Tetrahedron 74 (2018) 1024–1032

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Convenient synthesis of 10*H*-indolo[3,2-*b*]quinolines and 6*H*-indolo[2,3-*b*]quinolines by sequential chemoselective Suzuki reaction followed by double C-N coupling

Ghazwan Ali Salman [a, b, 1], Sophie Janke [a, c, 1], Ngo Nghia Pham [a, c, d], Peter Ehlers [a, c], Peter Langer [a, c, *]

[a] Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059, Rostock, Germany
[b] Department of Chemistry, College of Science, University Al-Mustansiriyah, Palestine St, Mustansiriya, Baghdad, Iraq
[c] Leibniz Institut für Katalyse an der Universität Rostock e.V., Albert-Einstein-Str. 29a, 18059, Rostock, Germany
[d] Faculty of Chemistry, VNU University of Science Hanoi (VNU-HUS), 19 Le Thanh Tong, Hoan Kiem, Hanoi, Viet Nam

ARTICLE INFO

Article history:
Received 23 October 2017
Received in revised form
3 January 2018
Accepted 5 January 2018
Available online 10 January 2018

Keywords:
Heterocycles
Cyclization
Palladium
Regioselectivity

ABSTRACT

A convenient and regioselective synthesis of two series of indolo[2,3-*b*]quinolines, namely 10*H*-indolo[3,2-*b*]quinolines and 6*H*-indolo[2,3-*b*]quinolines, has been developed. The synthesis, proceeds in moderate to high yields, involving chemoselective palladium catalyzed Suzuki reaction of 2,3-dihaloquinolines with 2-bromophenylboronic acid, followed by a double Buchwald-Hartwig C-N coupling.

1. Introduction

Indolo[2,3-*b*]quinoline and indolo[3,2-*b*]quinoline are fused scaffolds of quinoline and indole with biological importance. A number of derivatives have been discovered with antimalarial, antitumor and antiplasmodial activities, to name but a few.[1] A reason for their biological importance is their capability to form π-π stacking interactions in living systems.[2]

The synthesis of *N*-substituted indoloquinolines has gained increasing attention recently.[3] Theoretically, the substitution can occur at two positions, namely at the quinoline and the indole ring. The former is known for cryptolepine and neocryptolepine (Fig. 1), which have been found in several plants and have been known for antitumor and antimalarial activities.[4]

In comparison, *N*-substituted indolo[2,3-*b*]quinoline and indolo[3,2-*b*]quinoline have not been found in nature and has been solely synthesized in the laboratory instead.[5] A number of these compounds have been discovered with relevant biological activities (Fig. 2).

In recent years, we and others studied palladium catalyzed syntheses and functionalization of various heterocyclic systems.[10] In particular, we studied the combination of the regioselective Suzuki reaction of polyhalogenated heterocycles with 2-bromophenylboronic acid and subsequent double Buchwald-Hartwig reaction. Very recently, we reported the synthesis of 11*H*-indolo[3,2-c] quinolines based on the employment of 3,4-dihaloquinolines as starting material.[10a] In the present study, we report what is, to the best of our knowledge, a new synthesis of indolo[2,3-*b*]quinolines and indolo[3,2-*b*]quinolines which is based on chemoselective Suzuki reactions of 2,3-dihaloquinolines, followed by double C-N coupling (Scheme 1). Our methodology is high yielding and allows for a selective synthesis of two series of regioisomeric products based on the choice of the starting material.

2. Results and discussion

Our starting point was to identify suitable 2,3-dihaloquinolines

* Corresponding author. Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059, Rostock, Germany.
E-mail address: peter.langer@uni-rostock.de (P. Langer).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.tet.2018.01.010
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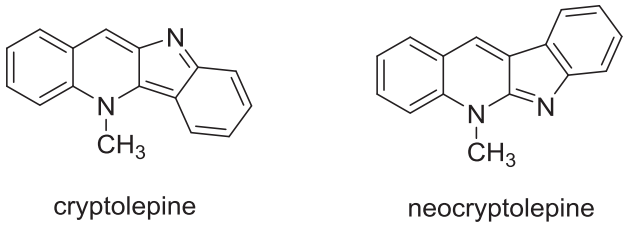


Fig. 1. Examples for *N*-substituted indolo[2,3-*b*]quinoline and indolo[3,2-*b*]quinoline.

as starting materials. 2-chloro-3-bromoquinoline (1a) was prepared according to a previously reported procedure.[11] Product 1a was then transformed to 2-iodo-3-bromoquinoline (1b).[11] In case of the synthesis of 1b, the addition of copper iodide was reported. In our hands, it was necessary to add copper iodide. The Suzuki reaction of 1a with 2-bromophenylboronic acid afforded the desired product 2a in 75% (Scheme 2). Changing the base (Cs_2CO_3, K_2CO_3), solvent (dioxane) or catalyst led to no improvements of the yields. The reaction proceeded with excellent chemoselectivity in favor of position 3. The selectivity can be explained by the fact that bromine is a better leaving group than chlorine. The leaving group ability obviously overrides electronic factors. Usually, position 2 of the quinoline moiety is more reactive than position 3 in palladium catalyzed cross-coupling reactions, because it is electronically more deficient. The reaction of 1b with 2-bromophenylboronic acid afforded the desired product 2b in 60%. The reaction proceeded chemoselectively at position 2 which is electronically more deficient than position 3 and also bears an iodine atom which is a better leaving group than bromine. 2,3-Dichloro- and 2,3-dibromoquinoline are less attractive starting materials, because of the lack of reactivity of chlorine located at position 3 and a less pronounced difference of the reactivity of positions 2 and 3 in these molecules.

Subsequently, we attempted to carry out the double carbon-nitrogen coupling reaction. For the optimization study, 2a and *p*-toluidine were chosen as model substrates (Table 1). In the presence of the catalyst Pd_2dba_3 with the base NaO*t*Bu in toluene, different sterically hindered, electron rich monodentate and bidentate ligands were applied which can be successfully applied in Buchwald-Hartwig reactions. Among them, $PtBu_3 \cdot HBF_4$ gave a very high yield (95%) making further optimization of the reaction conditions (solvent, base temperature) unnecessary. Furthermore, to rule out that the product is formed by nucleophilic aromatic substitution we performed the reaction without employment of the palladium catalyst under otherwise identical conditions. It was found that there is no formation of the desired product without catalyst, even the substitution at the highly reactive position 2 of the quinoline by the amine was not observed, proofing the reaction undergoes a double Buchwald-Hartwig C-N coupling.

With the optimized conditions in hand, the scope of the reaction

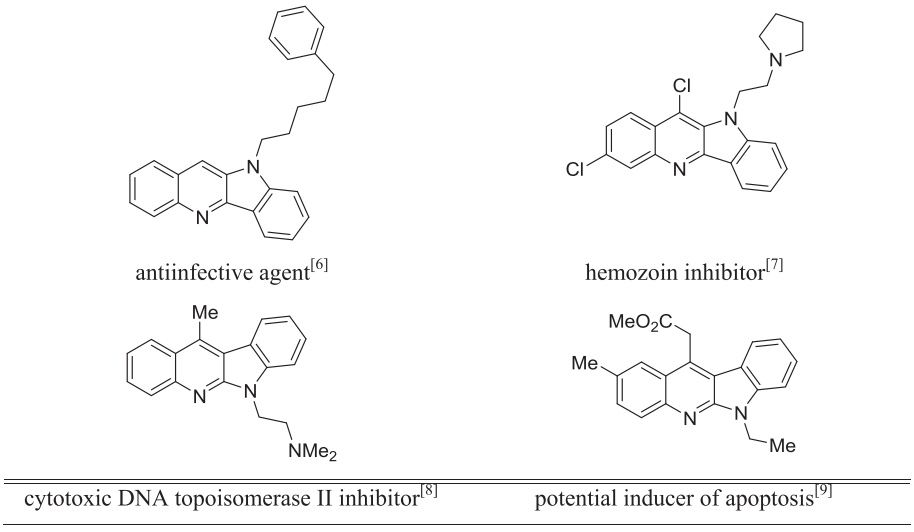
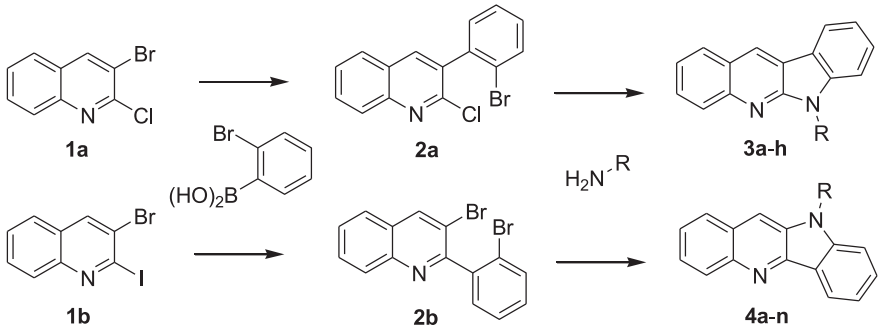


Fig. 2. Examples of synthesized *N*-substituted indoloquinolines with biological activities.[6–9]



Scheme 1. Synthetic strategy of the present paper.