Solvent-Free Pivalic Acid/Copper Chloride Jointly Promoted Chlorination of 1,2,3-Triazoles

Christophe Menendez,[a,b] Nathalie Saffon,[c] Christian Lherbet,*[a,b] Michel Baltas*[a,b]

[a] CNRS, Laboratoire de Synthèse et Physico-Chimie de Molécules d'Intérêt Biologique, SPCMIB, UMR-5068, 118 Route de Narbonne, 31062 Toulouse cedex 9, France

[b] Université de Toulouse, UPS, Laboratoire de Synthèse et Physico-Chimie de Molécules d'Intérêt Biologique, SPCMIB, 118 route de Narbonne, 31062 Toulouse cedex 9, France

[c] Université de Toulouse, UPS, and CNRS, ICT FR2599, 118 route de Narbonne, 31062 Toulouse, France
Fax +33(5)61556011; E-mail: lherbet@chimie.ups-tlse.fr; E-mail: baltas@chimie.ups-tlse.fr

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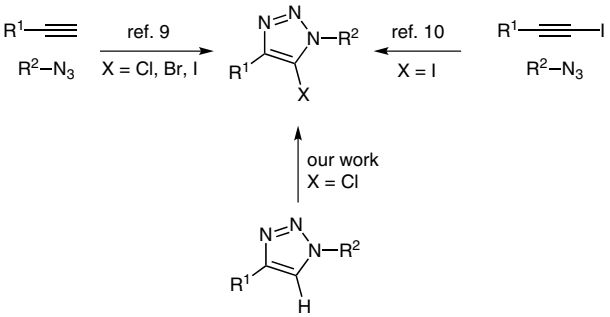
Abstract: A novel chlorination reaction on the 5-position of 1,2,3-triazoles, directly from 5*H*-substituted 1,2,3-triazoles was developed by using copper(II) chloride in pivalic acid. A series of triazoles were thus chlorinated in low to good yields.

Key words: chlorination, triazole, copper chloride, pivalic acid

1,2,3-Triazoles are fundamental motifs in numerous applications, particularly in biological areas.[1,2] Over the years, major advances have been accomplished for their synthesis, especially to improve regioselectivities and reduce reaction time through application of the Huisgen 1,3-dipolar cycloaddition reaction. Sharpless and Meldal reported that this reaction could be accelerated by the use of copper catalysts to afford 1,4-disubstituted 1,2,3-triazoles.[3,4] Recently, the family of catalytic alkyne-azide cycloaddition reactions has expanded with the use of ruthenium complexes [Cp*RuCl] enabling 1,5-disubstituted 1,2,3-triazoles to be obtained with high regioselectivities.[5]

With the increasing importance of triazoles in medicinal chemistry, it has become necessary to develop new techniques to obtain halogenated 1,2,3-triazoles. These compounds can be considered as useful synthons in the elaboration of 5-substituted 1,2,3-triazoles. Wu et al. reported a Suzuki cross-coupling reaction of iodo-1,2,3-triazoles with arylboronic acid catalyzed by palladium(0), affording 5-aryl-1,2,3-triazoles.[6] Interestingly, 5-halogenated 1,2,3-triazoles might be valuable compounds with biological activities, as was recently reported for halogenated aryl derivatives by Diederich et al.[7] The authors have reported the conception of halogenated compounds with higher affinities, depending on the nature of halogens, for the active site of human Cathepsin L and MEK1 kinase. In the same way, Leonidas et al. showed that halogen interactions could be used in the rational design of potent halogen derivatives of glucosyl(hydro)quinones that can be used to inhibit glycogen phosphorylase activity.[8] Various useful methodologies have been developed for the synthesis of 5-halogenated 1,2,3-triazoles (Scheme 1). Among them, the interception of 5-cuprated 1,2,3-triazoles with an electrophile, for example ICl or I_2, permits the desired 5-iodo-1,2,3-trisubstituted triazoles to be delivered.[9] Another method involves coupling functionalized alkynes (i.e., 1-iodoalkynes) with azides, as described by Fokin et al.[10]



Scheme 1 Synthetic approaches to halogenated triazoles

In this paper, we wish to report for the first time the chlorination of 1,2,3-triazoles at the 5-position, directly from 5*H*-triazoles. The reaction is performed in the presence of stoichiometric amounts of copper(II) chloride in pivalic acid.

We initially investigated the reaction of 4-hexyl-1-phenethyl-1*H*-1,2,3-triazole under various conditions. All reactions were followed by TLC until no further evolution was observed. Selected results are presented in Table 1. Copper(II) chloride was initially used as a source of halogen. The first experiment was carried out in the presence of $CuCl_2$ and pivalic acid in toluene to give the corresponding chlorinated product in 39% yield (entry 1). It is noteworthy that when halogenation was performed in the presence of $CuCl_2$ (1 equiv) in toluene, and in the absence of pivalic acid, no product was observed (entry 2). Interestingly, the same reaction conducted in the presence of only pivalic acid as additive led to successful halogenation of triazole; nevertheless a substantial amount of starting material was recovered (entry 3). Longer reaction time (46 h) afforded the product in 62% yield (entry 4). The presence of pivalic acid was crucial, because no reaction occurred when it was omitted (entry 5); when pivalic acid was replaced by acetic acid, only traces of the product

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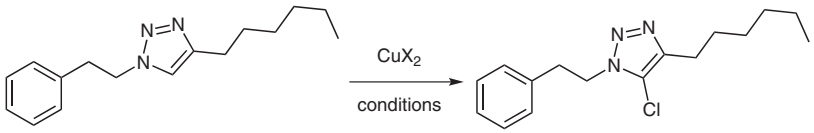
Table 1 Synthesis of 5-Chlorotriazole[a]



Entry	CuX_2 (equiv)	Additive (mg)	Solvent (mL)	Temp (°C)	Time (h)	Yield (%)[b]
1	$CuCl_2$ (1)	PivOH (500)	toluene (3)	140	23	39
2	$CuCl_2$ (1)	–	toluene (3)	Reflux	23	NR
3	$CuCl_2$ (1)	PivOH (500)	–	140	23	40[c]
4	$CuCl_2$ (1)	PivOH (500)	–	140	46	62
5	$CuCl_2$ (1)	–	–	140	46	NR
6	$CuCl_2$ (1)	AcOH (500)	–	Reflux	46	trace
7	$CuCl_2$ (2)	PivOH (500)	–	140	46	46
8	CuCl (1)	PivOH (500)	–	140	23	36
9	–	NaCl (2 equiv), PivOH (500)	–	140	23	0[d]
10	–	LiCl (2 equiv), PivOH (500)	–	140	23	0[d]
11	$CuCl_2$ (0.2)	LiCl (2 equiv), PivOH (500)	–	140	23	5
12	–	DDQ (2 equiv), LiCl (2 equiv)	toluene (3)	110	23	no product

[a] Substrate (0.3 mmol) was used.
[b] Isolated yield.
[c] Starting material (30%) was also recovered.
[d] Checked by HPLC.

were observed (entry 6). Increasing the amount of copper(II) salts afforded the desired monochlorinated compound in 46% yield along with unidentified side products (entry 7). Use of copper(I) salt did not result in a significant difference in yield compared with the result obtained using copper(II) (entry 8). Finally, other sources of halogen such as NaCl or LiCl, either in the presence or absence of copper, were not suitable for the reaction (entries 9–11).[11] Using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidant in the presence of LiCl (2 equiv) was found to be ineffective after 23 hours of reaction (entry 12).

The scope and limitations of this methodology were then explored by using different triazoles, as shown in Table 2.[12] All reactions were conducted for 46 h at 140 °C in the presence of pivalic acid. First, 1,4-disubstituted triazoles bearing an alkyl chain at the carbon or nitrogen atom were tested (entries 1–4). The chlorinated compounds were obtained in fair to moderate yields (43–62%). Starting material was observed by TLC along with degradation products that were not characterized.

Triazole systems possessing electron-rich arenes bearing one (or two) methoxy groups on the aromatic moiety were tested. Compounds bearing a single 4-OMe group on the phenyl ring led to moderate results (Table 2, entries 5 and 6). In contrast, the 2-methoxy-substituted compound (entry 7) afforded the corresponding chlorinated adduct in

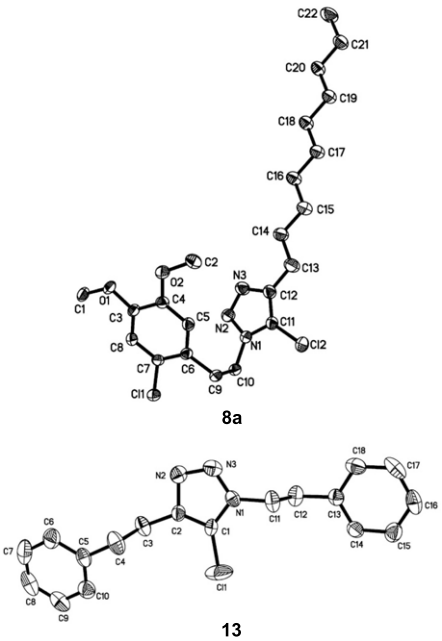
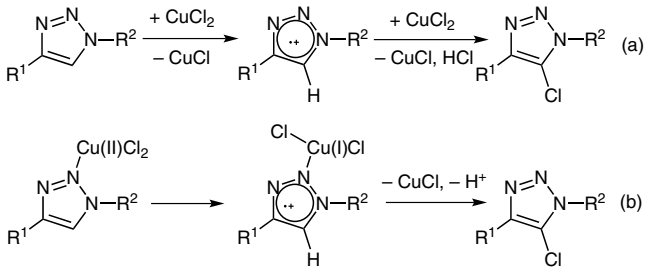


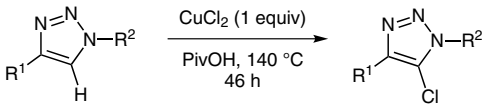
Figure 1 X-ray crystal structures of **8a** and **13**. Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms are omitted for clarity (crystallographic data for **8a** and **13** are provided in the Supporting Information).



Scheme 2 Proposed mechanisms for the chlorination of 1,2,3-triazoles

low yield (29%) along with degradation products. Finally, use of the triazole bearing a 3,4-dimethoxy electron-rich aryl moiety (entry 8) led to a mixture of compounds that were identified after purification by silica gel chromatography as the aryl halide **8b** (31% yield) and the dichlorinated derivative **8a** (53% yield) . The structure of the latter compound was confirmed by X-ray crystallographic analysis (Figure 1).[13] This result shows that halogenation of the aryl moiety is favored over the triazolo moiety. Stahl and co-workers[14] have recently reported mono- or dihalogenation of 1,3-dimethoxybenzene in the presence of $CuCl_2$ (25–200 mol%) in O_2 and acetic acid at 110 °C.

Table 2 Scope of the Reaction



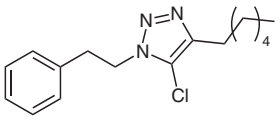
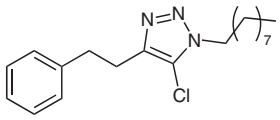
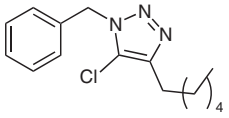
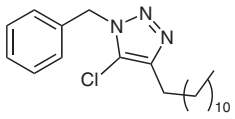
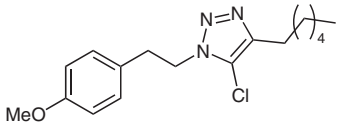
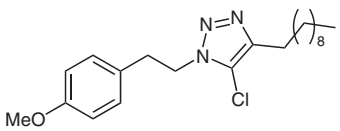
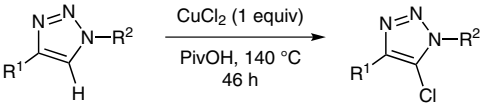
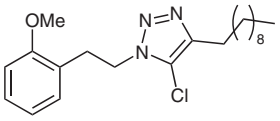
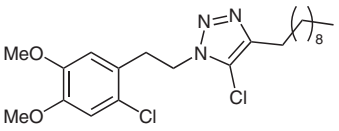
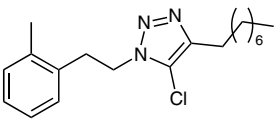
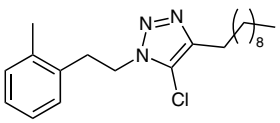
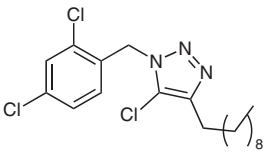
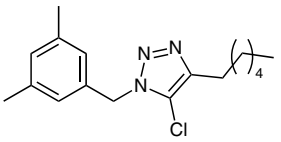
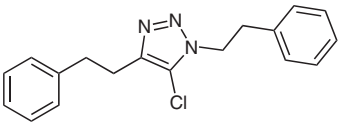
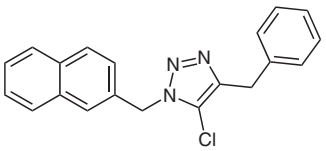
Entry	Product		Yield (%)
1		**1**	62
2		**2**	43
3		**3**	47
4		**4**	53
5		**5**	46
6		**6**	43

Table 2 Scope of the Reaction (continued)



Entry	Product		Yield (%)
7		**7**	29
8		**8a**	53 (X-ray)
		8b	31
9		**9**	53
10		**10**	60
11		**11**	49
12		**12**	30
13		**13**	39 (X-ray)
14		**14**	mixture

Triazoles for which the phenyl ring was substituted with methyl or chlorine groups were also evaluated and afforded the corresponding chlorinated compounds in either fair yields (Table 2, entries 9, 10, and 11) or low yields (entry 12). Finally, triazole systems possessing aromatic remote groups at both the 1- and 4-positions led to either a low yield or a mixture (entries 13 and 14). The structure of

compound **13** was also confirmed by X-ray crystallographic analysis.[15]

Although there is no precedent in the literature for direct chlorination of 1,2,3-triazoles, Stahl et al. indicated in a recently published review[16] various single electron transfer (SET) mechanisms for halogenation of electron-rich arenes. As substituted triazoles can be considered electron-rich heterocycles, we would tentatively propose two mechanisms. The first involves formation of a triazole radical cation that would undergo chlorination of the ring through reaction with $CuCl_2$ and loss of a proton, as proposed for electron-rich arenes (Scheme 2a).[17] The second possibility could be a reaction initiated by a SET from the tertiary amine function of triazole chelated to copper to form an amine radical cation that could undergo intramolecular chlorination and loss of a proton, as proposed for chelate directed C–H oxidation reactions (Scheme 2b).[18] Pivalic acid, which is more basic and has a higher boiling point than acetic acid, is crucial for the reaction to occur. It could intervene by forming a three partner intermediate (triazole/pivalate/copper), perhaps in a manner similar to palladium complexes in the concerted metalation-deprotonation (CMD) pathways.[19] Nevertheless, its exact role has still to be elucidated.

In conclusion, we have demonstrated that a series of substituted 1,2,3-triazoles could be chlorinated at the 5-position using copper chloride and pivalic acid under solvent-free conditions. Further mechanistic studies are required to fully explain the role of copper in the reaction. This transformation represents a useful method that provides access to 4,5-disubstituted 1,2,3-triazoles.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) Bromination of triazole was also performed with $CuBr_2$ without success.
(12) **General procedure**: To a solution of triazole (0.3 mmol, 1 equiv) in pivalic acid (500 mg), was added $CuCl_2$ (1 equiv) at room temperature. The reaction mixture was warmed to 140 °C and stirred under air for 46 h. Pivalic acid was evaporated under reduced pressure and the residue was dissolved in EtOAc. The organic layer was washed with water (3 × 20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography.
5-Chloro-4-hexyl-1-phenethyl-1*H*-1,2,3-triazole (1): Yield: 62%; light-yellow oil; ^{1}H NMR ($CDCl_3$): δ = 7.26 (m, 3 H), 7.12 (dd, *J* = 7.6, 1.8 Hz, 2 H), 4.50 (t, *J* = 7.5 Hz, 2 H), 319 (t, *J* = 7.2 Hz, 2 H), 2.62 (t, *J* = 6.9 Hz, 2 H), 1.67 (m, 2 H), 1.30 (m, 6 H), 0.89 (t, *J* = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ = 136.7, 128.72, 128.71, 127.0, 49.5, 36.0, 31.5, 28.7, 28.4, 24.5, 22.5, 14.0; HRMS: (DCI/CH_4): *m*/*z* calcd for $C_{16}H_{23}N_3Cl$: 292.1581; found: 292.1605.
1-Benzyl-5-chloro-4-hexyl-1*H*-1,2,3-triazole (3): Yield: 47%; yellow oil; ^{1}H NMR ($CDCl_3$): δ = 7.28 (m, 5 H), 5.48 (s, 2 H), 2.63 (t, *J* = 7.6 Hz, 2 H), 1.68 (m, 2 H), 1.30 (m, 6 H), 0.86 (t, *J* = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ = 144.1, 134.1, 128.9, 128.4, 127.7, 122.3, 51.9, 31.4, 28.8, 28.4, 24.6, 22.5, 14.0, HRMS: (DCI/CH_4): *m*/*z* calcd for $C_{15}H_{21}N_3Cl$: 278.1424; found: 278.1415.
(13) **Crystal data for compound 8a**: $C_{22}H_{33}Cl_2N_3O_2$; *M* = 442.41; monoclinic; space group $P2_1/c$; *a* = 27.1442(7) Å, *b* = 4.9516(1) Å, *c* = 17.6348(5) Å, *β* = 101.803(2)°; *V*=2320.13(10) Å^3; *Z* = 4; crystal size 0.28 × 0.10 × 0.03 mm^3; 26260 reflections collected (5307 independent, R_{int}=0.0494), 265 parameters, *R*1 [*I*>2σ(*I*)] = 0.0429, *wR*2 [all data] = 0.1004, largest diff. peak and hole: 0.267 and –0.234 e·Å^{-3}. CCDC 876301 (**8a**) contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(14) Yang, L.; Lu, Z.; Stahl, S. S. *Chem. Commun.* **2009**, 6460.
(15) **Crystal data for compound 13:** $C_{18}H_{18}ClN_3$; *M* = 311.80; monoclinic; space group *P* $2_1/c$; *a* = 8.7163(11) Å, *b* = 10.9837(13) Å, *c* = 17.052(2) Å, *β* = 98.365(6)°; *V* = 1615.2(3) Å^3; *Z* = 4; crystal size 0.30 × 0.20 × 0.12 mm^3; 24818 reflections collected (3975 independent, R_{int} = 0.0344), 254 parameters, 225 restraints, *R*1 [*I*>2σ(*I*)]= 0.0515, *wR*2 [all data] = 0.1599, largest diff. peak and hole: 0.428 and –0.240 e·Å^{-3}. CCDC 876302 (**13**) contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(16) For a review, see: Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 11062.
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