Chinese Chemical Letters Vol. 15, No. 3, pp 253-256, 2004
http://www.imm.ac.cn/journal/ccl.html

Bischler-Napieralski Reaction of 2-(3, 4-Dimethoxy-2-nitrophenyl)-N- [2-(3, 4-dimethoxyphenyl) ethyl]-N- [(S)-1-phenylethyl] acetamide Accompanied by Elimination of Chiral Auxiliary

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Abstract: Unexpected dealkylation of Bischler-Napieralski cyclization of 2-(3,4-dimethoxy-2-nitro-phenyl)-N-[2-(3,4-dimethoxyphenyl) ethyl]-N-[(S)-1-phenyl-ethyl] acetamide **3** was reported. The electronic effect of the substituent at 2-position of C ring was also discussed.

Keywords: Bischler-Napieralski reaction, elimination, (S)-1-phenylethylamine, 1-benzyltetra-hydroisoquinolines.

Chiral 1-benzyltetrahydroisoquinoline alkaloids can be asymmetrically synthesized *via* Bischler-Napieralski (B-N) cyclization followed by stereoselective $NaBH_4$ reduction (Polniaszek's method) of the N- (2-phenylethyl)-2-phenylacetamides bearing chiral auxiliary such as (S)-1-phenylethyl group on the nitrogen atom[1-4]. Recently Y. Ohishi and co-workers found an unusual B-N reaction on the carbon at 2-position of the A ring, which bears a bromine atom[5, 6]. They indicated that the steric effect of the substituent group at the 2- or 5-position of A ring interfered with B-N reaction to give product accompanied by cleavage of the chiral auxiliary. These prompt us to present the result of our work in this field. We also observed similar unusual B-N reaction accompanying elimination of the chiral auxiliary from acetamide **3**. At the same time we found that the electronic effect of the substituent at 2-position of C ring also interfered with B-N reaction, except the steric effect of the substitute group of A ring.

Our entry into this field was as follows. We attempted to synthesize a natural (-)-thalibealine, a novel tetrahydroprotoberberine-aporphine dimmer alkaloid, which could be prepared through improved Ullmann-type ether synthesis. The protoberberine monomer required in Ullmann reaction might be synthesized *via* chiral benzyl-tetrahydroisoquinoline **5** as a key intermediate. Based on the works of literatures[1-4], it was rationally expected that the chiral auxiliary of **3** would result in 1,3-asymmetric induction through Polniaszek's method, then the chiral 1S–benzyltetrahydroisoquinoline

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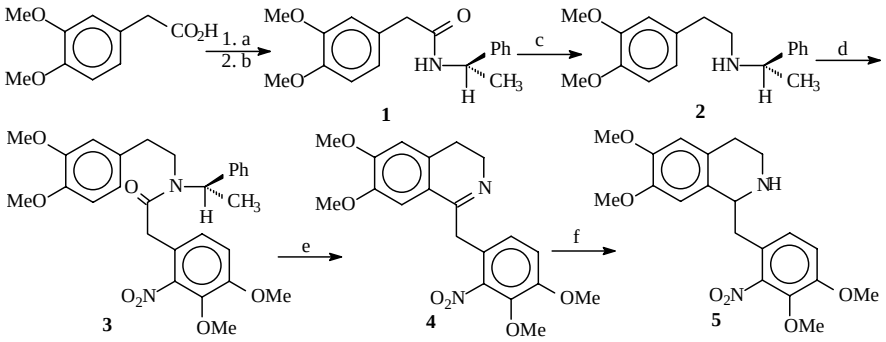
5 was obtained after eliminating the chiral auxiliary on the nitrogen atom.

The optical intermediate, 2-(3,4-dimethoxy-2-nitrophenyl)-N-[2-(3,4-dimethoxy-phenyl) ethyl]-N-[(S)-1-phenylethyl] acetamide **3** was prepared from 3,4-dimethoxy-phenylacetic acid as shown in **Scheme 1**. Treatment of 3,4-dimethoxy phenylacetic acid chloride with (S)-1-phenylethylamine afforded the optically active amide **1**. Reduction of **1** with BH_3-THF complex in the presence of BF_3-Et_2O complex gave the amine **2**, which was condensed with 3,4-dimethoxy-2-nitrophenylacetic acid chloride to yield the acetamide **3**. Treatment of the acetamide **3** with $POCl_3$ in dry MeCN (B-N reaction conditions) afforded a viscous substance **4**. Without purification the intermediate **4** was treated with $NaBH_4$ in MeOH at -78°C to give a yellow solid (77.3%). The structure of the product was assigned as racemic 1-(3,4-dimethoxy-2-nitro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **5** on the basis of its ^{1}H-NMR, ^{13}C-NMR and MS data[7].

Scheme 1



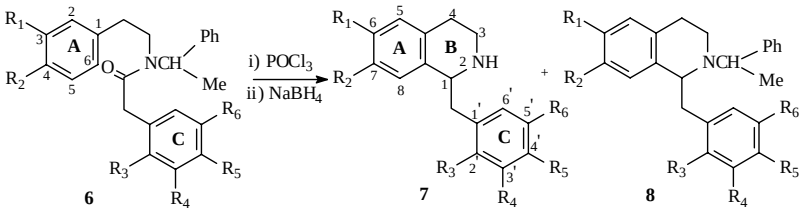
a) $SOCl_2$, 50℃, 1 hrs; b) (S)-1-phenylethyl amine, 5%Na_2CO_3, 0 ℃; c) BF_3-Et_2O/BH_3-THF; d) 3,4-dimethoxy-2-nitrophenylacetic acid chloride, 5% NaOH, 0 ℃; e) $POCl_3$, CH_3CN, reflux, 2.5 hrs; f) $NaBH_4$, MeOH, -78°C.

The B-N reaction intermediate was purified as usual to give 3, 4-dihydro-isoquinoline **4**, which was the only detectable product on thin layer chromatography. This proved that chiral auxiliary of the acetamide **3** was cleaved during the cyclization process. We also examined B-N reaction of the N-(2-phenylethyl)-2-phenylacetamides **6** bearing a chiral auxiliary on the nitrogen atom and found that B-N reaction of acetamide **6** having methoxy or hydrogen atom at 2-position of C ring afforded only the expected tetrahydroisoquinoline **8** in almost quantitative yield without the elimination of the chiral auxiliary[3, 4]. Partial loss of the chiral auxiliary was reported when the acetamide **6** has a bromine atom at 2-position of C ring, compound **7** (57.0%) was obtained together with compound **8** (20.0%)[6](**Scheme 2**). The acetamides without any substituent at the 2- or 5-position of A ring, gave different results because of the different substituent at 2-position of C ring. This suggested that the deterimining factor is the electronic effect of the substituent at 2-position of C ring.

In view of the reported and our results, a possible mechanism for the elimination of the chiral auxiliary can be postulated as shown in **Scheme 3**. The acetamide **3** would afford the intermediate iminium ion **9** upon treatment with $POCl_3$. The strong

electron-withdrawing nitro-group renders the hydrogen atoms of the methylene group much more acidic, which facilitates the loss of one molecule of HCl to give enamine **10**.

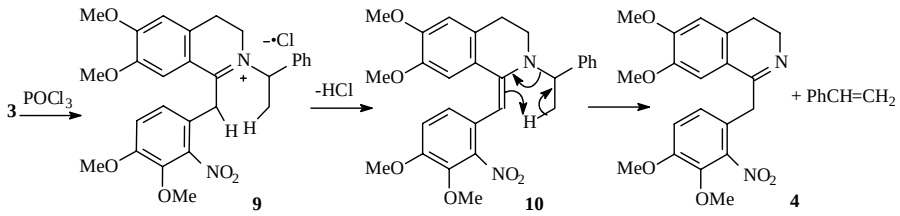
Scheme 2



The hydrogen atom at the methyl of the chiral auxiliary was attacked by the ethylenic bond of **10** then the more stable 3, 4-dihydroisoquinoline **4** was yielded accompanying elimination of styrene *via* a 6-membered ring transition state. The reported experiment results in **Scheme 2** can be explained with this mechanism reasonably. The hydrogen atoms of the benzyl CH_2-group were less acidic when there is no electron withdrawing group at 2-position of C ring so that the iminium ion formed from acetamide **6** was directly reduced with $NaBH_4$ to afford compound **8** without the elimination of the chiral auxiliary. Because bromine atom is a weak electron withdrawing group, partial of the iminium ion was converted to the enamine during B-N reaction, so two products **7** and **8** were obtained after the reduction reaction.

In conclusion, it was clarified that 2-(3,4-dimethoxy-2-nitrophenyl)-N-[2-(3,4-dimethoxyphenyl) ethyl]-N-[(S)-1-phenylethyl] acetamide **3** possessing a nitro group at 2-position of C ring afforded racemic 1-(3,4-dimethoxy-2-nitrobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **5** by Polniaszek's method because of the elimination of the chiral auxiliary at B-N cyclization step *prior to* 1,3-asymmetric reduction with $NaBH_4$. It can be concluded that the degree of the loss of chiral auxiliary during B-N reaction depends on the electron withdrawing ability of the substituent at 2-position of C ring.

Scheme 3



References and Notes

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7. Spectral data:
   4: mp 161-163°C. ^{1}H NMR (300MHz, $CDCl_3$, δ ppm) 2.66 (t, 2H, J=7.5Hz, CH_2CH_2), 3.72 (t, 2H, J=7.5Hz, CH_2CH_2), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.94 (s, 2H, CH_2C=N), 6.66 (s, 1H, Ar-H), 6.89 (d, 1H, J = 8.7Hz, Ar-H), 6.91 (s, 1H, Ar-H), 7.00 (d, 1H, J = 8.7Hz, Ar-H). EI-MS (*m/z*): 386.2 $(M)^+$, 340.3 (base), 309.2.
   5: ^{1}H NMR (300MHz, $CDCl_3$, δ ppm) 2.73-3.22 (m, 6H,CH_2×3), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.37 (dd, 1H, J_1=9.6Hz, J_2=4.2Hz, CHN), 6.50 (s, 1H, Ar-H), 6.57 (s, 1H, Ar-H), 6.98 (d, 1H, J = 8.7Hz, Ar-H), 7.07 (d, 1H, J = 8.7Hz, Ar-H). ^{13}C NMR (125MHz, $CDCl_3$, δ ppm): 29.1, 37.7, 39.7, 55.9, 56.0, 56.1, 56.5, 62.3, 109.7, 111.8, 114.1, 123.3, 126.5, 127.0, 129.5, 141.1, 147.1, 147.5, 147.9, 152.2. FAB-MS (*m/z*): 389.0 $(M+1)^+$, 192.0 (base).

Received 20 February, 2003