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

Yasutomo Yamamoto\textsuperscript{a, **}, Yasue Nakanishi\textsuperscript{b}, Ken-ichi Yamada\textsuperscript{b, 1}, Kiyoshi Tomioka\textsuperscript{a, *}

\textsuperscript{a} Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts, Kodo, Kyotanabe, 610-0395, Japan
\textsuperscript{b} Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto, 606-8501, Japan

\textsuperscript{*} Corresponding author.
\textsuperscript{**} Corresponding author.
E-mail addresses: yayamamo@dwc.doshisha.ac.jp (Y. Yamamoto), tomioka@pharm.kyoto-u.ac.jp (K. Tomioka).
\textsuperscript{1} Current address: Graduate School of Pharmaceutical Sciences, Tokushima University, Shomachi, Tokushima 770–8505, Japan.

Abstract

Aminolithiation–arylation tandem cyclization of N-(2-fluorophenyl)methylaminoalkylstyryls proceeded smoothly to give hexahydro-2H-pyrido[1,2-b]isoquinoline using a stoichiometric amount of \textit{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 \textit{C}==\textit{C} double bond is a versatile method for the synthesis of nitrogen-containing heterocycles.\textsuperscript{1} Lithium amide is useful in this context because the initial addition reaction of lithium amide to intramolecular \textit{C}==\textit{C} double bond\textsuperscript{2} affords reactive alkylolithium intermediates that can be further applied for a bond-forming reaction.\textsuperscript{3,4} We previously reported a consecutive cyclization of N-allylaminoalkene \textit{1} giving substituted indolizine \textit{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, \textit{R}\textsubscript{1} = Ph or SPh).\textsuperscript{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 alkylithium intermediate 6-Li using an intramolecular fluoroaryl group to yield hexahydro-2H-pyrido[1,2-b]isoquinoline 5 (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 \textit{4a} (Scheme 3). A Wittig reaction of benzaldehyde and phosphonium ylide \textit{7a}, generated in situ from the corresponding phosphonium bromide and LHMDS, gave \textit{8a} with an \textit{E}/\textit{Z} ratio of 9/1.\textsuperscript{7} \textit{LiAlH}_{4} reduction of carboxylic acid \textit{8a} yielded alcohol \textit{9a}, and subsequent mesylation gave \textit{10a}.\textsuperscript{7} \textit{N}-Boc amide \textit{12a} was prepared by Boc protection of commercially available benzylamine \textit{11a} by \textit{ZnBr}_{2}.\textsuperscript{8} We examined the cyclization reaction of \textit{4a} using a stoichiometric amount of \textit{n}-BuLi (Table 1). In THF, TLC analysis indicated that the reaction did not proceed at 0 °C, whereas substrate \textit{4a} was gradually consumed at room temperature. The desired cyclized product \textit{5a} was not obtained at all, however, and only monocyclized product \textit{6a} was obtained in 21% yield (entry 1). With the...
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 Et₂O and pentane/Et₂O (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 diastereoselectivity of the reaction were very high and (RS,SR)-5a was predominately obtained with a diastereomeric ratio of 96/4 (97/3) (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 alkyl lithium 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). The addition reaction of the benzyl anion that was generated after aminolithiation of 4a-Li to an intramolecular fluoroaryl 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 conformers B and C, 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 did not affect 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 stereo-determining pathway is isomerization of trans-5a to cis-5a through deprotonation of the benzylcine proton, because an excess amount of n-BuLi (1.5 equiv) caused deterioration of the diastereoselectivity (Table 1, entry 6). In fact, treatment with 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 (1 equiv) and HMPA (3 equiv) in pentane/Et₂O 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 4f (R = H), probably due to the low nucleophilicity of lithium anilide. A styrene moiety as an acceptor of aminolithiation was important in this reaction, and aminoaalkene 4ga (R = H) of the internal olefin, 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-2H-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. 1H NMR (500 MHz) and 13C NMR (125 MHz) were measured in CDCl3 unless otherwise mentioned. Chemical shift values were expressed in ppm relative to an internal reference of tetramethylsilane (0 ppm) in 1H NMR and