Pergamon

Tetrahedron Letters, Vol. 38, No. 40, pp. 6977-6980, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01668-7

SYNTHESIS OF ETHYL *N*-(DIPHENYL)METHYL-1,2,3,4-TETRAHYDROISOQUINOLINE-3-CARBOXYLATES

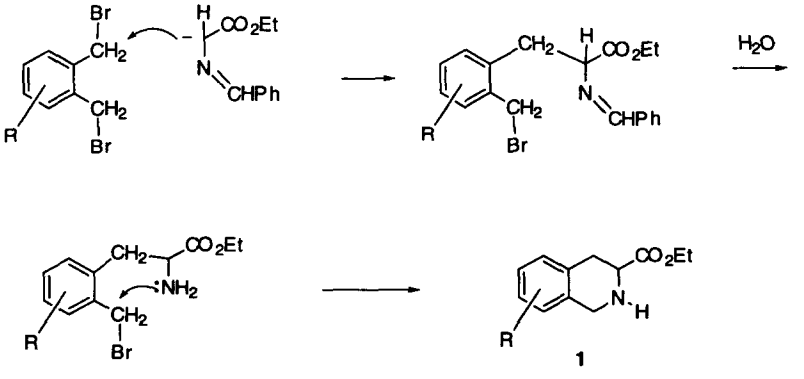
Eugene A. Mash*, Lawrence J. Williams, and Steven S. Pfeiffer

Department of Chemistry, The University of Arizona, Tucson, Arizona 85721-0041 USA

Abstract: A concise method for the synthesis of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives from α,α'-dibromo-*o*-xylenes via sequential C-alkylation and N-alkylation of a glycine anion is described. © 1997 Elsevier Science Ltd.

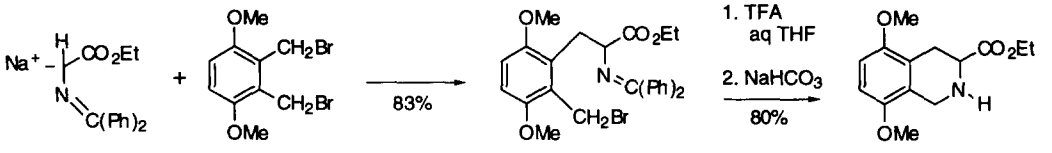
The 1,2,3,4-tetrahydroisoquinoline (THIQ) ring system is a structural component of many biologically active natural products[1] and is a useful template for construction of conformationally restricted analogs of aromatic α-amino acids.[2] Methods available for construction of THIQ derivatives include the Bischler-Napieralski reaction,[3a] the Pictet-Spengler reaction,[3b] and the Pomeranz-Fritsch reaction,[3c] among others.[4] While useful, these reactions have limitations, and so development of alternative syntheses of THIQ derivatives from readily available starting materials is important.

In the course of preparing 2-aminoindane-2-carboxylic acid derivatives by the method of Kuki and Kotha,[5] we were able to isolate minor products which were identified as the corresponding 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives **1**. It was hypothesized that, following the initial alkylation at carbon, the second alkylation at carbon had been incomplete, and so upon hydrolysis of the imine a small amount of a (bromomethyl)aryl amine was produced. Cyclization via alkylation at nitrogen gave **1**. As this process appeared to have significant synthetic potential, its optimization became a goal.[6,7]



1

The benzophenone imine of ethyl glycinate was deprotonated using sodium bis(trimethylsilyl)amide (NaBTMSA) in THF and the resulting enolate **2** allowed to react with a slight excess of α,α'-dibromo-*o*-xylene derivative **3a**.[8a] Following an extractive workup and chromatography on silica gel 60, imine **4** was isolated in 83% yield. Hydrolysis using trifluoroacetic acid in aqueous THF at room temperature, followed by basification with $NaHCO_3$, produced ethyl 5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **5** in 80% yield (66% from **2**).



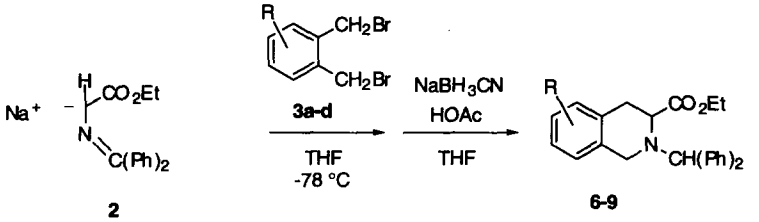
2 **3a** **4** **5**

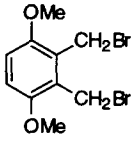
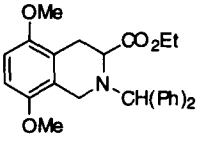
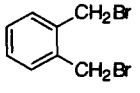
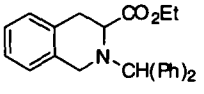
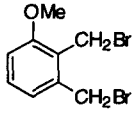
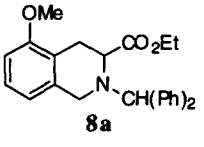
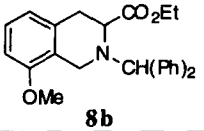
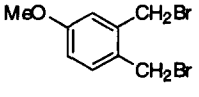
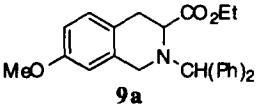
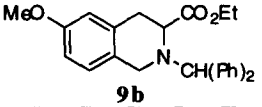
Following this encouraging result, we envisaged a concise one-pot synthesis of fully protected THIQ-3-carboxylic acid derivatives (Table 1). Enolate **2** was again allowed to react in THF with α,α'-dibromo-*o*-xylene derivative **3a**. When TLC analysis indicated the absence of **2**, $NaBH_3CN$ and acetic acid were added to the reaction mixture. Following an extractive workup and chromatography on silica gel 60, ethyl 5,8-dimethoxy-2-(diphenyl)methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**6**) was isolated in 72% yield. This result was consistently obtained on scales ranging from 100 mg to 5 g. In a similar manner, α,α'-dibromo-*o*-xylene (**3b**) was converted to THIQ-3-carboxylate derivative **7** in 69% yield. Dibromides **3c**[8b] and **3d**[8c] were employed to determine whether regioselectivity would result from preferential C-alkylation. A 1:1 mixture of THIQ derivatives **8a** and **8b** was obtained from dibromide **3c**, while a 3:1 mixture of THIQ derivatives **9a** and **9b** was obtained from dibromide **3d**. These product mixtures were not chromatographically separable, but were analyzed by 200 MHz ^1H NMR and 50.3 MHz ^{13}C NMR spectroscopy. In the case of **9a/9b**, the identity of the major diastereomer was not determined. Presumably, steric and electronic effects act in opposition in the case of **3c**, while electronic effects are responsible for the modest regioselectivity observed in the case of **3d**. Efforts to improve the regioselectivity are in progress.

This procedure[9] could make available THIQ derivatives which possess electron withdrawing substituents on THIQ carbons 5-8, which are difficult to synthesize by other methods.[3,4] Additionally, this procedure can be modified to provide access to enantiomerically enriched THIQ derivatives by incorporating the catalytic phase-transfer alkylation method of O'Donnell.[6] This synthesis of THIQ derivatives should be applicable to stereocontrolled syntheses of natural products and a variety of unnatural THIQ α-amino acid analogs.

Acknowledgment. Partial support of this research by the Howard Hughes Medical Institute and by the Office of Naval Research through the Center for Advanced Multifunctional Nonlinear Optical Polymers and Molecular Assemblies is gratefully acknowledged.

Table 1. Synthesis of Tetrahydroisoquinoline Derivatives **6-9**.



Xylene Dibromide	THIQ Product(s)	Yield,%	r.r.[a]
 **3a**	 **6**	72	na
 **3b**	 **7**	69	na
 **3c**	 **8a**  **8b**	71[b]	1:1[c]
 **3d**	 **9a**  **9b**	71[b]	3:1[c,d]

[a]Regioisomer ratio. [b]Products **8a/8b** and **9a/9b** were not separable by column chromatography. [c]The regioisomer ratio was determined by ^{1}H NMR and ^{13}C NMR spectroscopy. [d]The identity of the major diastereomer was not determined.

References and Notes

1. For examples, see Kametani, T. The Total Syntheses of Isoquinoline Alkaloids. In *The Total Synthesis of Natural Products*, vol. 3; ApSimon, J., Ed. John Wiley: New York, 1977; pp. 1-272.
2. (a) Hruby, V. J. *Biopolymers* **1993**, *33*, 1073-1082. (b) Liskamp, R. M. J. *Recl. Trav. Chim. Pays-Bas.* **1994**, *113*, 1-19. (c) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539-1650.
3. (a) Whaley, W. M; Govindachari, T. R. *Org. React.*, VI, 74-150 (1951). (b) Whaley, W. M; Govindachari, T. R. *Org. React.*, VI, 151-190 (1951). (c) Gensler, W. J. *Org. React.*, VI, 191-206 (1951).
4. Jones, G. Pyridines and their Benzo Derivatives: (v) Synthesis. In *Comprehensive Heterocyclic Chemistry*, vol. 2; Boulton, A. J. and McKillop, A., Eds. Pergamon: New York, 1984; pp. 395-510.
5. Kuki, A.; Kotha, S. *Tetrahedron Lett.* **1992**, *33*, 1565-1569.
6. To the best of our knowledge, this synthesis of THIQ derivatives has not been reported. For previous alkylations of benzophenone imines for the synthesis of α-amino acids, see O'Donnell, M. J.; Wu, S.; Huffman, J. C *Tetrahedron* **1994**, *50*, 4507-4518 and references cited therein.
7. For related synthetic approaches to THIQ derivatives, see (a) Seebach, D.; Dziadulewicz, E.; Behrendt, L.; Cantoreggi, S.; Fitzi, R. *Liebigs Ann. Chem.* **1989**, 1215-1232. (b) Kammermeier, B. O. T.; Lerch, U.; Sommer, C. *Synthesis* **1992**, 1157-1160.
8. (a) Eck, G.; Julia, M.; Pfeiffer, B.; Rolando, C. *Tetrahedron Lett.* **1985**, *26*, 4225-4228. (b) Box, V. G. S.; Yiannikouros, G. P. *Heterocycles* **1990**, *31*, 1261-1270. (c) Heffner, R. J.; Joullié, M. M. *Synthetic Communic.* **1991**, *21*, 1055-1069.
9. The synthesis of **6** is illustrative: In a flame-dried three neck flask was placed dry THF (6 mL). Stirring was commenced and the flask was cooled in a dry ice/acetone bath. Recrystallized Schiff base **2** (101.8 mg, 0.381 mmol) was added to the flask followed by a solution of NaBTMSA (1 M in THF, 0.4 mL, 0.4 mmol). The resulting yellow solution was stirred for 45 min. In a separate flame-dried flask a solution of recrystallized dibromide **3a** (159.9 mg, 0.495 mmol) in dry THF (6 mL) was stirred in an ice bath. The solution of the deprotonated Schiff base was transferred over 15 min via canula into the solution of dibromide **3a**. The resulting mixture was allowed to stir for 45 min at 0 °C at which time TLC analysis showed that **2** was absent. The reaction mixture was allowed to warm to room temperature and $NaBH_3CN$ (41.1 mg, 0.375 mmol) and glacial acetic acid (1.2 mL) were added. After 5 min the reaction mixture was poured into a mixture of sat NaCl solution (10 mL) and sat $NaHCO_3$ solution (30 mL) and the mixture was extracted with ether (4 x 30 mL). The extracts were combined, dried (Na_2SO_4), filtered, and concentrated in vacuo to give a yellow oil which was purified by column chromatography on silica gel 60 (300 mL, 70-230 mesh) eluted with 2% EtOAc/toluene. The yield of **6**, a pale yellow solid, mp 93-95 °C, R_f 0.45 (10% EtOAc/toluene), was 118.6 mg (0.274 mmol, 72%). ^1H NMR δ 1.17 (3, t, ^3J = 7.1 Hz), 2.91 (1, dd, ^2J = 16.9 Hz, ^3J = 6.6 Hz), 3.22 (1, d, ^2J = 16.9 Hz), 3.60 (3, s), 3.76 (3, s), 3.78-4.11 (5, m), 5.25 (1, s), 6.54 (1, d, ^3J = 8.9 Hz), 6.61 (1, d, ^3J = 8.9 Hz), 7.09-7.31 (6, m), 7.37-7.55 (4, m); ^{13}C NMR δ 14.1, 26.6, 44.9, 56.9, 57.2, 58.0, 60.0, 72.5, 106.5, 107.0, 123.2, 124.9, 126.9, 127.2, 127.5, 128.0, 128.5, 130.1, 132.3, 142.3, 143.0, 150.0, 151.1, 172.3, 197.8; HRMS (FAB+) calcd for $C_{27}H_{30}NO_4$ ($M+H^+$) 432.2195, observed 432.2192, calcd for $C_{27}H_{29}NO_4$ (M^+) 431.2117, observed 431.2087, calcd for $C_{27}H_{28}NO_4$ ($M+H^+-H_2$) 430.2038, observed 430.2030.

(*Received in USA* 18 *July* 1997; *revised* 5 *August* 1997; *accepted* 11 *August* 1997)