Tetrahedron Letters 52 (2011) 658–660

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Chemoselective preparation of disymmetric bistriazoles from bisalkynes

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ARTICLE INFO

Article history:
Received 30 September 2010
Revised 22 November 2010
Accepted 26 November 2010
Available online 2 December 2010

Keywords:
Huisgen's reaction
Click chemistry
Activation
Alkyne
Azide

ABSTRACT

Best of both worlds, molecules bearing two alkyne groups, activated and unactivated, can selectively react on the activated one in a copper-free version of Huisgen's reaction to form a first triazole ring, with a good selectivity toward the 1,4-isomer, which is solely isolated by a simple trituration procedure. The other alkyne function is then submitted to the selective reaction using a polymer-supported copper(I) catalyst to form a second triazole ring. This gave access to disymmetric bistriazoles without the need of protection using simple, easy, and fast procedures.

1. Introduction

Huisgen's [3+2] thermal cycloaddition between organic azides and alkynes, especially in it's copper(I)-catalyzed variation, has become a powerful tool for heterocycles construction; namely disubstituted 1,2,3-triazoles.[1,2] This reaction is perfectly meeting the requirements of the 'click-chemistry' concept by both its efficiency and wide scope.[3] Furthermore, the use of copper(I) catalysts not only increased the reaction kinetics, making it possible at lower temperatures, but also its selectivity giving rise only to the 1,4-substituted isomer (Fig. 1).[4]

During the course of our work on Huisgen's reaction,[5] we observed an increased reactivity of some electron-withdrawing bearing alkynes compared to unactivated ones, and this in the absence of solvent, heating, or copper catalysis.[6] Alkynes do not usually spontaneously react with azides in solution, with the exception of strained ones, as it was exemplified in in vivo click-chemistry using cyclooctynes and their α-*gem*-difluorinated analogs.[7]

We decided to explore and take advantage of this increased reactivity in order to access bistriazole bearing molecules from bisalkyne ones. The synthesis of some 1,1′-disubstituted-4,4′-bistriazoles has been reported using sequential approaches starting from mono- or di-silylated butadiynes, deprotection after a first copper-catalyzed Huisgen's reaction, followed by another one or in a one-pot fashion.[8] A similar approach was proposed from propargyl alcohol, followed by oxidation and Seyferth–Gilbert homologation onto the resulting triazolaldehyde before the formation of the other triazole.

2. Results and discussion

For this study, molecules incorporating both an activated and unactivated terminal alkyne were needed. We decided to study amides of propiolic acid substituted by a distal unactivated terminal alkyne on the N-substituent. The first molecule tested was *N*-propargylpropiolamide (**1a**) as depicted in Figure 2.

We found out that the alkyne bared by the amide carbonyl was exclusively reacting when **1a** was mixed with organic azides **2a–d** under solvent- and catalyst-free conditions at room temperature (Table 1). The resulting mono-triazoles **3a–d** were obtained in good yields (80–86%) as mixtures of 1,4- and 1,5-isomers, with a selectivity toward the 1,4 one (1,4/1,5 = ca. 80:20).

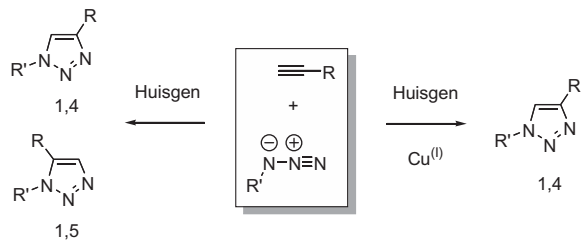

Figure 1. Huisgen's reaction between azides and alkynes: original thermal (1,4/1,5-isomers) and copper(I)-catalyzed (1,4-isomer) conditions.

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0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.11.141

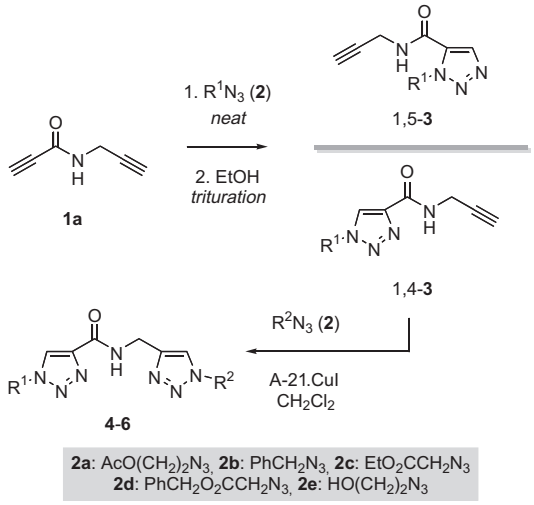

Figure 2. Sequential chemoselective preparation of bistriazoles from *N*-propargyl-propiolamide (**1a**) and azides **2**.

Fortunately, a simple trituration with ethanol gave pure 1,4-**3** as solids after filtration (52–61%), while the solvent contained mainly the 1,5-isomer (14–23%), together with a small amount of the 1,4 one (1,4/1,5 = ca. 25:75). In this first step, only the ethyl ester of azidoacetic acid (**2c**) failed to give a solid compound upon trituration (**3c**, 82% yield, 1,4/1,5 = 74:26). The use of its benzyl ester analog **2d**, however, circumvented the problem by giving a crystalline derivative.

Pure 1,4-**3a**, **3b**, and **3d** were then used for a second Huisgen's reaction, using this time a copper(I)-supported catalyst; Amberlyst A-21·CuI,[5a] in order to access bistriazoles **4**–**6** (Fig. 2, Table 1). Mono-triazoles **3** all reacted equally well with azides **2a**–**e** under these conditions, at room temperature, giving the corresponding bistriazoles **4**–**6**/**a**–**e** in a high average yield of 95%.[9]

The compounds were isolated as highly crystalline products after a simple filtration to remove the catalyst and evaporation of the reaction solvent. Furthermore, as for all copper(I)-catalyzed Huisgen's reactions, only the 1,4-isomer of the newly formed triazole was observed.

In order to make a first evaluation of the scope of this method, we decided to test the sequential procedure on propiolamides derived from *meta*- (**1b**) and *para*-ethynylaniline (**1c**), as illustrated in Figure 3. The bisalkynes **1b** and **1c** are very light solids that were not well in contact with the liquid azides **2a**–**c**. The procedure has thus to be changed to run it using some solvent. Acetone was selected, but only a few percent conversions were observed at room temperature for an over-night reaction. The reaction mixture was then heated to reflux and, to our surprise, only the activated alkyne on **1b** and **1c** reacted once again. This gave access to the first triazole nucleus, **7** and **8**, respectively, as isomeric mixtures (1,4/1,5 = ca. 80:20) with good yields between 61% and 87% (Table 2). Trituration of the crude in ethyl alcohol gave access to the pure crystalline 1,4-isomers of **7** and **8** in 48–72% yield and to the 1,5/1,4-isomers mix in solution.

Table 1
Results of preparation of bistriazoles **4**–**6** from **1a**

R^1N_3[a] —	**3** [%] (1,4/1,5)	1,5-**3**[b] [%] (1,4/1,5)	1,4-**3**[c] [%] —	R^2N_3[a] —	**4** [%]
2a	**3a**, 86 (84:16)	17 (26:74)	61	**2a**	**4a**, 99
				2b	**4b**, 96
				2c	**4c**, 95
				2d	**4d**, 98
				2e	**4e**, 92
2b	**3b**, 84 (79:21)	23 (24:76)	52	**2a**	**5a**, 96
				2b	**5b**, 95
				2c	**5c**, 94
				2d	**5d**, 92
				2e	**5e**, 93
2c	**3c**, 82 (74:26)	—	—	—	—
2d	**3d**, 80 (82:18)	14 (18:82)	60	**2a**	**6a**, 95
				2b	**6b**, 93
				2c	**6c**, 89
				2d	**6d**, 97
				2e	**6e**, 94

[a] For structures of **1a** and **2a**–**e**, see Figure 2.
[b] Contained in EtOH trituration solution.
[c] Solid isolated after EtOH trituration.

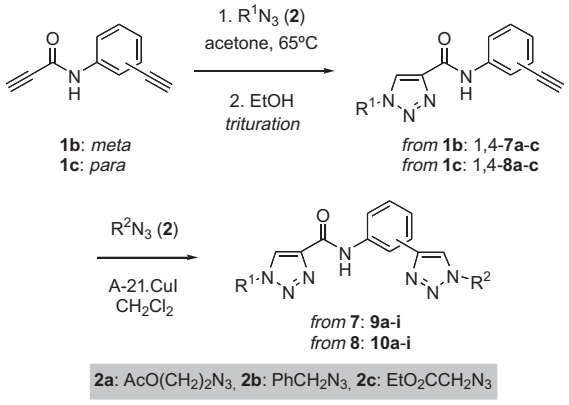

Figure 3. Sequential Huisgen's reactions of propiolamides of *meta*- (**1b**) and *para*-ethynylaniline (**1c**) with azides **2**.

Table 2
Results for the preparation of bistriazoles **9** and **10** from bisalkynes **1b** and **1c**

1	R^1N_3[a] —	**7**/**8** [%] (1,4/1,5)	1,5-**7**/**8**[b] [%] (1,4/1,5)	1,4-**7**/**8**[c] [%] —	R^2N_3[a] —	**9**/**10** [%]
1b	**2a**	**7a**, 78 (80:20)	12 (32:68)	61	**2a**	**9a**, 93
					2b	**9b**, 97
					2c	**9c**, 98
	2b	**7b**, 85 (78:22)	11 (21:79)	67	**2a**	**9d**, 99
					2b	**9e**, 96
					2c	**9f**, 92
	2c	**7c**, 74 (81:19)	15 (29:71)	56	**2a**	**9g**, 91
					2b	**9h**, 96
					2c	**9i**, 99
1c	**2a**	**8a**, 87 (83:17)	10 (24:76)	72	**2a**	**10a**, 96
					2b	**10b**, 95
					2c	**10c**, 99
	2b	**8b**, 61 (77:23)	9 (37:63)	48	**2a**	**10d**, 92
					2b	**10e**, 96
					2c	**10f**, 97
	2c	**8c**, 76 (85:15)	12 (34:66)	58	**2a**	**10g**, 94
					2b	**10h**, 98
					2c	**10i**, 96

[a] For structures of **1b**, **1c** and **2a**–**c**, see Figure 3.
[b] Contained in EtOH trituration solution.
[c] Solid isolated after EtOH trituration.

Each of the six mono-triazole 1,4-**7a**–**c** and **8a**–**c** were then reacted with the same azides (**2a**–**c**) using the above mentioned solid-phase catalyst for Husigen's reaction. The corresponding bistriazoles **9a**–**i** and **10a**–**i** were isolated in very good yields in each case, as their 1,4-isomers once again (average yield of 96%).[9]

3. Conclusion

We presented in this Letter a new approach for the synthesis of disymmetric bistriazoles starting from unprotected bisalkynes using Huisgen's reaction. The reactivity difference between what

was called an activated and unactivated alkyne, gave the opportunity to introduce chemoselectively a first triazole ring on the activated part of the molecule, in a catalyst-free way, with or without a solvent. The resulting mono-triazoles, obtained in good yields mainly as their 1,4-disubsituted isomers, were easily obtained pure after a simple trituration and filtration. The products were then submitted to a copper(I)-catalyzed Huisgen's reaction to form the second triazole ring on the unactivated alkyne, with exclusive 1,4 selectivity and in high yields. Further work on the application of this selective method is in progress and will be reported in due course.

Acknowledgments

This work is a part of the international thesis of H. Elamari—Université P. & M. Curie/Université du 7 Novembre à Carthage. It was supported by fellowships from Ministry of Education of Tunisia and UPCG; and Grants CNRS (UMR 8151) and INSERM (U 1022). We thank Dr. Marie-Nöelle Rager for NMR experiments and helpful discussions.

Supplementary data

Supplementary data associated with (complete experimental procedures, analyses and NMR spectra) this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.141.

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9. *Typical procedures*. *General procedure for solvent- and catalyst-free Huisgen's reaction on the activated alkyne*: To bisalkyne **1a** (0.5 mmol) was added azide **2** (0.55 mmol). The mixture was stirred 18 h at room temperature. The crude was triturated in EtOH (8 mL) and filtrated to obtain the solid 1,4-**3**. For the reactions conducted in solution, alkyne **1b–c** was dissolved in acetone (4 mL), azide **2** added and the solution heated at reflux (65 °C) for 24 h. The same work-up was made after evaporation of acetone. *General procedure for copper-catalyzed Huisgen's reaction on the unactivated alkyne*: Mono-triazole **3** (**7** or **8**) (0.2 mmol) was dissolved in CH_2Cl_2 (2 mL) and the azide **2** (0.22 mmol) and Amberlyst A-21·CuI (12 mg, 8 mol %) were sequentially added. The resulting suspension was stirred at room temperature until completion of the reaction (16–48 h), before being filtered and the polymer washed with CH_2Cl_2 (2 × 1 mL). Evaporation of the solvent gave the corresponding bistriazole **4–6** (**9** or **10**).