University of Applied Sciences and Arts Northwestern Switzerland
School of Life Sciences

Synthesis of di- and tri-(2*H*-1,2,3-triazol-2-yl)benzoic acids

Roth Remo
Bachelor thesis, Molecular Life Science

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ABSTRACT

The synthesis and characterization of seven N^2-substituted triazole derivatives of benzoic acids, benzaldehydes and benzene containing two to three triazole moieties is presented. The unknown target compounds were prepared from 4,5-dibromo-2*H*-1,2,3-triazole in a four-step sequence by N^2-selective nucleophilic aromatic substitutions with fluoronitrobenzenes, Pd-catalyzed hydrogenation, Sandmeyer and finally Grignard reaction. The synthetic sequence was successfully applied on 40-90 g scale, except the Grignard reaction, which was performed on 10 g scale, since only 5 g of the target compounds were desired.

INTRODUCTION

1,2,3-triazoles have been known for over a century and have become of increasing interest in medicinal chemistry because of their broad range of biological activities.[1]

For example, Suvorexant **1** (Figure 1) is a soporific, more specifically a dual orexin receptor antagonist, introduced on the marked by Merck in 2014. Orexin is a neurotransmitter located in the hypothalamus and plays an important role in the regulation of sleep and arousal states. This neuropeptide binds to two G protein-coupled receptors which are both inhibited by Suvorexant.[2][3]

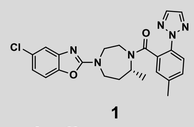
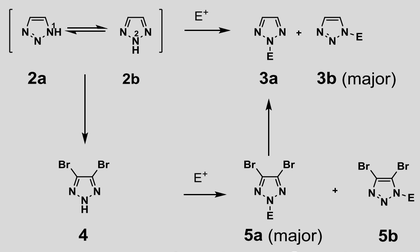


Fig. 1: Suvorexant

Idorsias interest is to develop more potent orexin antagonists by developing different N^2-substituted ortho-triazole benzoic acids and derivatives.

Whereas N^1-substituted triazoles can be easily accessed by thermal or copper(I)-catalyzed azide-alkyne cycloaddition, selective N^2-substitution remains a challenge.[4]

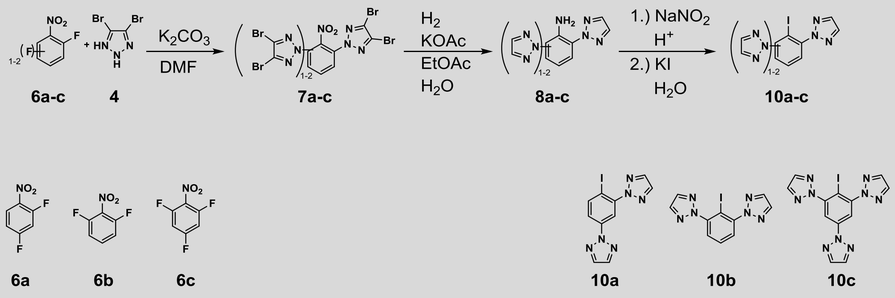
Here, it was achieved by following the procedure of Wang et al. [4] where 4,5-dibromo-2*H*-1,2,3-triazole **(4)** is used instead of 2*H*-1,2,3-triazole **(2)**. It is proposed that the 4,5-dibromo-substitution pattern provides sufficient steric hinderance and electrophilic deactivation to block a reaction at the N^1-position (Scheme 1).



Scheme 1: Selective N^2-substitution

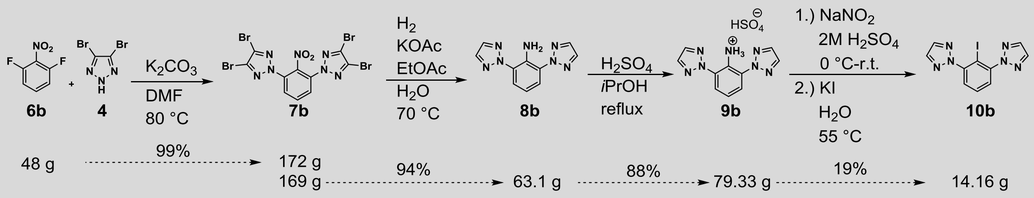
RESULTS

Synthesis of the iodides **10a-c** was performed by selective N^2-arylation of **4**, followed by hydrogenation and Sandmeyer reaction with KI (Scheme 2).



Scheme 2: Synthetic route to the iodides **10a-c**

Scheme 3 shows the whole scale-up process with **6b** as an example. The N^2-arylation and the Sandmeyer reaction were performed in a 4 L double-jacked reactor (Figure 2). Hydrogenations were performed in a 3 L Büchi Ecoclave in multiple batches (Figures 3 and 4).



Scheme 3: Scale-up process of **6b**

Figure 2: 4 L reactor

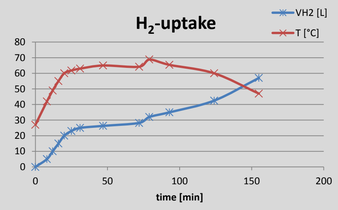
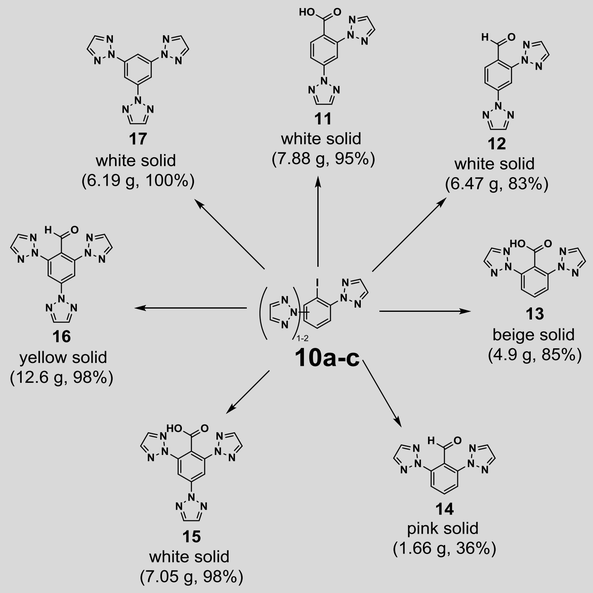


Figure 3: H_2-uptake

Figure 4: 3 L Büchi Ecoclave

The sulfates **9** could only be formed from **8a** and **8b**. Unfortunately, they were not as soluble as expected, which had a negative influence on the conversion to the iodides **10a** and **10b** during scale-up (19-57% yield). Alternatively, **8c** was converted to the iodide **10c** as free base with 2M HCl and with acetonitrile as a co-solvent. With these conditions, no solubility issues arose and the reaction could be scaled up with an overall yield of 79%.

The title compounds **11-17** were then prepared by halogen-metal exchange of the iodides **10a-c** and subsequent quenching with electrophiles like CO_2, DMF and NH_4Cl (Scheme 4).



Scheme 4: Grignard reaction of the iodides **10a-c**

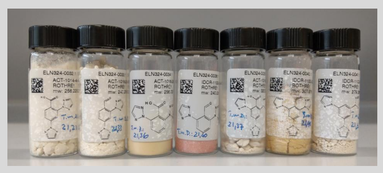


Fig. 5: Synthesized compounds **11-17**

CONCLUSION AND OUTLOOK

Selective N^2-arylation for mono-triazole substituted benzenes according to Wang et al. [4] could be successfully applied to the synthesis of poly-triazole substituted benzoic acids with excellent N^2-selectivity. Furthermore, scalability was demonstrated through the conversions of 40-90 g batches of 4,5-dibromo-2*H*-1,2,3-triazole **(4)**. Seven new compouds could be synthesized and characterized.

Proceeding from the iodides, further different functional groups like boronic acids, ketones or amines should be accessible.

REFERENCES

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