Synthesis of 2-Substituted Hexahydro-1*H*-1,4-diazepine Analogues

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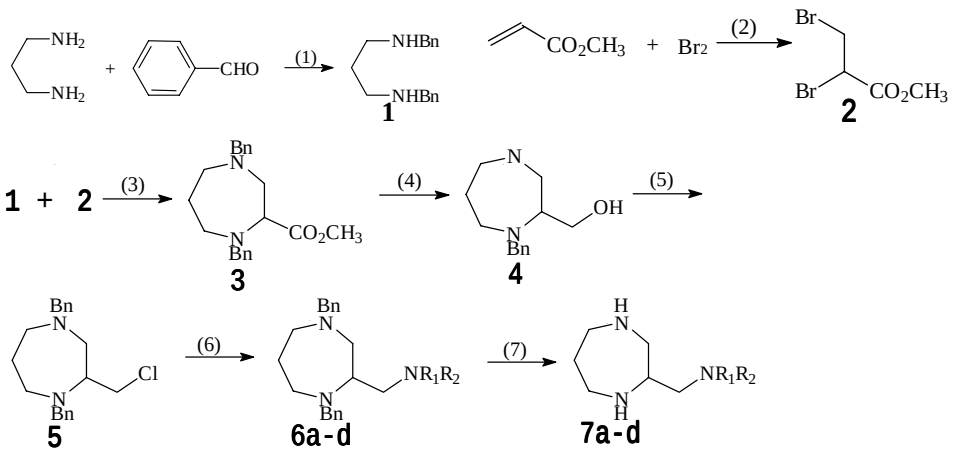
Abstract: 2-substituted hexahydro-1*H*-1,4-diazepine analogues were synthesized starting from N,N'-dibenzyl-1,3-propylene diamine and methyl-2,3-dibromo propionate through nucleophilic substitution, reduction, chlorination and debenzylation.

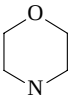
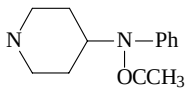
Keyords: Hexahydro-1*H*-1,4-diazepine analogues, synthesis, nucleophilic substitution, reduction, chlorination , debenzylation.

Opioids have attracted increasing research interest, primarily because of their powerful pain relieving properties and their potential for recreational abuse[1,2]. In order to get some selective κ -opioid receptor agonists, which can elicit analgesia while lacking serious side effects, a series of hexahydro-1*H*-1,4-diazepine analogues carrying the segment of (1-arylacetamide-2-tertiaryamine) ethane have been synthesized in our laboratory. The κ -opioid receptor antagonistic activity[3]of these compounds are now being tested. In the process of preparing these molecules, we devised the basic structures of 2-substituted hexahydro-1*H*-1,4-diazepine[4]. Herein, we report the synthesis of these novel compounds and the synthetic route is shown in the scheme below.

Scheme



Reagents and conditions: (1) Cat. p TS, CH_3OH; then KBH_4; (2) Br_2, CH_2Cl_2; (3) $PhCH_3$, NEt_3; (4) $LiAlH_4$, THF; (5) $SOCl_2$, $CHCl_3$; (6) HNR_1R_2, CH_3CN; (7) H_2, Pd-C, CH_3OH.

NR_1R_2= a  b  c  d 

Compounds **1** and **2** (yield, 81.2 and 95%) were prepared according to the literatures[5,6] as starting materials. The mixture of **1** and **2** in toluene solution was stirred at room temperature for 5 hrs then at 50-60℃ for 2 hrs in the presence of triethylamine. The extracted mixture was purified *via* silica gel with ethyl acetate-petroleum ether (7:1) as eluent to give yellow oil **3**, 1,4-dibenzyl-2-methoxycarbonyl hexahydro-1,4-diazepine, in yield 55.1%.

The reduction of compound **3** was carried out in THF *via* the addition of $LiAlH_4$ at 0°C. Then the mixture was stirred at room temperature for 8 hrs and the resulting mixture was separated *via* silica gel with ethyl acetate-petroleum ether (5:1 then 2:1) as eluent to give yellow liquid **4** (yield, 93.0%), 1,4-dibenzyl-2-hydroxymethyl hexahydro-1,4-diazepine.

Thionyl chloride was added into the chloroform solution of **4** (satured by dry HCl previously)and the mixture was stirred for 2 hrs at 50℃, the compound **5**, 1,4-dibenzyl-2-chloromethyl hexahydro-1,4-diazepine, was given in yield 81.2%. Under nitrogen atmosphere, compound **5** reacted with pyrrolidine, piperidine, morpholine and 4-(N-phenyl-N-acetyl)-amino piperidine respectively in acetonitrile in the presence of K_2CO_3 at 60℃ for 18 hrs. The extracted mixtures were isolated *via* silica gel with petroleum ether-ethyl acetate-methanol (1:1:0.1) as eluent to give **6a-d**, which were then catalyzed by Pd-C in water-methanol solution at 40-50℃ for 8 hrs. Finally the target compounds of **7a-d**[**7a** 2-(1-pyrrolidinyl)-methyl hexahydro-1*H*-1,4-diazepine; **7b** 2-(1-piperidyl)-hexahydro-1*H*-1,4-diazepine; **7c** 2-(1-morpholinyl)-hexahydro-1*H*-1,4-diazepine; **7d** 2-(1-(4-(N-phenyl-N-acetyl)amino)piperidyl)-hexahydro-1*H*-1,4-diazepine] were achieved through debenzylation of **6a-d**.

All products were characterized by NMR，EIMS, IR and elemental analysis[7].

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7. The spectral and analytical data of **7a-d** have been submitted to editoral department of CCL.

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