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

Roth Remo
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ABSTRACT

The synthesis and characterization of seven N²-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-2H-1,2,3-triazole in a four-step sequence by N²-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 (Figure 1) is a soporific, more specifically a dual orexin receptor antagonist, introduced on the market 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]

Idorsia’s interest is to develop more potent orexin antagonists by developing different N²-substituted ortho-triazole benzoic acids and derivatives.

Whereas N¹-substituted triazoles can be easily accessed by thermal or copper(I)-catalyzed azide-alkyne cycloaddition, selective N²-substitution remains a challenge.[4]

Here, it was achieved by following the procedure of Wang et al. [4] where 4,5-dibromo-2H-1,2,3-triazole (4) is used instead of 2H-1,2,3-triazole (2). It is proposed that the 4,5-dibromo-substitution pattern provides sufficient steric hindrance and electrophilic deactivation to block a reaction at the N¹-position (Scheme 1).

RESULTS

Synthesis of the iodosides 10a-c was performed by selective N²-arylation of 4, followed by hydrogenation and Sandmeyer reaction with KI (Scheme 2).

Scheme 3 shows the whole scale-up process with 6b as an example. The N²-arylation and the Sandmeyer reaction were performed in a 4 L double-jacketed reactor (Figure 2). Hydrogenations were performed in a 3 L Büchi Ecoclave in multiple batches (Figures 3 and 4).

CONCLUSION AND OUTLOOK

Selective N²-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 N²-selectivity. Furthermore, scalability was demonstrated through the conversions of 40-90 g batches of 4,5-dibromo-2H-1,2,3-triazole (4). Seven new compounds could be synthesized and characterized.

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

REFERENCES