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Deprotometalation–iodolysis and computed CH acidity of 1,2,3- and 1,2,4-triazoles. Application to the synthesis of resveratrol analogues

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ABSTRACT

1-Aryl- and 2-aryl-1,2,3-triazoles were synthesized by *N*-arylation of the corresponding azoles using aryl iodides. The deprotometalations of 1-phenyl-1,2,3-triazole and -1,2,4-triazole were performed using a 2,2,6,6-tetramethylpiperidino-based mixed lithium–zinc combination and occurred at the most acidic site, affording by iodolysis the 5-substituted derivatives. Dideprotonation was noted from 1-(2-thienyl)-1,2,4-triazole by increasing the amount of base. From 2-phenyl-1,2,3-triazoles, and in particular from 2-(4-trifluoromethoxy)phenyl-1,2,3-triazole, reactions at the 4 position of the triazolyl, but also ortho to the triazolyl on the phenyl group, were observed. The results were analyzed with the help of the CH acidities of the substrates, determined in THF solution using the DFT B3LYP method. 4-Iodo-2-phenyl-1,2,3-triazole and 4-iodo-2-(2-iodophenyl)-1,2,3-triazole were next involved in Suzuki coupling reactions to furnish the corresponding 4-arylated and 4,2′-diarylated derivatives. When evaluated for biological activities, the latter (which are resveratrol analogues) showed moderate antibacterial activity and promising antiproliferative effect against MDA-MB-231 cell line.

1. Introduction

Di- and triazoles are key elements present in compounds of biological interest[1] or in materials for a wide range of applications.[1a,b,2]

Aromatic deprotonative lithiation[3] is an efficient tool to functionalize regioselectively heterocycles.[4] Concerning 1-substituted 1,2,3- and 1,2,4-1*H*-triazoles, such a possibility has been developed, affording after subsequent trapping 5-substituted derivatives.[4q]

Combinations of lithium reagents and softer metal compounds have recently emerged as efficient tools to deprotometalate sensitive aromatic compounds.[5] In the framework of these studies, we developed efficient pairs of metal amides which complement each other in deprotometalation reactions. In particular, the TMP-based (TMP = 2,2,6,6-tetramethylpiperidino) lithium–zinc mixture,[6] prepared by mixing LiTMP with $ZnCl_2$·TMEDA (1/3 equiv, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) and supposed to be a 1:1 $Zn(TMP)_2$–LiTMP·2LiCl(±TMEDA) mixture,[7] was identified as a suitable reagent to functionalize sensitive aromatic compounds including heterocycles.

We herein describe our attempts to use the lithium–zinc combination above mentioned for the deprotometalation (followed by iodolysis) of the azole substrates **1** and **2** shown in Scheme 1. Earlier we have shown that the regioselectivity of the same reaction for the related substrates **3**[6f] and **4**[6h] is partly determined by the acidity of the different hydrogens in their molecules. As a consequence, we similarly tried to rationalize the reaction results using the CH acidities in THF of the heteroaromatic substrates calculated by using the homodesmic reaction approach within the density functional theory (DFT) framework. Finally, iodides generated by deprotometalation–iodolysis were involved in

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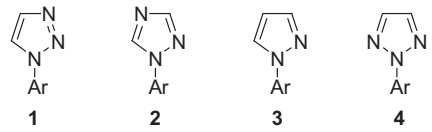


Scheme 1. Substrates for which the deprotometalation has been studied.

palladium-catalyzed Suzuki cross-coupling reactions, and the resulting arylated triazoles (which are resveratrol analogues) were evaluated for their biological activity.

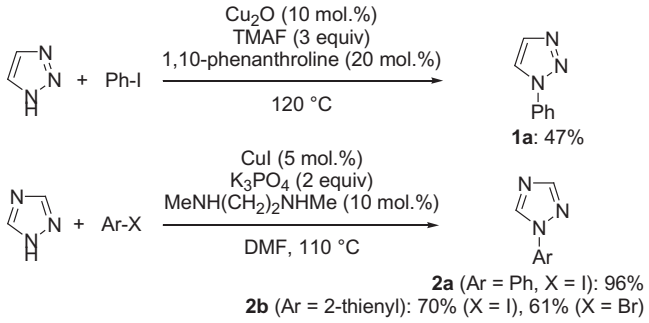
2. Results and discussion

2.1. Synthetic aspects

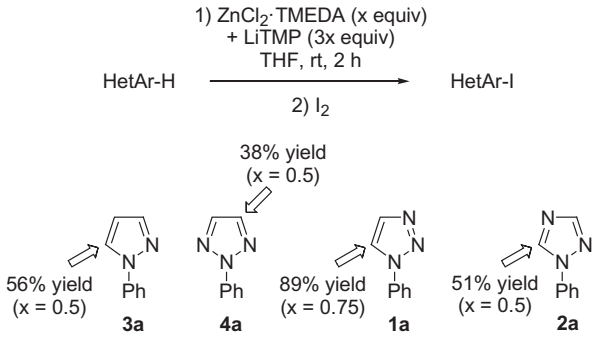
1-Phenyl-1*H*-1,2,3-triazole (**1a**) was prepared by adapting a procedure described.[8] To reach the target substrates **2**, the unsubstituted azoles were treated with aryl and heteroaryl halides under copper catalysis using the conditions reported by Buchwald and co-workers (Scheme 2).[9] Moderate to excellent yields were noted, with aryl iodides favoring the reaction as observed previously.[6l]

Upon treatment in THF for 2 h at room temperature with the lithium–zinc base, in situ prepared from $ZnCl_2$·TMEDA (x equiv) and LiTMP (3x equiv), 1-phenyl-1*H*-pyrazole (**3a**) is mainly deprotonated at its 5 position ($x = 0.5$), a result evidenced by subsequent interception with iodine.[6c,f] In addition, 2-phenyl-2*H*-1,2,3-triazole (**4a**) mainly led to the 4-iodo derivative under the same reaction conditions.[6h] It was thus of interest to attempt the reaction from 1-phenyl-1*H*-1,2,3-triazole (**1a**) and 1-phenyl-1*H*-1,2,4-triazole (**2a**). In both cases, the reaction took place at the 5 position of the triazolyl group, and the iodides **5a** ($x = 0.75$) and **6a** ($x = 0.5$) were isolated in 89% and 51% yield, respectively, (Scheme 3). The iodide **5a** was also isolated (80% yield) from **1a** after carrying out the reaction using LiTMP (1.5 equiv) in THF, but using a lower (−20 °C) reaction temperature.

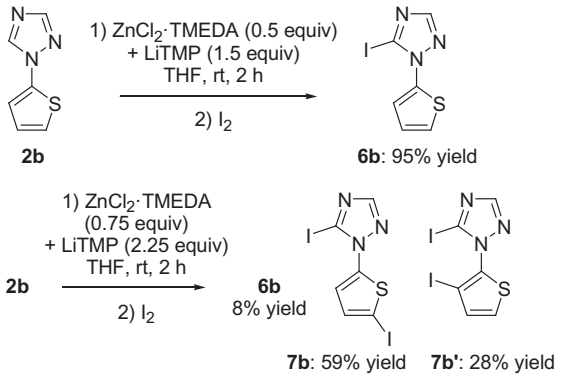
By replacing the phenyl group connected to the 1,2,4-triazole by a 2-thienyl group (substrate **2b**), a reaction at the 5 position of the aza-heterocycle was still observed, as demonstrated by the isolation of the corresponding iodide **6b** in 95% yield. By increasing the amount of base (0.75 equiv of $ZnCl_2$·TMEDA and 2.25 equiv of LiTMP instead of 0.5 equiv of $ZnCl_2$·TMEDA and 1.5 equiv of LiTMP), the iodide **6b** became the minor product formed (8% yield) due to competitive dideprotometalation, as previously noted in the other azole series.[6f,h] Indeed, the diiodides **7b** and **7b′** were obtained in 59% and 28% yield, respectively, (Scheme 4). The iodides **5a** and **6a**, as well as the major isomer **7b**, were identified unequivocally by X-ray structure analysis (Fig. 1).



Scheme 2. Synthesis of **1a**, **2a** and **2b**.



Scheme 3. Deprotometalation followed by iodolysis on *N*-phenylpyrazole and different *N*-phenyltriazoles.



Scheme 4. Deprotometalation of **2b** followed by iodolysis.

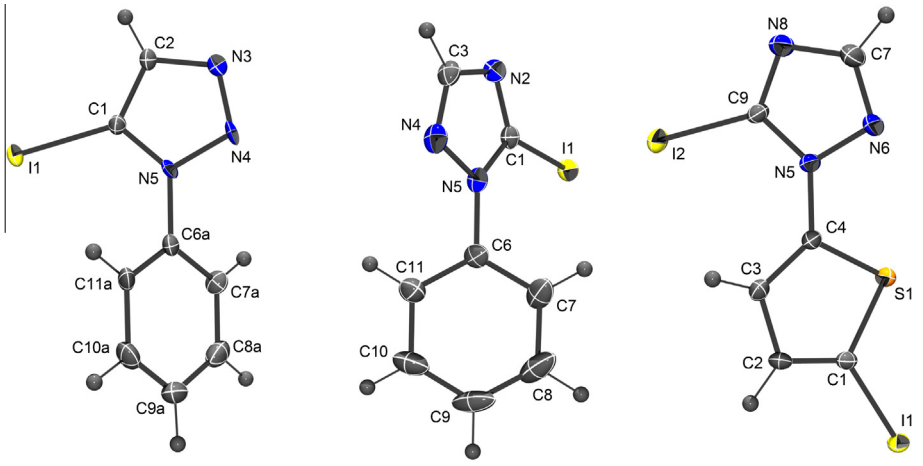


Figure 1. ORTEP diagram (50% probability) of **5a**, **6a** and **7b**.