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One-Pot Synthesis of 2,4-Benzodiazepin-1-ones Using Benzotriazole Methodology

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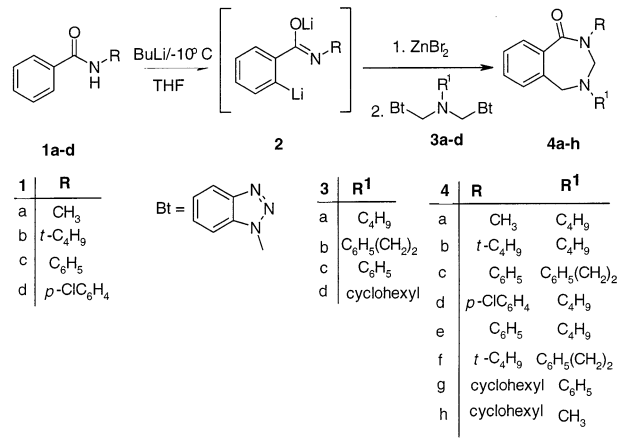
Abstract: 2, 4-Benzodiazepin-1-ones were prepared in moderate to good yields by reaction of bis(benzotriazolylmethyl)amines with ortho-metalated N-substituted benzamides.

Many benzodiazepines display potent pharmacological activity. 1,4-Benzodiazepine-2,5-diones are platelet glycoprotein antagonists IIb−IIIa[1] and anticonvulsant agents.[2] 1,4-Benzodiazepine is a "privileged scaffold"[3] with exceptional ability to mimic natural ligands. Additionally, many alkaloids are benzodiazepines.[4] Synthetic interest has so far focused on 1,4-benzodiazepines,[5] 1,5-benzodiazepines,[6] and 2,3-benzodiazepines.[7] Published synthetic routes to 2,4-benzodiazepines are scarce: 2,4-benzodiazepin-1,3-diones are formed by the palladium-catalyzed intramolecular cyclization of 1-butyl-1(*o*-iodobenzyl)-3-phenylurea,[8] and there is one reported synthesis of 2,3-benzodiazepin-1-one from 2-[(dimethylamino)methyl]benzamide.[9] We now describe a one-pot synthesis of 2, 4-benzodiazepin-1-ones utilizing benzotriazole strategy.

SCHEME 1



1	R
a	CH_3
b	t-C_4H_9
c	C_6H_5
d	p-ClC_6H_4

3	R^1
a	C_4H_9
b	$C_6H_5(CH_2)_2$
c	C_6H_5
d	cyclohexyl

4	R	R^1
a	CH_3	C_4H_9
b	t-C_4H_9	C_4H_9
c	C_6H_5	$C_6H_5(CH_2)_2$
d	p-ClC_6H_4	C_4H_9
e	C_6H_5	C_4H_9
f	t-C_4H_9	$C_6H_5(CH_2)_2$
g	cyclohexyl	C_6H_5
h	cyclohexyl	CH_3

N,*N*-Bis(benzotriazolylmethyl)alkylamines, easily prepared from primary amines, benzotriazole, and formaldehyde,[10] are useful for the synthesis of julolidines,[11] 1,3-oxazolidines,[12] and 3-aryl pyrrolidines.[13] Bis(benzotriazolylmethyl)amines are nitrogen-centered 1,3-dication synthons as is well exemplified in their application in the synthesis of substituted piperidines.[14] We now show that this concept combined with an ortho metalation process can lead to 2,4-benzodiazepin-1-ones.

Results and Discussions

N-Alkylbenzamides generate dianions in orthometalation chemistry.[15] When *N*-methylbenzamide **1a** was treated with butyllithium at −78 °C in diethyl ether and reacted with bisbenzotriazolyl derivative **3a**, only the starting materials were recovered after workup (Scheme 1). However, addition of $ZnBr_2$ to the reaction mixture caused the reaction to take place as desired. After addition of **3a**, the reaction mixture was stirred overnight at room temperature. Aqueous workup and isolation yielded the benzodiazepin-1-one **4a** in 22% yield. The yield of **4a** was improved to 64% by conducting the reaction at −10° C. The $ZnBr_2$ acts in this reaction as a Lewis acid; it activates the benzotriazole and thereby expedites the C−N bond scission. This is characteristic of benzotriazole chemistry.[14] Bis(benzotriazolylmethylalkyl)amines prepared from other primary amines also reacted similarly under the modified conditions giving the corresponding 2,4-benzodiazepin-1-one in good to moderate yields. The results are summarized in

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TABLE 1. 2, 4-Benzodiazepine-1-ones Prepared

entry	R	R^1	yield
4a	CH_3	C_4H_9	64
4b	^{t}Bu	C_4H_9	82
4c	C_6H_5	phenethyl	53
4d	pCl−C_6H_4	C_4H_9	57
4e	C_6H_5	C_4H_9	47
4f	^{t}Bu	phenethyl	36
4g	C_6H_5	cyclohexyl	74
4h	CH_3	cyclohexyl	57

Table 1. A variety of *N*-alkyl- and *N*-aryl-benzamides were also used for the generation of ortholithiated benzamides.

In conclusion, we describe a one-pot synthesis of 2,4-benzodiazepin-1-ones starting from easily affordable starting materials and utilizing simple chemistry.

Experimental Section

Melting points were determined using a hot-stage microscope and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a 300 MHz NMR spectrometer in chloroform-*d* solution. Column chromatography was performed on silica gel (300−400 mesh). THF was distilled from sodium-benzophenone ketal prior to use. All the reactions were performed under a nitrogen atmosphere and in flame-dried glasswares.

General Procedure for the Preparation of 2,4-Benzodiazepin-1-ones. The N-substituted benzamide (3 mmol) was dissolved in THF (30 mL). *n*-BuLi (6.6 mmol) was added dropwise at −10 °C. The mixture was gradually warmed to 0 °C and stirred for 30 min. After the mixture was cooled to −10 °C, $ZnBr_2$ (7 mmol) was added to the mixture followed by the addition of the *N*,*N*-bis(benzotriazolyl)amine (3 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched with 2 M NaOH, and the mixture was washed with brine and extracted with EtOAC. Column chromatography (Al_2O_3, from 10/1 to 6/1 hexanes/EtOAC) afforded the analytically pure benzodiazepines.

2-Methyl-4-butyl-2,3,4,5-tetrahydro-1*H*-2,4-benzodiazepin-1-one 4a: yellow oil (64%); ^{1}H NMR δ 7.77−7.74 (m, 1H), 7.44−7.40 (m, 2H), 7.26−7.24 (m, 1H), 4.09 (s, 2H), 3.64 (s, 2H), 3.27 (s, 3H), 2.71 (t, J = 7.3 Hz, 2H), 1.62−1.56 (m, 2H), 1.44−1.37 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ 171.1, 136.5, 134.4, 131.1, 129.0, 128.5, 128.2, 68.1, 55.2(2), 36.3, 30.1, 20.4, 13.9; HRMS (FAB) calcd for $C_{14}H_{20}N_2O$ (M + H) 233.1654, found 233.1629.

2-(*tert*-Butyl)-4-butyl-2,3,4,5-tetrahydro-1*H*-2,4-benzodiazepin-1-one 4b: isolated as a colorless oil (82%); ^{1}H NMR δ 7.76 (dd, J = 6.7, 2.2 Hz, 1H), 7.43−7.37 (m, 2H), 7.10 (dd, J = 6.5, 1.9 Hz, 1H), 3.78 (s, 4H), 2.31 (t, J = 7.0 Hz, 2H), 1.59 (s, 9H), 1.51−1.46 (m, 2H), 1.40−1.35 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 172.1, 138.3, 131.5, 130.8, 128.8, 128.2, 128.0, 63.2, 57.1, 53.6, 51.8, 30.1, 28.7, 20.5, 14.0. Anal. Calcd for $C_{17}H_{26}N_2O$: C, 74.41; H, 9.55; N, 10.21. Found: C, 74.35; H, 10.06; N, 10.40.

2-Phenyl-4-phenyethyl-2,3,4,5-tetrahydro-1*H*-2,4-benzodiazepin-1-one 4c: isolated as a yellow oil (53%); ^{1}HNMR δ 7.85 (dd, J = 6.9, 1.6 Hz, 1H), 7.50−7.40 (m, 6H), 7.39−7.17 (m, 5H), 6.98 (d, J = 6.7 Hz, 2H), 4.56 (s, 2H), 3.92 (s, 2H), 2.84−2.79 (m, 2H), 2.74−2.69 (m, 2H); ^{13}C NMR δ 170.7, 143.2, 139.4, 136.3, 134.0, 131.6, 129.3, 129.1, 129.1, 128.6, 128.4, 126.7, 126.2, 126.1, 68.1, 56.6, 55.3, 34.6. Anal. Calcd for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18. Found: C, 80.53; H, 6.46; N, 8.19.

2-(4-Chlorophenyl)-4-butyl-2,3,4,5-tetrahydro-1*H*-2,4-benzodiazepin-1-one 4d: isolated as a colorless oil (57%); ^{1}H NMR δ 7.52−7.39 (m, 6H), 7.33−7.26 (m, 2H), 4.65 (s, 2H), 4.00 (s, 2H), 2.55 (t, J = 7.3 Hz, 2H), 1.40−1.24 (m, 4H), 0.83 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 171.0, 136.0, 135.6, 130.9, 129.6, 128.6, 128.4, 127.5, 126.7, 126.3, 125.3, 66.0, 53.0, 52.3, 29.7, 20.3, 13.9. Anal. Calcd for $C_{19}H_{21}ClN_2O$: C, 69.4; H, 6.74; N, 8.52. Found: C, 69.3; H, 6.57; N, 8.52.

2-Phenyl-4-butyl-2,3,4,5-tetrahydro-1*H*-2,4-benzodiazepin-1-one 4e: isolated as a yellow oil (47%); ^{1}H NMR δ 7.84 (dd, J = 6.9, 1.9 Hz, 1H), 7.52−7.39 (m, 6H), 7.33−7.26 (m, 2H), 4.50 (s, 2H), 3.86 (s, 2H), 2.57 (t, J = 7.3 Hz, 2H), 1.43−1.38 (m, 2H), 1.29−1.22 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 170.8, 143.3, 136.4, 134.2, 131.6, 129.3, 129.1, 129.0, 128.5, 126.6, 126.2, 68.6, 55.2, 54.7, 29.8, 20.3, 13.8. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 76.57; H, 8.64; N, 9.43.

2-(*tert*-Butyl)-4-phenylethyl-2,3,4,5-tetrahydro-1*H*-2,4-benzodiazepin-1-one 4f: isolated as a yellow oil (36%); ^{1}H NMR δ 7.78−7.75 (m, 1H), 7.41−7.37 (m, 2H), 7.31−7.25 (m, 2H), 7.22−7.18 (m, 3H), 7.11−7.08 (m, 1H), 3.84 (s, 2H), 3.82 (s, 2H), 2.82 (t, J = 7.0 Hz, 2H), 2.58 (t, J = 7.0 Hz, 2H), 1.56 (s, 3H); ^{13}C NMR δ 172.1, 139.9, 138.2, 131.3, 130.9, 128.7, 128.6, 128.4, 128.2, 128.1, 126.2, 63.1, 57.1, 54.0, 53.7, 34.8, 28.6. Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 78.09; H, 8.19; N, 8.72.

2-Phenyl-4-cyclohexyl-2,3,4,5-tetrahydro-1*H*-2,4-benzodiazepin-1-one 4g: isolated as colorless crystals (EtOAc/hexane), 74%, mp 102−103 °C; ^{1}H NMR δ 7.98−7.81 (m, 1H), 7.58−7.25 (m, 8H), 4.62 (s, 2H), 3.96 (s, 2H), 2.55−2.40 (m, 1H), 1.90−1.45 (m, 6H), 1.20−1.05 (m, 4H); ^{13}C NMR δ 170.8, 142.6, 136.3, 134.9, 131.7, 129.3, 129.2, 129.0, 128.4, 126.6, 126.3, 64.8, 60.5, 52.8, 31.1, 25.8, 25.0. Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 76.01; H, 7.55; N, 7.96.

2-Methyl-4-cyclohexyl-2,3,4,5-tetrahydro-1*H*-2,4-benzodiazepin-1-one 4h: isolated as colorless liquid (57%); ^{1}H NMR δ 7.77−7.75(m, 1H), 7.46−7.39 (m, 2H), 7.25−7.37 (m, 1H), 4.21 (s, 2H), 3.75 (s, 2H), 3.24 (s, 3H), 2.65−2.55 (m, 1H), 2.17−2.07 (m, 2H), 1.90−1.78 (m, 2H), 1.38−1.21 (m, 6H); ^{13}C NMR δ 171.2, 136.4, 135.0, 131.3, 129.2, 128.4, 128.2, 64.4, 60.7, 52.4, 35.6, 31.3, 25.9, 25.3. Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 72.21; H, 9.75; N, 10.35.

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