Tetrahedron Letters 53 (2012) 846–848

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

A facile synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines

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ARTICLE INFO

Article history:
Received 4 November 2011
Revised 2 December 2011
Accepted 5 December 2011
Available online 9 December 2011

Keywords:
Tetrahydroisoquinoline
THIQ
Arylation
Dihydroisoquinolinone
Palladium

ABSTRACT

A facile and versatile palladium catalyzed α-arylation between dihydroisoquinolinones and various aryl halides is described. Combined with borane reduction, it provides a convenient way to prepare 4-aryl-1,2,3,4-tetrahydroisoquinolines.

Tetrahydroisoquinoline (THIQ) is an interesting structural motif that appears in a number of biologically active compounds.[1] In our efforts to find novel antidepressants, we decided to further explore the THIQ scaffold. During our study of structure–activity relationships (SAR) of aryl substitution at the C-4 position of the THIQ core (**1**, Fig. 1), we developed a facile procedure for making THIQs involving a palladium catalyzed α-arylation reaction between dihydroisoquinolinones and aryl halides followed by a borane reduction. The method is described in this Letter.

There are a number of existing methods to build 4-substituted THIQs (**2**). Several of them, shown in Scheme 1, include: (a) intramolecular Friedel–Craft cyclization of a benzylic alcohol (**3**); (b) Bischler–Napieralski cyclization of (**4**); and (c) a Suzuki coupling [between boronic acid (**5**) and an aryl halide] followed by a reduction sequence.[2] Even though these methods are robust and generally provide good yields, they have limitations in that they do not provide the flexibility of changing 4-aryl groups at a late synthetic stage, which is preferred for rapidly studying SAR on the C-4 position.

Palladium catalyzed arylation of the activated methylene groups of a ketone or ester with aryl or heteroaryl halides has been previously reported.[3] We envisioned that a successful α-arylation reaction between (**6**) and an aryl bromide would provide 4-aryl-dihydroisoquinolinone (**7**), which could be reduced to give the corresponding 4-aryl-tetrahydroisoquinoline (**2**) (Scheme 2). The route offers a quick and convergent approach toward 4-aryl-THIQs and provides the opportunity to change the 4-aryl group at a late stage of synthesis. There was no example of using a lactam, for example, dihydroisoquinolinone (**6**), in this type of reaction before our patented work.[4] This Letter expands on this work with additional details and examples for this important reaction sequence.

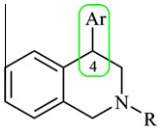

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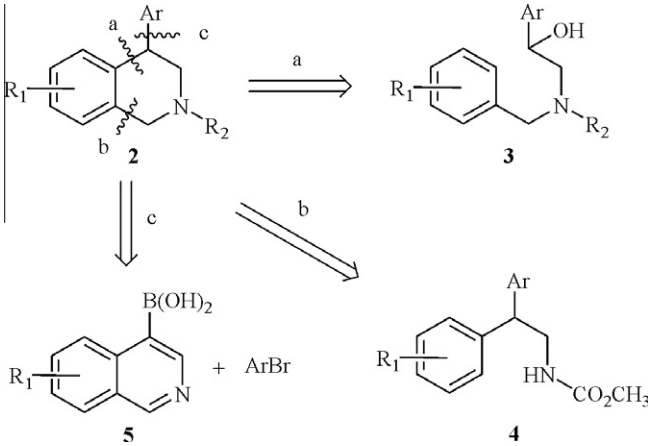
Figure 1. 4-Aryl-tetrahydroisoquinolines (**2**).



Scheme 1. General routes to synthesize of 4-aryl-tetrahydroisoquinoline (**2**).

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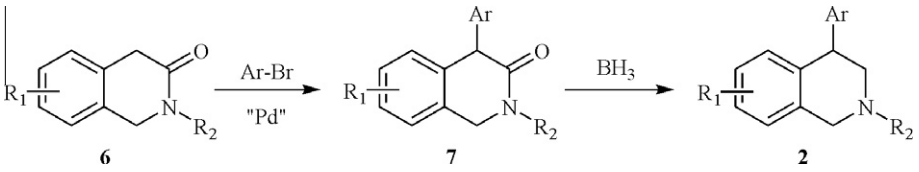
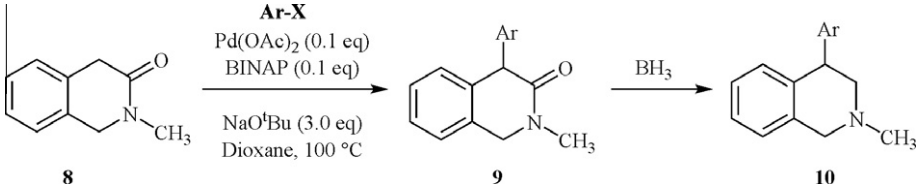
doi:10.1016/j.tetlet.2011.12.022



Scheme 2. Synthetic route toward 4-aryl-tetrahydroisoquinoline (**2**) via palladium mediated α-arylation reaction.

Table 1
Results of palladium catalyzed α-arylation reactions of **8** with arylhalides and subsequent borane reductions of **9** to **10**



Entry	Ar–Br	Yield of **9**[a] (%)	Yield of **10**[a] (%)
a	4-CH_3PhBr	83	80
b	4-ClPhBr	90	69
c	4-FPhBr	86	73
d	4-MeOPhBr	63	74
e	4-$MeSO_2$PhBr	n.d.[b]	51[c]
f	3-CH_3PhBr	75	71
g	2-CH_3PhBr	61	68
h	2-*i*PrPhBr	23	30
i	3-Bromoquinoline	36	20
j	5-Bromoquinoline	54	37
k	6-Bromoquinoline	72	37
l	6-Bromoimidazo[1,2-α]pyridine	59	41
m	2-Chloro-4-methoxypyridine	28	26
n	2-Bromopyrazine	0	n.a.[d]

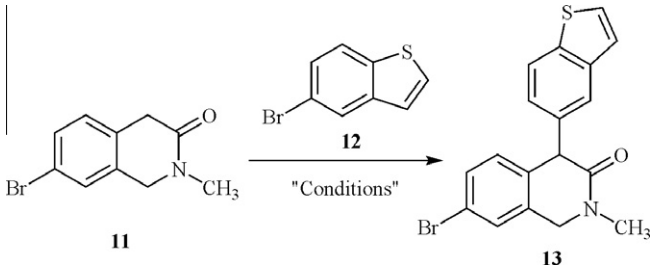
[a] Yield of isolated product.
[b] Not determined.
[c] Yield from **8**.
[d] Not available.

We first studied this arylation reaction using 2-methyl-1,2-dihydroisoquinolin-3(4*H*)-one (**8**). We were delighted to find that using $Pd(OAc)_2$ as the catalyst, BINAP as the ligand, and Na^{t}OBu as the base, **8** reacted well with a variety of aryl bromides or heteroaryl halides to give the corresponding dihydroisoquinolinones (**9**).[5] The results are shown in Table 1.

Para- and *meta*-substituted phenyl bromides reacted smoothly in the α-arylation reactions as shown in entries **a**–**f**. The electronic character of the substitution group on the phenyl ring did not have a profound effect on the reaction yields, as shown in entry **d** (4-methoxyl) and entry **e** (4-methylsulfonyl). On the other hand, the coupling reaction was affected by the steric environment near the reaction center. As shown in the table, the reaction yield dropped slightly for *o*-methyl substitution (entry **g**) and plunged for *o*-isopropyl substitution (entry **h**).[6] Some nitrogen-containing heteroaryls worked very well in this palladium catalyzed α-arylation reactions to give the desired 4-heteroaryl-dihydroisoquinolinone in moderate to good yield (entries **i**–**l**). However, reactions with some α-halogenated heteroaryls (entries **m** and **n**) were sluggish or unsuccessful.

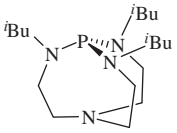
Borane reduction of these dihydroisoquinolinones (**9**) generally went smoothly to give the corresponding 4-aryl-tetrahydroisoquinolines (**10**) as shown in Table 1.[7]

We also examined the arylation reaction between 7-bromo-2-methyl-1,2-dihydroisoquinolin-3(4*H*)-one (**11**)[8] and 5-bromobenzothiophene (**12**) to see if this reaction can tolerate a reactive group, such as bromide, on the dihydroisoquinolinone (Scheme 3). The results are summarized in Table 2. With BINAP as the ligand (entry 1), the arylation reaction gave the desired product **13** in a modest 40% yield. However, it is important to point out that bromide **11** did not self react to form a dimer; instead, it reacted preferentially with 5-bromobenzothiophene (**12**) to provide **13**. Presumably, deprotonation of dihydroisoquinolinone (**11**) increased the electron density on the aromatic ring, therefore protecting the bromide on **11** from reacting in the cross-coupling reaction with itself. Using PCy_3 as the ligand gave a 30% yield (entry 2). Cossy et al. reported a palladium catalyzed coupling of zinc enolate (prepared from activated methylene using LHMDS and $ZnCl_2$)[9]; however, we were only able to achieve a 42% yield using this condition (entry 3). To our pleasant surprise, the proazaphosphatrane ($P(i\text{BuNCH}_2\text{CH}_2)_3\text{N}$)[10] gave **13** in a much improved 63% yield (entry 4).[11] Borane reduction of the resultant dihydroisoquinolinone (**13**) provided the corresponding tetrahydroisoquinoline in an 85% yield.



Scheme 3. Synthesis of 7-bromo-4-aryl dihydroisoquinolinone (**13**) using palladium catalyzed α-arylation between **11** and **12**.

Table 2
Summary of α-arylation conditions in the synthesis of **13** from **11** and **12**

Entry	Catalyst	Ligand	Base	Solvent	Temperature (°C)	Yield (%)[a]
1	$Pd(OAc)_2$ (10%)	BINAP (10%)	NaO^tBu (1.5 equiv)	Dioxane	100	40
2	$Pd(OAc)_2$ (10%)	PCy_3 (10%)	NaO^tBu (2.0 equiv)	Dioxane	50	30
3	$Pd(dba)_2$ (5%)	(*o*-NMe_2)Ph-Ph(*o*-PCy_2), (7.5%)	$ZnCl_2$ (2.0 equiv) LHMDS (2.0 equiv)	THF	Reflux	42
4	$Pd(OAc)_2$ (10%)	 (20%)	NaO^tBu (1.5 equiv)	Toluene	70	63

[a] Yield of the isolated product.

In summary, we have developed a convenient palladium catalyzed α-arylation between dihydroisoquinolinones and various aryl halides. The reaction conditions worked well for a diverse set of aryl halides. Combined with a borane reduction, this two-step sequence provided a facile way to prepare 4-aryl-1,2,3,4-tetrahydroisoquinolines (THIQs).

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5. General procedure for α-arylation using BINAP as the ligand: A suspension of dihydroisoquinolinone **8** (2.0 mmol), aryl/heteroaryl bromide (3.0 mmol), palladium acetate (0.2 mmol) and BINAP (0.2 mmol) in dioxane (10.0 mL) was degassed with argon. Then sodium *tert*-butoxide (3.0 mmol) was added. The reaction mixture was heated at 100 °C under argon for 1 h, and then it was cooled to room temperature, quenched with ammonium chloride, and extracted with EtOAc. The organic extract was washed with brine, dried over sodium sulfate, and concentrated in vacuo. The crude material obtained was purified by silica-gel flash column chromatography to give the desired dihydroisoquinolinone **9**.
6. Reaction with larger substitution on the nitrogen of dihydroisoquinolinone **8** (e.g., isopropyl vs methyl) also gave decreased yield (unpublished results).
7. General procedure for borane reduction: To a solution of dihydroisoquinolinone (**9**, 1.7 mmol) in anhydrous THF (10 mL) at 0 °C was added borane·dimethylsulfide complex (0.34 mL, 3.6 mmol). The reaction solution was stirred at 50 °C for 2 h and then it was cooled to room temperature, quenched with methanol (5.0 mL), and concentrated to dryness. The residue obtained was dissolved in dioxane (15 mL) and aqueous 6 N HCl (5 mL) and heated under reflux for 90 min. After cooling to room temperature, the reaction was quenched with aqueous sodium bicarbonate and extracted with EtOAc. The organic extract was dried over sodium sulfate and concentrated in vacuo. The crude product was purified by silica-gel flash column chromatography to give the desired 4-aryl-tetrahydroisoquinoline.
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11. A representative procedure for arylation reaction using P(*i*BuNCH$_2$CH$_2$)$_3$N as the ligand: To a solution of 5-bromobenzothiophene (**12**, 11.5 g, 45.1 mmol) in toluene (150 mL) under argon was added palladium acetate (0.84 g, 3.75 mmol), P(*i*BuNCH$_2$CH$_2$)$_3$N (2.6 g, 7.6 mmol), and sodium *tert*-butoxide (5.4 g, 56.3 mmol). The reaction mixture was stirred for 2 min at room temperature, and then 7-bromodihydroisoquinolinone (**11**, 9.0 g, 37.5 mmol) was added. The resultant solution was heated at 70 °C for 30 min, and then it was cooled to room temperature. The reaction was quenched with aqueous ammonium chloride and extracted with dichloromethane. The organic extract was washed with brine, dried over sodium sulfate, and concentrated in vacuo. The residue obtained was purified by flash column chromatography (eluent: 80/20 dichloromethane/EtOAc) to give the desired 4-(5-benzothiophenyl)dihydroisoquinolinone (**13**, 8.84 g, 63%) as a light yellow foam.