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SYNTHESIS OF BRIDGED BENZOAZABICYCLIC COMPOUNDS USING RADICAL TRANSLOCATION/ CYCLIZATION REACTIONS OF 1-ALKYNYL-2-(*o*-IODOBENZOYL)TETRAHYDROISOQUINOLINES

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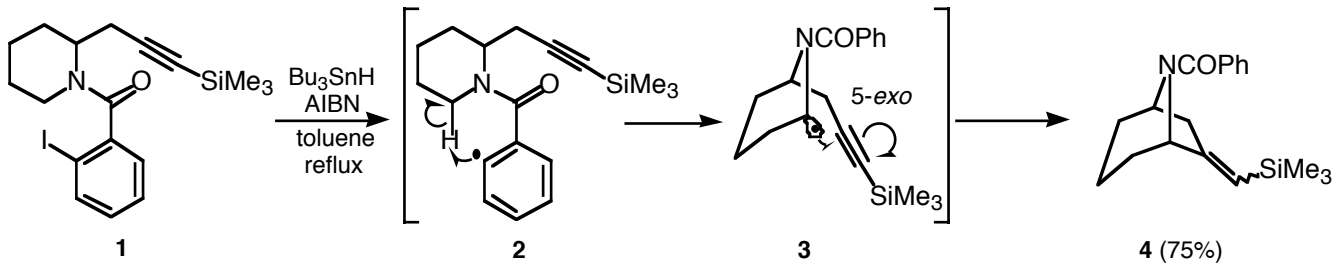
Abstract–Bu_3SnH-mediated radical translocation/cyclization reactions of 1-alkynyl-2-(*o*-iodobenzoyl)tetrahydroisoquinolines were examined. The 1-[3-(trimethylsilyl)prop-2-ynyl]- (**10a**) and 1-[4-(trimethylsilyl)but-3-ynyl]-1,2,3,4-tetrahydroisoquinoline derivatives (**10b**), with Bu_3SnH in the presence of azobis(isobutyronitrile) in boiling toluene, gave regioselectively the 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5,8-imine (**12a**) and 5,6,7,8,9,10-hexahydrobenzocycloocten-5,9-imine (**12b**), respectively.

In a series of papers,[1] we have reported that treatment of 1-(*o*-iodobenzoyl)-2-[3-(trimethylsilyl)prop-2-ynyl]piperidine (**1**) with tributyltin hydride (Bu_3SnH) in the presence of azobis(isobutyronitrile) (AIBN) in boiling toluene gave regioselectively the 8-azabicyclo[3.2.1]octane (**4**). The product was believed to arise *via* the α-acylamino radical (**3**), resulting from a 1,5-hydrogen transfer[2] of the initially formed aryl radical (**2**), which undergoes a 5-*exo-dig* cyclization.



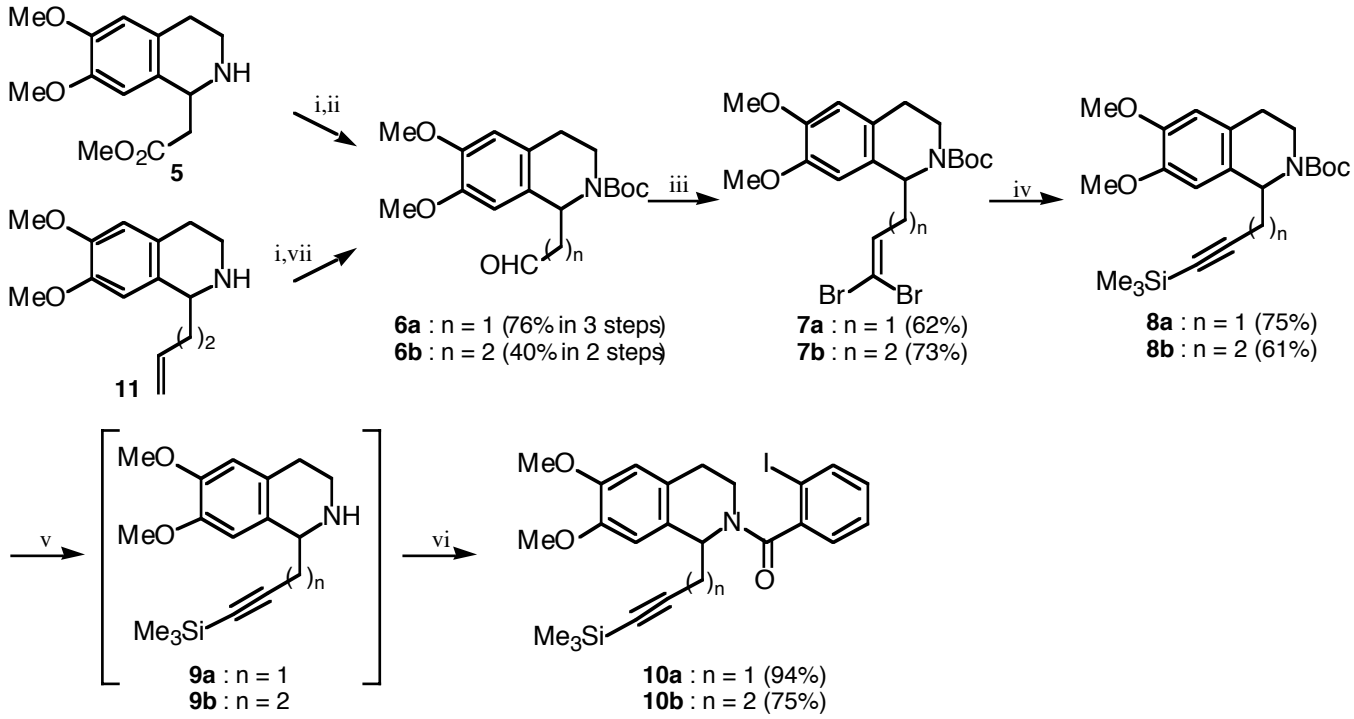
1 **2** **3** **4** (75%)

This paper is dedicated to Professor Teruaki Mukaiyama, Science University of Tokyo, on the occasion of his 73rd birthday.

We have now applied this reaction to the synthesis of the 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5,8-imine[3] and 5,6,7,8,9,10-hexahydrobenzocycloocten-5,9-imine ring systems,[4] which are of interest for the medicinal chemistry.

The radical precursor 2-(*o*-iodobenzoyl)-6,7-dimethoxy-1-[3-(trimethylsilyl)prop-2-ynyl]-1,2,3,4-tetrahydroisoquinoline (**10a**) was prepared starting from methyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetate (**5**).[5] Thus, protection of **5** with a *tert*-butoxycarbonyl (Boc) group followed by reduction with $LiAlH_4$ and oxidation of the resulting alcohol with pyridine-SO_3/DMSO gave the aldehyde (**6a**), which was treated with bromoform and triphenylphosphine in the presence of potassium *tert*-butoxide to give the dibromide (**7a**). Treatment of **7a** with butyllithium[6] and quenching with trimethylsilyl chloride gave *tert*-butyl 6,7-dimethoxy-1-[3-(trimethylsilyl)prop-2-ynyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (**8a**), which was converted into **10a** by deprotection followed by *N*-acylation of the resulting **9a** with *o*-iodobenzoyl chloride. The 6,7-dimethoxy-1-[4-(trimethylsilyl)but-3-ynyl]-1,2,3,4-tetrahydroisoquinoline derivative (**10b**) was prepared from 1-(but-3-enyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**11**).[7] Protection of **11** with the Boc group followed by OsO_4/$NaIO_4$ oxidation gave the aldehyde (**6b**). Repetition of the same sequence from the aldehyde (**6b**) as that described for the preparation of **10a** produced the radical precursor (**10b**).

Scheme 1



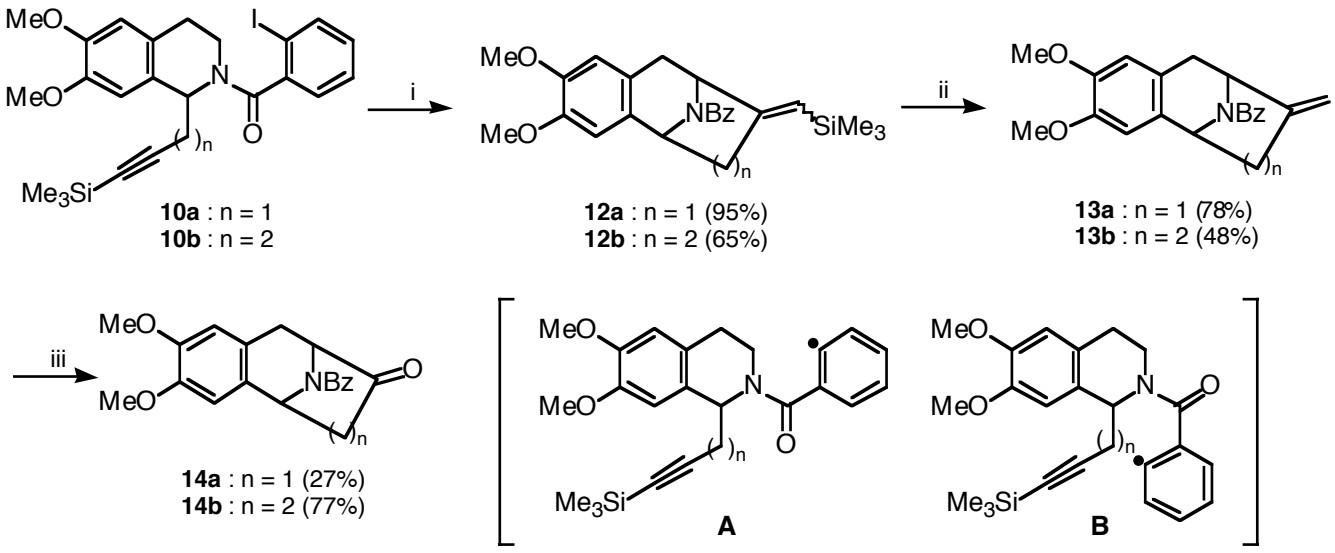
Reagents and Conditions : i, Boc_2O, Et_3N, DMAP, AcOEt, rt, 1 day; ii, (a) $LiAlH_4$, THF, rt, 1 h, (b) pyridine-SO_3, DMSO, Et_3N, CH_2Cl_2, 0 °C, 2 h; iii, PPh_3, $CHBr_3$, *t*-BuOK, toluene, -20 °C, 1 h; iv, *n*-BuLi, TMEDA, THF, -78 °C, 1 h then TMS-Cl, rt, 1 day; v, TMS-I, MeCN, rt, 15 min; vi, *o*-iodobenzoyl chloride, Et_3N, DMAP, benzene, rt, 1 day; vii, 4% aq. OsO_4, THF-H_2O, 0 °C, 15 min then $NaIO_4$, rt, 1 day.

A toluene solution of Bu_3SnH (1.25 equiv.) and a small amount of AIBN (0.1 equiv.) was added slowly to a boiling solution of **10a** in toluene over a period of 2 h, and the mixture was refluxed for an additional 2 h. The crude material was chromatographed on silica gel to give the 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5,8-imine (**12a**) in 87% combined yield as a diastereomeric mixture. The structure of **12a** was confirmed by the following chemical transformation. Treatment of **12a** with trifluoroacetic acid in dichloromethane gave the methylene derivative (**13a**), which was then oxidized with OsO_4 and $NaIO_4$ to afford the ketone (**14a**) as a viscous oil. The ketone (**14a**) showed a strong carbonyl absorption at 1758 cm^{-1} (a five-membered ketone) in addition to an absorption due to an *N*-benzoyl group at 1631 cm^{-1} in the IR spectrum.

A similar treatment of the compound (**10b**) with Bu_3SnH/AIBN gave exclusively the 5,6,7,8,9,10-hexahydrobenzocycloocten-5,9-imine (**12b**) in 65% yield as a diastereomeric mixture. The compound (**12b**) was again converted into the corresponding ketone (**14b**), mp 136-137 °C, *via* the methylene derivative (**13b**). The IR spectrum of **14b** showed two carbonyl absorption bands at 1720 (a six-membered ketone) and 1629 cm^{-1} (an amide).

The smooth *exo*-selective cyclization can be rationalized as follows: 1) the alkynyl group in the radicals derived from **10a**,**b** may occupy a quasi-axial position in order to avoid allylic 1,3-strain ($A^{1,3}$ strain) with the N=C double bond in the amide[8] and 2) the internal position of the alkynic bond is closer to the radical center formed at the 3-position of the tetrahydroisoquinoline ring than the external position is. The regioselective formation of the radical at the 3-position may arise from the preferred conformer **A** that minimizes steric interaction between the 1-alkynyl and benzoyl groups, rather than from the less favorable conformer **B**.

Scheme 2



10a : n = 1
10b : n = 2

12a : n = 1 (95%)
12b : n = 2 (65%)

13a : n = 1 (78%)
13b : n = 2 (48%)

14a : n = 1 (27%)
14b : n = 2 (77%)

Reagents and Conditions : i, Bu_3SnH, AIBN, toluene, reflux, 2 h; ii, TFA, CH_2Cl_2, rt, 2 h; iii, 4% aq. OsO_4, THF-H_2O, 0 °C, 15 min then $NaIO_4$, rt, 1 day.

ACKNOWLEDGEMENT

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7. Compound (**11**) was prepared by the Bischler-Napieralski reaction of *N*-[2-(3,4-dimethoxyphenyl)ethyl]-4-pentenamide ($POCl_3$ in benzene at 80 °C) followed by $NaBH_4$ reduction of the resulting imine,[9] and this compound was used in the next step without further purification.
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