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New Approach to Synthesis of Tetrahydroisoquino[2,1-c] [1,3]-benzodiazepine

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Abstract: A concise and efficient synthesis of the new compounds tetrahydroisoquino [2,1-c] [1,3] benzodiazepine **5** and **7** is reported.

Keywords: Tetrahydroisoquinoline, Mannich reaction, benzodiazepine, berberine.

It is known that intramolecular Mannich reaction of 1-benzyltetrahydroisoquinolines with formaldehyde is the most common and convenient procedure for the synthesis of tetrahydroprotoberberines[1-3]. We had an occasion to employ this reaction during the synthesis of aminotetrahydroprotoberberine from the corresponding isoquinoline derivative **4** which we desired to synthesize natural (-)-thalibealine. However, the expected aminoprotoberberine had not been obtained from isoquinoline derivative **4** by Mannich reaction. The structure of the product was confirmed by the spectral data to be tetrahydroisoquino[2,1-c] [1,3] benzodiazepine.

As seen in **Scheme 1**, Mannich reaction of isoquinoline derivative **4** with 37% formaldehyde in ethanol did not afford the expected aminoprotoberberine[1-3]. ^{1}H NMR、^{13}C NMR、FAB-MS and HRMS confirmed the product to be tetrahydroisoquino[2,1-c] [1,3] benzodiazepine **5**[4]. The desired tetrahydroprotoberberine was then tried to be synthesized from formamidine **6** in which the amino group was protected by N, N-dimethylformamide dimethyl acetal (DMF-DMA). Under the same reaction condition, compound **7** was isolated.

The starting material **1** in this reaction was synthesized by condensation of 3, 4-dimethoxy-β-phenethylamine with 3, 4-dimethoxy-2-nitrophenylacetyl chloride under the Schotten-Baumann reaction condition. Bischler-Napieralski cyclization of **1** in CH_3CN and $POCl_3$ furnished 3,4-dihydroisoquinoline **2**. $NaBH_4$ reduction of **2** in methanol afforded tetrahydroisoquinoline **3**. Reduction of **3** with stannous chloride dihydrate in acidic condition yielded the corresponding amino compound **4**. This base was refluxed with 37% formaldehyde solution in ethanol to afford tetrahydroisoquino [2,1-c] [1,3] benzodiazepine **5** (64%). After the amino group of isoquinoline derivative **4** was

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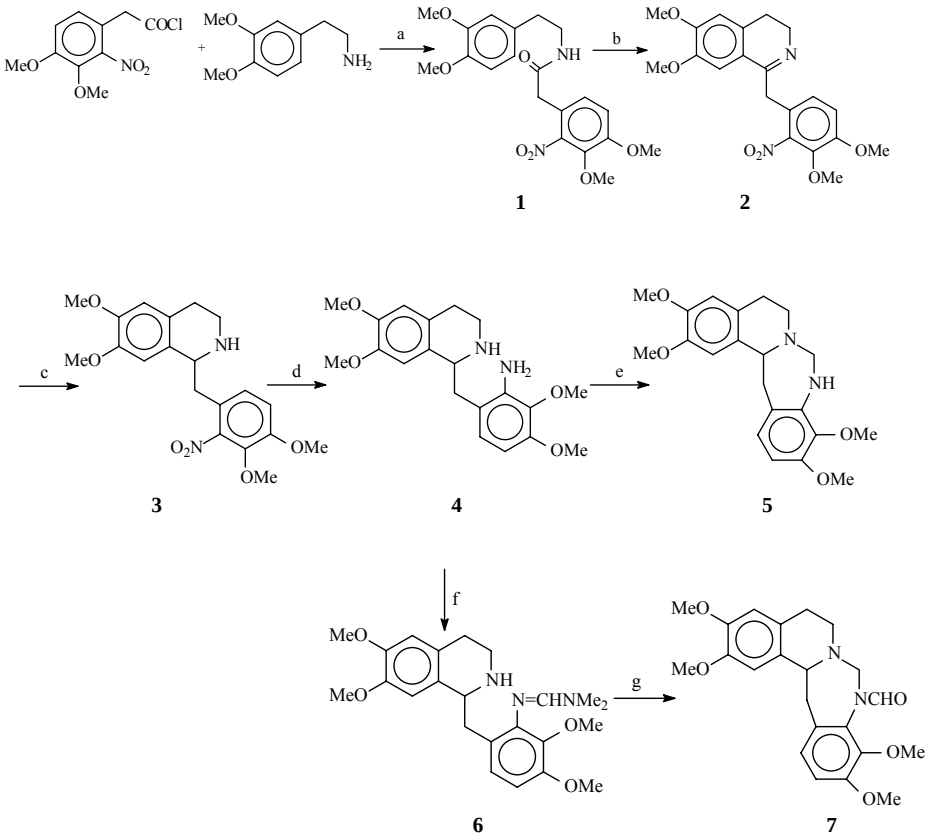
Scheme 1

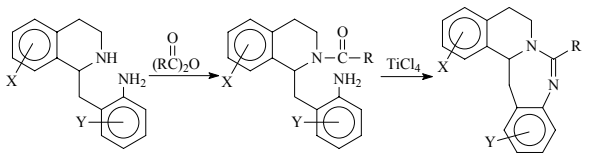


a) 5% NaOH, 0℃; b) $POCl_3$, CH_3CN, reflux; c) $NaBH_4$, MeOH, 0℃; d) $SnCl_2$, AcOH, HCl; e) 37% HCHO, EtOH, reflux; f) DMF- DMA, reflux, 16h; g) 37% HCHO, EtOH, reflux, 2h.

protected by DMF-DMA to form **6**, formamidine **6** was subjected to Mannich reaction condition, and the corresponding N-formyl derivative **7** (70%) was isolated.

Only one patent reported about the synthesis of tetrahydroisoquino [2,1-c][1,3]-benzodiazepines which was prepared as agents for treating memory dysfunctions characterized by decreased cholinergic function, such as Alzheimer's disease by L. L. Martin *et al*[5]. N-Acylated-*O*-toluidine and 3,4-dihydroisoquinoline were employed as starting materials and isoquinoline derivative as the key intermediate (**Scheme 2**). The harsh reaction conditions and low yield (26%) of the last step limited the use of patent method. Our methodology shows an obvious improvement over the literature method in terms of its convenient operation and high yield. It can be seen obviously that the seven-member ring of compounds **5** and **7** is different from that of compounds synthesized by L. L. Martin *et al*. The former is saturated methylene-diamine while the latter has C=N group.

Scheme 2



In summary, we developed a simple and efficient way of constructing the new skeleton of tetrahydroisoquino [2,1-c] [1,3] benzodiazepines. The study on the synthesis of its analogues is in progress based on this methodology.

References and Notes

1. D. S. Bhakuni, P. Kumar, *Indian Chem. Soc.*, **1988**, *LXV*, 417.
2. S. Ishiwata, K. Itakura, *Chem. Pharm. Bull.*, **1970**, *18*(4), 763.
3. G. Memetzidis, J. Stambach, L. Jung, *Heterocycles*, **1990**, *31*(2), 341.
4. Spectral data:
   4: ^{1}H NMR (300MHz, $CDCl_3$) δ ppm 2.82-3.33 (m, 6H,CH_2×3), 3.73 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.37 (t, 1H, J= 6.6 Hz, CHN), 6.28 (d, 1H, J = 8.4 Hz, Ar-H), 6.38 (s, 1H, Ar-H), 6.59 (s, 1H, Ar-H), 6.66 (d, 1H, J = 8.4 Hz, Ar-H). FAB-MS:*m/z* 359.2 (M+1), 357.2 (M-1), 192.1 (base), 166.1.
   5: mp 149-151℃. ^{1}H NMR (500MHz, $CDCl_3$) δ ppm 2.60 (d, 1H, J= 15.0 Hz, CH_2CH), 2.73-3.04, 3.62-3.67 (m, 4H, CH_2CH_2), 3.62 (m, 1H, CH_2CH), 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.86(s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.07 (d, 1H, J= 11.0 Hz, CHN), 4.16 (d, 1H, J= 13.0 Hz, CH_2NH), 4.37 (d, 1H, J= 13.0 Hz, CH_2NH), 4.54 (br, 1H, NH), 6.41 (d, 1H, J = 8.0 Hz, Ar-H), 6.60(s, 1H, Ar-H), 6.67 (s, 1H, Ar-H), 6.87 (d, 1H, J = 8.0 Hz, Ar-H); ^{13}C NMR ($CDCl_3$): 28.83 (t, CH_2), 40.87 (t, CH_2), 41.58 (t, CH_2), 55.76 (q, OCH_3), 55.79 (q, OCH_3), 56.11 (q, OCH_3), 59.82 (d, CH), 60.65 (q, OCH_3), 70.15 (t, CH_2), 103.80 (d, Ar-CH), 110.37 (d, Ar-CH), 111.19 (d, Ar-CH), 124.36 (s, Ar-C), 125.41 (d, Ar-CH), 126.41 (s, Ar-C), 131.04 (s, Ar-C), 137.82 (s, Ar-C), 144.97 (s, Ar-C), 147.14 (s, Ar-C), 147.64 (s, Ar-C), 150.85 (s, Ar-C); FAB-MS(*m/z*): 371.3 (M+1, base), 192.2, 185.2; IR (cm^{-1}, KBr): 3359 (NH); HRMS (FAB): calcd. for $C_{21}H_{26}N_2O_4$. 370.189258, found 370.189177.
   7: mp 166.5-168.5℃. ^{1}H NMR (300MHz, $CDCl_3$) δ ppm 2.55 (d, 1H, J=15Hz, CH$\underline{CH_2}$), 2.67-3.40 (m, 4H, CH_2CH_2N), 3.67 (dd, 1H, J=10.8Hz, 15Hz, CH$\underline{CH_2}$), 3.75 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.02 (d, 1H, J=13.5Hz, NCH_2N), 4.09 (d, 1H, J=10.8Hz, $\underline{CH}CH_2$), 5.72 (d, 1H, J=13.5Hz, NCH_2N), 6.59 (s, 2H, Ar-H), 6.80 (d, 1H, J = 8.4Hz, Ar-H), 7.01 (d, 1H, J = 8.4Hz, Ar-H), 8.33 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): 28.55 (t, CH_2), 39.84 (t, CH_2), 41.86 (t, CH_2), 55.76 (q, OCH_3), 56.08 (q, OCH_3), 56.16 (q, OCH_3), 59.36 (d, CH), 60.97 (q, OCH_3), 64.53 (t, CH_2), 110.23 (d, Ar-CH), 110.82 (d, Ar-CH), 111.19 (d, Ar-CH), 124.96 (d, Ar-CH), 126.16 (s, Ar-C), 130.10 (s, Ar-C), 130.90 (s, Ar-C), 135.98 (s, Ar-C), 143.82 (s, Ar-C), 147.28 (s, Ar-C), 147.90 (s, Ar-C), 152.04 (s, Ar-C), 164.09 (CHO); FAB-MS(*m/z*): 399.4 (M+1, base), 397.4 (M-1), 383.4 (M-CH_3), 369.4 (M-CHO), 367.4 (M-CH_2OH), 205.2, 192.2, 178.2, 93.1; HRMS (FAB): calcd. for $C_{22}H_{26}N_2O_5$ 398.184173, found 398.182222.
5. L. L. Martin, R. C. Allen, U. S. Patent 4,908,361, **1990**.

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