

One-Pot Procedure for Diazo Transfer and Azide-Alkyne Cycloaddition: Triazole Linkages from Amines

Henning S. G. Beckmann and Valentin Wittmann*

Fachbereich Chemie, Universität Konstanz, D-78457 Konstanz, Germany

SUPPORTING INFORMATION

General Methods

Syntheses under microwave irradiation were performed in sealed tubes using a *Biotage AB* SmithSynthesizer. TLC was performed on *Merck* Silica Gel 60 F₂₅₄ aluminum sheets. Reagents used for developing plates include Cer-Reagent (5 g molybdato-phosphoric acid, 2.5 g ceric sulphate tetrahydrate, 25 ml sulfuric acid and 225 ml water), ethanolic ninhydrine (3 % w/v), ethanolic sulfuric acid (15 % v/v) and detection by UV light was used when applicable. Flash column chromatography was performed on *Macherey-Nagel* Silica Gel 60 (0.04 – 0.063 mm; 230 – 400 mesh ASTM). ¹H and ¹³C NMR spectra were recorded at room temperature on a *Bruker* Avance DRX 600 instrument. ¹H chemical shifts are referenced to residual protic solvent (CDCl₃, δ_H = 7.26 ppm; DMSO-d₆, δ_H = 2.50 ppm). ¹³C chemical shifts are referenced to the solvent signal (CDCl₃, δ_C = 77.0 ppm; DMSO-d₆, δ_C = 39.4 ppm). ESI mass spectra were recorded on a *Bruker Daltonics* Esquire 3000 plus instrument. Combustion elemental analyses were performed on an *elementar* vario EL analyzer.

Warning: In the case of reactions with azide sources in dichloromethane, formation of explosive diazidomethane has been reported.¹ Therefore, the triflyl azide solution in dichloromethane should always be prepared freshly and the reaction time of 2 h should not be exceeded. Special caution should also be exercised during the workup procedure (especially during evaporation of the reaction mixture) due to excess triflyl azide and possibly formed copper azides, although we never observed any incident.

General Procedure 1: Sequential One-Pot Process for Diazo Transfer and Azide-Alkyne Cycloaddition Using CuSO₄ and Sodium Ascorbate

Triflyl azide (TfN₃) was freshly prepared prior to each reaction.² NaN₃ (6 eq per substrate amine) was dissolved in a minimum volume of water (solubility of NaN₃ in water is approximately 0.4 g/ml). At 0 °C an equal volume of dichloromethane was added and triflic anhydride (Tf₂O) (3 eq) was added dropwise to the vigorously stirred solution. After stirring for 2 h at 0 °C the aqueous phase was once

extracted with the same volume of dichloromethane. The combined organic phases were washed with sat. NaHCO₃ solution and used without further purification.

The substrate amine, CuSO₄ (2 mol%) and NaHCO₃ (1 eq) were dissolved/suspended in the same volume of water as the volume of the TfN₃ solution to be employed. The TfN₃ solution was added, followed by addition of methanol until the solution became homogeneous. The reaction was stirred at room temperature (ca. 30 min) until TLC showed complete conversion of the starting amine.

Then the acetylene component (1 or 1.1 eq), TBTA (5 mol%) and sodium ascorbate (10 mol% per substrate amine) were added and the reaction was heated to 80 °C in the microwave oven until TLC showed complete conversion of the azide intermediate (10 - 30 min).

The reaction mixture was diluted with water and the organic solvents were removed under reduced pressure. If the product precipitates, it was collected by filtration. If not, the water was removed by lyophilization. (In order to remove copper salts, it is advisable to stir the solution with CupriSorb resin and filter it before lyophilization.) The crude product was purified by flash chromatography.

1-Benzyl-4-phenyl-1H-1,2,3-triazole (3)

Method 1: According to General Procedure 1

Benzylamine **1** (54 mg, 0.50 mmol) and phenylacetylene **2** (55 μ l, 0.50 mmol) were reacted according to general procedure 1. After flash chromatography (petroleum ether / ethyl acetate 2:1) **3** was isolated as a white powder (105 mg, 94 %). The ¹H and ¹³C NMR spectroscopic data were in agreement with those published.³

Elemental Analysis: calcd. C 76.57 %, H 5.57 %, N 17.86 %; found: C 76.28 %, H 5.45 %, N 17.83 %.

Method 2: According to General Procedure 1 Using Toluene and Isopropyl Alcohol

The procedure is the same as described above except that toluene is used instead of dichloromethane and isopropyl alcohol instead of methanol. In this case 20 mol% sodium ascorbate was used.

Method 3: Sequential One-Pot Process for Diazo Transfer and Azide-Alkyne Cycloaddition Using CuSO₄ and Cu Powder

The procedure is the same as described in general procedure 1 except that 10 mol% CuSO₄ was used instead of 2 mol% and Cu powder (30 mol%) instead of sodium ascorbate.

Method 4: One-Step One-Pot Process for Diazo Transfer and Azide-Alkyne Cycloaddition Using Sodium Ascorbate or Cu Powder as Reducing Agent

TfN₃ was prepared as described above. The substrate amine, the acetylene component (1 eq) and NaHCO₃ (1 eq) were suspended in the same volume of water as the volume of the TfN₃ solution to be

employed. Then either 2 mol% CuSO₄, 5 mol% TBTA and 10 mol% sodium ascorbate per substrate amine or 10 mol% CuSO₄ and 30 mol% Cu powder per substrate amine were added. The TfN₃ solution was added, followed by addition of methanol until the solution became homogeneous. The reaction was heated to 80 °C in the microwave oven until TLC showed complete conversion of the starting material. The workup procedure is the same as described in general procedure 1.

1-(*p*-Methoxybenzyl)-4-phenyl-1*H*-1,2,3-triazole (**9**)

p-Methoxybenzylamine **4** (69 mg, 0.50 mmol) and phenylacetylene **2** (55 μ l, 0.50 mmol) were reacted according to general procedure 1 at 120 °C in the microwave oven. After flash chromatography (petroleum ether / ethyl acetate 2:1) **9** was isolated as a white powder (104 mg, 78 %). The ¹H and ¹³C NMR spectroscopic data were in agreement with those published.⁴

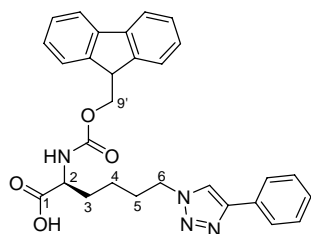
Elemental Analysis: calcd. C 72.43 %, H 5.70 %, N 15.84 %; found: C 72.43 %, H 6.08 %, N 16.13 %.

Ethyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl) acetate (**10**)

Glycine ethyl ester hydrochloride **5** (70 mg, 0.50 mmol) and phenylacetylene **2** (55 μ l, 0.50 mmol) were reacted according to general procedure 1 using 2 eq of NaHCO₃. After flash chromatography (petroleum ether / ethyl acetate 2:1) **10** was isolated as a white powder (94 mg, 81 %). The ¹H and ¹³C NMR spectroscopic data were in agreement with those published.⁵

Elemental Analysis: calcd. C 62.33 %, H 5.67 %, N 18.17 %; found: C 61.99 %, H 5.75 %, N 18.19 %.

(2*S*)-2-(9'-Fluorenylmethyloxycarbonylamino)-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)hexanoic acid (**11**)



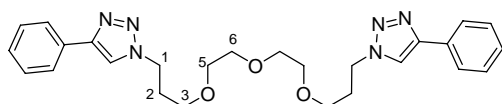
Fmoc-Lys-OH **6** (81 mg, 0.22 mmol) and phenylacetylene **2** (24 μ l, 0.22 mmol) were reacted according to general procedure 1 using 30 mol% Na ascorbate. After flash chromatography (CHCl₃/MeOH/AcOH 96:3:1) **11** (103 mg, 94 %) was isolated as a white powder.

¹H NMR (CDCl₃, 600 MHz): δ = 7.77 – 7.71 (m, 5 H; Ar-H and triazole-5), 7.58 – 7.53 (m, 2 H; Ar-H), 7.40 – 7.34 (m, 4 H; Ar-H), 7.32 – 7.29 (m, 1 H; Ar-H), 7.29 – 7.24 (m, 2 H; Ar-H), 5.63 – 5.58 (br. d, 1 H; NH), 4.54 – 4.24 (m, 5 H; H-2, H-6 and CH₂), 4.17 (t, *J* = 6.8 Hz, 1H; H-9'), 2.02 – 1.75 (m, 4 H; H-3, H-5), 1.51 – 1.34 (m, 2 H; H-4) ppm.

^{13}C NMR (CDCl_3 , 150.9 MHz): δ = 156.1 (C=O), 147.7 (triazole-4), 143.6 (Ar), 141.3 (Ar), 130.0 (triazole-5), 128.9, 128.4, 127.7, 127.1, 125.8, 125.1, 120.0, 119.8 (each Ar), 67.1 (OCH_2), 53.4 (C-2), 50.0 (C-6), 47.1 (C-9'), 31.5 (C-3), 29.5 (C-5), 21.9 (C-4) ppm.

MS (ESI, MeOH): m/z calcd. 495.2 [$M - \text{H}$] $^-$; found 495.3.

1,13-Bis(4-phenyl-1H-1,2,3-triazol-1-yl)-4,7,10-trioxatridecane (12)



4,7,10-Trioxa-1,13-tridecanediamine **7** (66 mg, 0.30 mmol) and phenylacetylene **2** (73 μl , 0.66 mmol) were reacted according to general procedure 1. After flash chromatography (ethyl acetate / MeOH 20:1) **12** (141 mg, 99 %) was isolated as a white powder.

^1H NMR (CDCl_3 , 600 MHz): δ = 7.84 (s, 2 H; triazole-5), 7.83 – 7.81 (m, 4 H; Ar-H), 7.42 – 7.38 (m, 4 H; Ar-H), 7.32 – 7.29 (m, 2 H; Ar-H), 4.48 (t, J = 6.8 Hz, 4 H; H-1), 3.67 – 3.64 (m, 4 H, H-5 or H-6), 3.59 – 3.57 (m, 4 H, H-6 or H-5), 3.42 (t, J = 5.8 Hz, 4 H; H-3), 2.17 – 2.12 (m, 4 H; H-2) ppm.

^{13}C NMR (CDCl_3 , 150.9 MHz): δ = 147.5 (triazole-4), 130.7, 128.7, 128.0, 125.6 (each Ar), 120.4 (triazole-5), 70.5 (C-4 or C-5), 70.3 (C-5 or C-4), 67.0 (C-3), 47.1 (C-1), 30.1 (C-2) ppm.

MS (ESI, MeOH): m/z calcd. 499.2 [$M + \text{Na}$] $^+$; found 499.4.

Elemental Analysis: calcd. C 65.53 %, H 6.77 %, N 17.63 %; found: C 65.32 %, H 6.95 %, N 17.60 %.

α,α' -Bis(4-phenyl-1H-1,2,3-triazol-1-yl)-*m*-xylylene (13)

α,α' -Diamino-*m*-xylylene **8** (42 mg, 0.31 mmol) and phenylacetylene **2** (75 μl , 0.68 mmol) were reacted according to general procedure 1. After flash chromatography (petroleum ether / ethyl acetate 2:1 to ethyl acetate / MeOH 20:1) **13** (106 mg, 88 %) was isolated as a white powder.

^1H NMR (DMSO, 600 MHz): δ = 8.62 (s, 2 H; triazole-5), 7.84 – 7.82 (m, 4 H, Ar-H), 7.44 – 7.37 (m, 6 H; Ar-H), 7.34 – 7.31 (m, 4 H; Ar-H), 5.66 (s, 4 H; CH_2) ppm.

^{13}C NMR (DMSO, 150.9 MHz): δ = 146.6 (triazole-4), 136.6, 130.6, 129.3, 128.8, 127.9, 127.7, 127.4, 125.1 (each Ar), 121.5 (triazole-5), 52.8 (CH_2) ppm.

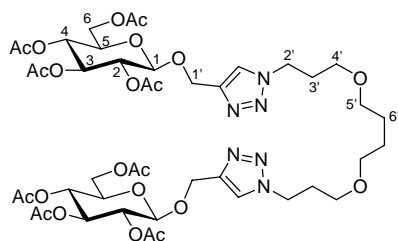
MS (ESI, MeOH): m/z calcd. 415.2 [$M + \text{Na}$] $^+$; found 415.1.

Elemental Analysis: calcd. C 73.45 %, H 5.14 %, N 21.41 %; found: C 73.44 %, H 5.08 %, N 21.61 %.

Propargyl 2,3,4,6-Tetra-O-acetyl- β -D-glucopyranoside (**15**)

2,3,4,6-Tetra-O-acetyl- α -D-glucopyranosyl-trichloroacetimidate⁶ (200 mg, 0.41 mmol) and propargyl alcohol were dissolved in 2 ml abs. CH₂Cl₂. Boron trifluoride etherate (14 μ l of a 0.80 M stock solution in abs. CH₂Cl₂, 0.011 mmol) was added at 0 °C and the reaction was stirred for 45 min at room temperature. Then, sat. NaHCO₃ solution was added at 0 °C. The aqueous phase was extracted once with dichloromethane. The combined organic phases were washed with water, dried over Na₂SO₄ and the organic solvent was removed under reduced pressure. After flash chromatography (petroleum ether / ethyl acetate 2:1) **15** (90 mg, 57 %) was isolated as a white powder. The ¹H and ¹³C NMR spectroscopic data were in agreement with those published.⁷

1,4-Bis(3-(4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyloxymethyl-1H-1,2,3-triazol-1-yl)-propoxy)-butane (**16**)



1,4-Bis(3-aminopropoxy)-butane (20 mg, 0.10 mmol) and **15** (90 mg, 0.23 mmol) were reacted according to general procedure 1 using 0.6 eq NaN₃. After flash chromatography (dichloromethane / MeOH 19:1) **16** (89 mg, 86 %) was isolated as a white powder.

¹H NMR (CDCl₃, 600 MHz): δ = 7.51 (s, 2 H; triazole-5), 5.16 (t, 2 H, J = 9.5 Hz; H-3), 5.07 (t, 2 H, J = 9.6 Hz; H-4), 4.99 (dd, 2 H, J = 8.0 and 9.6 Hz; H-2), 4.91 (d, 2 H, J = 12.6 Hz; H-1a'), 4.79 (d, 2 H, J = 12.5 Hz; H-1b'), 4.67 (d, 2 H, J = 8.0 Hz, H-1), 4.46-4.43 (m, 4 H; H-2'), 4.25 (dd, 2 H, J = 4.8 and 12.3 Hz; H-6a), 4.13 (dd, 2 H, J = 2.3 and 12.3 Hz; H-6b), 3.72 (ddd, 2 H, J = 2.4, 4.7 and 10.0 Hz), 3.43 – 3.38 (m, 8 H; H-4' and H-5'), 2.13 (quin., 4 H; H-3'), 2.07 (s, 6 H; C(O)CH₃), 2.00 (s, 6 H; C(O)CH₃), 1.97 (s, 6 H; C(O)CH₃), 1.96 (s, 6 H; C(O)CH₃), 1.64 – 1.61 (m, 4 H; H-6') ppm.

¹³C NMR (CDCl₃, 150.9 MHz): δ = 170.6, 170.1, 169.4, 169.3 (each C=O), 143.9 (triazole-4), 122.9 (triazole-5), 99.8 (C-1), 72.7 (C-3), 71.9 (C-5), 71.2 (C-2), 70.8 (C-5'), 68.3 (C-4), 66.7 (C-4'), 62.9 (C-1'), 61.8 (C-6), 47.4 (C-2'), 30.4 (C-3'), 26.4 (C-6'), 20.7, 20.6, 20.5 (each CH₃) ppm.

MS (ESI, MeOH): m/z [M + Na]⁺ calcd. 1051.4; found 1051.4.

Elemental Analysis: calcd. C 51.36 %, H 6.27 %, N 8.17 %; found: C 51.13 %, H 6.26 %, N 8.22 %.

(1) Hassner, A.; Stern, M. *Angew. Chem., Int. Ed.* **1986**, *25*, 478-479. Hassner, A.; Stern, M.; Gottlieb, H. E. *J. Org. Chem.* **1990**, *55*, 2304-2306. Dharanipragada, R.; VanHulle, K.; Bannister, A.; Bear, S.; Kennedy, L.; Hruby, V. J. *Tetrahedron* **1992**, *48*, 4733-4748. Bretherick, L. *Chem. Eng. News* **1986**, *64*

- (Dec. 22), 2. Peet, N. P.; Weintraub, P. M. *Chem. Eng. News* **1993**, 71 (Apr. 19), 4. Hruby, V. J.; Boteju, L.; Li, G. *Chem. Eng. News* **1993**, 71 (Oct. 11), 2.
- (2) Nyffeler, P. T.; Liang, C.-H.; Koeller, K. M.; Wong, C.-H. *J. Am. Chem. Soc.* **2002**, 124, 10773-10778. Lundquist, J. T.; Pelletier, J. C. *Org. Lett.* **2001**, 3, 781-783.
- (3) Raghavendra, M. S.; Lam, Y. *Tetrahedron Lett.* **2004**, 45, 6129-6132.
- (4) Abu-Orabi, S. T.; Atfah, M. A.; Jibril, I.; Mari'i, F. M.; Ali, A. A.-S. *J. Heterocyclic Chem.* **1989**, 26, 1461-1468.
- (5) Holzer, W. *Tetrahedron* **1991**, 47, 9783-9792.
- (6) Schmidt, R. R.; Michel, J. *Angew. Chem. Int. Ed. Engl.* **1980**, 19, 731-732.
- (7) Crombez-Robert, C.; Benazza, M.; Fréchou, C.; Demailly, G. *Carbohydr. Res.* **1998**, 307, 355-359.

