5-Formyltriazoles as Valuable Starting Materials for Unsymmetrically Substituted Bi-1,2,3-Triazoles

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Herein, we present the first synthetic methodologies toward non-symmetrical 5,5′-C, C-linked bi-1,2,3-triazoles starting from 5-formyl-1,2,3-triazole via two related pathways. In a first reaction, 5-formyl-1,2,3-triazole is successfully reacted with a variety of nitroalkanes and organic azides in a one-pot three-component fashion resulting in tetra-ortho-substituted bi-1,2,3-triazoles. In the second, closely related reaction, 5-formyl-1,2,3-triazole is initially converted with nitromethane to the corresponding nitroalkene, and then subsequently oxidatively cyclized with a number of organic azides toward 4-nitro substituted non-symmetrical tetra-ortho-substituted 5,5′-bi-1,2,3-triazoles. The scope of both reactions and further post-functionalizations are examined, and the atropisomeric properties of the obtained bi-1,2,3-triazoles are evaluated.

Keywords: bi-1,2,3-triazole, atropisomer, nitro compounds, 1,2,3-triazoles, 1,3-dipolar cycloadditions

INTRODUCTION

The synthesis of bi-1,2,3-triazole derivatives is scarcely reported, and hence their characteristics and potential applications in e.g., enantioselective synthesis, are strongly underexplored (Zheng et al., 2015; Dawood et al., 2018). The bi-1,2,3-triazoles that have been reported to date are divided into three groups in recent reviews, i.e., symmetrical and unsymmetrical 4,4′-bi-1,2,3-triazoles, and symmetrical 5,5′-bi-1,2,3-triazoles (Zheng et al., 2015; Dawood et al., 2018). For the latter type, the only used method is a modified copper(I)-catalyzed azide-alkyne cycloaddition reaction first reported by Burgess in 2007 (Angell and Burgess, 2007). Via this way, only symmetrical bi-1,2,3-triazoles can be obtained (Angell and Burgess, 2007; Oladeinde et al., 2010; González et al., 2011; Kwon et al., 2012; Zheng et al., 2012, 2015; Wang et al., 2014; Hoyo et al., 2015; Brassard et al., 2016; Etayo et al., 2017; Dawood et al., 2018; Li et al., 2018; Singh et al., 2018). Interestingly, Péricas et al. reported the preparation of 5,5′-bi-1,2,3-triazoles derived from an enantiopure and sterically encumbered propargylamine, but the target compound was only obtained in a poor yield of 8% (Etayo et al., 2017). These 5,5′-bi-1,2,3-triazoles exhibited a relatively high conformational stability (113−117 kJ/mol at 75°C in toluene-δ8), and were successfully applied in the scandium-catalyzed addition of indoles to isatin. Other axially chiral N,N-dimethylpropargylamine-derived bi-1,2,3-triazoles showed fast rotation at room temperature (79.5 kJ/mol at 25°C in n-hexane/ethanol) (Etayo et al., 2017). This was the first study of the conformational stability of 5,5′-bi-1,2,3-triazoles. Nonetheless, this field remains strongly underexplored. The lack of investigation in this area could be ascribed to the complicated syntheses...
of both starting materials (functionalized alkynes) and bi-1,2,3-triazoles themselves, and hence the cumbersome introduction of functional groups interesting for various applications (Zheng et al., 2015; Dawood et al., 2018). In regard with our current interests in sterically encumbered fully substituted (atropisomeric) 1,2,3-triazoles (Thomas et al., 2014, 2016; Vroemans et al., 2018; Krasniqi and Dehaen, 2019), we report what are to the best of our knowledge the first pathways toward novel unsymmetrically tetra-ortho-substituted 5,5′-bi-1,2,3-triazoles from easily accessible starting materials. The anticipated highly sterically hindered bi-1,2,3-triazoles could be decorated with various functional groups which can be introduced in a straightforward manner from ortho, ortho′(1,4-)disubstituted 5-formyl-1,2,3-triazoles, and nitroalkane derivatives.

RESULTS AND DISCUSSION

The common precursor that was envisaged for the synthesis of the desired tetra-ortho-substituted bi-1,2,3-triazoles 8 and 9 is 5-formyl-1,2,3-triazole 4, which itself can be easily prepared either from the commercially available methyl 4-methoxyacetoacetate 1 (Scheme 1; NMR spectra of all novel compounds are displayed in the Supplementary Material) or ethyl 4,4-diethoxy-3-oxobutanoate (Labbé and Dehaen, 1988; Pohkodylo et al., 2018). The aldehyde moiety serves as a versatile tool which can be employed in our in-house developed three-component reaction (Thomas et al., 2014), or can be converted to nitroalkene derivative 5 (Nomland and Hills, 2008) which can subsequently undergo the copper-catalyzed oxidative [3+2]-cycloaddition reaction reported by the group of Chen (Chen et al., 2015). Hence, we commenced by synthesizing starting materials 4 and 5, which was initiated by performing the Dimroth reaction with methyl 4-methoxyacetoacetate 1 and phenyl azide 2, and not starting from ethyl 4,4-diethoxy-3-oxobutanoate which needs to be prepared itself. The desired 5-methoxybenzyl analog 3 was easily obtained on multigram scale via subsequent precipitation and recrystallization. Next, aldehyde 4 was obtained via the photochemical conversion of the methyl ether with bromine in 65% yield. For the second procedure, i.e., the oxidative [3+2]-cycloaddition reaction, 5-formyl-1,2,3-triazole 4 was converted into nitroalkene derivative 5. With both aldehyde 4 and nitroalkene 5 available on gram scale, these could now be employed as starting materials in the subsequent synthesis of unsymmetrical tetra-ortho-substituted 5,5′-bi-1,2,3-triazoles 8 and 9.

Next, the three-component reaction was applied as described by our group on 5-formyl-1,2,3-triazole 4 with a variety of nitroalkanes 6a-d and organic azides 2, 7a-e (Figure 1). Firstly, various alkyl and aryl azides were employed with aldehyde 4 and ethyl nitroacetate 6a as model substrates. Good to excellent yields (56–87%) of bi-1,2,3-triazoles 8 were obtained for alkyl azides 7a-d. Interestingly, enantiopure chiral alkyl azide (R)-7b yielded a 2:25:1-diastereomeric mixture, which was successfully separated via silica gel chromatography into single diastereomers 8ba and 8bb. In general, the use of aryl azides 2 and 7e involved an extended reaction time and slightly decreased yields (21–36%) compared to alkyl azides, and the reaction even failed to afford any product when electron-deficient 4-nitrophenyl azide was employed. Secondly, other functional groups were introduced by varying nitroalkanes 6a-6d. Benzoyl- and phenylsulfonyl-appended bi-1,2,3-triazoles 8h and 8i, respectively, were both prepared in 54% yield. The direct three-component reaction toward bromo-derivative 8g seemed cumbersome, in which the formation of the intermediate bromonitroalkene did not proceed. Nevertheless, 8g was isolated in 64% via a two-pot procedure without intermediate purification of the in situ generated bromonitroalkene derivative.

The introduction of the nitro moiety on the 4-position of 1,2,3-triazoles is highly interesting in view of further transformations, yet tedious to accomplish with the three-component reaction since this would require the use of the hazardous dinitromethane at elevated temperatures. Hence, the copper-catalyzed oxidative [3+2]-cycloaddition reaction with 5-nitrovinyl-appended 1,2,3-triazole 5 serves as a complementary pathway toward highly interesting 4-nitro substituted non-symmetrical tetra-ortho-substituted 5,5′-bi-1,2,3-triazoles. 5-Nitrovinyl-appended 1,2,3-triazole 5 was subjected to the oxidative [3+2]-cycloaddition conditions with different alkyl and aryl azides 2, 7a-e (Figure 2). Derivatives 9a-d, obtained from alkyl azides 7a-d, were obtained in moderate to good yields (51–70%). Again, the use of (R)-7b yielded a diastereomeric mixture of 1:77:1, which were successfully separated via silica gel chromatography and furnished both isolated diastereomers 9ba and 9bb. The use of aryl azides 2 and 7e furnished derivatives 9e and 9f, whilst again 4-nitrophenyl azide did not furnish any desired product. In general, via this second pathway
solely nitro derivatives can be obtained, and the crude reaction mixtures are cleaner than the ones obtained from the three-component reaction with only the HNO$_2$-eliminated derivatives as minor side products.

Several of the obtained bi-1,2,3-triazoles now bear interesting functionalities that could serve as valuable starting point for further derivatization (Scheme 2). Bromo-derivative 8g was subjected to Buchwald-Hartwig amination conditions with pyrrolidine, yet surprisingly the reaction furnished hydrodehalogenated amide 10 in 60% yield. The reactivity of the ester moiety over the bromide of 8g was further exemplified in a substitution reaction with pyrrolidine, in which amide 11 constituting the bromide formed in excellent yields upon reaction at room temperature. Next, hydrolysis of the methyl ester moiety of 9a formed the highly versatile, yet possibly labile, carboxylic acid 12 in 92% yield. Hence, the carboxylic acid was in a next step subjected to heating in order to investigate its thermal stability. Carboxylic acid 12 displayed reasonable stability over the course of several weeks at room temperature, but at 140°C decarboxylation of 12 nicely furnished 13 in good yields (82%). Finally, the reduction of nitro derivative 9f was investigated. Under standard hydrogenation conditions using Pd/C, the versatile free 4-amino-appended derivative 14 was obtained. Further cyclization toward bis-1,2,3-triazolo-fused 2-pyridone 15 was achieved under acidic conditions at 80°C, in which 15 was obtained in 76% yield.

The newly prepared tetra-ortho-substituted 5,5’-bi-1,2,3-triazoles are fascinating structures in the viewpoint of obtaining novel 1,2,3-triazole-containing axially chiral derivatives. The presence of diastereotopic splitting displayed in the $^1$H NMR spectra of the synthesized products strongly indicates this existence of conformationally stable atropisomers (Figure 3). Hence, VT-NMR studies were conducted in tetrachloroethane-$_d_4$ for both 8a and 9a to have an estimate on the energy barrier to rotation for these novel bi-1,2,3-triazoles. At 25°C, both
FIGURE 2 | Scope of copper-catalyzed oxidative [3+2]-cycloaddition toward tetra-ortho-substituted 5,5′-bi-1,2,3-triazoles 9a–f, variations with respect to 5-nitrovinyl-1,2,3-triazole 5, and organic azides 2, 7a–e. 11 Reaction conditions: 5 (1 equiv), organic azides 2, 7a–e (1.5 equiv), Cu(OTf)₂ (0.1 equiv), air, DMF/AcOH (2.5 mL, 4:1), 110°C.

FIGURE 3 | (a) 5,5′-diethoxy-1,2,3-triazole 8a, (b) 4-nitrophe-1,2,3-triazole 9a, (c) 5-(n-decyl)-1,2,3-triazole 9b, (d) 5-[4-(4-fluorophenyl)-1,2,3-triazole 9c, (e) 5-[4-(3-methylphenyl)-1,2,3-triazole 9d, (f) 5-[4-(3,5-dimethylphenyl)-1,2,3-triazole 9e, (g) 5-[4-phenyl-1,2,3-triazole 9f.
Postfunctionalization reactions performed with bi-1,2,3-triazoles 8g, 9a, and 9f.

Rotational stability tests showed promising characteristics as bi-1,2,3-triazoles. Both reactions displayed a versatile scope toward various alkyl and aryl azides, and via the use of both aforementioned procedures various attractive functional groups can be incorporated. Postfunctionalizations further emphasized their peculiar and interesting chemistries for future applications. Rotational stability tests showed promising characteristics as
atropisomers, although the rotational barrier was still rather limited and could be further increased by implementing more sterically hindered ortho-substituents.

**DATA AVAILABILITY STATEMENT**

All datasets generated for this study are included in the article/Supplementary Material.

**AUTHOR CONTRIBUTIONS**

RV and TH carried out the experiments, analyzed the data, and wrote the manuscript. MV carried out some of the experiments and analyzed the data. WD directed the project and corrected the manuscript.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2020.00271/full#supplementary-material

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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