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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 8360–8362

Synthesis of new trifluoromethyl peptidomimetics with a triazole moiety

Julien Bonnamour, Julien Legros, Benoit Crousse* and Danièle Bonnet-Delpon

Laboratoire BioCIS-CNRS, Faculté de Pharmacie, Univ Paris-Sud, rue J. B. Clément, F-92296 Châtenay-Malabry, France

Received 26 June 2007; revised 27 July 2007; accepted 18 September 2007
Available online 21 September 2007

Abstract—*gem*-Chloroamine $CF_3CH(Cl)NHAc$ **1** reacts in a one-pot sequence with NaN_3 to afford trifluoromethyl azido compound **2** and further undergoes a Huisgen 1,3-dipolar cycloaddition with alkynes to yield 1,4-disubstitued 1,2,3-triazoles. The reaction is catalyzed by Cu(II) species ($Cu(OAc)_2$, 10 mol %) without any reducing agent, and the corresponding products are afforded in high yields (74–87%). This process offers thus an entry to new trifluoromethyl pseudopeptides.
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1,2,3-Triazoles are an important class of heterocycles which are found in various therapeutic agents.[1] On the other hand, trifluoromethyl moiety can greatly modify the physico-chemical features and thus the biological properties of a molecule (resistance to metabolic oxidation, modification of pK_a, lipophilicity, etc.).[2] In this line, accessing to peptide analogues with a CF_3 group is of major interest, as illustrated in the work of Zanda.[3] Over the last years, our research has been oriented toward the synthesis of new CF_3-containing amino compounds[4] starting from simple 'N-derivatives' of fluoral (imines, *N*,*O*-acetals, and oxazolidines), a rich source of functionalized trifluoromethyl molecules.[5] In reference to recent progress in the preparation of modified peptides by 'click chemistry',[6] we report herein the synthesis of new trifluoromethyl pseudopeptides with a triazole moiety[7] starting from the *gem*-chloroamine $CF_3CH(Cl)NHAc$ **1**,[5,8] an excellent electrophile previously used by Zard and Gagosz.[9]

1,2,3-Triazoles are generally prepared by 1,3-dipolar cycloaddition of azides and alkynes (also called Huisgen cycloaddition).[10] This reaction is typically performed in refluxing toluene. Thus, our first assessments were performed by reacting $CF_3CH(N_3)NHAc$ **2** (easily obtained from **1**)[11] with ethyl propiolate, a reactive terminal alkyne, under thermal conditions. At reflux of acetonitrile, the reaction was completed within 16 h to yield a mixture of 1,4- and 1,5-disubstituted isomers **3a** (85% yield, 70:30, respectively; Table 1, entry 2).[12] The lack of selectivity is well known under these conditions. To circumvent this problem and in order to use milder conditions for sensitive compounds, Sharpless and Fokin reported the use of copper(I) salts as catalyst for this reaction.[13] These conditions are so efficient (high yields, 1,4 complete selectivity) and easy to implement (room temperature, simple filtration for isolation of the product) that it is considered as the typical 'click' reaction.[14,15] Then, we turned our attention to the copper-catalyzed conditions (Table 1). According to the literature,[14a] the Cu(I) species can be used directly (e.g., CuI), or generated by oxidation or reduction of a Cu(0) or Cu(II) species, respectively. CuBr and CuI were first assessed as Cu(I) sources (10 mol %). Copper iodide showed a good activity with completion of the reaction within 16 h at room temperature and, as expected, only the 1,4-isomer was afforded (entry 4). In contrast, CuBr only showed very low catalytic activity (5% conversion, entry 3). We then switched to copper(II) species: while most of the reports involving Cu(II) describe the use of a reducing agent (e.g., sodium ascorbate with copper sulfate[13]), a single article by Kantam reported the direct use of $Cu^{II}(OAc)_2$ as catalyst (20 mol %) for the same purpose, albeit with a lower efficiency than Cu(I).[16] Surprisingly, in our case also, $Cu(OAc)_2{\cdot}H_2O$ revealed to be the most efficient catalyst, with a complete conversion of the starting material into **3** in only 3 h (entry 6), while with $CuSO_4$ almost no conversion was observed (entry 5). The difference of efficiency between CuI and $Cu(OAc)_2{\cdot}H_2O$ is striking in favor of the Cu(II) salt.[17]

Keywords: Copper; Catalysis; Fluorine; Heterocycle; Click chemistry.
* Corresponding author. Fax: +33 1 46 83 57 40; e-mail: benoit.crousse@u-psud.fr

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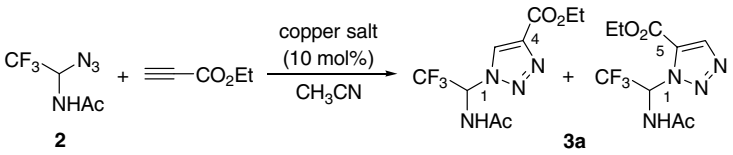
doi:10.1016/j.tetlet.2007.09.118

Table 1. 1,3-Dipolar cycloaddition between azide **2** and ethyl propiolate[a]

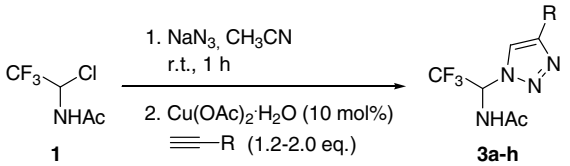


Entry	Copper salt	Temperature (°C)	Time (h)	Conv.[b] (%)	1,4/1,5[c]
1	—	20	16	0	—
2	—	80	16	100[d]	70:30
3	CuBr	20	16	5	n.d.
4	CuI	20	16	100	100:0
5	$CuSO_4$	20	16	5	n.d.
6	$Cu(OAc)_2{\cdot}H_2O$	20	3	100	100:0

[a] Reaction conditions: **2** (0.5 mmol), ethyl propiolate (0.6 mmol) with copper salt (0.06 mmol) in MeCN.
[b] Measured by ^{19}F NMR. Only products from 1,3-dipolar cycloaddition were detected.
[c] Measured by ^{19}F NMR.
[d] 85% isolated yield by flash chromatography on neutral alumina.

Having optimal conditions for this reaction ($Cu(OAc)_2{\cdot}H_2O$, 10 mol %, in CH_3CN at rt), it was decided to improve the process starting directly from chloride **1**, and thus to perform in the same pot the synthesis of azide **2** and the Huisgen reaction. The two-step reaction proceeded very well and the product was isolated in 81% yield (Table 2, entry 1).[18] The scope of reagents was then extended to other acetylenic partners: with all alkynes, the conversion into the expected 1,4-disubstituted triazoles was complete (Table 2).[19] Phenylacetylene gave good results (80%, entry 2), while with hexyne the reaction was sluggish (16 h at 40 °C) but the product was also isolated in very good yield (83%, entry 3). The use of functionalized alkynes, such as propargyl alcohol and some derivatives (entries 4–7), as well as the Boc-protected propargyl amine (entry 8) also gave very good results (good to high yields, short reaction times). In the case of 3-butyn-2-ol as reaction partner (entry 6), we were expecting to obtain a mixture of diastereomers. However, in all NMR experiments (^1H, ^{13}C, and ^{19}F), only a diastereomer (as a racemate) was detected for the product **3f**. Although NMR experiments did not bring a definitive evidence, we considered that **3f** was obtained as a diastereomer (racemic).

Table 2. One-pot azide **2** synthesis/copper(II)-catalyzed synthesis of 1,4-disubstituted triazoles **3**[a]



Entry	R	Temperature (°C)	Time (h)	Product	Yield[b] (%)
1	$-CO_2Et$	20	3	**3a**	81
2	–Ph	20	2	**3b**	80
3	$-C_4H_9$	40	16	**3c**	83
4	$-CH_2OTBDMS$	20	2	**3d**	74
5	$-CH_2OH$	20	2	**3e**	85
6	$-CH(Me)OH$[c]	20	2	**3f**	87
7	$-C(Me)_2OH$	40	20	**3g**	85
8	$-CH_2NHBoc$	20	3	**3h**	77

[a] Reaction conditions: see Ref. 18.
[b] Yield over 2 steps, after purification.
[c] Only one diastereomer was detected by NMR.

Finally, as triazole moieties '*share useful topological and electronic features with nature's ubiquitous amide connectors but, unlike amides, they are not susceptible to cleavage*',[15] we assessed the stability of compound **3a** in aqueous solution at physiological pH. After 24 h, ^{19}F NMR monitoring did not show any transformation of the substrate confirming thus the expected stability of the compound and its possible interesting application as pseudopeptide.

In summary, this work reports the synthesis of new peptidomimetics bearing both a triazole and a trifluoromethyl moiety. They are easily synthesized by using a one-pot azido compound synthesis/copper(II)-catalyzed version of the Huisgen 1,3-dipolar cycloaddition reaction, starting from a readily available trifluoromethylaed starting material. The range of acetylenic partners is large and allows the access to new CF_3-containing pseudopeptides.

Acknowledgments

Samy Chabane (undergraduate student, University Paris XII) is gratefully acknowledged for his active participation in this work, as well as Michèle Ourévitch for NMR experiments. Central Glass is thanked for the kind gift of fluoral hydrate.

References and notes

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11. *Synthesis of N-(1-azido-2,2,2-trifluoroethyl)-acetamide* (**2**): A mixture of chloro compound **1** (2.4 g, 13.6 mmol) and NaN_3 (884 mg, 13.6 mmol) in EtOH or MeCN (20 mL) was stirred for 1 h at room temperature. Then Et_2O was added to the reaction mixture followed by filtration. The filtrate was recovered and the solvents were evaporated to afford **2** as a colorless oil. ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$ as internal standard): δ −79.0 (d, CF_3, $J = 5.5$ Hz); ^1H NMR (188 MHz, $CDCl_3$): δ 6.5 (br, 1H), 6.1 (m, 1H, CF_3CH), 2.2 (s, 3H, CH_3); ^{13}C NMR (188 MHz, $CDCl_3$): δ 171.2 (CH_3CO), 123.0 (q, $^1J_{C-F} = 286$ Hz, CF_3), 63.7 (q, CH, $^2J_{C-F} = 35$ Hz), 22.8 (CH_3CO). Anal. Calcd for $C_4H_5F_3N_4O$ (182.10): C, 26.38; H, 2.77; N, 30.77. Found: C, 26.59; H, 2.95; N, 31.05.
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17. There is currently no evidence on the nature of the active catalytic species in our reactions. While unlikely (Cu^{II} salts are often purer than Cu^{I} salts, see Ref. 13), the presence of Cu^{I} species cannot be ruled out.
18. *Typical procedure for the synthesis of ethyl 1-(1-acetamido-2,2,2-trifluoroethyl)-1H-1,2,3-triazole-4-carboxylate* (**3a**): Chloro compound **1** (1 mmol, 176 mg) and NaN_3 (1.05 mmol, 68 mg) were dissolved in CH_3CN (1.5 mL), and the resulting mixture was stirred for 1 h (clear brown color). Then, a solution of ethyl propiolate (1.2 mmol, 118 mg) in MeCN (1.5 mL), followed by $Cu(OAc)_2{\cdot}H_2O$ (0.1 mmol, 20 mg) were added to the previous solution. After completion of the reaction (3 h, ^{19}F NMR monitoring), the mixture was filtered onto a short pad of neutral alumina and eluted with methanol. The solvents were then removed in vacuo, and the pure product was afforded as a white solid (185 mg, 81%). Mp: 124 °C (toluene/methanol); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$ as internal standard): δ −77.1 (d, CF_3, $J = 5.3$ Hz); ^1H NMR (400 MHz, $CDCl_3$): δ 8.6 (s, 1H, H_{vinyl}), 8.2 (d, $J = 10$ Hz, 1H, NH), 7.1 (m, 1H, CF_3CH), 4.4 (q, $J = 7.2$ Hz, 2H, CH_2), 2.2 (s, 3H, CH_3CO), 1.4 (t, $J = 7.2$ Hz, 3H, CH_3CH_2); ^{13}C NMR (400 MHz, $CDCl_3$): δ 170.2 (CH_3CO), 160.2 ($COOEt$), 140.5 ($C{=}CH$), 128.4 ($C{=}CH$), 121.3 (q, $^1J_{C-F} = 282$ Hz, CF_3), 63.5 (q, CH, $^2J_{C-F} = 37$ Hz), 61.7 (CH_2), 22.6 (CH_3CO) 14.1 (CH_3); Anal. Calcd for $C_9H_{11}F_3N_4O_3$ (280.08): C, 38.58; H, 3.96; N, 20.00. Found: C, 38.38; H, 4.07; N, 19.81.
19. The stereochemistry of the molecule **3a** obtained under copper catalysis was determined by HMBC experiments: a correlation was clearly observed between the carbon $C{=}CH$ and the proton $CHCF_3$. The stereochemistry of all the other compounds was assumed by analogy with **3a**.