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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7923–7925

Regioselective synthesis of 1-(2,2-dimethoxyethyl)-1,2,3-triazoles by copper(I)-catalyzed [3+2] cyclization of 2-azido-1,1-dimethoxyethane with alkynes

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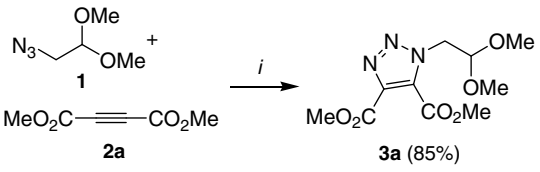
Received 14 July 2007; revised 10 September 2007; accepted 11 September 2007
Available online 15 September 2007

Abstract—1-(2,2-Dimethoxyethyl)-1,2,3-triazoles are regioselectively prepared by copper(I)-catalyzed [3+2] cyclizations of 2-azido-1,1-dimethoxyethane with alkynes.

2-Azido-1,1-dimethoxyethane (ADE) represents a small, but versatile C_2-building block containing a masked aldehyde and a masked amino group. It can be readily prepared by reaction of 1-chloro- or 1-bromo-2,2-dimethoxyethane with sodium azide.[1,2] Despite its structural simplicity and potential synthetic usefulness, there are only a few reports related to the reactions of ADE. The reaction of ADE with *p*-toluenesulfonic acid in acetone and water afforded azidoacetic aldehyde.[3] Two pyrroles were prepared by $TiCl_4$-mediated condensation of ADE with silyl enol ethers and subsequent reductive cyclization.[4] We reported the synthesis of functionalized 2-alkylidenepyrrolidines and pyrroles based on Me_3-SiOTf-catalyzed reactions of ADE with 1,3-bis(silyl enol ethers) and subsequent cyclization by the Staudinger–aza-Wittig reaction.[2] The Staudinger–aza-Wittig reaction of 2-azido-1,1-diethoxyethane with 1,3-dicarbonyl compounds afforded 3-(1-aza-3,3-diethoxypropyl)alk-2-en-1-ones, which were subsequently transformed into a variety of functionalized pyrroles.[5] The Staudinger–aza-Wittig reaction of ADE with aldehydes was reported to give iminoacetals.[1] Herein, we report what are, to the best of our knowledge, the first [3+2] cycloaddition reactions of ADE. These reactions provide a convenient approach to 1-(2,2-dimethoxyethyl)-1,2,3-triazoles. To the best of our knowledge, only one example of this type of molecule has been reported so far.[6] It has been previously reported that acetals, aldehydes and ketones are inert during the formation of triazoles by [3+2] cyclizations.[7] We believe that the triazoles reported herein will be useful synthetic building blocks in organic and medicinal chemistry. In fact, 1,2,3-triazoles are emerging as powerful pharmacophores.[8]

Our starting point was the reaction of ADE (**1**) with dimethyl acetylenedicarboxylate. The reaction of an ethanol solution of the starting materials in a pressure tube (2 h, 120 °C) afforded 1,2,3-triazole **3a** in excellent yield (Scheme 1). The structure of **3a** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[9]

The thermal [3+2] cyclization of azides with terminal alkynes often suffers from low regioselectivities.[10] 1,4-Disubstituted 1,2,3-triazoles can be regioselectively prepared by copper(I)-catalyzed [3+2] cyclization of azides with terminal alkynes.[11] The reaction of ADE (**1**) and methyl propynoate (**2b**), dissolved in a 1:1 mixture of



Scheme 1. Synthesis of 1,2,3-triazole **3a**. Reagents and conditions: (i) EtOH, 2 h, 120 °C.

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doi:10.1016/j.tetlet.2007.09.069

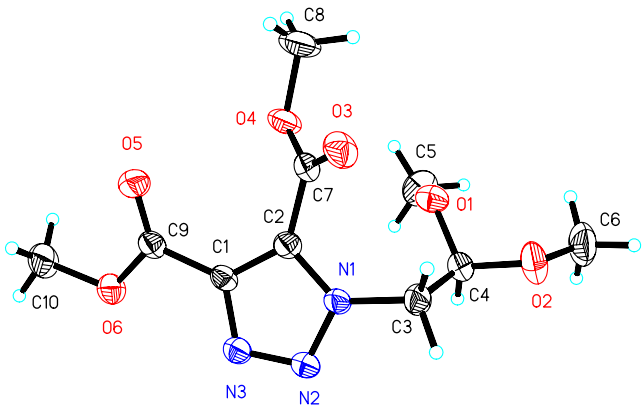
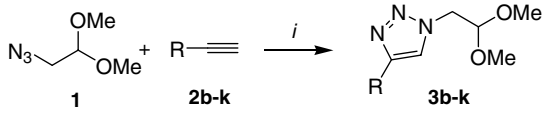


Figure 1. Ortep plot of **3a**.



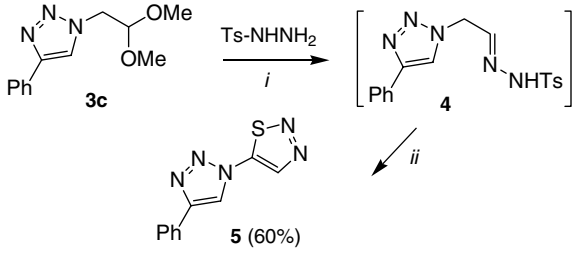
Scheme 2. Synthesis of 1,2,3-triazoles **3b–k**. Reagents and conditions: (i) $Cu/CuSO_4$ (5 mol %), H_2O, *t*-BuOH, 2 h, 110 °C.

water and *tert*-butanol (2 h, 110 °C), gave 1-(2,2-dimethoxyethyl)-1,2,3-triazole **3b** in excellent yield (Scheme 2, Table 1).[12] Likewise, the cyclization of ADE with alkynes **2c–k** afforded the 1-(2,2-dimethoxyethyl)-1,2,3-triazoles **3c–k**. All products were formed in excellent yields and with very good regio- and chemoselectivity. It is noteworthy that a number of different functional groups (acetal, hydroxyl, amino and trimethylsilyl groups) proved to be compatible with the reaction conditions. The structure of products **3b–k** was confirmed by 2D NMR experiments.

Table 1. Products and yields

3	R	%[a]
b	CO_2Me	84
c	Ph	75
d	4-(*n*BuO)C_6H_4	76
e	CH_2Ph	80
f	$(CH_2)_2OH$	82
g	CH(OH)Et	85
h	CH(OH)*c*Hex	89
i	$C(OH)Me_2$	84
j	$N(Me)CH_2Ph$	72
k	$SiMe_3$	88

[a] Yields of isolated products.



Scheme 3. Synthesis of 1,2,3-thiadiazole **5**. Reagents and conditions: (i) concd HCl, EtOH, reflux, 12 h; (ii) $SOCl_2$, neat, 20 °C, 2 h.

The acetal group of 1-(2,2-dimethoxyethyl)-1,2,3-triazoles **3** can be further functionalized as exemplified by the following experiment. The reaction of **3c** with tosylhydrazine in the presence of hydrochloric acid and subsequent treatment with thionyl chloride[13] afforded 1,2,3-thiadiazole **5** (Scheme 3).[14]

Acknowledgement

Financial support by the state of Mecklenburg-Vorpommern is gratefully acknowledged.

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12. *Typical procedure:* Phenylacetylene (500 mg, 4.89 mmol) and 2-azido-1,1-dimethoxyethane (705 mg, 5.38 mmol) were suspended in a 1:1 mixture of water and *tert*-butanol

(5 mL each). To this mixture was added copper turning (50 mg) and an aqueous solution of copper sulfate (1 M, 5 mol %) and the mixture was heated at 110 °C for 2 h. After cooling, the reaction mixture was diluted with water (20 mL). The precipitated product was filtered off and washed with cold water (20 mL) and subsequently with petroleum ether to give **3c** as a colourless solid (851 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.99$ (s, 6H, OCH_3), 4.06 (d, $^{3}J = 5.2$ Hz, CH_2), 4.24 (t, $^{3}J = 5.2$ Hz, CH), 6.81–7.01 (m, 3H, Ph), 7.31–7.40 (m, 2H, Ph), 7.41 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 51.9$ (CH_2), 55.1 (OCH_3), 102.7 (CH), 120.8, 15.6, 128.0, 130.5 (CH_{Ph}), 132.3, 147.8 (C). IR (KBr): $\tilde{\nu} = 3126$ (s), 2996 (m), 2894 (s), 1466 (s), 1364 (m), 1222 (s), 1124 (s), 1079 (s), 1018 (s), 924 (s), 772 (s), 836 (s), 768 (s), 693 (s), 542 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%): 233 (M^+, 16), 173 (13), 116 (19), 75 (100), 47 (18). Elemental Anal. Calcd for $C_{12}H_{15}N_3O_2$ (233.27): C, 61.79; H, 6.48; N, 18.03. Found: C, 61.75; H, 6.44; N, 17.78.

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14. *5-(4-Phenyl-1H-1,2,3-triazol-1-yl)-1,2,3-thiadiazole* (**5**). Colourless solid, yield: 60%; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 7.36$–5.51 (m, 3H, Ph), 7.85–7.88 (m, 2 H, Ph), 9.44 (s, 1H, CH), 9.44 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO): $\delta = 121.3$ (CH), 125.5 (CH_{Ph}), 128.9 (C), 129.0 (CH_{Ph}), 129.1 (C), 129.2, (CH_{Ph}), 138.7 (CH), 147.9 (C). IR (KBr): $\tilde{\nu} = 2996$ (m), 2894 (s), 1466 (s), 1364 (m), 1222 (s), 1124 (s), 1079 (s), 1018 (s), 924 (s), 772 (s), 836 (s), 768 (s), 693 (s), 542 (m) cm^{-1}. Elemental Anal. Calcd for $C_{10}H_7N_5S$ (229.26): C, 52.39; H, 3.08; N, 30.50. Found: C, 52.67; H, 3.44; N, 30.11.