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A novel 3,4-dihydroisoquinoline annulation: expedient access to isoquinoline heterocycles

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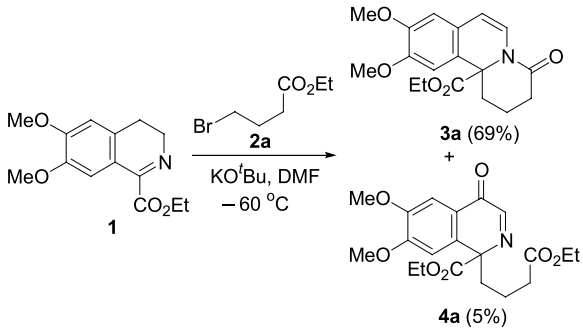
Abstract—3,4-Dihydroisoquinoline carboxylate **1** undergoes a smooth annulation with ω-bromopropionate, butyrate or *ortho*-bromomethyl benzoate **2** to afford the isoquinoline heterocycle **3** upon treatment with potassium *tert*-butoxide in DMF at −60 °C. This novel annulation constitutes a formal direct synthesis of cyclic Reissert equivalent compounds, thus offers an expedient access towards certain medicinally important isoquinoline heterocycles and relevant natural alkaloids, that is, of berberine and erythrina types.

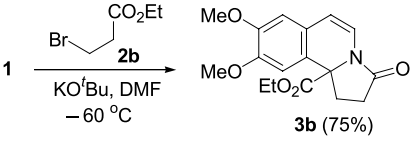
1. Introduction

In connection with our recent studies on the total synthesis of cephalotaxine,[1] we observed an unusual annulation reaction as shown in Scheme 1. An attempted Claisen condensation of 3,4-dihydroisoquinoline 1-carboxylate **1**[2] with ethyl 4-bromobutyrate (**2a**) using 1 equiv of potassium *tert*-butoxide (KO^{t}Bu) as base in DMF at −60 °C led to the formation of a majority tricyclic product in ca. 20% yield, which was identified spectroscopically as an isoquinoline annulation adduct **3a**. By employing 2 equiv of KO^{t}Bu at −60 °C in degassed DMF, the yield of the annulation product **3a** was increased to 69% on a 1 mmol scale reaction, along with a small portion (ca. 5%) of oxidized α-alkylation product characterized as **4a**.

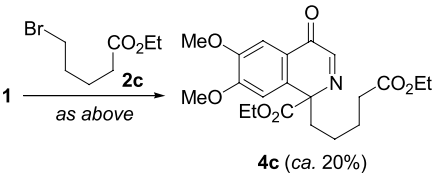


Scheme 1.

The scope of this novel annulation reaction[3] of 3,4-dihydroisoquinoline in terms of product ring-size was then examined by using ethyl 3-bromopropionate (**2b**) and ethyl 5-bromovalerate (**2c**) as the alkylating components under identical conditions (2 equiv KO^{t}Bu, degassed DMF, see Eqs. 1 and 2). It is interesting to note that, although the 5-membered ring annulation product **3b** was produced cleanly in 75% yield, the reaction of **1** with 5-bromovalerate **2c** was sluggish and the expected 7-membered annulation product **4b** was not detected. A major isolable product **4c**, a structural analog of **4a**, was obtained instead in low yield after an extended reaction time.[4] Apparently, this annulation reaction is limited to the synthesis of 5- and 6-membered annulation adducts.



(1)



(2)

Nonetheless, this unusually facile and simple annulation reaction constitutes an alternative direct synthesis of the cyclic (annulated) Reissert compound equivalents, and to a certain extent, is complementary to the conventional Reissert synthesis,[5] for the 5-membered cyclic Reissert

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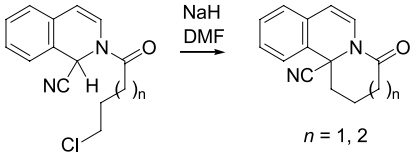
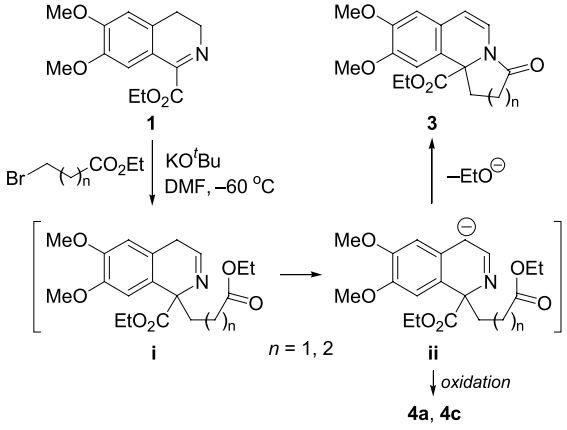
equivalent compound of type **3b** which cannot be obtained directly via the intramolecular alkylative cyclization of the corresponding Reissert precursors (Eq. 3, $n \neq 0$ and 3) as demonstrated by Popp and co-workers.[6] It is equally interesting to note that the Popp method is applicable to the synthesis of 7-membered cyclic Reissert compounds, but not to 5- and 8-membered annulation products.[7]



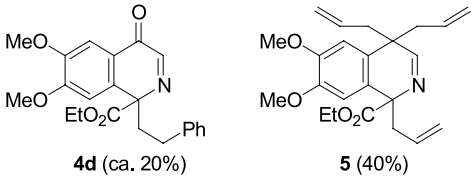
(3)

A possible reaction pathway of this base-mediated alkylative annulation is depicted in Scheme 2. The initial α-alkylation intermediate **i** may undergo intramolecular *N*-acylation through an intermediary imino benzylic anion **ii** generated by deprotonation[8] of **i**; mesomerism of **ii** and by 5- or 6-exo-trig ring-closure[9] of the corresponding enaminate leads to **3**. The oxidative products (i.e., **4a** and **4c**) might result from the imino benzylic anion **ii** by aerial oxidation.[4] The delicate increase of ring-strain may be responsible for the reluctant 7-exo-trig ring-closure to form the corresponding 7-membered annulation product from the anionic intermediate **ii** ($n=3$) after the initial α-alkylation of **1** with 5-bromovalerate.

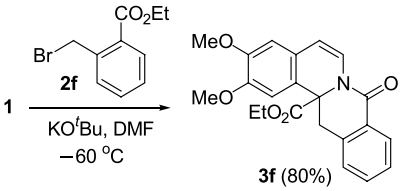


Scheme 2.

Simple alkyl bromide, phenethyl bromide (**2d**), reacted with **1** sluggishly under identical reaction conditions to give a low yield of oxidative product isoquinolinone **4d**, whilst the more reactive electrophile, allyl bromide (**2e**), led to tris-alkylated product **5** (mp 75–77 °C) in moderate yield. The use of other electrophiles, such as ethyl acrylate,[10] did not give any desired annulation product (i.e., **3b**), and the use of 1,3-dibromopropane and 1,4-dibromobutane did not give any intramolecular bis-alkylated products either. Some other reaction conditions have been examined by varying the bases and solvents[11] used, among which KO^{t}Bu in DMF was found to be the solvent system of choice. Typical phase transfer conditions involving the use of 50% aqueous KOH solution as base and *n*-tetrabutylammonium bromide (TBAB) as a phase transfer catalyst in CH_2Cl_2 or toluene also failed to promote the production of any detectable annulation product.

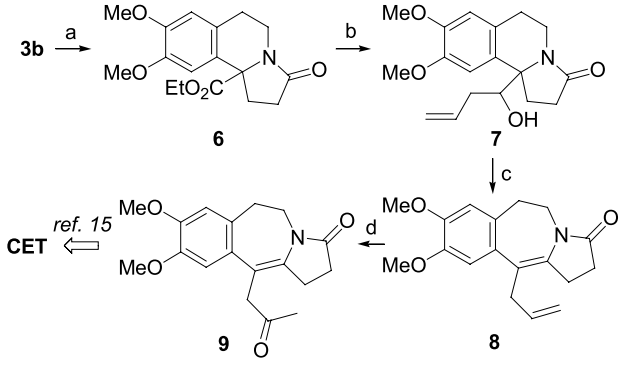


Other electrophiles, such as ethyl *ortho*-bromomethyl benzoate (**2f**), was annulated with **1** to afford an isoquinoline adduct **3f** (mp 145–147 °C) in 80% yield (Eq. 4). Analogous annulation reactions with substituted 3,4-dihydroisoquinoline and electrophiles would provide an efficient and simple method for the synthesis of berberinetype[12] and related alkaloid heterocycles (vide infra).



(4)

The annulated isoquinoline derivatives can be hydrogenated quantitatively to the corresponding dihydro compounds under usual catalytic hydrogenation conditions. For example, the dihydro derivative **6**, which possesses the basic pyrroloisoquinoline ring systems, appears as the major structural motif of erythrina-type alkaloids.[13] Compound **6** can be transformed into a benzazepine intermediate **9** as shown in Scheme 3, which may serves as an advanced precursor[14] in the total synthesis of cephalotaxine (CET),[15] by the following sequence: (1) carboxylate reduction by DIBAL-H to the corresponding aldehyde followed by allyl Grignard addition to give alcohol **7** (mixture of diastereomers); (2) sulfuryl chloride (SO_2Cl_2)-mediated ring-opening rearrangement[15] to give an allyl benzazepine intermediate **8**; and (3) standard Wacker oxidation to furnish the tricyclic methyl ketone **9**.



Scheme 3. (a) Conditions: (a) H_2, 10% Pd–C, MeOH, 100%. (b) (i) DIBAL-H, CH_2Cl_2, −78 °C, 72%; (ii) Allyl-MgBr, THF, −20 °C, 80%. (c) SO_2Cl_2, Et_3N, Pyr, CH_2Cl_2, −78 °C, 80%. (d) $PdCl_2$ (10 mol%), $CuCl_2$, DMF–H_2O (4:1), O_2, 40 °C, 67%.

Similarly, dihydro derivative **10** (mp 144 °C) obtained from **3f** can also be converted (Scheme 4) to a benzazepine heterocycle **12**, a structural analog of relevant natural alkaloids (i.e., lennoxamine and chilenine).[16] Further transformation of the annulation product **10** to 8-oxoprotoberberines **13** and **14**, key intermediates for the synthesis of