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ORIGINAL PAPER

Simple and efficient preparation of 3-substituted 6-(4-chlorophenyl)-9-methyl-12*H*-[1]benzofuro[3,2-*e*][1,2,4]-triazolo[4,3-*b*][1,2]diazepines via a silylation–amination reaction

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Abstract A series of new 3-substituted 6-(4-chlorophenyl)-9-methyl-12*H*-[1]benzofuro[3,2-*e*][1,2,4]triazolo-[4,3-*b*][1,2]diazepines was synthesized from the corresponding bicyclic 1-(4-chlorophenyl)-3,5-dihydro-8-methyl-4*H*-[1]benzofuro[2,3-*d*][1,2]diazepin-4-one. The synthesis strategy makes use of silylation–amination as the key step, allowing a wide range of derivatives to be prepared.

Keywords Cyclizations · Fused diazepines · Hexamethyldisilazane · Silylation–amination

Introduction

2,3-Benzodiazepines are a class of heterocyclic compounds that can interact with glutamate receptors and AMPA (2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid)-type receptors in a noncompetitive manner. These compounds are of great interest due to their pharmacological effects against acute and chronic neurodegenerative diseases such as ischemia and epilepsy [1–5]. Pharmacological studies have revealed that tricyclic 11*H*-[1,2,4]triazolo[4,3-*c*][2,3]benzodiazepines possess anticonvulsant activity, which is comparable to that of their bicyclic precursors [3–5]. Generally, the synthesis of 11*H*-[1,2,4]triazolo[4,3-*c*][2,3]benzodiazepines involves the condensation of 3,5-dihydro-4*H*-2,3-benzodiazepin-4-thiones with appropriate hydrazides [3] (Scheme 1). Because such transformations have not been described for the [1]benzofuran series, we decided to see if triazolodiazepines can be prepared from derivatives with a [1]benzofuran fragment according to this route.

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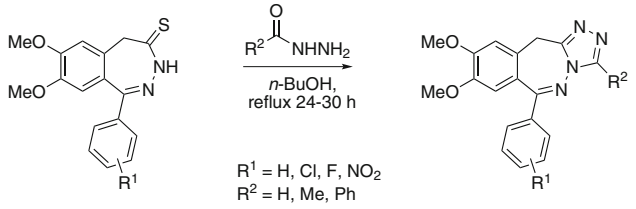
Results and discussion

1-(4-Chlorophenyl)-3,5-dihydro-8-methyl-4*H*-[1]benzofuro [2,3-*d*][1,2]diazepine-4-one (**1**) was transformed into the corresponding thione **2** by reaction with Lawesson's reagent in heated toluene as described elsewhere [6]. Diazepine-4-thione **2** reacts with an appropriate amount of hydrazides by heating at reflux in *n*-butanol ("Method A," Scheme 2). New compounds **3a**–**3e** were obtained as stable solids in good yield.

Much attention has recently been paid to an important synthetic transformation consisting of the direct conversion of diazepine-4-one **1** into triazolodiazepines **3a**–**3e**. However, we found no examples of such methodology being used to prepare triazolodiazepines. Generally, the direct conversion of diazepine-4-one **1** to triazolodiazepines **3** can be accomplished by silylation–amination methods [7–9], in which 1,1,1,3,3,3-hexamethyldisilazane (HMDS) is the key reagent. Recently, the silylation–amination reaction was successfully applied to the preparation of 3-aminobenzofuro[2,3-*c*]pyridines [10]. On the basis of our prior work, we expected the formation of triazolodiazepines **3a**–**3e** to also occur under these conditions. In fact, we found that compound **1** reacts readily with hydrazides of benzoic acids and HMDS in the presence of *p*-toluenesulfonic acid monohydrate to afford triazolodiazepines **3a**–**3e** ("Method B," Scheme 2). The yields of **3a**–**3e** (from **1** and from **2**) obtained by using both procedures are given in Table 1.



Scheme 1

A possible mechanism for the silylation–amination reaction has already been described elsewhere [9]. We assume the following reaction sequence: HMDS reacts with a molecule of diazepinone **1** to produce reactive species **A**, and intermediate **A** then interacts with hydrazide leading to intermediate **B**. Further cyclization of intermediate **B** results in the formation of the corresponding triazolodiazepines **3** (Scheme 3).

Conclusion

A highly efficient and practical one-pot synthesis of triazolodiazepines has been developed in this work. The procedure outperforms the existing processes, allowing us to produce several pharmacologically useful triazolodiazepine derivatives in a clearly shorter synthetic sequence.

Experimental

Melting points were determined in non-sealed capillaries using a Bellstone apparatus. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 (400 MHz) using tetramethylsilane (TMS) as an internal standard. Mass spectra were acquired on a Finnigan MAT INCOS 50, operating in the electron-impact mode (EI) at 70 eV. The CHNS elemental analysis was performed using a Fisons AE1108 analyzer, and the results were in good agreement (±0.25%) with the calculated values. Methyl [2-(4-chlorobenzoyl)-6-methyl-1-benzofuran-3-yl]acetate and compound **1** were obtained as reported elsewhere [11].

Table 1 Synthesis of 3-substituted 6-(4-chlorophenyl)-9-methyl-12*H*-[1]benzofuro[3,2-*e*][1,2,4]triazolo[4,3-*b*][1,2]diazepines **3a**–**3e**

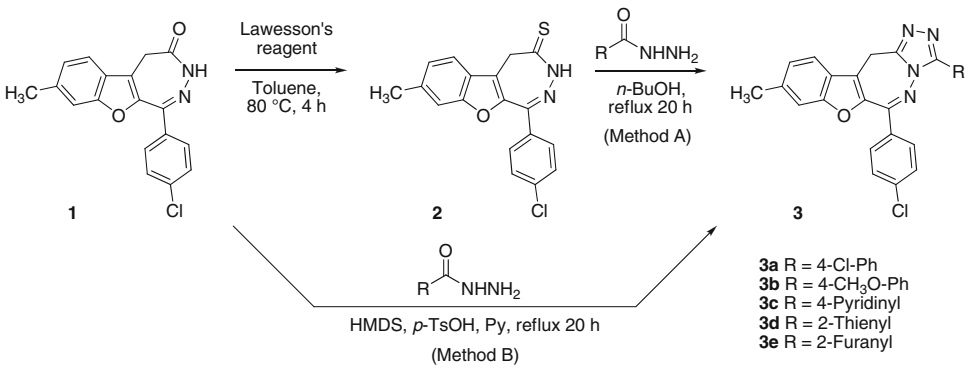
Compound	R	M.p. (°C)	Yield (%)	
			"Method A"	"Method B"
3a	4-Cl-Ph	238–239	87	54
3b	4-CH_3O-Ph	231–232	90	57
3c	4-Pyridinyl	245–246	80	51
3d	2-Thienyl	249–250	79	55
3e	2-Furanyl	246–247	78	50

1-(4-Chlorophenyl)-3,5-dihydro-8-methyl-4H-[1]-benzofuro[2,3-d][1,2]diazepine-4-thione
(**2**, $C_{18}H_{13}ClN_2OS$)
Lawesson's reagent (0.5 mmol) was added to a solution of compound **1** (1 mmol) in 5 cm^3 dry toluene. The reaction mixture was heated at 100 °C for 2 h. The solution was cooled, and the product crystallized from the reaction mixture. The precipitate was collected by filtration and washed with dry toluene to afford compound **2**. Yield: 85%; m.p.: 204–205 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.50$ (s, 3H, CH_3), 4.09 (s, 2H, CH_2), 7.21 (d, $J = 8.0$ Hz, 1H, H-7), 7.34 (s, 1H, H-9), 7.46 (d, $J = 8.0$ Hz, 2H, H-3′, H-5′), 7.20 (d, $J = 8.0$ Hz, 1H, H-6), 7.80 (d, $J = 8.0$ Hz, 2H, H-2′, H-6′), 12.86 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 21.50$, 37.82, 111.76, 119.70, 121.76, 122.76, 125.09, 128.21, 129.99, 132.98, 135.65, 137.97, 142.75, 149.78, 156.21, 193.31 ppm; MS (EI, 70 eV): $m/z = 340$ (M^+).

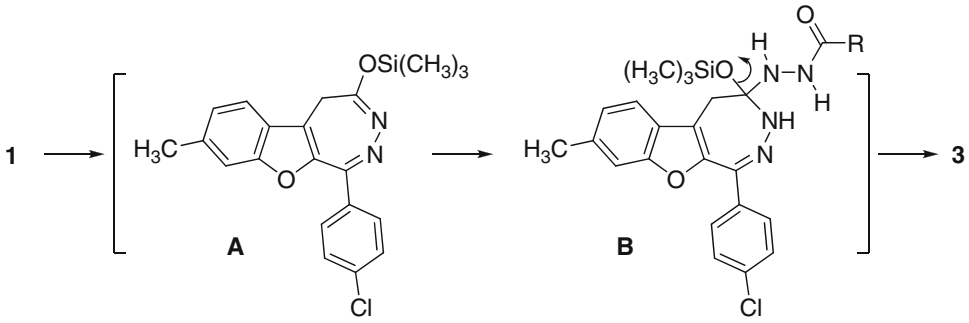
*General procedures for synthesis of 3-substituted 6-(4-chlorophenyl)-9-methyl-12H-[1]benzofuro[3,2-e]-[1,2,4]triazolo[4,3-b][1,2]diazepines **3a**–**3e***

Method A
A solution of diazepine-4-thione **2** (1 mmol) and the hydrazide of the corresponding acid (1.25 mmol) in 15 cm^3

Scheme 2



Scheme 3



n-butanol was refluxed for 20 h. The solution was cooled, and the products **3** crystallized from the reaction mixture. The precipitate was collected by filtration and washed with *n*-butanol to afford compounds **3**.

Method B

A solution of diazepine-4-one **1** (1 mmol), the hydrazide of corresponding acid (1.1 mmol), and HMDS (1.5 mmol) in 15 cm^3 pyridine with a catalytic amount of *p*-toluenesulfonic acid monohydrate (0.1 mmol) was refluxed for 20 h. The solution was then evaporated to dryness, and the residue was washed with water, dried, and recrystallized from 2-propanol/dimethylformamide (1:1) to afford compounds **3**.

3,6-Bis(4-chlorophenyl)-9-methyl-12H-[1]benzofuro-[3,2-e][1,2,4]triazolo[4,3-b][1,2]diazepine
(**3a**, $C_{25}H_{16}Cl_2N_4O$)
M.p.: 238–239 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.50$ (s, 3H, CH_3), 4.61 (s, 2H, CH_2), 7.27 (d, $J = 8.0$ Hz, 1H, H-7), 7.38 (s, 1H, H-9), 7.57 (d, $J = 8.0$ Hz, 2H, H-3′,H-5′), 7.60 (d, $J = 8.0$ Hz, 2H, H-3″, H-5″), 7.76 (d, $J = 8.0$ Hz, 2H, H-2′, H-6′), 7.95 (d, $J = 8.0$ Hz, 1H, H-6), 7.98 (d, $J = 8.0$ Hz, 2H, H-2″, H-6″) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 19.73$, 21.56, 111.61, 120.71, 123.43, 124.90, 125.39, 128.22, 128.39, 130.26, 130.93, 132.83, 135.00, 136.35, 138.86, 141.40, 149.65, 152.06, 152.65, 155.42 ppm; MS (EI, 70 eV): $m/z = 458$ (M^+).

6-(4-Chlorophenyl)-3-(4-methoxyphenyl)-9-methyl-12H-[1]benzofuro[3,2-e][1,2,4]triazolo[4,3-b][1,2]diazepine
(**3b**, $C_{26}H_{19}ClN_4O_2$)
M.p.: 231–232 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.52$ (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.57 (s, 2H, CH_2), 7.07 (d, $J = 8.0$ Hz, 2H, H-3″, H-5″), 7.26 (d, $J = 8.0$ Hz, 1H, H-7), 7.35 (s, 1H, H-9), 7.54 (d, $J = 8.0$ Hz, 2H, H-3′, H-5′), 7.77 (d, $J = 8.0$ Hz, 2H, H-2′, H-6′), 7.89 (d, $J = 8.0$ Hz, 2H, H-2″, H-6″), 7.92 (d, $J = 8.0$ Hz, 1H, H-6) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 19.64$, 21.30, 55.16, 111.82, 113.77, 118.93, 120.71, 123.36, 124.95, 125.48, 128.54, 130.40, 131.06, 133.15, 135.89, 139.04, 141.55, 149.71, 152.45, 153.14, 155.29, 160.43 ppm; MS (EI, 70 eV): $m/z = 454$ (M^+).

6-(4-Chlorophenyl)-9-methyl-3-(pyridin-4-yl)-12H-[1]-benzofuro[3,2-e][1,2,4]triazolo[4,3-b][1,2]diazepine
(**3c**, $C_{24}H_{16}ClN_5O$)
M.p.: 245–246 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.46$ (s, 3H, CH_3), 4.69 (s, 2H, CH_2), 7.30 (d, $J = 8.0$ Hz, 1H, H-7), 7.50 (s, 1H, H-9), 7.65 (d, $J = 8.0$ Hz, 2H, H-3′, H-5′), 7.79 (d, $J = 8.0$ Hz, 2H, H-3″, H-5″), 7.98 (d, $J = 8.0$ Hz, 2H, H-2′, H-6′), 8.02 (d, $J = 8.0$ Hz, 1H, H-6), 8.80 (d, $J = 8.0$ Hz, 2H, H-2″, H-6″) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 19.68$, 21.33, 111.87, 120.81, 122.74, 125.05, 125.61, 128.62, 131.19, 133.01, 133.93, 134.73, 136.31, 139.33, 140.96, 149.83, 150.74, 152.45, 152.94, 155.47 ppm; MS (EI, 70 eV): $m/z = 425$ (M^+).

6-(4-Chlorophenyl)-9-methyl-3-(2-thienyl)-12H-[1]-benzofuro[3,2-e][1,2,4]triazolo[4,3-b][1,2]diazepine
(**3d**, $C_{23}H_{15}ClN_4OS$)
M.p.: 249–250 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.51$ (s, 3H, CH_3), 4.61 (s, 2H, CH_2), 7.22 (t, $J = 4.0$ Hz, 1H, H-4″), 7.26 (d, $J = 8.0$ Hz, 1H, H-7), 7.34 (s, 1H, H-9), 7.59 (d, $J = 8.0$ Hz, 2H, H-3′, H-5′), 7.70 (d, $J = 4.0$ Hz, 1H, H-5″), 7.90–7.93 (m, 4H, H-6, H-2′, H-6′, H-3″) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 19.77$, 21.54, 111.65, 120.81, 123.43, 124.79, 125.44, 126.88, 127.20, 128.44, 128.59, 129.15, 131.17, 132.97, 136.24, 139.03, 141.41, 148.72, 149.03, 152.77, 155.49 ppm; MS (EI, 70 eV): $m/z = 430$ (M^+).

6-(4-Chlorophenyl)-3-(2-furanyl)-9-methyl-12H-[1]-benzofuro[3,2-e][1,2,4]triazolo[4,3-b][1,2]diazepine
(**3e**, $C_{23}H_{15}ClN_4O_2$)
M.p.: 246–247 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.52$ (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 6.66 (t, $J = 4.0$ Hz, 1H, H-4″), 7.20 (d, $J = 4.0$ Hz, 1H, H-5″), 7.25 (d, $J = 8.0$ Hz, 1H, H-7), 7.31 (s, 1H, H-9), 7.56 (d, $J = 8.0$ Hz, 2H, H-3′, H-5′), 7.80 (d, $J = 4.0$ Hz, 1H, H-3″), 7.83 (d, $J = 8.0$ Hz, 2H, H-2′, H-6′), 7.90 (d,

$J = 8.0$ Hz, 1H, H-6) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 19.59$, 21.30, 111.73, 111.84, 113.13, 120.83, 123.31, 124.92, 125.54, 128.60, 131.17, 133.06, 136.01, 139.26, 140.75, 141.42, 144.86, 146.16, 149.29, 153.09, 155.42 ppm; MS (EI, 70 eV): $m/z = 414$ (M^+).

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