Tetrahedron Letters 51 (2010) 4350–4353

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Regioselective synthesis of 2,3-dihydrospiro[1,4]dioxino[2,3-*b*]pyridine derivatives

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ARTICLE INFO

Article history:
Received 31 March 2010
Revised 2 June 2010
Accepted 11 June 2010
Available online 17 June 2010

ABSTRACT

2-Chloropyridines and an aryl bromide underwent palladium-catalyzed intramolecular C–O bond forming reactions to provide 2,3-dihydrospiro[1,4]dioxino[2,3-*b*]pyridine derivatives and a benzodioxin, regioselectively.

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2,3-Dihydro-1,4-benzodioxins occur widely as important structural units in natural products.[1] They are utilized extensively in many pharmaceutically important compounds such as the α-adreno receptor antagonist WB 4101,[2a] serotonic 5-HT (5-hydroxytryptamine) receptor agonists,[2b] and as antipsychotic[2c] and antigastric[2d] agents. 1,4-Benzodioxane derivatives also show high potency against 5-lipoxygenases.[2e]

Replacement of a phenyl group by its bioisostere pyridine is an established approach in drug discovery and is used widely in lead optimization studies.[3] 2,3-Dihydro-1,4-dioxino[2,3-*b*]pyridines are important structural motifs in many therapeutic agents with anti-tumor activity[4a] such as the farnesyltransferase inhibitor **1a**[4b] (Fig. 1) and 5-HT_{1A} receptor agonists.[4c,d] The 2,3-dihydro-1,4-dioxino[2,3-*b*]pyridine system is conceived as a 1,4-benzodioxane bioisostere and limited literature is available for the synthesis of such compounds.[5] Selective introduction of substituents on the pyridine ring of 1,4-dioxino[2,3-*b*]pyridines has been studied previously.[6] Further advancement in the synthesis of 2,3-dihydrospiro[1,4]-dioxino[2,3-*b*]pyridine would be useful for the preparation of therapeutically important compounds.[7] The introduction of spirocycles creates a rigid three dimensional arrangement and this type of conformational restriction strategy was utilized to develop selective high affinity ligands for vesicular acetylcholine trasnsporters,[8a] σ_1 receptor ligands,[8b] anti-ischemic activators of mitochondrial ATP-sensitive potassium channels,[8c] potent non-peptidic inhibitors of caspase-3,[8d] and the positive allosteric modulator[8e] **1b**.

As a part of our drug discovery program we were interested in the synthesis of 2,3-dihydrospiro[1,4]dioxino[2,3-*b*]pyridines **2** and **3**. We were also interested in the preparation of 2,2′-spiro-1,4-benzodioxins **4** (Fig. 2) which are analogs of spirobenzofuran[9a] and 3,4-dihydrospirobenzopyrans.[9b]

The synthesis of compounds **2** and **3** has been previously described in the literature,[7] however, the reported synthesis of **2** suffers from a lack of regioselectivity and difficulties in the purification and separation of regioisomeric mixtures (Scheme 1). The only reported synthesis of spiro[1,4]benzodioxin **4** suffers from harsh reaction conditions and low yields.[10] In this Letter, we describe a versatile approach for the regioselective synthesis of 3-substituted-2,3-dihydrospiro[1,4]dioxino[2,3-*b*]pyridine derivatives and 2,2′-spiro-1,4-benzodioxin via a palladium-catalyzed S_NAr reaction.

In our initial studies the reaction of commercially available 2-chloro-3-pyridinol (**5a**) with epoxide **6a**[11a] in DMF and K_2CO_3 as base, afforded the tertiary alcohol **7a** as the only product, as expected. The analytical data obtained was in agreement with the literature report.[7]

When the cyclization of **7a** was performed according to the literature[7] using various base/solvent combinations, either spirocycle **9a** or an inseparable mixture of **8a** and **9a** in variable yields were obtained (Scheme 1, Table 1). The obtained analytical data for **8a** and **9a** were in agreement with the literature.[7] The CH_2–O group of **9a** (δ 4.09) was shifted downfield after cyclization with respect to **7a** (δ 3.88) but for **8a** (δ 3.92) the change in the chemical shift for

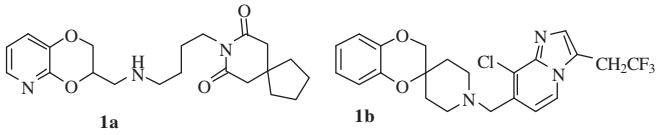

Figure 1. 2,3-Dihydro-[1,4]dioxino[2,3-*b*]pyridine **1a** and spiro[1,4]benzodioxin **1b** derivatives.

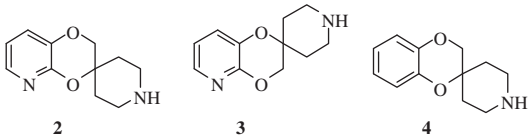

Figure 2. Spirocyclic pyridinedioxins and benzodioxins.

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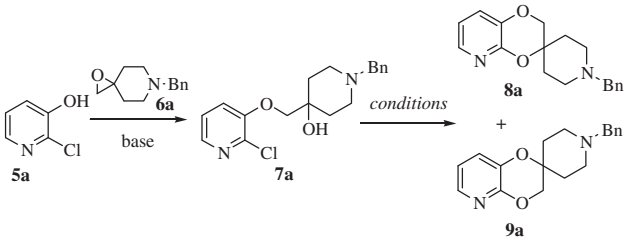
doi:10.1016/j.tetlet.2010.06.061



Scheme 1. Conventional S_NAr reactions for the synthesis of spirocycles **8a** and **9a**.

Table 1
Conditions and product ratios for the cyclizations of **7a** and **10**

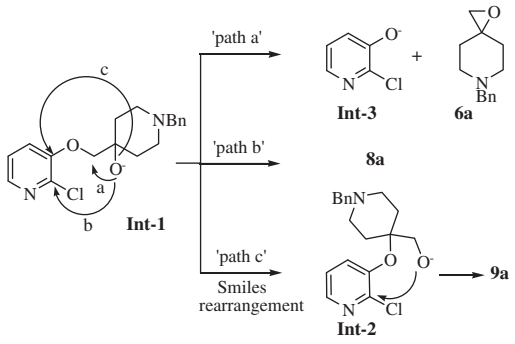
Substrate	Base/solvent	Temp (°C)	**8a**/**9a**	**11**/**12**
7a	NaH/DMF	80	0/100[a]	
7a	KO*t*-Bu/*t*-BuOH	80	0/100[a]	
7a	NaH/2-MeTHF	70	65/35	
7a	NaH/THF	70	50/50	
7a	KOH/toluene, 18-crown-6	80	0/100	
10	Cs_2CO_3/DMF	70		0/100
10	Cs_2CO_3/acetone	70		0/100
10	NaH/DMF	0		0/100
10	NaH/DME	25		0/100
10	NaH/THF	25		35/65
10	NaH/2-MeTHF	25		50/50

[a] A substantial amount of epoxide **6a** was also isolated.

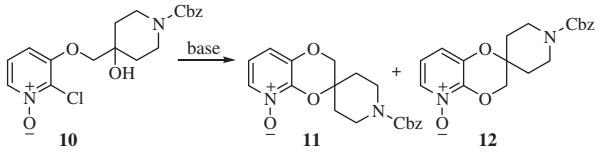
CH_2–O group was negligible.[7] A combination of strong base and polar solvent always provided substantial amounts of epoxide **6a** (Scheme 2). The formation of **6a** was suppressed when the reaction was performed in toluene, a non-polar aprotic solvent. The best product ratio for spirocyclic compounds **8a**/**9a** was observed with NaH/2-methyltetrahydrofuran (Table 1).

Product **9a** is formed through a Smiles rearrangement intermediate (**Int-2**, Scheme 2) as is commonly observed[7,12] with electronically deactivated pyridines under strongly basic conditions. Three different competitive reactions are potentially in operation; pathway 'a' results in the retro-epoxide opening leading to the **Int-3** and epoxide **6a** whereas pathways 'b' and 'c' furnish the spirocyclic compounds **8a** and **9a**, respectively.

2-Halopyridine N-oxides are known to undergo S_NAr processes at C-2 at low temperatures.[13] Consequently, we envisioned 2-halopyridine N-oxide as a substrate for the regioselective cyclization to provide **11** following reaction pathway 'b'. Assuming that the Smiles rearrangement might be avoided if the reaction was performed at lower temperatures, we attempted the cyclization of *N*-Cbz-protected pyridine-N-oxide[14] **10** at 0 °C. Base-mediated cyclization of **10** at 0 °C afforded a mixture of regioisomers **11**



Scheme 2. Plausible pathways for the competitive reactions occurring during the formation of products **8a** and **9a**.



Scheme 3. Intramolecular cyclization of 2-chloropyridine N-oxide **10**.

and **12** (Scheme 3, Table 1). Similar to **8a** and **9a**, the structures for spirocycles **11** and **12** were also tentatively assigned based on the chemical shift of the CH_2–O group before and after cyclization. For **12** the CH_2–O group (δ 4.24) was shifted downfield after cyclization with respect to **10** (δ 3.92) but for **11** (δ 3.99) the change in the chemical shift for CH_2–O group was negligible. These observations indicated that any conventional S_NAr reaction conditions on substrates **7a** and **10** would result in a regioisomeric spirocyclic product mixture from the competitive reactions.

Transition metal catalyzed cross-coupling reactions have emerged as a powerful tool for the formation of carbon–carbon[15] and carbon-heteroatom[16] (X = N, O, S) bonds. The importance of metal-catalyzed reactions in the construction of heterocycles has been reviewed.[17] Buchwald reported the intramolecular coupling reaction of various secondary and tertiary alcohols with aryl bromides to provide oxygen-containing heterocycles via a palladium-catalyzed C–O bond forming reaction.[18] We were interested to test the feasibility of the palladium-mediated intramolecular C–O bond forming conditions on **7a** to furnish the desired spiro-dioxinopyridines **8a**, regioselectively. Following treatment of tertiary alcohol **7a** under Buchwald's conditions[18] (5 mol % $Pd(OAc)_2$, BINAP, K_2CO_3, toluene) in a sealed tube, only trace amounts of **8a** were observed. However, when the catalyst loading was increased from 5 to 10 mol %, the 3,3′-spiro-1,4-dioxino[2,3-*b*]pyridine **8a** was formed as a single regioisomer in good yield (Table 2, entry 1). The obtained analytical data was in agreement with the literature.[7]

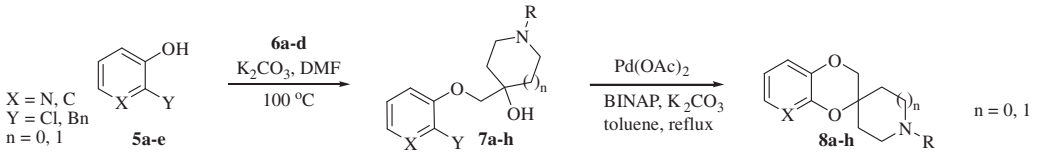
In order to probe the scope and limitations of the synthesis, a number of substituted chloropyridines, chloroquinolines and a bromophenol were subjected to epoxide opening and subsequent cyclization reactions. The requisite epoxides **6a–d**[11a] and the 2-chloro-3-pyridinols **5c** and **5d** and 3-hydroxy-2-chloroquinoline (**5b**) were prepared by literature methods. Epoxides **6a–d** were readily obtained from corresponding piperidone and pyrrolidinone by the literature procedures.[11a,b] 3-Hydroxy-2-chloroquinoline (**5b**) was synthesized from 2-quinolone according to the procedure reported by Quéguiner.[19] 5-Phenyl-3-chloro-2-pyridinol (**5c**) was prepared from 3,5-dibromopyridine in four steps.[20] 6-Methyl-2-chloro-3-pyridinol (**5d**) was prepared by chlorination of 6-methyl-3-pyridinol using sodium hypochlorite.[21]

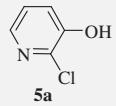
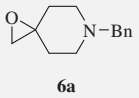
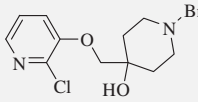
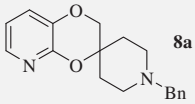
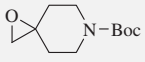
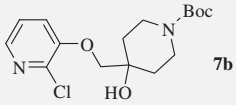
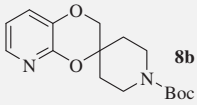
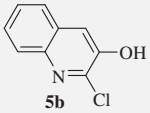
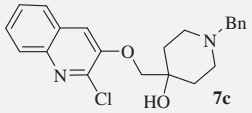
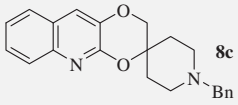
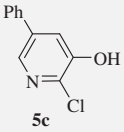
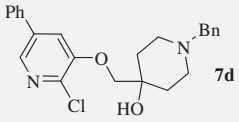
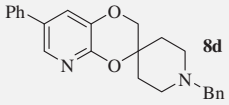
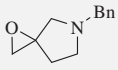
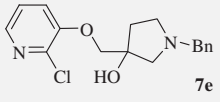
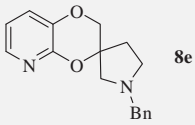
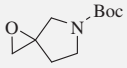
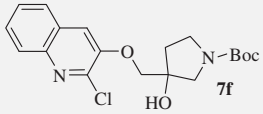
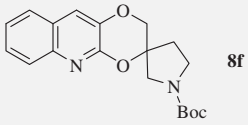
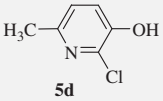
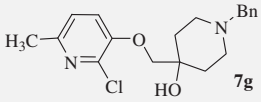
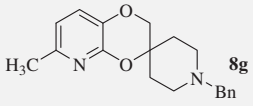
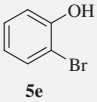
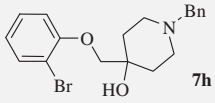
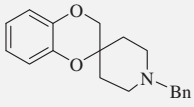
The optimized epoxide opening reaction conditions were then applied to the ring-opening of **6a–d** with aromatic and heteroaromatic alcohols **5b**–**e** to afford the tertiary alcohols **7b–h** as the only products[22] (Table 2). These relatively mild conditions (K_2CO_3/DMF/100 °C) compared to the literature method (NaH/DMF/100 °C)[7] improved significantly the product yield especially for pyrrolidine epoxides **6c** and **6d** (entries 5 and 6, Table 2).

The structures of products **7b–h** were confirmed from ^{1}H NMR data. The presence of two singlets between δ 3.60–3.65 ppm (CH_2–N) and δ 3.80–3.90 ppm (CH_2–O) confirmed the desired epoxide opening at the less-hindered carbon of the epoxide.

The alcohols **7b–h** were then subjected to our optimized cyclization conditions. The reaction proved to be general across a number of substituted pyridines, quinoline and a phenyl.[23] Further both piperidine (six-membered) and pyrrolidine (five-membered) derivatives underwent smooth cyclization. Similar to **8a**, the chemical structures for spirocycles **8b–g** were assigned based on the

Table 2
C–O bond forming reactions in 2-chloropyridines and an aromatic bromide leading to spirocyclic compound **8**



Entry	Substrate[a]	Epoxide	Intermediate	Yield[b] (%)	Product[c]	Yield[d] (%)
1	 **5a**	 **6a**	 **7a**	80	 **8a**	80
2	**5a**	 **6b**	 **7b**	75	 **8b**	68
3	 **5b**	**6a**	 **7c**	80	 **8c**	83
4	 **5c**	**6a**	 **7d**	70	 **8d**	65
5	**5a**	 **6c**	 **7e**	65	 **8e**	68
6	**5b**	 **6d**	 **7f**	85	 **8f**	76
7	 **5d**	**6a**	 **7g**	75	 **8g**	70
8	 **5e**	**6a**	 **7h**	78	 **8h**	60

[a] Reactions were carried out with 1–2 mmol if **5**.
[b] Isolated yields of intermediate **7a–h**.
[c] Reaction were carried out with 0.50–1.0 mmol of **7**.
[d] Isolated yield of products **8a–h**.

chemical shift of the CH_2–O group before and after cyclization. For all spirocycles **8b–g** the changes in the chemical shift for CH_2–O group was negligible before and after cyclization indicating exclusive desired spirocycle formation (see Supplementary data). The analytical data for **8h** was in full agreement with the data available in the literature.[10]

In conclusion, a convenient and regioselective synthetic pathway to 3-substituted-2,3-dihydro-spiro[1,4]dioxino[2,3-*b*]pyridine derivatives via efficient epoxide opening and a subsequent palladium-catalyzed cyclization sequence is described. To the best of our knowledge, this is the first report on the selective synthesis of spirocycles of type **8a–h** in good yields. The methodology worked well with a variety of substituents on the pyridine rings.

Supplementary data

Supplementary data (^{1}H NMR and mass spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.061.

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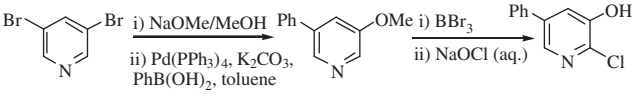
20. 

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23. *Representative procedure for the palladium-catalyzed intramolecular C–O bond formation*: A solution of **7a–h** (0.50 mmol) in toluene (5.0 mL) was added to a Schlenck tube and degassed under argon for 15 min. Then $Pd(OAc)_2$ (0.05 mmol), BINAP (0.06 mmol) and, K_2CO_3 (0.60 mmol) were added and the mixture was heated at 125 °C for 5–8 h. When the reaction was complete, the mixture was filtered through a short pad of Celite. The filtrate was concentrated in vacuo and purified by silica-gel chromatography to give compounds **8a–h**.