Tetrahedron xxx (2018) 1–10

Contents lists available at ScienceDirect

Tetrahedron

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

Aminolithiation–arylation consecutive cyclization of *N*-(2-fluorophenyl)methylaminoalkylstyryls giving aryl-substituted pyrido[1,2-*b*]isoquinolines

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ARTICLE INFO

Article history:
Received 27 February 2018
Received in revised form
24 May 2018
Accepted 29 May 2018
Available online xxx

Keywords:
Aminolithiation
Lithium amide
Cyclization
Tandem reaction
Heterocycles

ABSTRACT

Aminolithiation–arylation tandem cyclization of *N*-(2-fluorophenyl)methylaminoalkylstyryls proceeded smoothly to give hexahydro-2*H*-pyrido[1,2-*b*]isoquinoline using a stoichiometric amount of *n*-BuLi with high *trans* selectivity. The arylation reaction was highly accelerated by the addition of HMPA. Both pyrido- and pyrrolo-[1,2-*b*]isoquinoline were successfully constructed by this tandem reaction.

1. Introduction

The addition of nitrogen nucleophiles to intramolecular C=C double bond is a versatile method for the synthesis of nitrogen-containing heterocycles.[1] Lithium amide is useful in this context because the initial addition reaction of lithium amide to intramolecular C=C double bond[2] affords reactive alkyllithium intermediates that can be further applied for a bond-forming reaction.[3,4] We previously reported a consecutive cyclization of *N*-allylaminoalkene **1** giving substituted indolizine **3** through an aminolithiation (**1-Li** to **2-Li**) and carbolithiation (**2-Li** to **3-Li**) process, where carbanion **2-Li** was stabilized by adjacent phenyl or phenylthio group (Scheme 1, R^1 = Ph or SPh).[5]

In the course of our studies of tandem cyclization reactions triggered by aminolithiation, we planned to combine aminolithiation with other bond-forming reactions. We designed a trap for reactive alkyllithium intermediate **6-Li** using an intramolecular fluoroaryl group to yield hexahydro-2*H*-pyrido[1,2-*b*]isoquinoline **5**[6] (Scheme 2). Herein we report the consecutive cyclization of *N*-(2-fluorophenyl)methylaminoalkene **4** giving **5** through an aminolithiation–arylation process.

2. Results and discussion

We first prepared the cyclization precursor of aminoalkene **4a** (Scheme 3). A Wittig reaction of benzaldehyde and phosphonium ylide **7a**, generated in situ from the corresponding phosphonium bromide and LHMDS, gave **8a** with an *E*/*Z* ratio of 9/1.[7] $LiAlH_4$ reduction of carboxylic acid **8a** yielded alcohol **9a**, and subsequent mesylation gave **10a**.[7] *N*-Boc amide **12a**, prepared by Boc protection of commercially available benzylamine **11a**, was alkylated with mesylate **10a** in DMF to give **13a**. Finally, Boc deprotection of **13a** by $ZnBr_2$[8] afforded aminoalkene **4a**.

We examined the cyclization reaction of **4a** using a stoichiometric amount of *n*-BuLi (Table 1). In THF, TLC analysis indicated that the reaction did not proceed at 0 °C, whereas substrate **4a** was gradually consumed at room temperature. The desired cyclized product **5a** was not obtained at all, however, and only monocyclized product **6a** was obtained in 21% yield (entry 1). With the

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https://doi.org/10.1016/j.tet.2018.05.085
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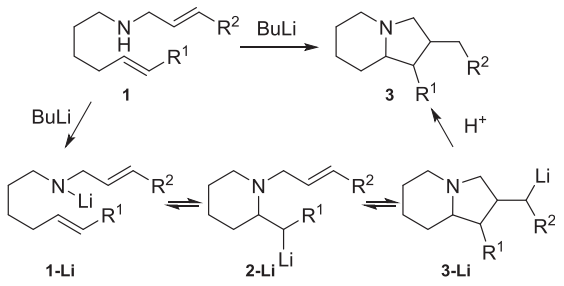
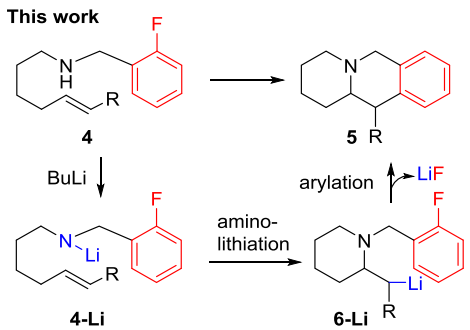
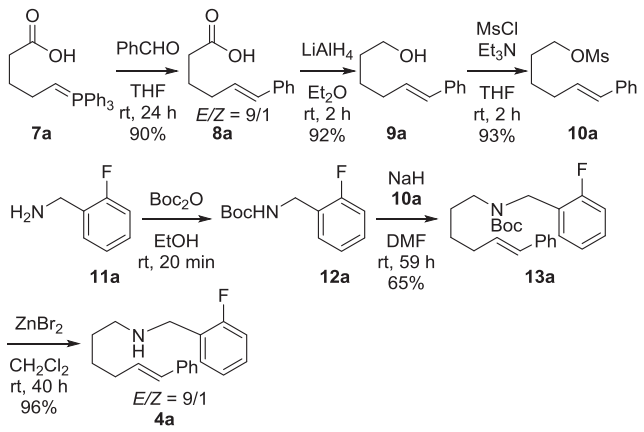


Scheme 1. Consecutive aminolithiation–carbolithiation of *N*-allylaminoalkene **1**.



Scheme 2. Consecutive aminolithiation–arylation.



Scheme 3. Synthesis of cyclization precursor **4a**.

addition of 3 equiv of HMPA, the reaction proceeded even at 0 °C, and the desired cyclized product **5a** was obtained in 36% yield along with **6a** in 50% yield after 6.5 h (entry 2). Changing the solvents to Et_2O and pentane/Et_2O (3/2) improved the yield of **5a** to 54% and 59%, respectively (entries 3 and 4). Increasing the reaction time to 16.5 h did not improve the yield of the desired **5a**, and mono-cyclized product **6a** (21%) was still obtained (entries 4 and 5). The diastereoselectivities of the reaction were very high and (*RS*,*SR*)-**5a** was predominately obtained with a diastereomeric ratio of 96/4–97/3[9] (entries 3–5). When we used 1.5 equiv of *n*-BuLi, the yield of the desired **5a** slightly improved to 62%, but the diastereoselectivity decreased to 85/15.

We postulated that aminolithiation of **4a-Li** (Scheme 2) proceeded before completing the deprotonation of **4a** by *n*-BuLi, and a part of the reactive alkyllithium intermediate **6a-Li** was protonated by substrate **4a** to yield **6a**. To complete the deprotonation, **4a** was first treated with *n*-BuLi at −78 °C for 0.5 h without HMPA, and then HMPA was added and the reaction mixture was warmed up to 0 °C. As expected, the yield of the desired **5a** improved to 65% and the production of **6a** was suppressed to 10% (Table 2, entry 1). When the reaction was carried out in toluene, the desired **5a** was obtained in 65% yield and **6a** was obtained in 17% yield (entry 2). Prolonging the deprotonation time to 1 h at −78 °C in toluene before adding HMPA gave best results, and the desired **5a** was obtained in 75% yield with a diastereomeric ratio of 97/3 (entry 3). Further extending the deprotonation time did not improve the yield of **5a** (entry 4).

The relative stereochemistry of the major diastereomer of *trans*-**5a** was unequivocally determined by X-ray crystallographic analysis (Fig. 1).[10] The addition reaction of the benzyl anion that was generated after aminolithiation of **4a-Li** to an intramolecular fluorophenyl group via **A**, in which the phenyl group was arranged in an equatorial position, afforded the major diastereomer of *trans*-**5a** (Scheme 4). In contrast, cyclization via conformer **B**, which afforded the minor diastereomer, was unfavorable due to the 1,3-diaxial steric repulsion between the two aromatic groups. It is important to note that *E*/*Z* ratio of substrate **4a** not affected the diastereoselectivity of product **5a**. Thus, **4a** of *E*/*Z* 6/4 also afforded **5a** with dr 97/3 (*trans*/*cis*). This result indicated the presence of equilibrium between benzyl anion **A** and **B**.

Another possible stereodeterminig pathway is isomerization of *trans*-**5a** to *cis*-**5a** through deprotonation of the benzylic methine proton, because an excess amount of *n*-BuLi (1.5 equiv) caused deterioration of the diastereoselectivity (Table 1, entry 6). In fact, treatment of *trans*-**5a** with *n*-BuLi and HMPA at 0 °C caused partial isomerization (Scheme 5).

Cyclization of (2-bromophenyl)methylaminoalkene **4b** was examined (Scheme 6). With *n*-BuLi (1equiv) and HMPA (3 equiv) in pentane/Et_2O at 0 °C for 6.5 h, the same reaction conditions as in entry 4 of Table 1, the desired cyclized product **5a** was not obtained at all. Instead, mono-cyclized product **6b** (9%) and its debrominated product **14** (26%) were obtained. These results indicated that the lithium-bromine exchange proceeded preferentially over the arylation reaction.

The substrate scope was examined next (Scheme 7). Cyclization of **4c** proceeded through 5-*exo* aminolithiation–arylation to afford pyrrolo[1,2-*b*]isoquinoline **5c** in 57% yield and **6c** in 13% yield. By using **4d** with a 5-trifluoromethyl group on the aromatic ring, the desired product **5d** was obtained in 37% yield along with recovered **4d** (11%). The reaction of **4e** with a 2,6-difluorophenyl group gave the desired **5e** in 59% yield and substrate **4e** (30%) was recovered. The reaction did not occur at all with aniline derivative **4fa** (R = H), probably due to the low nucleophilicity of lithium anilide.[11] A styrene moiety as an acceptor of aminolithiation was important in this reaction, and aminoalkene **4ga** (R = H) of the internal olefin,[11,12] **4h** of the terminal olefin, and **4i** of the terminal alkyne did not afford the corresponding cyclized products **5** or **6**.

3. Conclusion

In conclusion, a tandem aminolithiation–arylation process was successfully achieved to afford the hexahydro-2*H*-pyrido[1,2-*b*]isoquinoline skeleton with high diastereoselectivity. Both a styrene moiety, as an acceptor of aminolithiation, and a fluoroaryl group were important for the reaction. The method is also applicable for the synthesis of pyrrolo[1,2-*b*]isoquinoline.

4. Experimental section

All melting points are uncorrected. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were measured in $CDCl_3$ unless otherwise mentioned. Chemical shift values were expressed in ppm relative to an internal reference of tetramethylsilane (0 ppm) in ^{1}H NMR and

Please cite this article in press as: Yamamoto Y, et al., Aminolithiation–arylation consecutive cyclization of *N*-(2-fluorophenyl) methylaminoalkylstyryls giving aryl-substituted pyrido[1,2-*b*]isoquinolines, Tetrahedron (2018), https://doi.org/10.1016/j.tet.2018.05.085