Synthesis of a Substituted Benzazepin-2-one Dihydrate

Sathish K. Boini,* Radhe K. Vaid, Kenneth P. Moder, David Mitchell

Chemical Product Research and Development, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA
Fax +1(317)2764507; E-mail: s.boini@lilly.com

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Abstract: Synthesis of the title compound was accomplished via coupling of (*S*)-alaninyl-(*S*)-1-amino-3-methyl-4,5,6,7-tetrahydro-2*H*-3-benzazepin-2-one with the activated trimethylsilyl ester of (*S*)-2-trimethylsilyloxy-3-methylbutyric acid, followed by deprotection and crystallization in situ. The starting material was prepared by the condensation of (*S*)-1-amino-3-methyl-4,5,6,7-tetrahydro-2*H*-3-benzazepin-2-one with activated *N*-(2-methoxycarbonyl-1-methylvinyl)-(*S*)-alanine sodium salt in the form of the mixed carboxylic carbonic anhydride, followed by enamine hydrolysis using methanesulfonic acid.

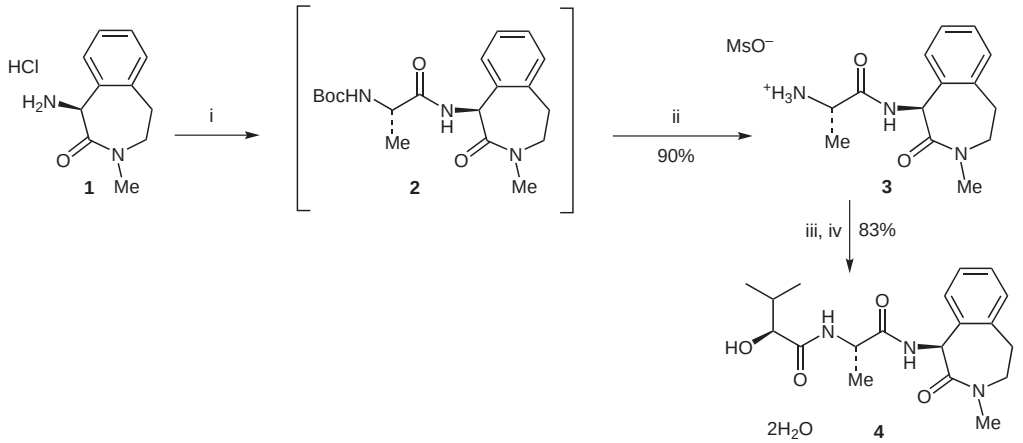
Key words: trimethylsilyl, (*S*)-2-hydroxy-3-methylbutyric acid, mixed anhydride, Dane salt

The title compound (**4**) is being developed for inhibition of β-amyloid peptide release as a method for treating Alzheimer's disease.[1] The enabling synthesis of **4**, shown in Scheme 1, involved two peptide coupling reactions to form intermediate **3** and the target compound **4** using *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) as a coupling agent, in the presence of 1-hydroxy benzotriazole (HOBT), followed by crystallization.[1] This process involved various solvent exchanges, pH adjustment and multiple extractions.

We were interested in developing a more streamlined, cost-effective and environmentally friendly process for the synthesis of **4**. This manuscript details an alternate synthesis of the title compound.

A survey of the literature revealed that activation of *N*-(2-methoxycarbonyl-1-methylvinyl)-(*S*)-alanine sodium salt can be accomplished using a variety of reagents such as chloroformates.[2] The synthesis of **4** requires the penultimate intermediate **3**, the potential route to which might involve the use of *N*-(2-methoxycarbonyl-1-methylvinyl)-(*S*)-alanine sodium salt (**6**) – the Dane salt of (*S*)-alanine – instead of *N*-Boc-(*S*)-alanine. The enamine moiety of the Dane salt can be easily removed under mild acidic aqueous conditions to unmask the amine functionality. Thus, compound **6** was prepared from readily available and inexpensive starting materials: methyl acetoacetate, (*S*)-alanine and sodium hydroxide, in methanol solvent, following a literature procedure.[2]

Based on our recent work,[3] we demonstrated the straightforward synthesis of **3** via activation of **6** as its mixed carboxylic-carbonic anhydride **7** in DMF at –48 °C, followed by coupling with free amine **5**, generated in-situ from **1**. Workup and hydrolysis of enamine **8** using aqueous methanesulfonic acid and product isolation, gave **3** in 93% yield from **1** with a chiral purity of 99.5% (Scheme 2). After the successful synthesis of **3**, we focused our efforts on finding an alternate coupling approach to the synthesis of **4**. The first synthetic approach incorporated mixed anhydride formation (for activation towards acylation) and simultaneous protection of the α-hydroxy group of **9** as a carbonate or ester (Scheme 3).



Scheme 1 Enabling synthesis of **4**. *Reagents and conditions*: (i) Boc-(*S*)-alanine, EDC, HOBT, CH_2Cl_2; (ii) $MeSO_3H$, CH_2Cl_2–MTBE; (iii) (*S*)-2-hydroxy-3-methylbutyric acid, EDC, HOBT, CH_2Cl_2; (iv) acetone–H_2O.

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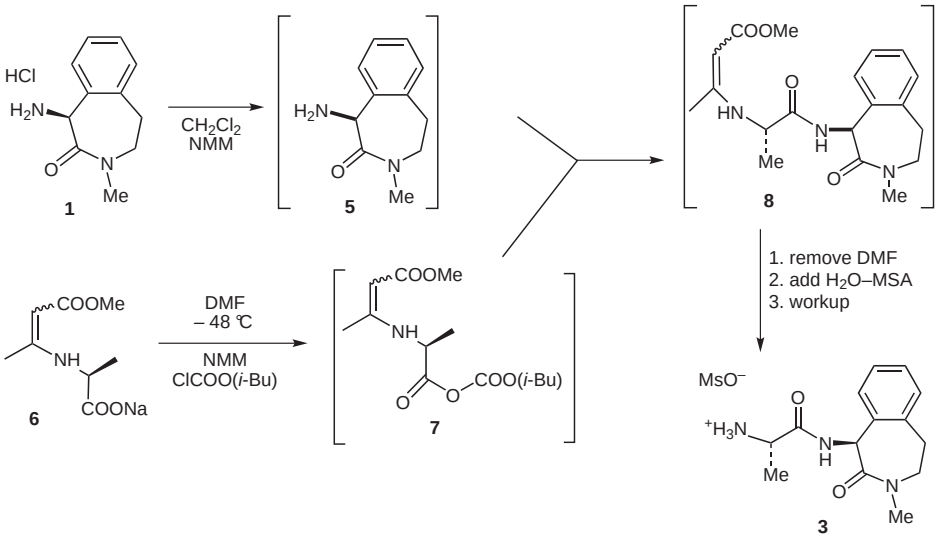
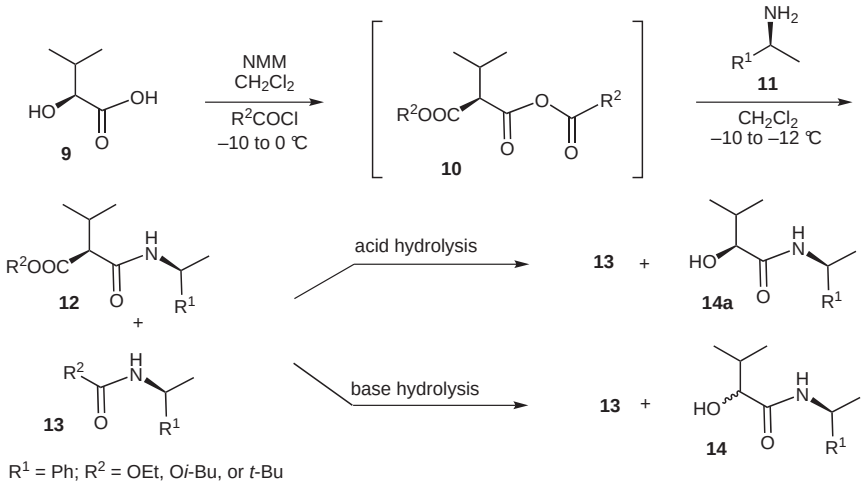


Scheme 2 Synthesis of **3** via mixed carboxylic-carbonic anhydride activation of the Dane salt



Scheme 3

(*S*)-α-Methylbenzylamine (**11**) was chosen as a model amine. Several chloroformates were examined, such as, ethyl chloroformate and isobutyl chloroformate. However, the anticipated problem with this route was the potential competition for the amine between the carbonyl groups in **10** and the carbonate functionality. The products of the acylation reactions were thus examined by HPLC in order to determine the ratio of **12** to **13** (Table 1).

Table 1 Impact of Acid Activating Agent on Product Formation[a]

Amine	Acid activating agent	Ratio (product/by-product)
11	$ClCO_2Et$	5:1
11	$ClCO_2$(*i*-Bu)	5:1
11	*t*-BuCOCl	16:1
3a	*t*-BuCOCl	1:1
3a	$ClCO_2Et$	3:2

[a] Reaction performed in CH_2Cl_2.

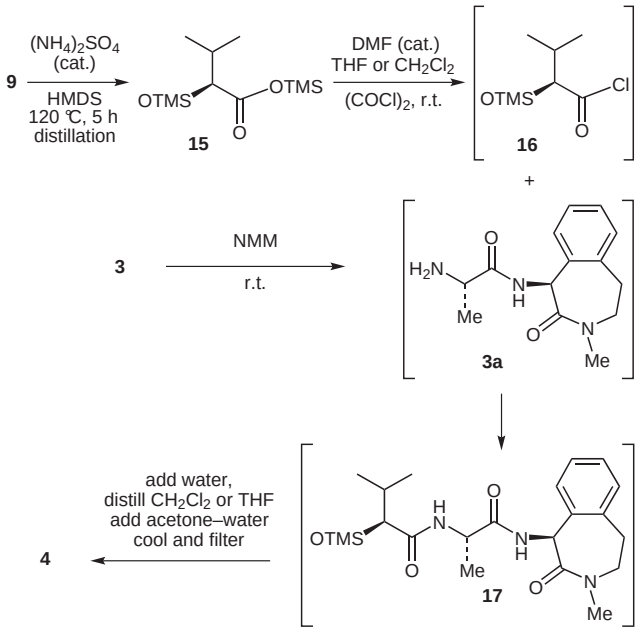
We planned to deprotect the carbonate or ester functionality via acid or base hydrolysis. However, treatment of a mixture of **12** and **13** with methanolic potassium carbonate lead to epimerization and formation of **14**, as indicated by the resonances in the proton spectrum resulting from the methyl group of the α-methyl benzyl moiety. Hydrolysis of the same mixture under acidic conditions (HCl or H_2SO_4) provided a mixture of **14a** and **13**. As the best result for acylation of **11** was obtained using pivaloyl chloride (*t*-BuCOCl), amine **3a** was subjected to acylation under the same conditions. However, since analysis of the reaction mixture indicated a product to by-product ratio of 1:1, indicating poor selectivity in acylation of **3a**, this approach was not further investigated.

Another classical acylation strategy was to convert **9** into the (*S*)-2-trimethylsilyloxy-3-methylbutyric acid silyl ester (**15**), followed by its conversion into the corresponding acid chloride (**16**) using oxalyl chloride, as previously demonstrated in the literature,[4] followed by coupling with **3a**. This approach was superior to the carbonate route

since silyl protection of the alcohol moiety would not predispose this site to side reactions.

Compound **9** was converted into its corresponding bis-trimethylsilyloxy-protected derivative **15** by heating in the presence of hexamethyldisilazane (HMDS) and catalytic ammonium sulfate, followed by distillation. Conversion of **15** with oxalyl chloride in the presence of catalytic *N*,*N*-dimethylformamide, in either dichloromethane or tetrahydrofuran, resulted in the formation of acid chloride **16**. Coupling of **3a** with **16** led to the formation of intermediate **17**, which was converted into **4** by hydrolysis in situ. Since compound **4** can be crystallized from acetone–water, the solvent was exchanged with acetone after the acylation reaction and before deprotection. Finally, compound **4** was crystallized in 82% yield from the acetone solvent by addition of water.

In conclusion, a streamlined, cost-effective and environmentally friendly process for the synthesis of **4** has been developed, as shown in Scheme 4.



Scheme 4 Alternate synthesis of **4** using TMS protection

HMDS, methyl acetoacetate, $ClCO_2$(*i*-Bu), (*S*)-alanine, Boc-(*S*)-alanine, (*S*)-2-hydroxy-3-methybutyric acid, EDC, HOBT, *N*-methylmorpholine (NMM), methanesulfonic acid (MsOH), DMF, THF, CH_2Cl_2 and NaOH pellets were all used as received from commercial suppliers without purification.

^{1}H NMR spectra were recorded on a 300 MHz Bruker Avance spectrometer. Chemical shifts (d) are reported in ppm downfield from TMS. HPLC analysis was performed using an Agilent HPLC 1100 series instrument. Melting points were measured on Buchi R-535 apparatus and are uncorrected. HRMS were recorded using a Waters LCT instrument with electrospray ionization. IR spectra were recorded using a Nicolet Magna 550-FTIR spectrophotometer.

Preparation of Mixed Anhydride 7

To a 100 mL 3-necked round-bottomed flask fitted with a mechanical stirrer and temperature probe, was added the Dane salt of (*S*)-alanine (**6**; 2.29 g, 0.0110 M) and DMF (13 mL, 5.68 vol). The slurry was stirred for 20–25 min at r.t. under a nitrogen atmosphere to obtain a clear solution, then cooled to between –48 °C and –50 °C. NMM (0.03 mL, 0.0003 M) and $ClCO_2$(*i*-Bu) (1.40 mL, 0.0107 M) were added sequentially, while maintaining the temperature at –48 °C during addition [$ClCO_2$(*i*-Bu) addition caused an exothermic reaction]. The reaction was stirred at –48 °C for an additional 30 min then used immediately as described below.

Preparation of Free Amine 5

To a 25 mL round-bottomed flask equipped with a thermocouple and magnetic bar, was added **1** (2.26 g, 0.01 M) and CH_2Cl_2 (10 mL). The contents were stirred for 10 min and then cooled to –10 °C, NMM (1.01 g, 0.01 M) was added and the reaction was stirred for 10 min and then cooled to –20 °C.

Preparation of Enamine 8

The free base slurry of **5** (prepared as described above) at –48 °C, was added to a pre-cooled solution of the mixed anhydride **7** at –48 °C as soon as possible. CH_2Cl_2 (4 mL) was used to rinse the flask. The reaction temperature rose to –39 °C. The temperature of the reaction mixture was allowed to slowly rise to r.t. over 4.5 h to give a thick slurry. CH_2Cl_2 was removed at atmospheric pressure using a rotary evaporator and then DMF was removed under vacuum. CH_2Cl_2 (40 mL) and H_2O (30 mL) were added to the reaction mixture and the contents were stirred at r.t. to dissolve the solids. The organic layer was taken and concentrated to obtain a white solid, which was suspended in acetone (9.5 mL), filtered and dried in a vacuum oven.

Yield: 93%; white solid; mp 212–214 °C.

IR (KBr): 3299, 1647, 1597 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.3 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.95 (s, 3 H, CH_3), 2.93 (s, 3 H, NCH_3), 3.3–3.6 (m, 3 H, 3 × CH), 3.7 (s, 3 H, $COOCH_3$), 4.19 (m, 1 H, CH), 4.4 (s, 2 H, CH, =CH), 4.6 [m, 1 H, C*H*(CH_3)], 6.2 (d, *J* = 6.3 Hz, 1 H, CH), 7.2 (m, 4 H, ArH), 8.6 (d, *J* = 7.7 Hz, 1 H, NH), 8.8 (d, *J* = 7.7 Hz, 1 H, NH).

HRMS: *m*/*z* calcd for $C_{19}H_{25}N_3O_4$: 359.4288; found: 359.4283.

Preparation of 3

The enamine **8** obtained above, was dissolved in CH_2Cl_2 (70 mL) under reflux conditions. Solvent exchange with acetone (70 mL) was performed. The reaction mixture was cooled to 12–15 °C, and MsOH (0.85g, 0.0088M) and H_2O (0.16 mL) were added. After stirring for 10 min, white solids appeared. The contents were stirred for 3–4 h then filtered and washed with acetone (18 mL). The product was dried in a vacuum oven at 50 °C.

Yield: 93.56%; white solid; mp >260 °C; chiral purity 99.5% (determined by chiral HPLC).

IR (KBr): 3274, 3077–2803, 1646 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.39 (d, *J* = 6.9 Hz, 3 H, CH_3), 2.28 (s, 3 H, OSO_2CH_3), 2.92 (s, 3 H, NCH_3), 2.91 (m, 2 H, 2 × CH), 3.81 (m, 1 H, CH), 4.23 (m, 2 H, 2 × CH), 6.21 (d, *J* = 7.9 Hz, 1 H, CH), 7.18 (m, 4 H, ArH), 8.10 (br, 3 H, $^+NH_3$), 8.94 (d, *J* = 7.7 Hz, 1 H, CONH).

HRMS: *m*/*z* calcd for $C_{14}H_{20}N_3O_2$: 262.1556; found: 262.1556.

Preparation of 15

To a 250 mL 3-necked round-bottomed flask equipped with a magnetic stir bar, condenser, thermocouple, and nitrogen purge, was added **9** (20.2 g, 0.171 M), HMDS (80 mL, 0.3836 M), and NH_4SO_4 (80 mg). Upon addition of the HMDS, the reaction mixture became a solid mass. The mass was heated to 124–126 °C whereupon the solids dissolved to form a homogeneous solution. The solution was refluxed for 6 h and then allowed to cool to r.t. Excess HMDS was

removed by vacuum distillation and the product was collected at 40–45 °C (1.4–1.8 torr).

Yield: 90%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.89 (d, *J* = 5.7 Hz, 1 H), 2.058 (m, 1 H), 0.917 (d, 1 H), 0.866 (d, *J* = 6.9 Hz, 3 H), 0.296 (s, 9 H), 0.152 (s, 9 H).

Preparation of 16

To a 250 mL 3-necked round-bottomed flask equipped with a magnetic stir bar, thermocouple, and septum, was added **15** (5.32 g, 0.0203 M), CH_2Cl_2 (21 mL), and DMF (3 drops). The solution was agitated for 5 min at r.t., then $(COCl)_2$ (1.77 mL, 0.0203 M) was added via syringe drive over 45 min at r.t. After the addition, the solution was stirred at r.t. for 2 h.

Preparation of 4

To a separate 250 mL single-necked round-bottomed flask equipped with a magnetic stir bar, was added **3** (5.58 g, 0.0156 M) and CH_2Cl_2 (67 mL). To this agitated slurry at r.t., was added NMM (4.62 mL, 0.0422 M) over 3 min. The slurry was stirred at r.t. for 2 h, and then added to a solution of **16** (prepared as described above) at r.t. To ensure complete transfer of **3a**, the flask was rinsed with CH_2Cl_2 (10 mL). The reaction mixture was agitated at r.t. for 4 h, then H_2O (40 mL) was added to the reaction mixture. The mixture was distilled with an internal set point of 60 °C at atmospheric pressure, to afford a white slurry. To the slurry at 47–53 °C, was added a mixture of H_2O (60 mL) and acetone (10 mL). The slurry was allowed to cool to r.t. over 2 h, then the solids were filtered and washed with H_2O (20 mL). The product **4** was dried in a vacuum oven at ambient temperature.

Yield: 85.2%; solid; mp 208–212 °C; chiral purity: 99.5% (determined by chiral HPLC).

IR (KBr): 3323, 1687, 1654 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.43 (d, *J* = 7.8 Hz, 1 H), 7.92 (d, *J* = 7.7 Hz, 1 H), 7.19 (m, 4 H), 6.22 (d, *J* = 7.9 Hz, 1 H), 5.46 (br, 1 H), 4.62 (t, *J* = 7.0 Hz, 1 H), 4.21 (m, 1 H), 3.71 (s, 1 H), 3.23 (m, 6 H), 2.90 (s, 3 H), 2.00 (t, *J* = 6.9 Hz, 1 H), 1.30 (d, *J* = 6.9 Hz, 3 H), 0.81 (dd, *J* = 6.9, 6.9 Hz, 6 H).

HRMS: *m*/*z* calcd for $C_{19}H_{28}N_3O_4$: 362.2080; found: 362.2084.

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