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Parallel synthesis of 4,5-dihydro-1*H*-1,4-benzodiazepine-2,3-diones

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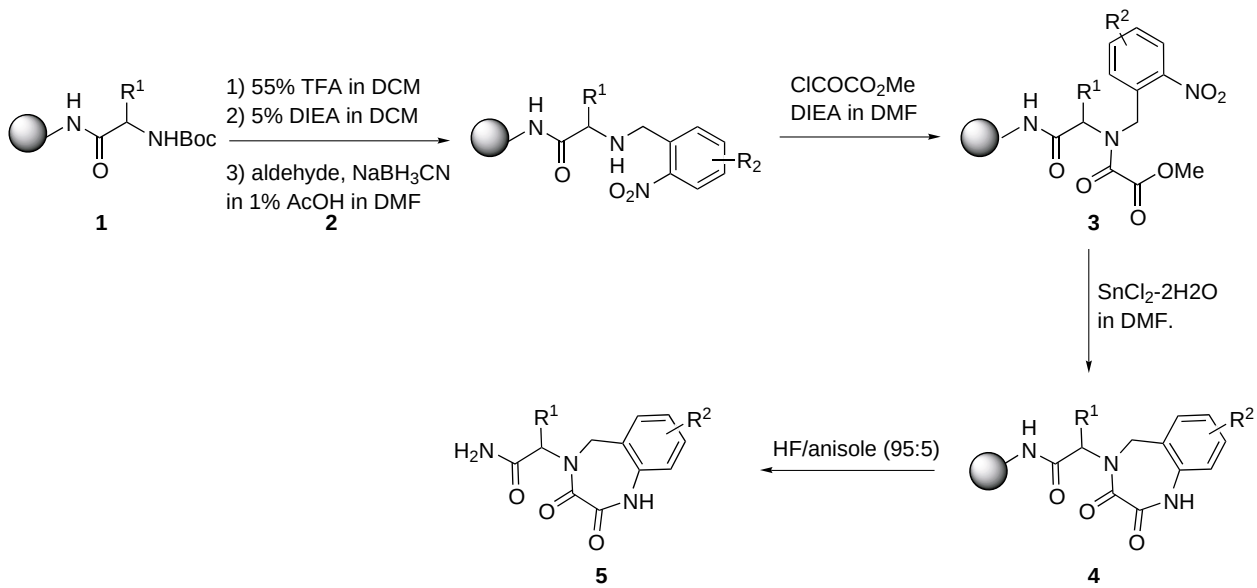
Abstract—An efficient strategy for the parallel solid-phase synthesis of 4,5-dihydro-1*H*-1,4-benzodiazepine-2,3-diones is described. The reductive alkylation of resin-bound primary amine with different substituted *o*-nitrobenzaldehydes generated a secondary amine, which was treated further with methyl chlorooxoacetate. The nitro group was reduced with tin(II) chloride. During the overnight reduction, an in situ intramolecular cyclization occurred to provide, following HF cleavage, the desired 4,5-dihydro-1*H*-1,4-benzodiazepine-2,3-dione.

Benzodiazepine derivatives are an important group of therapeutic agents.[1] One of the most interesting aspects of the benzodiazepine is their striking anticonvulsant properties in a variety of experimental models of epilepsy.[2] All known 1,4-benzodiazepines have the same profile of broad pharmacological activity, including antianxiety, sedative/hypnotic, anticonvulsant, muscle-relaxing actions and tranquilizing properties.[3] The benzodiazepines are also well absorbed following oral administration.[4] Many benzodiazepine drugs bind extensively to plasma and tissue proteins. The use of benzodiazepines in therapeutic applications has increased exponentially over the last 20 years. Benzodiazepines are now the most commonly prescribed group of drugs.



Scheme 1. Synthesis of 4,5-dihydro-1*H*-1,4-benzodiazepine-2,3-diones.

Keywords: parallel synthesis; solid-phase synthesis; benzodiazepine-2,3-diones.

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Many papers have been published describing the synthesis of benzodiazepine derivatives. Most of the papers focused on the synthesis of the 1,4-benzodiazepine-2-ones and 1,4-benzodiazepine-2,5-diones.[5] Herein, we describe an efficient approach for the solid-phase synthesis of a new class of benzodiazepine derivatives, the benzodiazepine-2,3-diones.

The parallel synthesis of 4,5-dihydro-1*H*-1,4-benzodiazepine-2,3-diones **5** (Scheme 1) was carried out on the solid-phase using the 'tea-bag' methodology.[6] Starting from *p*-methylbenzhydrylamine (MBHA) resin-bound *N*-terbutyloxycarbonyl (Boc) amino acid **1**, the Boc group was removed using 55% trifluoroacetic acid (TFA) in dichloromethane (DCM). Following neutralization, the free amine was reductively alkylated with different commercially-available substituted *o*-nitrobenzaldehydes in the presence of sodium cyanoborohydride in an acidic solution of dimethylformamide (DMF).[7] The generated secondary amine **2** was then treated with methyl chlorooxoacetate in DMF in the presence of diisopropylethylamine (DIEA) to provide the corresponding resin-bound methyl aminooxoacetate **3**. The nitro group was reduced in the presence of tin chloride ($SnCl_2$–$2H_2O$) in DMF.[8] To verify the completion of reduction of the nitro group, samples of resin controls were cleaved and the crude products were analyzed by LC–MS. As expected, in most cases, an in situ intramolecular cyclization occurred during the overnight nitro reduction allowing the formation of the desired resin bound seven member ring benzodiazepine **4**. The cyclization was complete for most cases and a small quantity of non-cyclized product was observed with some compounds. We decided to cleave all resins,

Table 1. Examples of 4,5-dihydro-1*H*-1,4-benzodiazepine-2,3-diones synthesized. The products were run on a Vydac column, gradient 5–95% of 0.05% TFA in ACN in 7 min. The purity was estimated on analytical traces at 214 nm. In all cases, the crude yields were higher than 80% relative to the initial loading of the resin

Compound #	R_1	R_2	MW (expected)	MW (found)	Purity (%)
$\mathbf{5_1}$	(*S*)-CH_3	H	247.1	247.6 (MH^+)	83
$\mathbf{5_2}$	(*S*)-CH_2Ph	H	323.1	323.8 (MH^+)	75
$\mathbf{5_3}$	H	9-OMe	263.1	263.6 (MH^+)	72
$\mathbf{5_4}$	H	7-Cl	267.0	267.6 (MH^+)	85
$\mathbf{5_5}$	(*S*)-$CH(CH_3)$Et	7-Cl	323.1	323.7 (MH^+)	82
$\mathbf{5_6}$	(*S*)-$CH(CH_3)$Et	6-Cl	323.1	323.7 (MH^+)	75
$\mathbf{5_7}$	(*S*)-$CH(CH_3)$Et	H	289.1	289.6 (MH^+)	87
$\mathbf{5_8}$	(*S*)-$(CH_2)_4$-NH_2	7-Cl	338.1	338.9 (MH^+)	91
$\mathbf{5_9}$	(*S*)-$CH_2CH(CH_3)_2$	7-Cl	323.1	323.7 (MH^+)	86
$\mathbf{5_{10}}$	(*S*)-$CH_2CH(CH_3)_2$	H	289.1	289.7 (MH^+)	83
$\mathbf{5_{11}}$	(*S*)-$CH(CH_3)_2$	7-Cl	309.1	309.1 (MH^+)	72
$\mathbf{5_{12}}$	(*S*)-$CH(CH_3)_2$	6-Cl	309.1	309.1 (MH^+)	78
$\mathbf{5_{13}}$	(*S*)-*p*-Hydroxybenzyl	7-Cl	373.7	374.5 (MH^+)	77
$\mathbf{5_{14}}$	(*R*)-CH_3	7-Cl	281.0	281.5 (MH^+)	76
$\mathbf{5_{15}}$	(*R*)-CH_3	H	247.1	247.6 (MH^+)	80
$\mathbf{5_{16}}$	(*R*)-CH_2Ph	6-Cl	357.1	357.9 (MH^+)	65
$\mathbf{5_{17}}$	(*R*)-$CH_2(CH_3)$Et	7-Cl	323.1	323.7 (MH^+)	81
$\mathbf{5_{18}}$	(*R*)-$CH(CH_3)_2$	H	289.1	289.7 (MH^+)	79
$\mathbf{5_{19}}$	(*R*)-$CH(CH_3)_2$	7-Cl	309.1	309.6 (MH^+)	87
$\mathbf{5_{20}}$	(*R*)-$CH(CH_3)_2$	6-Cl	309.1	309.7 (MH^+)	83
$\mathbf{5_{21}}$	(*R*)-$CH(CH_3)_2$	H	275.1	275.6 (MH^+)	92
$\mathbf{5_{22}}$	(*R*)-*p*-Hydroxybenzyl	7-Cl	373.7	342.8 (MH^+)	65
$\mathbf{5_{23}}$	(*R*)-*p*-Hydroxybenzyl	H	339.1	340.7 (MH^+)	77
$\mathbf{5_{24}}$	(*S*)-CH_2CH_3	7-Cl	295.7	296.5 (MH^+)	73
$\mathbf{5_{25}}$	(*S*)-CH_2CH_3	H	261.2	261.6 (MH^+)	79
$\mathbf{5_{26}}$	(*S*)-$CH_2CH_2CH_3$	7-Cl	309.7	310.6 (MH^+)	75
$\mathbf{5_{27}}$	(*S*)-$CH_2CH_2CH_3$	H	275.3	275.6 (MH^+)	75
$\mathbf{5_{28}}$	(*R*)-$CH_2CH_2CH_3$	7-Cl	309.7	310.6 (MH^+)	80
$\mathbf{5_{29}}$	(*S*)-$(CH_2)_3CH_3$	7-Cl	323.7	323.7 (MH^+)	73
$\mathbf{5_{30}}$	(*S*)-$(CH_2)_3CH_3$	H	289.3	289.7 (MH^+)	93
$\mathbf{5_{31}}$	(*R*)-$(CH_2)_3CH_3$	7-Cl	323.7	324.7 (MH^+)	78
$\mathbf{5_{32}}$	(*R*)-$(CH_2)_3CH_3$	H	289.3	289.7 (MH^+)	79
$\mathbf{5_{33}}$	(*S*)-$(CH_2)_3$-NH_2	7-Cl	324.7	324.8 (MH^+)	69
$\mathbf{5_{34}}$	(*S*)-$(CH_2)_3$-NH_2	6-Cl	324.7	324.9 (MH^+)	74
$\mathbf{5_{35}}$	(*S*)-Phenyl	7-Cl	343.0	343.7 (MH^+)	66
$\mathbf{5_{36}}$	(*S*)-Phenyl	H	309.1	309.8 (MH^+)	75
$\mathbf{5_{37}}$	(*R*)-Phenyl	H	309.1	309.8 (MH^+)	76
$\mathbf{5_{38}}$	(*S*)-CH_2-Cyclohexyl	7-Cl	363.1	363.5 (MH^+)	69
$\mathbf{5_{39}}$	(*S*)-CH_2-Cyclohexyl	H	329.1	329.9 (MH^+)	88
$\mathbf{5_{40}}$	(*R*)-CH_2-Cyclohexyl	7-Cl	363.1	363.7 (MH^+)	71
$\mathbf{5_{41}}$	(*R*)-CH_2-Cyclohexyl	H	329.1	329.9 (MH^+)	92

and all compounds were analyzed by LC–MS. Selected compounds were analyzed by ^{1}H NMR.[9] Using 40 amino acids (a combination of natural and non-natural amino acids) and five aldehydes, we prepared 200 individual 4,5-dihydro-1*H*-1,4-benzodiazepine-2,3-diones. As shown in Table 1, good purity ranging from 65 to 92% was obtained for all compounds. The purity was determined by RP-HPLC. Using the 6 nitro-piperonal (not included in the table), a mixture of the dihydroxybenzodiazepine and dioxolobenzodiazepine was obtained for all compounds.[10] The treatment of the mixture with a 2N hydrochloride solution drove the mixture to the dihydroxybenzodiazepine.

In summary, we have developed facile and efficient combinatorial approach for the solid-phase synthesis of different substituted 1,4-benzodiazepine-2,3-dione derivatives.[11]

Acknowledgements

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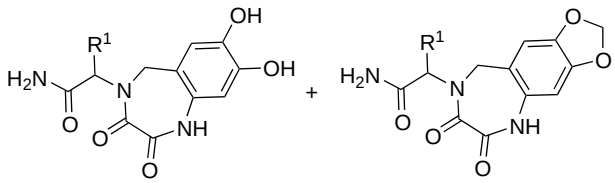
9. ^{1}H NMR of 2-(9-methoxy-2,3-dioxo-1,2,3,5-tetrahydro-4*H*-1,4-benzodiazepin-4-yl)propanamide (R^1=(*S*)-Me, R^2=9-OMe): 10.11 (s, 1H); 7.53 (s, 1H); 7.21 (s, 1H); 6.97–7.18 (m, 3H); 4.92 (m, 1H); 4.42 (s, 2H); 3.81 (s, 3H); 1.25 (d, J=7.1 Hz, 3H). ^{1}H NMR of 2-(6-chloro-2,3-dioxo-1,2,3,5-tetrahydro-4*H*-1,4-benzodiazepin-4-yl)-4-methylpentanamide (R^1=(*S*)-CH_2-$CHMe_2$, R^2=6-Cl): 11.34 (1s, 1H); 7.75 (s, 1H); 7.53–7.41 (m, 3H); 7.26 (m, 2H); 5.02 (d, J=16.7 Hz, 1H); 4.47 (d, J=16.4 Hz, 1H); 1.82 (m, 1H); 1.58 (m, 1H); 0.71(d, J=5.5 Hz, 3H); 0.56 (d, J=4 Hz, 3H).
10. 
11. General procedure for the solid-phase synthesis of individual 4,5-dihydro-1*H*-1,4-benzodiazepine-2,3-dione **5**. 50 mg of *p*-methylbenzhydrylamine (MBHA) (substitution: 1.1 mmol/g) was contained in a polypropylene mesh packet. Following neutralization with a solution of 5% diisopropylethylamine (DIEA) in dichloromethane (DCM), the resin was washed with DCM. The first Boc amino acid (6 equiv., 0.1 M) was coupled in the presence of diisopropylcarbodiimide (DICI) (6 equiv., 0.1 M) and hydroxybenzotriazole (HOBt) (6 equiv., 0.1 M) in dimethylformamide (DMF). Upon removal of the Boc group with 55% trifluoroacetic acid (TFA) in DCM (30 min), the resin was washed, neutralized with a solution 5% DIEA in DCM and washed three times with DCM. Prior to the reductive alkylation, the packet was washed with a 2% solution of acetic acid in anhydrous DMF. The resin-bound amino acid was treated with substituted *o*-nitrobenzaldehydes (10 equiv., 0.1 M) in a solution of DCM/MeOH/trimethylorthoformate (TMOF)/AcOH (74:20:5:1) followed by an in situ addition of sodium cyanoborohydride (10 equiv.) predissolved in anhydrous DMF. The generated secondary amine was then treated with methyl chlorooxoacetate (5 equiv., 0.1 M) in anhydrous DMF in the presence of diisopropylethylamine (10 equiv.) overnight. The resin was washed with DMF (6×) and DCM (4×). The nitro group was reduced in the presence of tin chloride ($SnCl_2$–$2H_2O$) (2 M) in anhydrous DMF overnight. Following washing with DMF (10×), DCM (2×) and isopropanol (2×), a sample of the resin was cleaved and the crude product was analyzed by LC–MS. As expected, an in situ intramolecular cyclization occurred during the overnight nitro reduction allowing the formation of the desired resin bound seven-membered ring benzodiazepine. Following cleavage of the resin with HF/anisole (95:5), the desired product was extracted with acetic acid/water (95:5), and lyophilized. The product was characterized by LC–MS.