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An efficient synthesis of 3-triazolyl-2(1*H*)-quinolones by CuTC-catalyzed azide–alkyne cycloaddition reaction

Samir Messaoudi*, Marie Gabillet, Jean-Daniel Brion and Mouâd Alami*

A facile and efficient Cu(I)-catalyzed azide–alkyne cycloaddition reaction for the synthesis of a series of 3-triazolyl-2(1*H*)-quinolones 3 have been developed using 3-azido-quinolin-2(1*H*)-one as the coupling partner. The optimized reaction conditions involve the use of eco- friendly ethanol as the solvent in the presence of copper(I) thiophene-2-carboxylate as the catalyst, to afford good to excellent yields of 3-triazolyl-2(1*H*)-quinolone derivatives of biological interest. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: triazole; quinolin-2(1*H*)-one; CuTC; hsp90 inhibitors

Introduction

In recent years, the copper-catalyzed [3 + 2] azide–alkyne cycloaddition (CuAAC) reaction has attracted considerable attention.[1] This reaction, discovered independently by Tornøe *et al*.[2] and Rostovtsev *et al*.,[3] constitutes a substantial improvement of the classical Huisgen thermal 1,3-dipolar cycloaddition.[4] The resulting 1,4-disubstituted 1,2,3-triazoles are obtained in high yields with exclusive regioselectivity under mild conditions. The wide scope of CuAAC is firmly demonstrated by its use in different areas,[5] including synthetic and medicinal chemistry,[6] surface and polymer chemistry,[7] as well as bioconjugation applications.[8]

In an ongoing medicinal chemistry program directed toward hsp90,[9] an exciting target in cancer drug discovery, we identified 4TCNA[10] as a simplified denoviose analogue of novobiocin (Nvb). Biological evaluation revealed that 4TCNA manifested micromolar anti-proliferative activities and exhibited higher potency than Nvb itself to induce client–protein degradation.[11] Further structure–activity relationships (SAR) studies led us, very recently, to discover 6BrCaQ as a lead compound in which the coumarin unit has been replaced by a 2-quinoleinone moiety (Fig. 1). 6BrCaQ displayed the most potent antiproliferative activity against a panel of cancer cell lines, and manifested down-regulation of several hsp90 client proteins. Moreover, 6BrCaQ induced a high level of apoptosis in MCF-7 breast cancer cells by activation of caspases, and the subsequent cleavage of PARP.[12] Modifications to both the quinolin-2(1*H*)-one core and benzamide side chain has been pursued, resulting in the production of preliminary SAR. However, modifications to the geometry of the amide bond have not been realized. Thus we proposed the synthesis of a series of 6BrCaQ analogues replacing the amide bond with a triazole ring, which could facilitate SAR analysis for the aryl side chain. Triazoles have been shown to possess a number of desirable features in the context of medicinal chemistry. For example, the 1,2,3-triazole ring may act as bioisoster of the amide moiety[13] due to similarities in both electronic and spatial characteristics. In addition, it is metabolically stable to hydrolysis.[14] Finally, the substitution with a triazole ring would have the great advantage of making these analogues suitable for combinatorial chemistry. To the best of our knowledge, except for our previous result[15] there is no report describing the synthesis of targeted 3-triazolyl-2(1*H*)-quinolone derivatives of type A (Fig. 1).

During our recent studies on the functionalization of heterocycles via transition metal-catalyzed reactions,[16] we have developed an *in situ* direct amination of (hetero)aryl halides using sodium azide as the amino source.[15] The catalytic system based on Cu-powder/pipecolinic acid/ascorbic acid proved to be highly efficient and versatile for the preparation of various (hetero)aromatic amines, including 3-aminoquinolinones. In addition, we have demonstrated through a preliminary result that the use of CuI (10 mol%) together with pipecolinic acid (30 mol%) and ascorbic acid (20 mol%) enabled cycloaddition of 3-azidoquinolin-2(1*H*)-one (**1a**) with 4-methoxyphenylacetylene (**2a**) in a good 80% yield (Table 1, entry 1). Given the practical importance of efficient 3-triazolylquinolones synthesis for the purpose of our hsp90 medicinal chemistry program, attention was consequently paid to improving our reported protocol,[15] and to extend the scope of the Cu-catalyzed CuAAC reactions with 3-azidoquinolones. In this paper we wish to detail our progress in this reaction, which provides a wide range of 3-triazolylquinolones **A** of biological interest.

Results and Discussion

At the outset, we were keen to determine the optimized reaction conditions using **1a** and **2a** as model substrates. Thus a variety of

* *Correspondence to: S. Messaoudi, Laboratoire de Chimie Thérapeutique, Faculté de Pharmacie, Université Paris-Sud, CNRS, BioCIS, UMR 8076, LabEx LERMIT, rue J. B. Clément F-92296 Châtenay-Malabry, France. E-mail: samir.messaoudi@u-psud.fr or: mouad.alami@u-psud.fr*

Laboratoire de Chimie Thérapeutique, Faculté de Pharmacie, Université Paris-Sud, Châtenay-Malabry, France

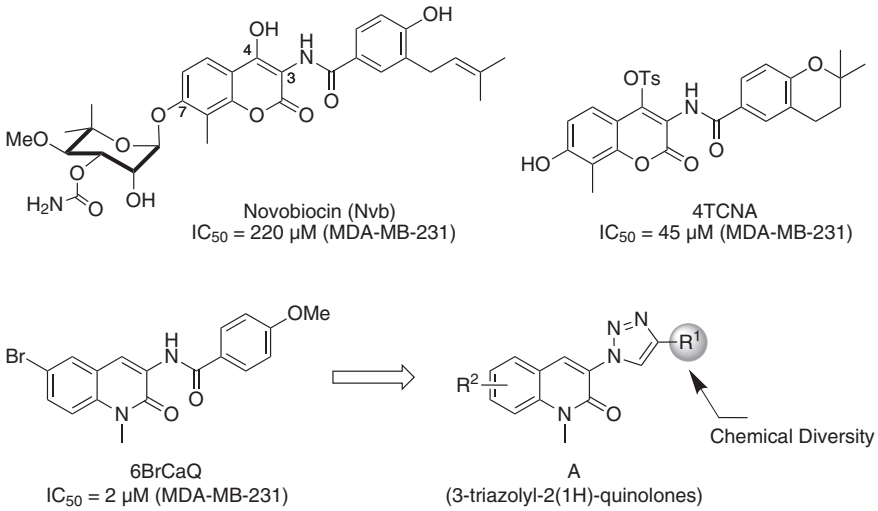
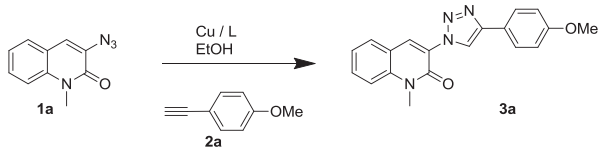


Figure 1. Nvb, 4TCNA, 6BrCaQ and the targeted 3-triazolyl-quinolones of general structure **A**.

reaction conditions were screened. In contrast to our previously reported conditions[15] (Table 1, entry 1), we found that the addition of a ligand or an additive was unnecessary since the reaction of **1a** with **2a** (2 equiv.) in the presence of CuI (10 mol%) and sodium ascorbate (entry 2) or pipecolinic acid (entry 3) in EtOH at 40°C led to the triazole **3a** in comparable yields. Interestingly, a similar result was observed when running the reaction in the absence of both sodium ascorbate and pipecolinic acid, suggesting that these reactants had no beneficial effect on the formation of **3a** (entry 4). Further optimization with respect to the copper source (entries 4–13) showed that copper(I) thiophene-2-carboxylate (CuTC)[17] was the best catalyst, providing **3a** in 91% yield within only 3 h (entry 8). The developed reaction conditions constitute a clear simplification and improvement when compared to our previous report, particularly the absence of additives and ligand.

Table 1. Optimization of the copper-catalyzed formation of triazole **3a**[a]



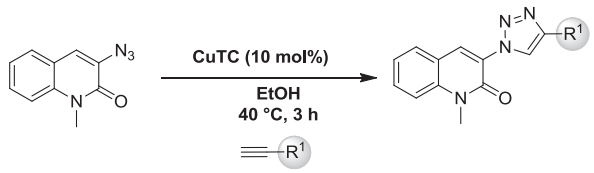
Entry	[Cu]	Ligand	Additives	Time (h)	Yield[b] (%)
1	CuI	Pipecolinic acid	NaAsc[c]	6	80
2	CuI	—	NaAsc	6	79
3	CuI	Pipecolinic acid	—	9	77
4	CuI	—	—	9	76
5	$Cu(SO_4)_2.5H_2O$			6	70
6	Cu	—	—	6	19
7	Cu_2O	—	—	9	65
8	**CuTc**[d,e]	—	—	**3**	**91**
9	$Cu(OAc)_2$	—	—	3	77
10	CuCN	—	—	3	25
11	$CuNO_3$	—	—	3	31
12	CuBr.DMS	—	—	3	10
13	CuCl	—	—	3	8

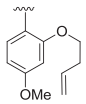
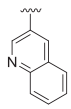
[a]Reaction conditions: **1a** (1 mmol), **2a** (2 mmol), [Cu] (10 mol%); Additive (20 mol%) in EtOH (6 ml) was heated in a sealed Schlenk tube at 40°C.
[b]Isolated yield of **3a**.
[c]NaAsc, sodium ascorbate.
[d]CuTC, copper(I) thiophene-2-carboxylate.
[e]For control experiments, no conversion at all was observed in the absence of CuTc.

With a viable CuAAC procedure in hand, we became interested to explore the scope of the reaction with various commercially available terminal alkynes (**2**) possessing different steric and electronic properties. As can be observed in Table 2, a variety of terminal alkynes, including aromatic, heteroaromatic and aliphatic derivatives, participated in the cycloaddition reaction, furnishing the corresponding triazoles in moderate to excellent yields, and high purity after simple filtration. Notably, electron-rich and electron-deficient, *meta*- and *para*-substituted arylalkynes all underwent efficiently the 1,3-dipolar cycloaddition in good yield (entries 1–3 and 7–10). In addition, the sterically demanding *ortho* substitution pattern was tolerated toward the CuAAC reaction of **1a**, leading to triazoles **3d–f** in yields ranging from 35% to 88% (entries 4–6). Interestingly, this cycloaddition also proceeded successfully in the case of heteroaromatic alkynes, such as 3-quinoleinylylacetylene (**2k**) and 2-pyridylacetylene (**2l**), leading to triazoles **3k** and **3l** in 60% and 70% yields, respectively (entries 11 and 12). The scope of our protocol was next examined with aliphatic terminal alkynes. Thus hept-1-yne (**2m**) was more sluggish to react, with incomplete conversion, leading to only 20% of triazole **3m** (entry 13). Finally, challenging functionalized substrates, such as *tert*-butyldimethyl(prop-2-ynyloxy)silane (**2n**), trimethylsilyl-acetylene (**2o**) and methyl propiolate (**2p**), were also investigated and found competent in this reaction, producing corresponding triazoles in reasonable to good yields (72%, 50%, and 80%, respectively).

Upon construction of the 3-triazolyl-2(1*H*)-quinolone derivatives, the newly synthesized compounds were subjected to antitumor evaluation against MCF-7 (estrogen-receptor positive breast cancer cells) cell lines *in vitro*. Unfortunately, in comparison to previously described quinolone-containing analogues,[12] our

Table 2. Click 1,3-cycloaddition toward the synthesis of 3-triazolyl-2(1*H*)-quinolones **3**[a]



Entry	R^1		Product **3** yield (%)[b]	
1	*p*-MeO-Ph	**2a**	**3a**	91
2	*p*-Me_2N-Ph	**2b**	**3b**	75
3	Ph **2c**	**2c**	**3c**	68
4	*o*-MeO-Ph	**2d**	**3d**	45
5		**2e**	**3e**	88
6	1-Np	**2f**	**3f**	35
7	2,3,4, MeO-Ph	**2g**	**3g**	64
8	*p*-F-Ph	**2h**	**3h**	60
9	*m*-F-Ph	**2i**	**3i**	74
10	*m*-Cl-Ph	**2j**	**3j**	65
11		**2k**	**3k**	60
12	2-Py	**2l**	**3l**	70
13	$(CH_2)_4$-CH_3	**2m**	**3m**	20
14	CH_2-OTBS	**2n**	**3n**	72
15	Me_3Si	**2o**	**3o**	50
16	CO_2Me	**2p**	**3p**	80

[a]Reaction conditions: **1a** (1.0 equiv.), aryl alkyne (2.0 equiv.), CuTc (10 mol%), in EtOH (6 ml) were heated in a sealed Schlenk tube at 40°C (time: see experimental section).

[b]Isolated yields of **3**.

newly synthesized triazole derivatives exhibited lower cytotoxicity against the tested tumor cell line (IC_{50} >100 μM). These compounds were not sufficiently active to be selected for the next valuation concerning their ability to induce degradation of Hsp90-dependent client proteins.

Conclusion

In summary, we reported a CuAAC reaction of 3-azidoquinolones with alkynes using CuTC as the catalyst without the need for exogenous ligand and/or additives. The disclosed method offers a quick and reliable route for the synthesis of various unknown 3-triazolyl-2(1*H*)-quinolone derivatives (**3**). The procedure works well with a wide variety of alkynes including aromatic, heteroaromatic and aliphatic, as well as challenging functionalized substrates. All the products were rapidly isolated by simple filtration from the reaction mixture with no further purification. Studies are currently under way for the synthesis of a library of substituted 3-triazolyl-2(1*H*)-quinolones related to 6BrCaQ and will be reported in due course.

Experimental

General Experimental Methods

All glassware was oven-dried at 140°C and all reactions were conducted under a nitrogen atmosphere. Solvents for chromatography – cyclohexane, ethyl acetate (EtOAc) – were technical grade.

All compounds were identified by the usual physical methods, i.e. ^{1}H NMR, ^{13}C NMR, IR and elemental analysis. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ or DMSO-d_6 with a Bruker ARX 400 or Bruker Avance 300 and chemical shifts are reported in ppm. The following abbreviation are used: m (multiplet), s (singlet), br s (broad singlet), d (doublet), t (triplet), dd (doublet of doublet), td (triplet of doublet), q (quadruplet). IR spectra were measured on a Bruker Vector 22 spectrophotometer (neat, cm^{-1}). Elemental analyses were performed with a PerkinElmer 240 analyzer. Analytical thin-layer chromatography was performed on Merck pre-coated silica gel 60F plates. Merck silica gel 60 (230–400 mesh) was used for column chromatography.

Experimental Procedure for CuAAC Synthesis of 3-Triazolyl-2(1*H*)-Quinolones

A flame-dried resealable 2–5 mL Pyrex reaction vessel was charged with the solid reactant(s): CuTc (10 mol%), 3-azidoquinolin-2(1*H*)-one (**1a**) (1 mmol) and alkyne **2** (2 mmol) in EtOH (6 mL). The reaction vessel was capped with a Teflon screw cap. The reaction vessel was sealed and then heated at 40°C. The resulting suspension was cooled to room temperature and filtered, and the resulting solid product was washed with H_2O (30 ml) and *c*-hexane (200 ml).

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