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Synthesis of 3, 7-Disubstituted 1, 4-Benzodiazepin-2-one

Sheng Biao WAN, Zong Ru GUO*

Department of Medicinal Chemistry, Institute of Materia Medica,
Chinese Academy of Medical Science & Peking Union Medical College, Bejing 100050

Abstract: A series of 3-methoxycarbonylpropoxy-7-(imidazol-4-ylpropinamide)-1, 3-dihydrogen-1-methyl-5-phenyl-2*H*-1, 4-benzodiazepin-2-ones, as farnesyltransferase(Ftase) inhibitors, were synthesized. The preparation of the key intermediate, 7-amino-3-methoxycabonylpropoxy-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one, was improved.

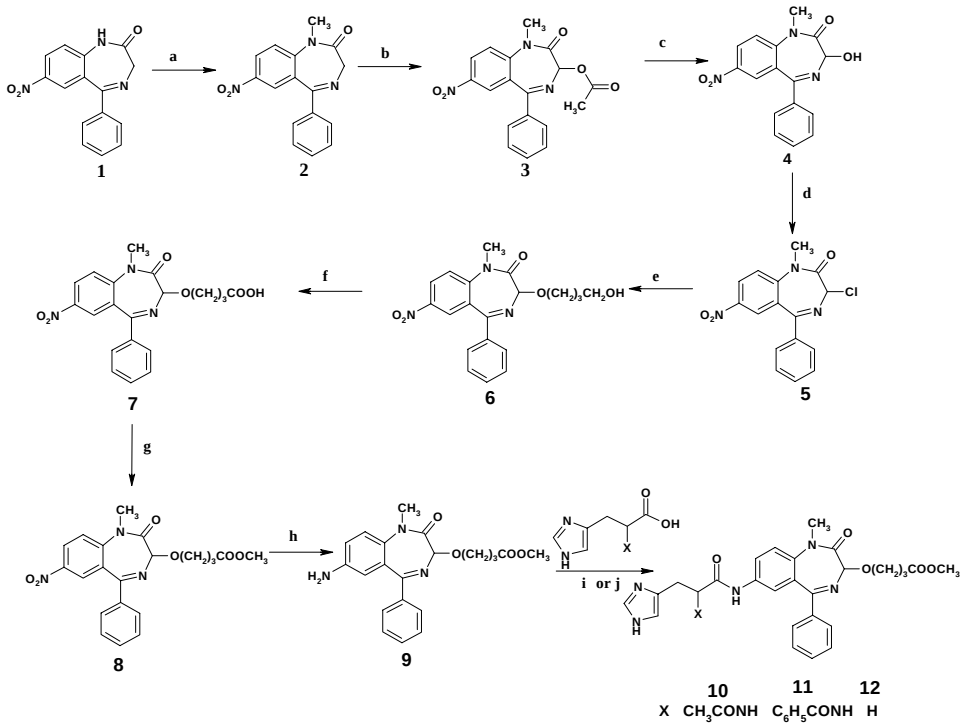
Keywords: Benzodiazepine, farnesyltransferase.

Benzodiazepines were considered as privileged structure in intelligent drug design and synthesis[1]. One of the advantadges is that various substituents can be linked at the positions of 1, 3, 4, and 7 respectively. The 1, 3-dihydrogen-1-methyl-5- phenyl-2*H*-1, 4-benzodiazepin-2-one, substituted by imidazole-containing groups at C-7 and carboxylate-containing groups at C-3[2], were designed and synthesized as novel FTase inhibitors[3-4]. The synthetic route was shown in **Scheme 1**. The analogues of 3-methoxycarbonylpropoxy-1, 4-benzodiazepin-2-one **8** has been prepared by Bell and coworkers[5] but in low yields. The improved preparation method of analogues of 3-carboxylpropoxy-1, 4-ben-zodiazepin-2-one **7** was also described in the literature[2]. We used the improved preparation method and found that the intermediates **7** and **8** are sensitive to acid under high temperature.

Methylation of nitrazepam[6] **1** with methyl sulfate gave methyl substituted compound **2** which was treated by $Pb(AcO)_4$ in glacial acetic acid to afford acetoxy-derivative **3**. **3** was hydrolyzed[7] to hydroxyl compound **4**. Reaction of **4** with thionyl chloride gave the 3-chloro compound **5** quantitatively as a pale yellow solid which slowly hydrolyzed back to **1** in exposure to moisture. The chloro-compound **5** was added slowly into excess 1, 4-dibutanol with vigorous stirring at room temperature, the resulting precipitate was collected and washed with water to afford exclusively the product **6**.

Oxidation of **6** with Jones regent furnished the acid **7**. **7** was activated by DCC and reacted with methanol at room temperature to give the ester **8**. Using the traditional method of esterification (MeOH, TsOH in benzene, reflux), however, we failed to obtain the methyl ester of **8** but 3-methoxy compounds **13** (**Figure 1**). This is probably due to substitution of 3-caboxylpropoxy group by methoxy group in the present of the acid.

Scheme 1

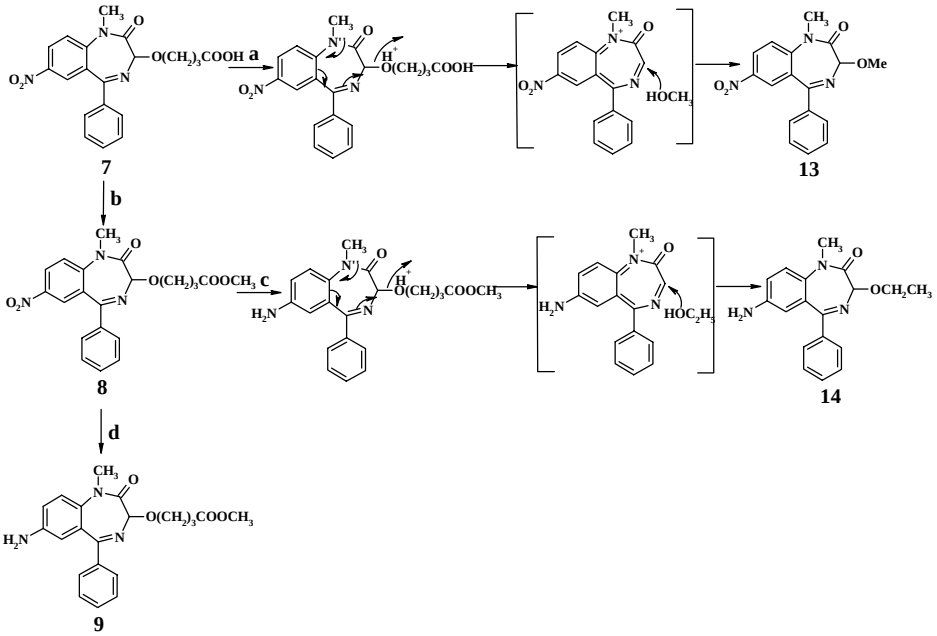


a) $(CH_3)_2SO_4/K_2CO_3$, 50℃; b) $(CH_3CO)_2O/PdAcO_4/I_2$, 105℃; c) $NaOCH_3$, RT; d) $SOCl_2$, 0℃ 1h then RT 2h; e) $HOCH_2CH_2CH_2CH_2OH$, RT; f) CrO_3/H_2SO_4, 0℃; g) CH_3OH/DCC, 0℃ 2h then RT overnight; h) $SnCl_2$/ Dioxane/CH_2Cl_2, RT; i) DCC/HOBt, 0℃ 2h then RT overnight; j) NEt_3/DMF/CH_2Cl_2, RT.

The ester **8** was reduced by stannous chloride in dioxane and methylene dichloride to give amine **9** at room temperature. If the reduction was conducted in ethanol at 70°C[8], it gave the by-product **14**. The mechanism was assumed to be similar to the formation of **13** (**Figure 1**). The compound **9** was coupled with imidazole compounds[9-10] to afford three target compounds.

The structures of compound **4**, **9**, **13** and **14** were identified by ^{1}HNMR and EI-MS, the structure of the three target compounds **10**, **11** and **12** were identified by ^{1}HNMR HR-MS[11].

Figure 1 Presumable mechanisms of production **13** and **14**



a) CH_3OH/benzene/ p-toluenesulfonic acid; b) CH_3OH/DCC, 0°C 2h then RT overnight; c) $SnCl_2{\cdot}2H_2O$/95% C_2H_5OH, RT, 70°C; d) $SnCl_2{\cdot}2H_2O$/Dioxane/CH_2Cl_2, RT;

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11. Data of the synthetic compounds:
    4: mp 179-181°C; EI-MS(*m/z*) 311(M^+); ^{1}HNMR (300MHz, $CDCl_3$, δppm) 3.57(s, 3 H, CH_3), 4.97(s, 1H, CH), 7.42-7.62(m, 6H, Ar-H) , 8.43-8.46(m, 2H, Ar-H).
    9: mp 172-174°C; EI-MS(*m/z*) 381(M^+); ^{1}HNMR (300MHz, $CDCl_3$, δppm) 1.35-1.40(m, 1H, CH_2), 2.03-2.17(m, 2H, CH_2), 2.56-2.61(m, 1H, CH_2), 3.35(s, 3H, CH_3), 3.66(s, 3H, CH_3), 3.69-3.76(m, 1H, CH_2), 3.85-3.93(m, 1H, CH_2), 4.795(s, 1H, CH), 6.64-7.71(m, 8H, Ar-H).
    10: mp 163-165°C; EI-HRMS:(M^+) Calcd. 560.2383, Found. 560.2384; ^{1}HNMR (300MHz DMSO-d_6, δppm) 1.79 (s, 3H, CH_3), 1.79-1.88(m, 2H, CH_2), 2.41-2.49(m, 2H, CH_2), 2.71-2.92(m, 2H, CH_2), 3.30(s, 3H, CH_3), 3.49-3.58(m, 1H, CH_2-A), 3.58(s, 3H, CH_3), 3.67-3.75 (m, 1H, CH_2-B), 4.48-4.55 (m, 1H, CH), 4.71(s, 1H, CH), 6.76(s, 1H, Im-H), 7.43-7.97(m, 9H, Ar-H), 8.12-8.15(d, 1H, NH), 10.26-10.27(d, J=13Hz, 1H, NH).
12. mp 132-134°C; EI-HRMS:(M^+) Calcd. 622.2500, Found. 622.2513; ^{1}HNMR (300MHz DMSO-d_6, δppm) 1.83-1.90(m, 2H, CH_2), 2.43-2.51(m, 2H, CH_2), 3.01-3.03 (m, 2H, CH_2),

3.30(s, 3H, CH_3), 3.51-3.56(m, 1H, CH_2-A), 3.69-3.76(m, 1H, CH_2-B), 3.59(s, 3H, CH_3), 4.71-4.76(m, 2H, 2H), 6.85(s, 1H, Im-H), 7.43-8.01(m, 14H, Ar-H), 8.71-8.73(d, 1H, NH), 10.358(s, 1H, NH).

13. mp 109-111°C; EI-HRMS:(M^+) Calcd. 503.2182, Found. 503.2184; ^{1}HNMR (300MHz DMSO-d_6, δppm) 1.95-1.88 (m, 2H, CH_2), 2.42-2.48(m, 2H, CH_2), 2.49-2.57(m, 2H, CH_2), 2.72-2.77 (m, 2H, CH_2), 3.28(s, 3H, CH_3), 3.58(s, 3H, CH_3), 3.50-3.58 (m, 1H, CH_2-A), 3.68-3.77 (m, 1H, CH_2-B), 4.71(s, 1H, CH), 6.70(s, 1H, Im-H), 7.43-7.91(m, 9H, Ar-H), 10.143(b, 1H, NH).

14. mp 160-162°C; EI-MS(*m/z*) 325(M^+); ^{1}HNMR (300MHz, $CDCl_3$, δppm) 3.51 (s, 3H, CH_3), 4.66(s, 1H, CH), 3.64(s, 3H, CH_3), 7.41-8.45 (m, 8H, Ar-H).
14: mp 262-264°C; EI-MS(*m/z*) 309(M^+); ^{1}HNMR (300MHz, $CDCl_3$, δppm) 1.35-1.40(t, J=8.0, 3H, CH_3), 3.36(s, 3H, CH_3), 3.67-3.77 (m, 1H, CH_2-A), 3.85-3.93(m, 1H, CH_2-B), 4.81(s, 1H, CH), 6.59-7.720 (m, 8H, Ar-H).

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