Chem.* **1992**, *29*, 1203. (b) Ohta, S.; Kawasaki, I.; Uemura, T.; Yamashita, M.; Yoshioka, T.; Yamaguchi, S. *Chem. Pharm. Bull.* **1997**, *45*, 1140. (c) Uhlmann, P.; Felding, J.; Vedsø, P.; Begtrup, M. *J. Org. Chem.* **1997**, 9177. (d) Felding, J.; Uhlmann, P.; Kristensen, J.; Vedsø, P.; Begtrup, M. *Synthesis* **1998**, 1181. (e) Krasiński, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett.* **2004**, *6*, 1237.

(8) Wu, Y.-M.; Deng, J.; Li, Y.; Chen, Q.-Y. *Synthesis* **2005**, 1314.

(9) Leroy, J. *Synth. Commun.* **1992**, 576.

(10) The regiochemistry was determined via reduction to the 5-hydrogen-1,2,3-triazole, using *i*-PrMgCl and subsequent quenching with MeOH, followed by comparison to the known 1,4-disubstituted triazole.

(11) Heating of the reaction mixture to temperatures higher than 50 °C led to the formation of small amounts of the 1,5-regioisomer, which was probably formed via a thermal [3+2] cycloaddition.

(12) Wu, Y.-M.; Deng, J.; Li, Y.; Chen, Q.-Y. *Synthesis* **2005**, 1314.

(13) Kuijpers, B. H. M.; Groothuys, S.; Keereweer, A. R.; Quaedflieg, P. J. L. M.; Blaauw, R. H.; van Delft, F. L.; Rutjes, F. P. J. T. *Org. Lett.* **2004**, *6*, 3123.