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Catalysis

Facile, High-Yielding Synthesis of 4-Functionalised 1,2,3-Triazoles via Amino- and Aryloxycarbonylation

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4-Iodo-1,2,3-triazoles were synthesised via azide-alkyne cycloaddition of alkynyl Grignard reagent and benzyl azide followed by iodination reaction. The aminocarbonylation and aryloxycarbonylation of 4-iodo-1,2,3-triazoles were carried out in the presence of various *N*- and *O*-nucleophiles, resulting in the corresponding triazole-based 4-carboxamides and 4-esters, respectively. Both high-yielding reactions were carried out under mild conditions (atmospheric CO pressure, 70 °C).

1. Introduction

The facile functionalization of heterocycles in homogeneous catalytic reactions[1] or their multistep synthesis is still in the forefront of the investigation of practically important skeletons. 1,2,3-Triazole-based derivatives are among the most investigated ones.[2] Due to our long interest in the synthesis of carboxamides in palladium-catalysed aminocarbonylation,[3,4] and recently in the functionalization of heterocycles,[5] novel synthetic procedures targeting 4-carboxamido-1,2,3-triazoles of high synthetic and biological (pharmaceutical) importance were considered. Various 1,4-disubstituted 1,2,3-triazoles were published showing antiaggregating and antithrombotic[6] and antiepileptic[7] activities.

Our synthetic approach is based on the combination of two efficient catalytic reactions, namely, the azide-alkyne (3 + 2) cycloaddition reaction[8–10] and the palladium-catalysed aminocarbonylation discovered by Heck ('Heck carbonylation').[11] While the 'click' reaction revolutionized the synthesis of triazoles,[10] the abovementioned aminocarbonylation enabled the synthesis of even hardly available carboxamides.

In this paper, a facile synthetic procedure for the synthesis of 4-carboxamido-1,2,3-triazoles, as well as their close analogues, 4-aryloxycarbonyl-1,2,3-triazoles will be described. Our approach is based on the application of conventional high-yielding reactions as well as the above homogeneous catalytic reaction, carbonylation reactions in the presence of *N*- and *O*-nucleophiles.

2. Results and Discussion

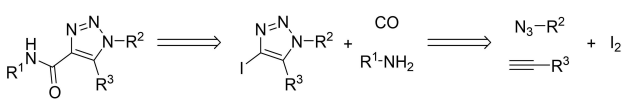
2.1. Synthesis of 4-Iodotriazoles

The retrosynthetic analysis of the 4-carboxamido-1,2,3-triazoles (Scheme 1) revealed that the application of a highly efficient carbonylation as a final step requires the synthesis of the corresponding 4-iodo-1,2,3-triazole. Since the azide-alkyne cycloaddition reaction of iodoalkynes[12] is perfectly regioselective resulting in the formation of 5-iodo-1,2,3-triazoles[13] and consequently, resulted in the formation of the corresponding 5-carboxamido-1,2,3-triazoles,[14] a different strategy had to be applied for the synthesis of 4-carboxamido-1,2,3.triazoles.

In our approach, the target sterically more congested 4-iodotriazoles (**7** and **8**) were synthesised via Grignard reagents. First the azide-alkyne cycloaddition reaction of benzyl azide and alkynyl Grignard reagents (**3** and **4**), obtained from the corresponding alkynes (**1** and **2**), was carried out. The reaction is highly regioselective providing the target 1,5-disubstituted derivatives containing the magnesium fragment in 4-position (**5** and **6**). Their 4-iodo derivatives (**7** and **8**) were obtained in iodination reaction (Scheme 2.). The above procedure was carried out in a one-pot procedure with a total yield of 52 %.

2.2. Aminocarbonylation of 4-Iodotriazoles (7 and 8)

The 4-iodotriazole substrates were aminocarbonylated under atmospheric pressure using various primary amines as *N*-nucleophiles *tert*-butylamine (**a**), *n*-decylamine (**b**), aniline (**c**), benzylamine (**d**), 1-phenylethylamine (**e**), 2-, 3- and 4-picolyl-



Scheme 1. Retrosynthetic analysis of the synthesis of 4-carboxamido-1,2,3-triazoles.

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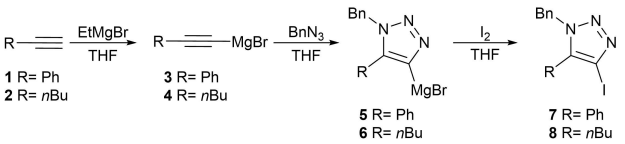


Scheme 2. Synthesis of 4-iodotriazoles in one-pot reaction.

amine (**f, g, h**), 2-furylmethylamine (**i**), 2-thiophenylmethylamine (**j**), 2-, 3- and 4-aminopyridine (**k, l. m**) in the presence of palladium catalysts (Scheme 3). A highly active and conveniently used Pd(0) catalyst, prepared 'in situ' from $Pd(OAc)_2$ and Xantphos, was used. Its formation was previously discussed.[15]

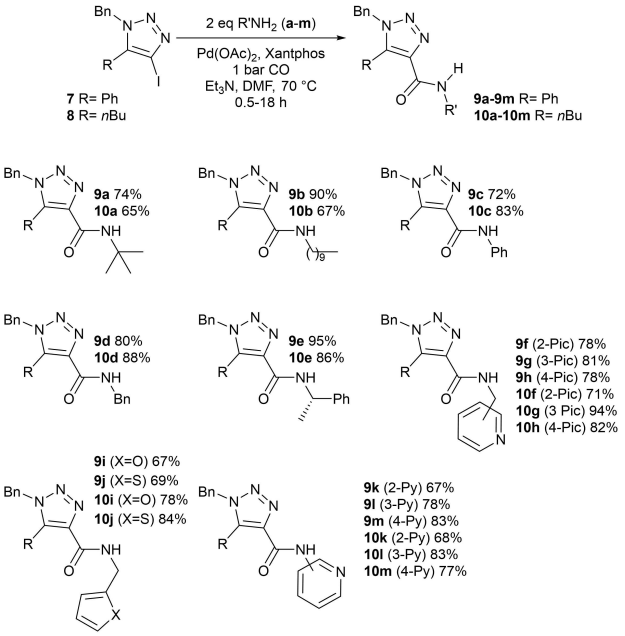
The corresponding 4-carboxamidotriazoles (**9a–9m** and **10a-10m**) were obtained as the only carbonylated products, *i.e.*, no formation of the 2-ketocarboxamide products, due to double CO insertion, was observed.

It is worth noting that the above aminocarbonylation reaction had to be carried out at slightly higher reaction temperature (70 °C) than usually applied in similar reactions (for instance in aminocarbonylation of conventional iodoaromatics).[3] At lower temperature (50 °C) the carbonylation reaction is accompanied by deiodination. The corresponding product **8′**[16] was identified in a mixture of **10a:8′** (53:47), as determined by ^{1}H NMR but not isolated in analytically pure form (Scheme 4).

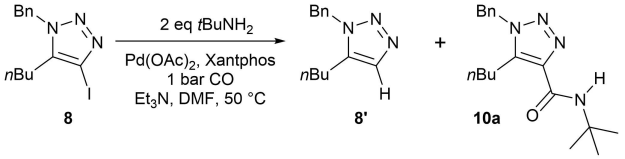
The loss of the iodoarene functionality can be rationalized on the basis of the reaction mechanism. At lower temperature the formation of the aryl-palladium(II) intermediates (**A** and **B**, Scheme 7) is not followed by carbon monoxide insertion but a competitive aminolysis might take place, *i.e.*, a reduction process by the primary amine leads to the formation of **8′**.

The 4-carboxamides were prepared as analytically pure compounds in moderate to high yields (65-95%). It is worth noting that the reaction is not influenced dramatically by the basicity of the N-nucleophile, *i.e.*, amines with high basicity (for instance, **a**) gave similar results with less basic aryl amines such as **c** and **k**, **l**, **m**.

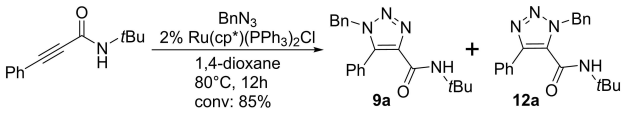
Regarding the mechanistic details, the facile formation of the Pd(II)-NHR amido complex, as well as a fast reductive elimination of the Pd(II)–acyl-amido complex in the product-forming step can be supposed. It Is worth noting that an alternative synthetic strategy could also be used for the introduction of the 4-carboxamido functionality. In particular, the ruthenium-catalysed 2 + 3 cycloaddition of the azide and the alkyne carboxamide was supposed to result in the formation of 4-carboxamido-1,2,3-triazoles.[8,17] However, in our



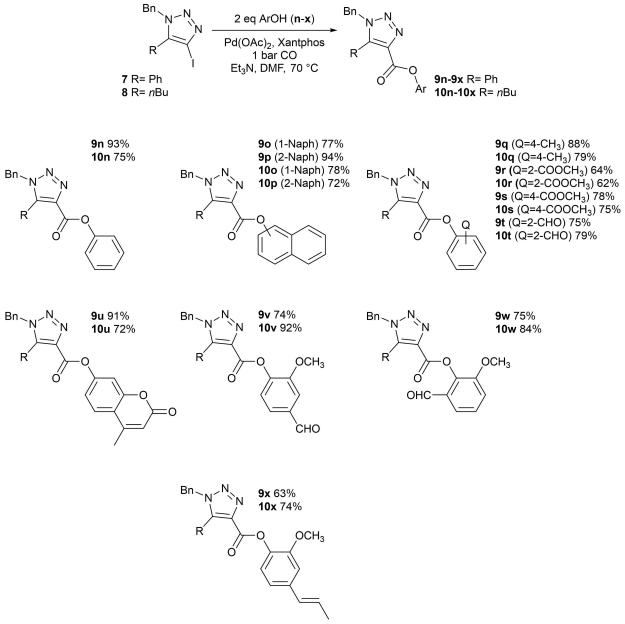
Scheme 3. Aminocarbonylation of iodotriazoles (**7** and **8**).



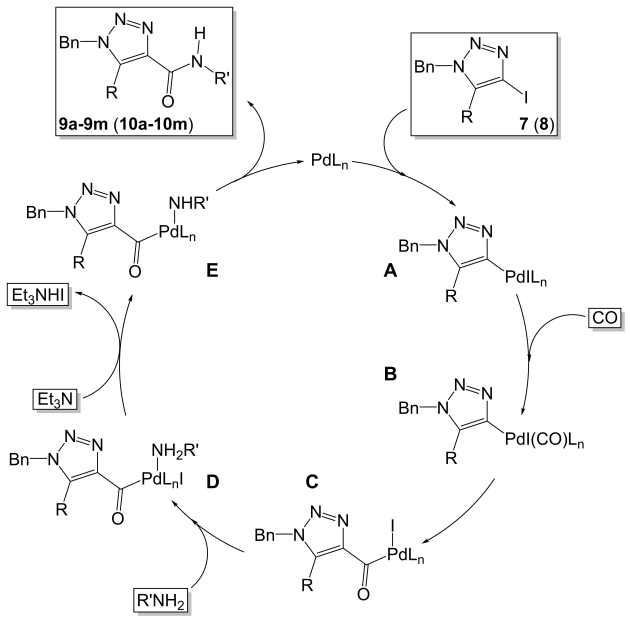
Scheme 4. A deiodination reaction of **8**.



Scheme 5. Ruthenium-catalysed 2 + 3 cycloaddition of an alkynamide and azide.



Scheme 6. Aryloxycarbonylation of iodotriazoles (**7** and **8**).



Scheme 7. A simplified catalytic cycle of the aminocarbonylation of iodotriazoles.

case conversion was far from complete and a mixture of the two regioisomers (**9a**:**12a** = 82:18) was obtained. (Scheme 5).

The previously reported synthesis of 5-carboxamido-1,2,3-triazoles[14] and that of the 4-carboxamido-1,2,3-triazoles described in this work differ substantially.

In particular, while the 3 + 2 cycloaddition of 1-iodoalkynes and triazole gave 5-iodo-1,2,3-triazoles (as specified above), the use of 'alkynyl-Grignard reagents **3**–**4** afforded 4-iodotriazoles **7**–**8**, directing the R substituent of the alkyne to position 5 selectively.

As for the final step, palladium-catalysed aminocarbonylation of 4-iodo-1,2,3-triazole substrates requires higher temperature (70 °C) than that of the corresponding 5-iodo compounds (50 °C).[14] A similar behaviour, *i.e.* decreased reactivity of the iodoheteroaromatics was observed when the iodo substituent adjacent to non-substituted nitrogen (for instance 2-iodopyridine, iodopyrazine)[18] were used. In addition, these substrates have shown also the lack of double carbon monoxide insertion. Mechanistically, the coordination of the nitrogen to the palladium centre might be responsible for these phenomena.

The most characteristic structural difference between 4- and 5 -carboxamido-1,2,3-triazoles is the presence and absence of hydrogen bonding. While the amide-NH ^{1}H NMR chemical shifts of 5-carboxamides are in the range of 4–6 ppm, the NH signals are shifted to the aromatic region in case of 4-carboxamides due to the interaction of NH with non-substituted N of the triazole ring (See Supporting Information).

2.3. Aryloxycarbonylation of 4-Iodotriazoles

The carbonylation of the iodotriazoles (**7** and **8**) was also carried out using phenol (**n**) and its derivatives possessing varied structures (1-naphthol (**o**), 2-naphthol (**p**), 4-methylphenol (**q**), methyl salicylate (**r**), 4-methoxycarbonylphenol (**s**), salicylaldehyde (**t**), 7-hydroxy-4-methylcoumarine (**u**), 2-methoxy-4-formylphenol (**v**), 2-methoxy-6-formylphenol (**w**) and 2-methoxy-4-allylphenol (**x**) as *O*-nucleophiles in the presence of the above highly durable palladium-containing catalytic system (Scheme 6).

The aryl esters (**9n**–**9x** and **10n**–**10x**) were obtained as the only products in moderate to high yields of up to 94%. Furthermore, it has to be added that in case of allylphenyl nucleophile (**x**) complete isomerization of the allyl fragment to 1-propenyl-substituent took place and **9x** and **10x** were isolated accordingly.

The formation of 4-carboxamidotriazols can be rationalized as depicted in Scheme 7. The oxidative addition of **7** (or **8**) onto palladium(0) species results in the formation of the palladium (II)-aryl intermediate (**A**). The activation of CO as a terminal carbonyl (**B**) is followed by its insertion yielding the corresponding palladium(II)-acyl intermediate (**C**). The coordination of the amine nucleophile (**D**), followed by hydrogen iodide abstraction by the base (Et_3N), resulted in the formation of the amido-acyl-palladium(II) complex (**E**) which provides carboxamides **9a**–**9m** (or **10a**–**10m**) by reductive elimination in the product forming step.

3. Conclusions

It has been proved that palladium-catalysed aminocarbonylation and aryloxycarbonylation are useful synthetic procedures for the synthesis of 1,2,3-triazoles possessing either carboxamido or ester functionality in 4-position. A highly active palladium-catalyst bearing large bite-angle Xantphos ligand was used in this study, The practically complete conversion and high chemoselectivity toward carboxamides and esters enabled facile isolation of the target products.

Supporting Information Summary

The Supporting Information (SI) is available free of charge on the website at. The SI provides the general methods and instrumentation, describes the synthesis of 4-iodotriazoles and target 4-functionalised carboxamides and esters. In addition, full characterization of all compounds and their ^{1}H and ^{13}C NMR spectra are attached.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Aminocarbonylation · carbon monoxide · carbonylation · palladium · triazole

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