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Article

Synthesis of 3-Substituted 1,4-Benzodiazepin-2-ones

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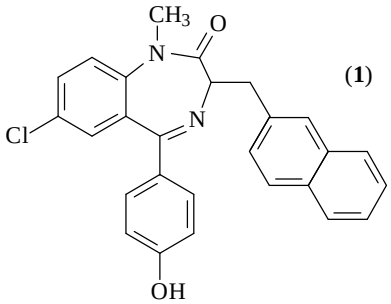
A preparação de benzodiazepínicos 1,4 substituídos na posição 3 é explorada a partir da alquilação de enolatos benzodiazepínicos. Empregando-se tal abordagem, vários gramas de benzodiazepínicos **1** foram preparados para estudos em animais, visando avaliar uma nova abordagem no tratamento da doença auto-imune lúpus eritematoso (LE).

The preparation of 3-substituted 1,4-benzodiazepines by benzodiazepine enolate alkylation has been explored. Employing this approach, multigram quantities of benzodiazepine **1** have been prepared for animal studies to evaluate a new approach for the treatment of the autoimmune disease systemic lupus erythematosus (SLE).

Keywords: *benzodiazepine enolate-alkylation, systemic lupus erythematosus*

Introduction

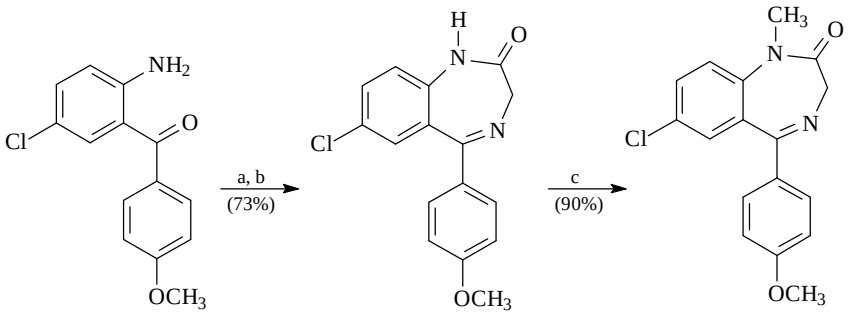
Benzodiazepines are one of the most important classes of therapeutic agents. For example, different benzodiazepines have anxiolytic, anticonvulsant and antihypnotic activities[1], serve as cholecystokinin A and B antagonists[2], opioid receptor ligands[3], platelet-activating factor antagonists[4], HIV trans-activator Tat antagonists[5], HIV reverse transcriptase inhibitors[6] and ras farnesyltransferase inhibitors[7]. Due to the biological importance of benzodiazepines, we have carried out the solid-phase synthesis of libraries of over 10,000 unique 1,4-benzodiazepines derivatives[8-12]. These libraries have been assayed against a number of receptor and enzyme targets. In one study, benzodiazepine **1** was identified as the first small molecule inhibitor of autoantibody•DNA interactions in lupus-prone mice[13]. Related autoantibody•DNA interactions have been implicated in the autoimmune disease systemic lupus erythematosus (SLE)[14]. Blocking this interaction could potentially provide the first effective treatment of SLE. In order to perform animal studies to evaluate this potential strategy for treatment, large quantities of benzodiazepine **1** were required. Herein, we report an efficient synthesis route to multigram quantities of **1** and further describe the scope and limitations of this approach for the preparation of other 3-substituted benzodiazepine derivatives.



(**1**)

Results and Discussion

Most synthesis routes to 3-substituted benzodiazepin-2-ones rely on the incorporation of amino acids into the benzodiazepine structure[1,15]. Accordingly, benzodiazepine **1** can be prepared from the nonproteinogenic amino acid β-naphthylalanine. However, due to the high cost of β-naphthylalanine, an alternative route was prefered for the preparation of large quantities of **1**. Alkylation of the enolate of benzodiazepine **4** (Scheme 1) with 2-naphthylmethyl bromide could potentially provide a cost effective route to **1**. Although Sternbach has documented the propensity for 1,4-benzodiazepines enolates to rearrange to isoindols[16], other researchers in limited reports have described successful benzodiazepine enolate alkylations.[17,18] In order to explore this approach, benzodiazepine **4** was prepared in three steps from aminobenzophenone **2**[19]. Treatment of **2** with bromoacetyl bromide in diethyl ether followed by amination and cyclization under acidic conditions provided **3** in 73% overall yield (Scheme 1).[1,20] *N*-Methylation with



2 **3** **4**

Scheme 1. (a) bromoacetyl bromide, diethyl ether, 0 °C; (b) i. NH_3/MeOH, diethyl ether, rt, ii. 5% HOAc in *tert*-butyl alcohol, 50 °C, 15 h; (c) K_2CO_3, CH_3I, MeOH/THF (1:1), rt.

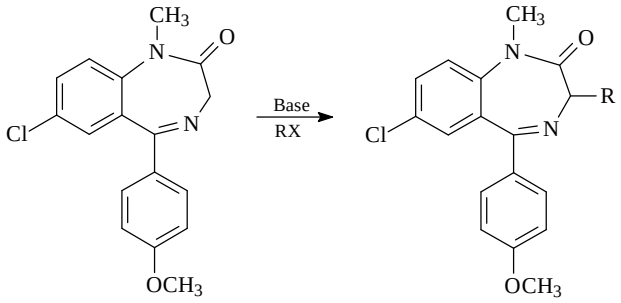
methyl iodide using potassium carbonate as a base then provided benzodiazepine **4** in 90% yield.

Next, we turned our attention to enolate alkylation of **4**. Reaction conditions were optimized by evaluating a number of bases, reaction temperatures, and reagent stoichiometries. Benzodiazepine **5a** (Table 1) was obtained in good yield (78%) using potassium *tert*-butoxide as base with THF as solvent at -78 °C (Method A). In order to evaluate the generality of these reaction conditions, several other benzodiazepine derivatives were also prepared (Table 1). Notably, with less reactive alkylating agents (entries **5d-5g**), potassium bis(trimethylsilyl)amide should be used as the base (Method B). Under these conditions, moderate yields of the benzodiazepine products are observed.

Demethylation of **5a** using aluminum tribromide in ethanethiol[21] proceeded in 86% yield, thereby providing benzodiazepine **1**. Greater than 50 g of benzodiazepine **1** has been prepared by this synthesis sequence.

Conclusion

Multigram quantities of benzodiazepine **1** have efficiently been prepared with the key step being enolate alkylation of benzodiazepine **4**. The scope and generality of preparing substituted benzodiazepines by enolate alkylation has also been established.



4 **5** (1)

Table 1. Enolate alkylation of benzodiazepine 4.

Entry[a]	RX	Yield (%)[b]	Rxn conditions[c]
5a	2-(Bromomethyl)naphthalene	78	A
5b	Benzyl bromide	72	A
5c	Iodomethane	98	A
5d	Allyl bromide	66	B
5e	Ethyl bromide	62	B
5f	1-Bromo-2-methylpropane	39	B
5g	(Bromomethyl)cyclohexane	48	B

[a]All products were fully characterized by ^{1}H-NMR, ^{13}C-NMR, and HRMS analysis. [b]Yields of pure compounds after chromatography. [c]See experimental section for reaction procedures.

Experimental

General

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran and diethyl ether were distilled under N_2 from sodium/benzophenone immediately prior to use. Flash column chromatography was carried out using Merck 60 230-400 mesh silica gel. ^{1}H-NMR spectra were obtained with a University of California at Berkeley Bruker AM-400 or AM-500 FT spectrometer. Proton-decoupled ^{13}C-spectra were obtained at 100 or 125 MHz with the same instruments. Chemical shifts are reported in ppm. High resolution mass spectra were obtained at the University of California at Berkeley mass spectrometry laboratory using fast atom bombardment (FAB) with 3-nitrobenzyl alcohol as matrix solvent.

7-Chloro-5-(4-methoxyphenyl)-1,4-benzodiazepin-2-one

To a solution of 2-amino-5-chloro-4'-methoxybenzophenone **2** (12 g, 46 mmol) in diethyl ether (200 mL) at 0 °C were added bromoacetyl bromide (5.2 mL, 60 mmol) and about 50 g of ice in one portion. After 1 h the white precipitate was filtered and washed with cold diethyl ether (3 x 50 mL) to afford the α-bromoacetamide intermediate. Without further purification, the white powder was dissolved in a mixture of 100 mL of diethyl ether and 700 mL of a 13% (w./w.) solution of ammonia in methanol. After stirring overnight the solution was concentrated *in vacuo* to dryness. The white residue was dissolved in 300 mL of 10% acetic acid in *tert*-butanol and the reaction solution was heated to 60 °C 15 h. The acidic solution was concentrated *in vacuo*. The residue was diluted with 500 mL of ethyl acetate, filtered through a silica gel pad, and concentrated *in vacuo*. The white powder was recrystallized from methanol to provide 10 g of product (73% yield), mp 198-199 °C: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 10.1 (s, 1H), 7.47 (dt, *J* = 9, 3 Hz, 2H), 7.42 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.31 (d, *J* = 2.5 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 6.89 (dt, *J* = 9, 3 Hz, 2H), 4.19-4.35 (br s, 2H), 3.83 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 172.4, 169.1, 161.6, 137.5, 131.7, 131.3, 131.2, 130.7, 128.6, 122.8, 113.7, 56.4, 55.4. LRMS (FAB) *m/e* 301 $(M+H)^+$; HRMS (FAB) *m/e* 301.0744 [$(M+H)^+$, calcd for $C_{16}H_{14}O_2N_2Cl$: 310.0749].

7-Chloro-5-(4-methoxyphenyl)-1-methyl-1,4-benzodiazepin-2-one

To a solution of **3** (16 g, 53.2 mmol) in 160 mL of methanol-THF (1:1) were added potassium carbonate (44 g, 318 mmol) and iodomethane (10 mL, 161 mmol). After stirring overnight the mixture was filtered through a Celite pad and concentrated *in vacuo* to afford 15 g of **4** (90%) as a white solid: mp 68-70 °C; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.54 (dt, *J* = 9, 3 Hz, 2H), 7.48 (dd, *J* = 9, 2.5 Hz, 1H), 7.26-7.29 (m, 2H), 6.89 (dt, *J* = 9, 3 Hz, 2H), 4.74 (d, *J* = 10.9 Hz, 1H), 3.82 (s, 3H), 3.71 (d, *J* = 10.9 Hz, 1H), 3.35 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.1, 168.6, 161.6, 142.5, 131.2, 131.0, 130.7, 130.2, 130.0, 129.1, 122.5, 113.7, 56.7, 55.4, 34.7; LRMS (FAB) *m/e* 315 $(M+H)^+$; HRMS (FAB) *m/e* 315.0900 [$(M+H)^+$, calcd for $C_{17}H_{16}O_2N_2Cl$: 315.0894].

Benzodiazepine enolate alkylation

Method A

To a solution of **4** (15 g, 48 mmol) in 200 mL of THF at -78 °C was added 122 mL of 0.59 M potassium *tert*-butoxide in THF. After 10 min, a solution of 2-(bromomethyl)naphthalene (13.7 g, 62 mmol) in THF (20 mL) was added by cannula. The solution was stirred for 1 h and quenched with 100 mL of saturated NH_4Cl solution. The aqueous layer was extracted with ethyl acetate (3 x 150 mL), and the combined organic layer was washed with water, brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was recrystallized from methanol to provide 16.8 g of **5a** (78%) as a white solid.

Method B

To a solution of **4** (100 mg, 0.32 mmol) in 2.0 mL of THF at -20 °C was added 0.83 mL of 0.5 M potassium hexamethyldisilazide (KHMDS) in toluene. The solution was allowed to warm to –5 °C and a solution of alkyl bromide (0.42 mmol) in THF (1 mL) was added by cannula. After stirring overnight, the solution was quenched with saturated NH_4Cl solution and then the work-up procedure described for Method A was followed.

*7-Chloro-5-(4-methoxyphenyl)-1-methyl-3-(2-naphthylmethyl)-1,4-benzodiazepin-2-one (**5a**)*

Mp 98-100 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.75-7.85 (m, 4H), 7.39-7.55 (m, 6H), 7.26 (dd, *J* = 13, 6.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 3.85 (s, 3H), 3.70-3.89 (m, 3H), 3.41 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$); δ 170.2, 166.3, 161.6, 142.2, 136.9, 133.5, 132.1, 131.3, 131.2, 130.7, 130.5, 129.8, 129.1, 128.6, 128.2, 127.54, 127.49, 125.8, 125.2, 122.7, 113.7, 65.2, 55.4, 38.2, 35.2. HRMS (FAB) *m/e* 455.1526 [$(M+H)^+$, calcd for $C_{28}H_{24}O_2N_2Cl$: 455.1528].

*7-Chloro-5-(4-methoxyphenyl)-1-methyl-3-benzyl-1,4-benzodiazepin-2-one (**5b**)*

Mp 194 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.9 Hz, 2H), 7.41-7.51 (m, 1H), 7.13-7.40 (m, 7H), 6.90 (d, *J* = 8.9 Hz, 2H), 3.83 (s, 3H), 3.73 (t, *J* = 6.3 Hz, 1H), 3.55-3.69 (m, 2H), 3.39 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.3, 166.2, 161.6, 142.2, 139.4, 131.3 131.2, 130.8, 130.5, 129.9, 129.9, 129.1, 128.2, 126.2, 122.8,

113.8, 65.1, 55.4, 38.2, 35.2. HRMS (FAB) *m/e* 405.1370 [(M+H)$^+$, calcd for $C_{24}H_{22}O_2N_2Cl$: 405.1368].

*7-Chloro-5-(4-methoxyphenyl)-1-methyl-3-methyl-1,4-benzodiazepin-2-one (**5c**)*

Mp 106-108 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.7 Hz, 2H), 7.41-7.51 (m, 1H), 7.21-7.38 (m, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 3.65 (q, *J* = 6.4 Hz, 1H), 3.36 (s, 3H), 1.67 (d, *J* = 6.4 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.4, 166.1, 161.6, 142.3, 131.3, 131.1, 130.8, 129.7, 129.0, 122.6, 113.7, 58.6, 55.4, 35.1, 17.5. HRMS (FAB) *m/e* 329.1057 [(M+H)$^+$, calcd for $C_{18}H_{18}O_2N_2Cl$: 329.1065].

*7-Chloro-5-(4-methoxyphenyl)-1-methyl-3-allyl-1,4-benzodiazepin-2-one (**5d**)*

Mp 152 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.7 Hz, 2H), 7.42-7.53 (m, 1H), 7.0-7.35 (m, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.89-6.03 (m, 1H), 5.14 (d, *J* = 17.2 Hz, 1H), 5.05 (d, *J* = 10.2 Hz, 1H) 3.82 (s, 3H), 3.54 (t, *J* = 6.8 Hz, 1H), 3.37 (s, 3H), 2.96 (t, *J* = 6.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.3, 166.2, 161.6, 142.3, 135.6, 131.3 131.2, 130.8, 130.6, 129.8, 129.1, 122.7, 117.0, 113.7, 63.3, 55.4, 36.3, 35.1. HRMS (FAB) *m/e* 355.1213 [(M+H)$^+$, calcd for $C_{20}H_{20}O_2N_2Cl$: 355.1212].

*7-Chloro-5-(4-methoxyphenyl)-1-methyl-3-ethyl-1,4-benzodiazepin-2-one (**5e**)*

Mp 108-110 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.8 Hz, 2H), 7.48 (dd, *J* =8.8 Hz, 2.5 Hz, 1H), 7.25-7.39 (m, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 3.37 (s, 3H) 3.32-3.40 (m, 1H) 2.15-2.30 (m, 2H) 1.01 (t, *J* = 7.4 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.7, 166.3, 161.6, 142.4, 131.2 131.1, 130.9, 130.7, 129.8, 129.0, 122.7, 113.7, 64.8, 55.4, 35.0, 24.9, 10.7. HRMS (FAB) *m/e* 343.1213 [(M+H)$^+$, calcd for $C_{19}H_{20}O_2N_2Cl$: 343.1209].

*7-Chloro-5-(4-methoxyphenyl)-1-methyl-3-isobutyl-1,4-benzodiazepin-2-one (**5f**)*

Mp 185-186 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.48-7.53 (m, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.24-7.30 (m, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H), 3.50-3.59 (m, 1H), 3.38 (s, 3H), 2.23-2.32 (m, 1H), 1.89-2.00 (m, 2H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.79 (d, *J* = 6.4 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.9, 166.2, 161.2, 142.4, 131.3, 131.1 131.0, 130.6, 129.7, 129.0, 122.6, 113.7, 61.4, 55.4, 40.3, 35.1, 24.6, 23.5, 22.0. HRMS (FAB) *m/e* 371.1526 [(M+H)$^+$, calcd for $C_{21}H_{24}O_2N_2Cl$: 371.1528].

*7-Chloro-5-(4-methoxyphenyl)-1-methyl-3-(methylcyclohexyl)-1,4-benzodiazepin-2-one (**5g**)*

Mp 155-156 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.9 Hz, 2H), 7.45-7.53 (m, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.22-7.30 (m, 1H), 6.89 (d, *J* = 8.9 Hz, 2H), 3.82 (s, 3H), 3.57 (dd, *J* = 9.0 Hz, 5.2 Hz, 1H), 3.37 (s, 3H), 2.17-2.29 (m, 1H), 1.9-2.02 (m, 1H), 1.45-1.80 (m, 5H), 0.9-1.31 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.9, 166.1, 161.5, 142.4, 131.3, 131.1 131.0, 130.6, 129.7, 129.0, 122.7, 113.7, 60.8, 55.4, 39.0, 35.1, 34.1, 32.7, 26.6, 26.4, 26.3. HRMS (FAB) *m/e* 411.1839 [(M+H)$^+$, calcd for $C_{24}H_{28}O_2N_2Cl$: 411.1836].

7-Chloro-5-(4-hydroxyphenyl)-1-methyl-3-(2-naphthylmethyl)-1,4-benzodiazepin-2-one

To a solution of **5a** (17 g, 37 mmol) in ethanethiol (300 mL) at 0 °C was added 222 mL of 1 M aluminum bromide in dibromomethane. The mixture was allowed to warm to room temperature and stirred for 3 h. The pale yellow solution was poured into about 100 g of ice in one portion and the precipitate was filtered. The white powder was partitioned between 200 mL of 1 M HCl solution and 400 mL of methanol-$CHCl_3$ (1:1). The mixture was concentrated *in vacuo*. The aqueous layer was extracted with ethyl acetate (3 x 200 mL), the combined extracts were washed with water, brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was recrystallized from methanol to furnish 14 g of **1** (86%) as a white solid: mp 153-155 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 7.71-7.83 (m, 4H), 7.32-7.63 (m, 5H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 2.2 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 2H), 3.77 (br t, *J* = 7.2 Hz, 1H), 3.47-3.51 (m, 2H), 3.29 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 170.1, 166.0, 160.3, 142.5, 137.3, 133.5, 132.1, 131.8, 131.4, 130.4, 129.2, 129.1, 129.0, 128.34, 128.25, 127.9, 127.81, 127.78, 126.3, 125.7, 124.4, 115.6, 64.9, 38.3, 35.1; LRMS (FAB) *m/e* 441 (M+H)$^+$; HRMS (FAB) *m/e* 441.1370 [(M+H)$^+$, calcd for $C_{27}H_{22}O_2N_2Cl$: 441.1379].

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