Tetrahedron Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of 3-amino-3,4-dihydro-1*H*-quinolin-2-ones through regioselective palladium-catalyzed intramolecular cyclization

François Hallé [a], Olivier Van der Poorten [b,c], Christelle Doebelin [a], Marie Niederst [a], Séverine Schneider [a], Martine Schmitt [a], Steven Ballet [b,c], Frédéric Bihel [a,*]

[a] UMR CNRS/UdS 7200, Faculté de Pharmacie, Université de Strasbourg, 74 route du Rhin, 67401 Illkirch, France
[b] Department of Bioengineering Sciences, Vrije Universiteit Brussel, Pleinlaan 2, B-1050 Brussels, Belgium
[c] Department of Chemistry, Vrije Universiteit Brussel, Pleinlaan 2, B-1050 Brussels, Belgium

ARTICLE INFO

Article history:
Received 18 January 2016
Revised 23 February 2016
Accepted 25 February 2016
Available online xxxx

Keywords:
Bridged peptide
BTPP
Buchwald–Hartwig
Dihydroquinolinone
Indoline

ABSTRACT

In this Letter we explored the regioselective cyclization of 2-bromophenylalanine derivatives to access enantiopure dihydroquinolinones via an intramolecular regioselective Buchwald–Hartwig cyclization using $Pd_2(dba)_3$/XPhos as a catalytic system in the presence of BTPP as organic base. This procedure represents a promising strategy for the direct synthesis of bridged Phe-Xaa dipeptides.

Introduction

The 3-amino-3,4-dihydro-1*H*-quinolin-2-one scaffold has been used in multiple biologically active compounds, such as converting enzyme inhibitors (**1**),[1] glycogen phosphorylase inhibitors (**2**),[2–4] cholecystokinin antagonists (**3**),[5] DPP-IV inhibitors (**4**), or anticoagulants (**5**),[6] all in either (*R*) or (*S*) configurations (Fig. 1).

The enantiopure core structure can be accessed via asymmetric phase-transfer catalyzed alkylation of glycine analog **6** by nitrobenzyl bromide, followed by the reduction of the nitro group in **7** and subsequent cyclization of the in situ formed 2-aminophenylalanine into 3-amino-3,4-dihydroquinolin-2-one **8** (Fig. 2).[7,8] This efficient two-step synthesis allows the access to unsubstituted dihydroquinolinone **8**, readily available for further N-alkylation with various alkylhalides and alkyl α-haloacetates. However, this method does not permit the insertion of an amino acid-like substituent exhibiting a chiral center at the alpha position of the nitrogen thus limiting the scope of the accessible structures. As shown in Figure 1, compounds **1**, **2**, **3**, and **5** show indeed a glycine residue at the *N*-position of the dihydroquinolinone scaffold.

In this Letter, an alternative strategy was envisaged based on an intramolecular palladium-catalyzed Buchwald–Hartwig

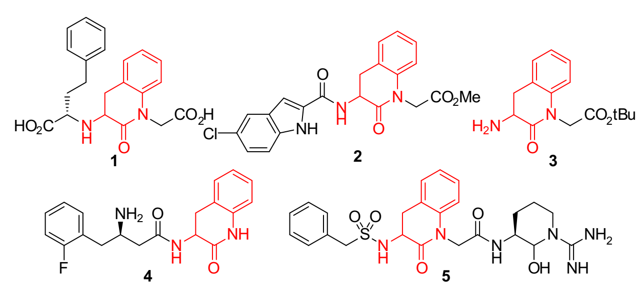


Figure 1. Selected examples of lactam-constrained peptidomimetics containing the 3-amino-3,4-dihydro-1*H*-quinolin-2-one core.

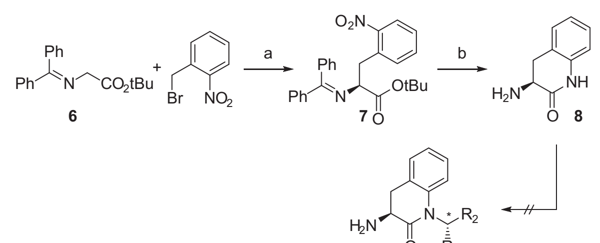
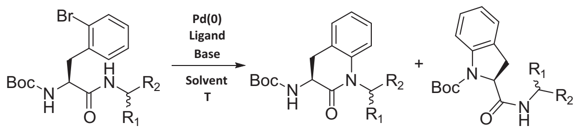


Figure 2. Method developed by Hulin et al. (a) Cinchonidine-derived catalyst, $CsOH{\cdot}H_2O$, CH_2Cl_2, −30 °C, 92%; (b) H_2, Pd/C, MeOH, 2 M HCl, 65%.

* Corresponding author.
E-mail address: fbihel@unistra.fr (F. Bihel).

http://dx.doi.org/10.1016/j.tetlet.2016.02.094
0040-4039/



9 10 11

Figure 3. Synthesis of dihydroquinolinone **10** and/or indoline **11** via an intramolecular Pd(0)-catalyzed Buchwald–Hartwig aryl amidation or carbamation reaction.

cyclization (Fig. 3).[9–13] Starting from Boc-protected dipeptide *tert*-butyl ester **9**, cyclization can occur in two different ways to afford either the six-membered dihydroquinolinone **10** or the five-membered indoline **11**. While establishing the reaction scope, our objective was to find a convenient, mild, and racemization-free protocol, favorable for the synthesis substituted 3-amino-3,4-dihydro-1*H*-quinolin-2-ones of type **10**.

Results and discussion

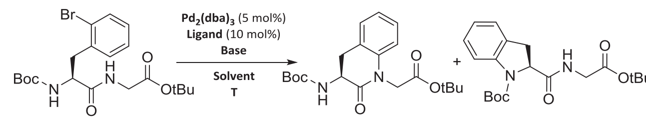
Dipeptide substrate Boc-2-Br-L-Phe-Gly-O*t*Bu **9a** was synthesized by standard coupling of commercially available Boc-2-Br-L-Phe-OH and H-Gly-O*t*Bu using HATU-activation. This model substrate was engaged in a Buchwald–Hartwig amidation reaction under anhydrous and oxygen-free conditions. To determine the optimal reaction conditions that could selectively lead to dihydroquinoline **10a** or indoline **11a**, different reaction parameters were screened for the envisaged intramolecular Pd(0)-catalyzed Buchwald–Hartwig aryl amidation reaction. This optimization process is summarized in Table 1.[14]

Although complete conversion of the starting material was obtained under standard coupling conditions with $Pd_2(dba)_3$ and the bidentate ligands XantPhos or BINAP, no or poor selectivity was observed between both cyclization directions **10a** and **11a** (entries 1 and 2). Next, monodentate ligands were screened under the same reaction conditions. Use of simple dialkylbiaryl phosphines such as JohnPhos or CyJohnPhos did not provide the targeted compounds in satisfying amounts (entries 4 and 5), whereas the addition of bulky isopropyl substituents on the inferior phenyl of dialkylbiaryl ligands (i.e., in case of XPhos) favored the formation of dihydroquinolinone **10a** (entry 6). In contrast, the presence of electron-donating groups on the applied biaryl phosphines systematically favored the formation of indoline **11a** (entries 7–12). A similar observation was made for BrettPhos, which is an analog of XPhos that exhibits two additional methoxy groups on the biphenyl moiety (entry 11). Ultimately, XPhos was the only ligand capable of promoting the formation of the six-membered ring **10a** over indoline **11a**. It was found that bulky *tert*-butyl substituted phosphines (*t*BuXPhos) showed no reaction (entry 7), neither did the use of second generation palladacycles of SPhos and XPhos.[15,16]

The replacement of toluene by 1,4-dioxane increased the yield of **10a**, while more polar solvents as THF, EtOAc, or DME did not affect selectivity (entries 14–16). Conversion was diminished in polar solvents as DMF, DMSO, or acetonitrile (entries 17–19). Initially performed at 100 °C, the reaction could be completed at 50 °C, but at this temperature, the reaction rate was lowered to 15 h and selectivity for a specific reaction product was lost (entry 23). As regioselectivity started to appear at 65 °C (entry 22), 80 °C was chosen as the optimal temperature (entry 21), allowing the completion of the reaction and maximal retention of regioselectivity within 6 h (66% of **10a** vs 34% of **11a**).

In the next step, a base screening was performed in 1,4-dioxane at 80 °C (entries 24–28), whereas inorganic bases such as Na_2CO_3, K_2CO_3, or K_3PO_4 did not result in reaction completion, BTPP (P_1-*t*-Bu-tris(tetramethylene), Fig. 4), a strong and soluble organic superbase,[17,18] afforded dihydroquinolinone **10a** in 65% yield after 4 h. Although the use of BTPP in Buchwald–Hartwig cross-coupling reactions is not yet described in literature, it allowed the expected intramolecular cyclization to proceed in mild conditions and short reaction times.

Table 1
Optimization of the reaction conditions for the intramolecular Buchwald–Hartwig cyclization of dipeptide **9**



9a 10a 11a

#	Ligand	Base	Equiv	Solvent	*T* (°C)	Time (h)	% **10a**[a]	% **11a**[a]
1	XantPhos	Cs_2CO_3	2	Toluene	100	24	50	50
2	BINAP	Cs_2CO_3	2	Toluene	100	24	22	50
3	DPEPhos	Cs_2CO_3	2	Toluene	100	24	9	68
4	JohnPhos	Cs_2CO_3	2	Toluene	100	24	2	6
5	CyJohnPhos	Cs_2CO_3	2	Toluene	100	24	5	14
6	XPhos	Cs_2CO_3	2	Toluene	100	24	63	34
7	*t*BuXPhos	Cs_2CO_3	2	Toluene	100	24	1	4
8	SPhos	Cs_2CO_3	2	Toluene	100	24	15	73
9	RuPhos	Cs_2CO_3	2	Toluene	100	24	23	67
10	MeO-SPhos	Cs_2CO_3	2	Toluene	100	24	36	63
11	BrettPhos	Cs_2CO_3	2	Toluene	100	24	8	64
12	DavePhos	Cs_2CO_3	2	Toluene	100	24	13	39
13	XPhos	Cs_2CO_3	2	Dioxane	100	24	71	12
14	XPhos	Cs_2CO_3	2	THF	100	24	68	6
15	XPhos	Cs_2CO_3	2	EtOAc	100	24	66	4
16	XPhos	Cs_2CO_3	2	DME	100	24	66	17
17	XPhos	Cs_2CO_3	2	DMF	100	24	34	0
18	XPhos	Cs_2CO_3	2	DMSO	100	24	0	0
19	XPhos	Cs_2CO_3	2	MeCN	100	24	47	0
20	XPhos	Cs_2CO_3	2	Dioxane	100	6	65	35
21	XPhos	Cs_2CO_3	2	Dioxane	80	6	66	34
22	XPhos	Cs_2CO_3	2	Dioxane	65	6	61	39
23	XPhos	Cs_2CO_3	2	Dioxane	50	15	49	51
24	XPhos	Na_2CO_3	1.1	Dioxane	80	4	3	3
25	XPhos	K_2CO_3	1.1	Dioxane	80	4	14	12
26	XPhos	Cs_2CO_3	1.1	Dioxane	80	4	41	39
27	XPhos	K_3PO_4	1.1	Dioxane	80	4	30	20
28	XPhos	BTPP	1.1	Dioxane	80	4	65	35
29	XPhos	BTPP	1.1	Dioxane	65	4	63	33

[a] Determined by HPLC quantification. Experimental procedure in footnote 14.

Since BTPP acts as a strong base, the potential racemization of dihydroquinolinone **10a** was evaluated. The Boc group was deprotected by acidolysis, and the resulting amine was subsequently coupled with (1*R*)-(+)-camphanic acid (Fig. 5). A single diastereoisomer was observed. A comparison with the racemic mixture obtained from Boc-2-Br-L/D-Phe-Gly-O*t*Bu was made by HPLC.[19] As expected, no racemization was observed when Cs_2CO_3 was used as base.

Having identified mild and racemization-free conditions favoring the formation of the six-membered ring **10a**, the insertion of other amino acids bearing a side chain in the second position was explored. L-Alanine and L-phenylalanine were selected and the corresponding dipeptides **9b** and **9c** were synthesized using HATU-activation (Table 2).

Unfortunately, the presence of an alkyl group in α-position of the C-terminal amino acid led to a complete inversion of regioselectivity, affording only the five-membered indolines **11b** and **11c** (Table 2, entries 1–3). Based on this result, the influence of various alkyl amides (entries 4–17) on regioselectivity was examined. Passing from glycine to a methyl moiety (**9d**) allowed the conservation of the previously established selectivity for the dihydroquinoline, whereas ethyl or propyl homologs **9e** and **9f** remarkably inverted this tendency toward indoline formation