Palladium(II)-Mediated Coupling Reactions of Bromo- and Iodo-1*H*-1,4-benzodiazepine-2,5-diones. A Route to Functionalized Benzodiazepinediones

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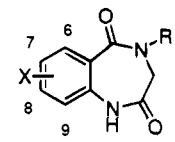
Received May 19, 1995[⊗]

A series of 7-, 8-, and 9-bromo- and iodo-1,4-benzodiazepine-2,5-diones have been prepared and examined as substrates for palladium(II)-mediated coupling reactions with alkenes, alkynes, arylstannanes, and heteroarylstannanes. The benzodiazepinediones **6a,e,g** were prepared from the reaction of *o*-nitrobenzoyl chlorides **3a–c** and methyl *tert*-butylglycinate followed by nitro reduction and cyclization. Regioselective halogenation gave **6c,d,f**. Bromo- and iodobenzodiazepinediones **6c,d,f,g** were then converted to alkenyl-, alkynyl-, aryl-, and heteroaryl-substituted benzodiazepinediones in moderate to good yield in the presence of palladium(II).

Compounds containing the 1*H*-1,4-benzodiazepine-2,5-dione ring system are known to elicit a wide range of biological activity. Synthetic 1,4-benzodiazepine-2,5-diones have been studied as anxiolytic agents,[1] anticonvulsants,[2] antitumor compounds,[3] and recently as potential glycoprotein antagonists.[4] Naturally occurring compounds containing this ring system include the nephrotoxic (+)-iforrestine[5] and the antitumor antibiotic oxotomaymycin.[6] In addition to the broad scope of pharmacological activity, these compounds have also been found to possess fungicidal and plant growth regulating activity.[7] Recently, we began to evaluate 1,4-benzodiazepine-2,5-diones for their herbicidal activity.[8]

In connection with a synthesis program directed toward the preparation of benzodiazepinediones of type **1** as potential herbicides, we desired an efficient route to a variety of benzenoid-substituted analogs. A number of approaches to this ring system have been described in the literature. Most often, the benzenoid portion of the molecule is derived from a suitably functionalized isatoic anhydride[1,4,7,9] or *o*-nitrobenzoyl chloride.[2b,3,10] Other methods have also been employed.[2a,11,12] The present study details our efforts to introduce alkenyl, alkynyl, aryl, and heteroaryl substituents at C-7 through C-9 of the benzodiazepinedione skeleton. It was reasoned that the most practical way to obtain these compounds would be through palladium-catalyzed coupling of alkenes, alkynes, and arylstannanes with appropriately functionalized bromo- or iodobenzodiazepinediones.



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Results and Discussion

Bromo- and Iodo-1,4-benzodiazepine-2,5-diones. Our initial goal was the preparation of compounds of type **1** (X = 7, 8, or 9 bromo or iodo) containing a *tert*-butyl group at C-4 of the benzodiazepinedione ring. The commercial availability of a variety of functionalized anthranilic acids makes the formation of the benzodiazepinedione ring from isatoic anhydrides attractive, since the former can be readily converted to the isatoic anhydride in one step.[13] In general, nonhindered amines react with isatoic anhydrides to afford benzodiazepinediones in excellent yield. As the steric bulk around the

[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1995.

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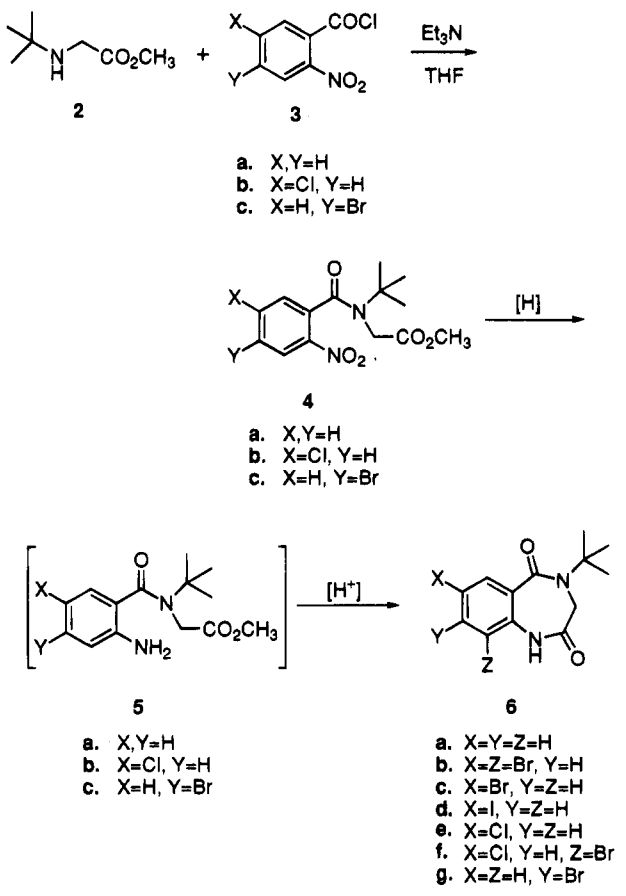
Scheme 1



amino nitrogen increases, the yield decreases.[14] Unfortunately, the reaction of amino ester **2** with isatoic anhydride afforded little, if any desired product.[15] In contrast, amino ester **2** reacted smoothly with *o*-nitrobenzoyl chloride **3a** to give nitroamide **4a** in 60% yield. Catalytic reduction of the nitro group was followed by heating the crude aminoamide **5a** with aqueous acid in THF to furnish benzodiazepinedione **6a** in 78% yield (Scheme 1).

Methods for the selective halogenation of **6a** were then examined. Attempted bromination using NBS in either CCl_4 or THF gave rise to a number of products. Treatment of **6a** with 100 mol % of benzyltrimethylammonium chlorobromate[16] gave the dibrominated product **6b** as the major product. A small amount of monobrominated **6c** was also obtained along with unreacted **6a**. Reaction of **6a** with bromine (100 mol %) in AcOH resulted in a slow conversion to **6c**. Upon prolonged heating at 50 °C, a number of additional products began to form. Cleavage of the *tert*-butyl group was found to take place under these conditions. Compound **6c** could be obtained cleanly in 72% yield upon treatment of **6a** with excess bromine in AcOH at room temperature using sodium acetate as an HBr scavenger.

With a method for the selective C-7 bromination in hand, preparation of the analogous iodo compound was examined next. Benzyltrimethylammonium dichloroiodate has been reported as an effective iodinating agent for acetamides.[17] However, no iodination was observed upon reaction with **6a**. Treatment of **6a** with iodine monochloride and sodium acetate in AcOH at room temperature was ineffective, while prolonged heating caused degradation. When **6a** was treated with iodine in the presence of oxidants such as mercuric(II) oxide and silver(I) acetate, no reaction took place. However, when bis(trifluoroacetoxy)phenyliodine[18] was used as the oxidant, clean C-7 iodination was effected, affording **6d** in 78% yield.[19]

Preparation of the analogous 8- and 9-halobenzodiazepinediones were sought next. The observation that some bromination took place at C-9 led to the expectation that halogenation could be directed to C-9 selectively if C-7 were blocked. 7-Chlorobenzodiazepinedione **6e** which had been previously prepared was chosen as the substrate. Compound **6e** was prepared in analogous fashion to **6a**. Reaction of amino ester **2** and *o*-nitrobenzoyl chloride **3b** gave nitroamide **4b** in 81% yield. Reduction of the nitro group was followed by cyclization to the benzodiazepinedione **6e** in 61% yield. In order to effect complete C-9 bromination of **6e**, more forcing conditions were required than for the C-7 bromination of **6a**. The reaction was carried out at 40 °C with 500 mol % of bromine in aqueous AcOH/sodium acetate, giving **6f** in 75% yield. When the optimized iodination conditions were applied to **6e** in an effort to iodinate at C-9, no reaction took place.[20]

Since direct halogenation at C-8 of the benzodiazepinedione skeleton did not appear trivial, the halogen was incorporated prior to ring formation. Although treatment of 4-bromo-2-nitrotoluene with sodium dichromate/H_2SO_4 failed to give the expected *o*-nitrobenzoic acid, potassium permanganate[21] gave the desired benzoic acid, albeit in low yield. Conversion to benzoyl chloride **3c** followed by reaction with amino ester **2** gave **4c** in 60% yield. Reduction to **5c** was unexpectedly sluggish *via* catalytic hydrogenation (H_2/Pt–C). Heating the crude reaction mixture with sodium dithionite effected complete reduction and concominant cyclization to **6g** in 50% yield.

Palladium-Mediated Coupling Reactions of Bromo- and Iodo-1,4-benzodiazepine-2,5-diones. The 7-, 8-, and 9-halobenzodiazepinediones prepared were subjected to palladium-mediated coupling reactions.[22,23] One of the modifications of interest to the benzodiazepinedione moiety was the incorporation of unsaturated substrates via palladium-catalyzed alkynylation. The alky-

(14) Secondary amines such as prolines have been reported to afford benzodiazepinediones in ca. 60–80% yield when there is no branching at C-5 of the proline (ref 9c–g). As the branching at C-5 increases, there is a pronounced decrease in yield (ref 1).

(15) Increasing the bulk of the nucleophile often favors attack at the C-2 carbonyl of isatoic anhydrides, affording ureido acids as products. Due to the polar nature of the products obtained, we believe that some product of this type formed upon reaction of **2** with isatoic anhydride. Methods reported to favor C-4 attack of isatoic anhydrides were unsuccessful upon reaction with amino ester **2**. For recent methods, see (a) Venuti, M. C. *Synthesis* **1982,** 266. (b) Hinman, C.; Vaughan, K. *Synthesis* **1980,** 719.

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(20) C-9 iodination of a similar benzodiazepinedione has been reported (ref 9a). However, under the strongly acidic conditions used, cleavage of the *tert*-butyl group would be anticipated.

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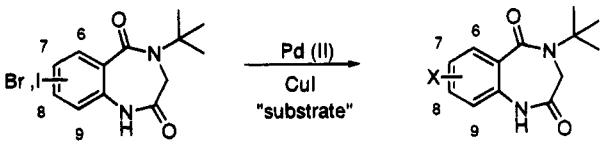
(23) During the course of these studies, alkynylations of a 7-iodobenzodiazepinedione were reported (ref 4).

Table 1. Palladium-Mediated Coupling Reactions of Halobenzodiazepinediones with Various Substrates

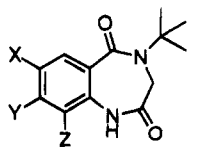


entry	halogen position	substrate	product (X)	% yield[a]
1	7-I	$C_6H_5C{\equiv}CH$	7-$C_6H_5C{\equiv}C$ (**7**)	69
2	7-Br	$C_6H_5C{\equiv}CH$	7-$C_6H_5C{\equiv}C$	37
3	7-I	$HC{\equiv}CSiMe_3$	7-$Me_3SiC{\equiv}C$ (**8**)	58
4	7-I	$H_2C{=}CHSiMe_3$	7-$H_2C{=}CH$ (**10**)	50
			7-(*E*)-$Me_3SiHC{=}CH$ (**11**)	15[b]
			7-$H_2C{=}CSiMe_3$ (**12**)	8[b]
5	7-I	$C_6H_5SnMe_3$	7-C_6H_5 (**13**)	43
6	7-I	(2-pyridyl)$SnMe_3$ (**14**)	7-(2′-pyridyl) (**15**)	70
7	7-I	(2-furyl)$SnMe_3$ (**16**)	7-(2′-furyl) (**17**)	72
8	8-Br	$HC{\equiv}CSiMe_3$	8-$Me_3SiC{\equiv}C$ (**18**)	41
9	7-Cl, 9-Br	$HC{\equiv}CSiMe_3$	7-Cl, 9-$Me_3SiC{\equiv}C$ (**20**)	72
10	7-Cl, 9-Br	(2-pyridyl)$SnMe_3$	7-Cl, 9-(2′-pyridyl) (**22**)	57[c]
11	7-Cl, 9-Br	(2-furyl)$SnMe_3$	7-Cl, 9-(2′-furyl) (**23**)	53[d]

[a] Yields are isolated yields by flash chromatography and are not optimized. [b] Isolated as an inseparable mixture; yields based on ^1H NMR integration. [c] In addition, 23% of **6f** was recovered. [d] In addition, 28% of **6f** was recovered.

nylation of aryl halides has been shown to be a reaction of great preparative importance.[22d,24] Stirring 7-iodobenzodiazepinedione **6d** with phenylacetylene at rt in the presence of 2 mol % dichlorobis(triphenylphosphine)-palladium(II) and 4 mol % copper(I) iodide smoothly gave the desired **7** in 69% yield (Table 1, entry 1). In contrast, the 7-bromo analog **6c** (entry 2) failed to give any **7** at rt, although it could be obtained in 37% yield by prolonged heating of the reaction mixture in the presence of excess phenylacetylene. These results are in support of the greater ease of aryl iodides to undergo oxidative addition to palladium.[25]

Alkynylation using (trimethylsilyl)acetylene was then studied (entries 3, 8, and 9). Treatment of **6d** with (trimethylsilyl)acetylene in the presence of palladium-(II) and Cu(I) at rt gave **8** in 58% yield. Removal of the TMS-protecting group was accomplished by alkaline hydrolysis,[24] affording the free acetylene **9** in 85% yield. Reaction of 8-bromobenzodiazepinedione **6g** with (trimethylsilyl)acetylene was slow at rt, but heating gave the trimethylsilyl-protected **18** in 41% yield after purification. TMS-deprotection gave the free acetylene **19** in 86% yield. Upon heating 7-chloro-9-bromobenzodiazepinedione **6f** with (trimethylsilyl)acetylene, alkynylation took place regiospecifically at C-9 as expected, furnishing **20** in 72% yield. TMS-deprotection afforded **21** in 67% yield.



8 X= $Me_3Si{-}{\equiv}$, Y=Z=H
9 X= $H{-}{\equiv}$, Y=Z=H
18 X=Z=H, Y=$Me_3Si{-}{\equiv}$
19 X=Z=H, Y=$H{-}{\equiv}$
20 X=Cl, Y=H, Z=$Me_3Si{-}{\equiv}$
21 X=Cl, Y=H, Z=$H{-}{\equiv}$
22 X=Cl, Y=H, Z=2-pyridyl
24 X=Y=H, Z=2-pyridyl

To test the applicability of direct vinylation of the benzodiazepinedione nucleus, the 7-iodo compound **6d** was chosen. Heating **6d** with vinyltrimethylsilane in a sealed tube[26] in the presence of 2 mol % palladium(II) acetate and 4 mol % triphenylphosphine gave the desired 7-vinyl analog **10** in 50% yield. In addition, a chromatographically inseparable mixture of byproducts containing trimethylsilyl residues was also isolated. The structures of the compounds were determined from the ^1H NMR coupling constants. The major component showed a coupling constant of 19.2 Hz for the two vinyl protons indicating vicinal coupling, *i.e.*, the (*E*)-(β-trimethylsilyl)-styrene **11**. The 2.6 Hz vinyl proton coupling constants for the minor component was indicative of the geminal coupling of the α-(trimethylsilyl)styryl analog **12**.[27] It was not initially apparent if the desired product **10** resulted from the cleavage of the vinyl–silicon bond during the coupling reaction or resulted from desilylation of **11** or **12**. When the mixture of **11** and **12** was resubjected to the reaction conditions, none of compound **10** was detected after heating for 23 h at 80 °C. The desilylation of **11** and **12** do not, therefore, appear to contribute to the formation of **10**.

To further examine the utility of palladium-mediated coupling reactions in the preparation of functionalized benzodiazepinediones, the bromo- and iodobenzodiazepinediones were reacted with aryl- and heteroarylstannanes. The stannanes could be prepared by generating the lithioaromatic compound and quenching with trimethyltin chloride.[28] When 7-iodobenzodiazepinedione **6d** was treated with a slight excess of phenyltrimethylstannane[29] in THF in the presence of 2 mol % dichlorobis-(triphenylphosphine)palladium(II), compound **13** was obtained in 43% yield. The cross-coupling reaction was rather sluggish; after heating at reflux for 29 h, a small amount of **6d** was still present. When the cross-coupling between **6d** and 2-pyridyltrimethylstannane **14** was carried out under similar conditions, product formation was also slow. Addition of a small amount of copper(I)

(24) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980,** 627.
(25) Tunney, S. E.; Stille, J. K. *J. Org. Chem.* **1987,** *52,* 748.
(26) Hallberg, A.; Westerlund, C. *Chem. Lett.* **1982,** 1993.
(27) β-(*E*)-(trimethylsilyl)styrenes have been reported as byproducts in the vinylation of aryl halides (ref 26). No mention is made of compounds containing the α-(trimethylsilyl)styryl configuration.
(28) For general procedures suitable for the generation of aryl- and heteroarylstannanes, see Brandsma, L.; Verkruijsse, H. In *Preparative Polar Organometallic Chemistry;* Springer Verlag: New York, 1987.
(29) Bailey, T. R. *Tetrahedron Lett.* **1986,** *27,* 4407.

iodide[30] greatly accelerated the reaction, whereby compound **15** was isolated in 70% yield after heating in THF for a few hours. In similar fashion, reaction of 2-furylstannane **16** with **6d** gave compound **17** in 72% yield. In contrast, cross-coupling reactions involving the dihalobenzodiazepinedione **6f** proved to be more problematic. After heating **6f** with 2-pyridylstannane **14** in THF for approximately 30 h, compound **22** was isolated in 57% yield. An additional 23% of unreacted **6f** was also isolated. Similarly, heating the 2-furylstannane **16** with **6f** for 30 h gave **23** in 53% yield along with 28% recovered starting material. Although the coupling reactions took place at C-9 exclusively, cross-coupling of **6f** was considerably slower than with **6d**. It was rationalized that the sluggish rate of reaction could be attributed to the greater steric demand of the 9-position as well as cross-coupling with a less reactive haloarene.

Removal of the 7-chloro group, which was originally exploited for the selective introduction of bromine at C-9, was then examined. Catalytic hydrogenation of **22** over Pd–C was ineffective. Carrying out the reduction *via* transfer hydrogenolysis (Pd/C, ammonium formate), however, gave the dechlorinated compound **24** in 68% yield. Thus the utility of the 7-chloro group as an easily removable blocking group, at least in the absence of other reductively sensitive functionality, has been demonstrated.

Summary

A series of bromo- and iodobenzodiazepinediones have been prepared from the reaction of *o*-nitrobenzoyl chlorides and methyl *tert*-butyl glycinate followed by nitro reduction and cyclization, and in the case of **6c,d,f**, subsequent regioselective halogenation. These compounds were found to be suitable substrates for the palladium-mediated coupling reactions to generate alkenyl-, alkynyl-, aryl-, and heteroaryl-substituted benzodiazepinediones in moderate to good yield. Of the compounds prepared, only the 7-acetylene analog **9** demonstrated herbicidal activity comparable to the halogenated precursors, i.e., **6c** and **6d**.

Experimental Section

General. All reactions requiring anhydrous conditions were carried out under an atmosphere of N_2. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Dichloromethane (CH_2Cl_2), dimethylformamide (DMF), and tetrahydrofuran (THF) were stored over 4A sieves. Mol % (mole percent) refers to the stoichiometry of the reaction components. Organic layers from aqueous extractions were dried over $MgSO_4$ and concentrated *in vacuo*. Melting points are uncorrected. ^1H NMR spectra were measured in $CDCl_3$ or DMSO-d_6. ^1H-Coupling constants, J, are reported in hertz. IR spectra were measured as Nujol mulls. Chemical ionization mass spectra (CIMS) are reported in units of *m/z*. Flash chromatography was performed on 230–400 mesh silica gel. Analytical thin-layer chromatography was done with glass-backed silica plates, 250 μm (Analtech).

Methyl *tert*-Butyl Glycinate (2).[31] A solution of methyl bromoacetate (7.10 mL, 75 mmol, 100 mol %) in Et_2O (30 mL) was added dropwise over 15 min to *tert*-butylamine (31.5 mL, 300 mmol, 400 mol %), previously cooled to 0 °C. The resultant thick slurry was stirred for 2.5 h and then filtered. After washing the precipitated salts with additional portions of Et_2O, the filtrate was washed with cold 0.1 M NaOH, dried, and then concentrated to 10.52 g of a clear liquid (97%): ^1H NMR ($CDCl_3$) δ 3.69 (s, 3H), 3.37 (s, 2H), 1.52 (br s, 1H), 1.06 (s, 9H).

Methyl *β-tert*-Butyl-2-nitrohippurates. General Procedure. A 1 M solution of *o*-nitrobenzoyl chloride **3a–c**[32] in toluene (115 mol %) was added dropwise to a 0 °C solution of **2** (100 mol %) and triethylamine (230 mol %) in THF (0.5–1 M). The heterogeneous reaction mixture was allowed to reach ambient temperature, stirred for ca. 16 h, and then diluted with EtOAc. The reaction mixture was washed successively with H_2O, two to three portions of saturated $NaHCO_3$, and brine. The organic phase was dried and concentrated, and the resultant crude products were purified by recrystallization ($EtOH/H_2O$).

Methyl *β-tert*-Butyl-2-nitrohippurate (4a). Reaction of acid chloride **3a** and **2** gave **4a** as a white solid in 60% yield: mp 120–121 °C; ^1H NMR ($CDCl_3$) δ 8.08 (d, J = 8.4, 1H), 7.64–7.43 (m, 3H), 4.07 (d, J = 18.3, 1H), 3.77 (d, J = 18.3, 1H), 3.63 (s, 3H), 1.54 (s, 9H); CIMS 295 (MH^+). Anal. Calcd for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.52. Found: C, 56.99; H, 6.09; N, 9.48.

Methyl *β-tert*-Butyl-5-chloro-2-nitrohippurate (4b). Reaction of acid chloride **3b** and **2** gave **4b** as white needles in 81% yield: mp 155–156 °C; ^1H NMR ($CDCl_3$) δ 8.05 (d, J = 7.8, 1H), 7.46–7.42 (m, 2H), 4.06 (d, J = 18.6, 1H), 3.72 (d, J = 18.6, 1H), 3.68 (s, 3H), 1.54 (s, 9H); CIMS 329 (MH^+). Anal. Calcd for $C_{14}H_{17}ClN_2O_5$: C, 51.15; H, 5.21; N, 8.52. Found: C, 51.24; H, 5.17; N, 8.51.

Methyl 4-Bromo-*β-tert*-butyl-2-nitrohippurate (4c). Reaction of acid chloride **3c** and **2** gave **4c** as tan needles in 60% yield: mp 145–146 °C; ^1H NMR ($CDCl_3$) δ 8.25 (d, J = 1.5, 1H), 7.74 (dd, J = 1.8, 8.4, 1H), 7.38 (d, J = 8.4, 1H), 4.09 (d, J = 18.0, 1H), 3.74 (d, J = 18.0, 1H), 3.67 (s, 3H), 1.54 (s, 9H); IR 1750, 1639, 1532 cm^{-1}; CIMS 373, 375 (MH^+). Anal. Calcd for $C_{14}H_{17}BrN_2O_5$: C, 45.06; H, 4.59; N, 7.51. Found: C, 45.09; H, 4.50; N, 7.46.

4-*tert*-Butyl-1*H*-1,4-benzodiazepine-2,5-dione (6a). A solution of **4a** (18.35 g, 62.4 mmol) in 300 mL of THF/EtOH (1/2, v/v) was hydrogenated over 10 % Pd–C (3.67 g, 20 wt %) in a Parr shaker at 50 psi until H_2 uptake ceased (ca. 1 h 40 min). The catalyst was removed, and the filtrate was concentrated to an oil. The crude intermediate (**5a**) was taken up in THF (100 mL) and 1 M H_2SO_4 (100 mL), heated at reflux for 40 min, and then cooled to rt. EtOAc was then added, and the solution was washed successively with H_2O and brine. The organic phase was then dried and concentrated to give 11.3 g (78%) of a fluffy white solid: mp 183–184 °C; ^1H NMR (DMSO-d_6) δ 10.44 (br s, 1H), 7.77 (d, J = 7.8, 1H), 7.47 (t, J = 7.5, 1H), 7.19 (t, J = 7.5, 1H), 7.09 (d, J = 7.8, 1H), 3.81 (br s, 2H), 1.48 (s, 9H); IR 1693, 1632 cm^{-1}; CIMS 233 (MH^+). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.24; H, 6.98; N, 12.11.

4-*tert*-Butyl-7-chloro-1*H*-1,4-benzodiazepine-2,5-dione (6e). A solution of **4b** in THF/EtOH was hydrogenated and cyclized in the manner described for **4a** substituting 5% Pt–C (20 wt %) as the catalyst. The crude solid obtained was purified by recrystallization (EtOAc/hexanes) to give **6e** as white needles in 61% yield: mp 177–178 °C; ^1H NMR ($CDCl_3$) δ 9.77 (br s, 1H), 7.92 (d, J = 2.4, 1H), 7.35 (dd, J = 2.4, 8.7, 1H), 6.96 (d, J = 8.7, 1H), 3.90 (br s, 2H), 1.55 (s, 9H); CIMS 267 (MH^+). Anal. Calcd for $C_{13}H_{15}ClN_2O_2$: C, 58.54; H, 5.67; N, 10.50. Found: C, 58.71; H, 5.66; N, 10.53.

8-Bromo-4-*tert*-butyl-1*H*-1,4-benzodiazepine-2,5-dione (6g). A solution of **4c** (5.12 g, 13.7 mmol) in THF/EtOH (150 mL, 1/1) was hydrogenated over 5% Pt–C (1.02 g, 20 wt %) at 50 psi for 21 h, the reaction was filtered, and the reaction was charged with an additional 1.50 g of 5% Pt–C (30 wt %).

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(32) The acid chlorides **3a–c** were prepared by heating a toluene solution of the acid (100 mol %) containing thionyl chloride (200 mol %) and a catalytic amount of DMF at 80 °C for ca. 16 h. After cooling to rt, the solution was concentrated and two additional portions of toluene were sequentially added and concentrated. It was convenient to store the acid chlorides as a 1 M solution in toluene.

Hydrogenation was continued for an additional 7 h at which time TLC analysis of the filtrate showed a few polar spots. The catalyst was filtered, sodium dithionite (5.0 g, 29 mmol) was added to the filtrate, and the reaction was heated at reflux for 3 h and then cooled to rt. The crude reaction mixture was poured into EtOAc and washed with H_2O and brine, and the organic phase was dried and concentrated to an off-white solid. The solid was triturated in hot THF and filtered hot to remove the inorganics. The cooled filtrate was dried and concentrated to give 2.15 g (50%) of an off-white solid. A small sample was purified by recrystallization from EtOH/H_2O: mp > 260 °C; ^{1}H NMR ($CDCl_3$) δ 8.74 (br s, 1H), 7.84 (d, J = 8.4, 1H), 7.36 (dd, J = 1.8, 8.4, 1H), 7.14 (d, J = 1.8, 1H), 3.90 (br s, 2H), 1.58 (s, 9H); IR 1718, 1620, 1592 cm^{-1}; CIMS 311, 313 (MH^+). Anal. Calcd for $C_{13}H_{15}BrN_2O_2$: C, 50.18; H, 4.86; N, 9.00. Found: C, 50.19; H, 4.72; N, 8.96.

7-Bromo-4-*tert*-butyl-1*H*-1,4-benzodiazepine-2,5-dione (6c). Compound **6a** (3.30 g, 14.2 mmol, 100 mol %) was dissolved in acetic acid (35 mL) and was treated with sodium acetate (2.91 g, 35.5 mmol, 250 mol %) and bromine (1.83 mL, 35.5 mmol, 250 mol %). After stirring at rt for 17 h, the reaction mixture was concentrated to a paste, dissolved in EtOAc, and washed sequentially with 1 M sodium thiosulfate, H_2O, saturated sodium bicarbonate, and brine. Drying and concentrating the organic phase left a white solid which was purified by recrystallization from EtOH/H_2O affording 3.18 g (72%) of a white solid: mp 205–208 °C; ^{1}H NMR ($CDCl_3$) δ 9.62 (br s, 1H), 8.07 (d, J = 2.1, 1H), 7.49 (dd, J = 2.1, 8.7, 1H), 6.89 (d, J = 8.7, 1H), 3.89 (br s, 2H), 1.55 (s, 9H); CIMS 311, 313 (MH^+). Anal. Calcd for $C_{13}H_{15}BrN_2O_2$: C, 50.18; H, 4.86; N, 9.00. Found: C, 50.17; H, 4.95; N, 9.07.

4-*tert*-Butyl-7-iodo-1*H*-1,4-benzodiazepine-2,5-dione (6d). To a solution of **6a** (11.3 g, 48.7 mmol, 100 mol %) and bis(trifluoroacetoxy)phenyliodine (23.0 g, 53.6 mmol, 110 mol %) in CH_2Cl_2 (100 mL) was added iodine (12.4 g, 48.7 mmol, 100 mol %). After stirring for 18 h at rt the dark solution was washed with saturated sodium bicarbonate, 1 M sodium thiosulfate, and brine. Each of the aqueous phases were back-extracted with CH_2Cl_2, and the combined organic phases were dried and concentrated to give a tan solid. Trituration in EtOAc/hexanes (40/60) followed by filtration gave 13.6 g (78%) of a cream-colored solid. Flash chromatography (EtOAc/hexanes, 20–33%) gave an analytically pure sample: mp 230–232 °C; ^{1}H NMR (DMSO-d_6) δ 10.47 (br s, 1H), 7.99 (d, J = 1.8, 1H), 7.68 (dd, J = 1.8, 8.1, 1H), 6.85 (d, J = 8.1, 1H), 3.78 (br s, 2H), 1.42 (s, 9H); CIMS 359 (MH^+). Anal. Calcd for $C_{13}H_{15}IN_2O_2$: C, 43.59; H, 4.22; N, 7.82. Found: C, 43.82; H, 4.08; N, 7.59.

9-Bromo-7-chloro-4-*tert*-butyl-1*H*-1,4-benzodiazepine-2,5-dione (6f). A suspension of **6e** (7.20 g, 27.1 mmol, 100 mol %), sodium acetate (11.1 g, 135 mmol, 500 mol %), bromine (7.0 mL, 135 mmol, 500 mol %) and ferric bromide (0.40 g, 1.35 mmol, 5 mol %) in 100 mL of acetic acid/H_2O (7/3, v/v) was heated at 40 °C for 21 h. The crude reaction mixture was partitioned between EtOAc and H_2O, the aqueous phase was removed, and the organic layer was washed successively with three portions of 0.1 M NaOH and one portion each of 1 M sodium thiosulfate and brine. The organic layer was dried and concentrated, and the resultant solid was triturated in 30 mL of EtOAc/hexanes (1/2) to give, after filtration, 7.0 g (75%) of a tan solid. Flash chromatography (EtOAc/hexanes, 20/80) gave an analytically pure sample: mp 176–178 °C; ^{1}H NMR (DMSO-d_6) δ 9.84 (br s, 1H), 7.96 (d, J = 2.4, 1H), 7.68 (d, J = 2.4, 1H), 3.90–3.80 (m, 2H), 1.45 (s, 9H); CIMS 345, 347 (MH^+). Anal. Calcd for $C_{13}H_{14}BrClN_2O_2$: C, 45.18; H, 4.08; N, 8.10. Found: C, 45.28; H, 3.93; N, 8.08.

Palladium-Mediated Alkynylation of Halobenzodiazepinediones. General Procedure. A degassed suspension of halobenzodiazepinedione (100 mol %) and alkyne (120 mol %) in triethylamine (0.1–0.2 M) was stirred at the temperature and time indicated below in the presence of 2 mol % dichlorobis(triphenylphosphine)palladium(II) and 4 mol % copper(I) iodide. The reaction mixture was diluted with EtOAc, washed with H_2O and brine, and then dried and concentrated to afford the crude products, purified as indicated below.

4-*tert*-Butyl-7-(2′-phenylethynyl)-1*H*-1,4-benzodiazepine-2,5-dione (7). Stirring compound **6d** with phenylacetylene at rt for 20 h gave crude **7** which was purified by recrystallization (EtOH/H_2O), affording light amber crystals in 69% yield: mp 233–234 °C; ^{1}H NMR (DMSO-d_6) δ 10.62 (br s, 1H), 7.89 (d, J = 2.2, 1H), 7.62 (dd, J = 2.2, 8.5, 1H), 7.57–7.52 (m, 2H), 7.44–7.39 (m, 3H), 7.10 (d, J = 8.5, 1H), 3.84 (br s, 2H), 1.46 (s, 9H); CIMS 333 (MH^+). Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06; N, 8.43. Found: C, 75.68; H, 5.89; N, 8.39.

4-*tert*-Butyl-8-[2′-(trimethylsilyl)ethynyl]-1*H*-1,4-benzodiazepine-2,5-dione (18). Compound **6g** was heated with (trimethylsilyl)acetylene for 6 h at reflux whereupon an additional 30 mol % of (trimethylsilyl)acetylene was added and heating was continued for an additional 3 h. The crude **18** was purified by flash chromatography (EtOAc/hexanes, 20/80) to give a light yellow solid in 41% yield: mp 200–202 °C; ^{1}H NMR ($CDCl_3$) δ 8.47 (br s, 1H), 7.88 (d, J = 8.1, 1H), 7.28 (dd, J = 1.5, 8.1, 1H), 7.02 (d, J = 1.5, 1H), 3.88 (br s, 2H), 1.55 (s, 9H), 0.22 (s, 9H); IR 1717, 1626, 1606 cm^{-1}; CIMS 329 (MH^+). Anal. Calcd for $C_{18}H_{24}N_2O_2Si$: C, 65.82; H, 7.36; N, 8.53. Found: C, 65.39; H, 7.41; N, 8.23.

4-*tert*-Butyl-7-chloro-9-[2′-(trimethylsilyl)ethynyl]-1*H*-1,4-benzodiazepine-2,5-dione (20). Compound **6f** was heated with (trimethylsilyl)acetylene at reflux for 30 min and then cooled to rt. The crude **20** was purified by flash chromatography (EtOAc/hexanes, 20/80) to afford an amber oil in 72% yield which solidified on standing: mp 60–63 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (br s, 1H), 7.86 (d, J = 2.4, 1H), 7.50 (d, J = 2.4, 1H), 3.87 (br s, 2H), 1.52 (s, 9H), 0.26 (s, 9H); IR 1714, 1657, cm^{-1}; CIMS 363 (MH^+). Anal. Calcd for $C_{18}H_{23}ClN_2O_2Si$: C, 59.57; H, 6.39; N, 7.72. Found: C, 59.97; H, 6.52; N, 7.33.

4-*tert*-Butyl-8-ethynyl-1*H*-1,4-benzodiazepine-2,5-dione (19). The trimethylsilyl-protected **18** (0.67 g, 2.04 mmol) was dissolved in 10 mL of MeOH and treated with 2.25 mL of 1 M NaOH. After stirring at rt for 6 h, the reaction mixture was partitioned in EtOAc and H_2O. The aqueous phase was removed and the organic layer was washed with additional H_2O and brine. After drying and concentrating the organic phase, the crude product was purified by flash chromatography (EtOAc/hexanes, 15/85) to give 0.45 g (86 %) of a light brown solid: mp 205–206.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.06 (br s, 1H), 7.93 (d, J = 8.4, 1H), 7.35 (dd, J = 1.5, 8.4, 1H), 7.05 (d, J = 8.4, 1H), 3.90 (br s, 2H), 3.20 (s, 1H), 1.57 (s, 9H); IR 1695, 1620 cm^{-1}; CIMS 257 (MH^+). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 69.85; H, 5.97; N, 10.59.

4-*tert*-Butyl-7-chloro-9-ethynyl-1*H*-1,4-benzodiazepine-2,5-dione (21). Compound **20** was treated in essentially the same manner as described above except the reaction was complete after 2 h. Flash chromatography (EtOAc/hexanes, 20/80) gave a light yellow solid in 67% yield: mp 145–148 °C; ^{1}H NMR ($CDCl_3$) δ 7.99 (br s, 1H), 7.93 (d, J = 1.8, 1H), 7.56 (d, J = 1.8, 1H), 3.89 (br s, 2H), 3.56 (s, 1H), 1.54 (s, 9H); IR 1689, 1643, cm^{-1}; CIMS 291 (MH^+). Anal. Calcd for $C_{15}H_{15}ClN_2O_2$: C, 61.97; H, 5.20; N, 9.63. Found: C, 61.84; H, 5.17; N, 9.44.

Vinylation of 6d. A solution consisting of **6d** (3.50 g, 9.78 mmol, 100 mol %), triethylamine (1.83 mL, 13.2 mmol, 135 mol %), palladium(II) acetate (0.05 g, 0.20 mmol, 2 mol %), and triphenylphosphine (0.10 g, 0.39 mmol, 4 mol %) in DMF (15 mL) was placed in a sealable Pyrex tube and was bubbled with a stream of N_2 for 2 min. Vinyltrimethylsilane (3.77 mL, 24.5 mmol, 250 mol %) was added, and the tube was then sealed and lowered into an 80 °C oil bath and heated for 22 h. After cooling to rt, the reaction mixture was diluted with EtOAc and washed with H_2O and brine. The organic phase was dried and concentrated, and the crude product was chromatographed (EtOAc/hexanes, 20–25%) to afford an inseparable mixture of **11** and **12** (less polar) and compound **10** (more polar).

11 and **12**: Isolated as a yellow solid in a combined yield of 23% (2:1); mp 170–190 °C; CIMS 331 (MH^+). Anal. Calcd for $C_{18}H_{26}N_2O_2Si$: C, 65.41; H, 7.93; N, 8.43. Found: C, 65.50; H, 7.63; N, 8.28. **11**: ^{1}H NMR (DMSO-d_6) δ 10.48 (br s, 1H), 7.82 (d, J = 1.9, 1H), 7.60 (dd, J = 2.3, 8.5, 1H), 7.03 (d, J =

8.5, 1H), 6.90 (d, J = 19.2, 1H), 6.48 (d, J = 19.2, 1H), 3.80 (br s, 2H), 1.45 (s, 9H), 0.13 (s, 9H). **12**: ^{1}H NMR (DMSO-d_6) δ 10.43 (br s, 1H), 7.59 (d, J = 2.2, 1H), 7.32 (dd, J = 2.2, 8.4, 1H), 7.04 (d, J = 8.4, 1H), 5.88 (d, J = 2.6, 1H), 5.61 (d, J = 2.6, 1H), 3.80 (br s, 2H), 1.45 (s, 9H), 0.15 (s, 9H).

10: Isolated as a light yellow solid in 50% yield; mp 174–175.5 °C; CIMS 259 (MH^+); ^{1}H NMR (DMSO-d_6) δ 10.46 (br s, 1H), 7.78 (br s, 1H), 7.60 (d, J = 8.4, 1H), 7.04 (d, J = 8.4, 1H), 6.73 (dd, J = 10.8, 17.7, 1H), 5.79 (d, J = 17.7, 1H), 5.23 (d, J = 10.8, 1H), 3.81 (br s, 2H), 1.45 (s, 9H); CIMS 259 (MH^+). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.43; H, 7.00; N, 10.57.

4-*tert*-Butyl-7-phenyl-1*H*-1,4-benzodiazepine-2,5-dione (13). A degassed solution of **6d** (1.50 g, 4.19 mmol, 100 mol %) and phenyltrimethylstannane (1.11 g, 4.61 mmol, 110 mol %) in THF (15 mL) was heated at reflux in the presence of dichlorobis(triphenylphosphine)palladium(II) for 29 h. The dark reaction mixture was cooled to rt, diluted with Et_2O, and filtered. The filtrate was washed with H_2O, saturated sodium bicarbonate, and brine, and after drying and concentrating, the resultant residue was chromatographed (EtOAc/hexanes, 25–30%) to give 0.55 g (43%) of a white solid: mp 230.5–233 °C; ^{1}H NMR (DMSO-d_6) δ 10.52 (br s, 1H), 8.01 (d, J = 2.4, 1H), 7.79 (dd, J = 2.1, 8.1, 1H), 7.67 (d, J = 8.7, 2H), 7.47 (t, J = 7.5, 2H), 7.36 (t, J = 7.5, 1H), 7.17 (d, J = 8.1, 1H), 3.86 (br s, 2H), 1.48 (s, 9H); CIMS 309 (MH^+). Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.66; H, 6.53; N, 8.99.

Palladium-Mediated Heteroarylation of Halobenzodiazepinediones. General Procedure. A degassed solution of the halobenzodiazepinedione (100 mol %) and heteroarylstannane (110 mol %) was heated in THF in the presence of dichlorobis(triphenylphosphine)palladium(II) (5 mol %) and copper(I) iodide (5 mol %) for the time indicated below. The crude reaction mixture was then diluted with EtOAc and filtered. The filtrate was concentrated, and the crude product was purified by flash chromatography.

4-*tert*-Butyl-7-(2′-pyridyl)-1*H*-1,4-benzodiazepine-2,5-dione (15). Heating **6d** and 2-pyridyltrimethylstannane **14**[28,33] in THF at reflux for 3 h followed by flash chromatography (EtOAc/hexanes, 40–60 %) gave **15** as a light yellow powder in 70% yield: mp 209–211 °C dec; ^{1}H NMR (DMSO-d_6) δ 10.57 (br s, 1H), 8.65 (dd, 1.2, 3.9, 1H), 8.49 (d, J = 2.1, 1H), 8.18 (dd, J = 2.1, 5.4, 1H), 7.97 (d, J = 7.8, 1H), 7.87 (dt, J = 2.1, 7.8, 1H), 7.36–7.31 (m, 1H), 7.18 (d, J = 8.7, 1H), 3.86 (br s, 2H), 1.49 (s, 9H); CIMS 310 (MH^+).

4-*tert*-Butyl-7-(2′-furyl)-1*H*-1,4-benzodiazepine-2,5-dione (17). Heating **6d** and 2-furyltrimethylstannane **16**[28,34] in THF at reflux for 6 h followed by flash chromatography (EtOAc/hexanes, 20–25 %) and trituration of the residue (EtOAc/hexanes, 10/90) gave **17** as a beige solid in 72% yield. Recrystallization (EtOH/H_2O) afforded an analytically pure sample: mp 232–234 °C; ^{1}H NMR (DMSO-d_6) δ 10.50 (br s, 1H), 8.04 (d, J = 2.4, 1H), 7.78 (dd, J = 2.4, 8.7, 1H), 7.74 (d, J = 1.8, 1H), 7.11 (d, J = 8.7, 1H), 6.96 (d, J = 3.0, 1H), 6.58 (dd, J = 1.8, 3.0, 1H), 3.84 (br s, 2H), 1.47 (s, 9H); CIMS 299 (MH^+). Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.03; H, 6.04; N, 9.27.

4-*tert*-Butyl-7-chloro-9-(2′-pyridyl)-1*H*-1,4-benzodiazepine-2,5-dione (22). Compound **6f** and 2-pyridyltrimethylstannane **14**[28,33] were heated at reflux in THF for 33 h. Flash chromatography (EtOAc/hexanes, 25-30%) gave recovered **6f** (23%) followed by **22** as a white solid in 57% yield. Recrystallization (EtOH/H_2O) afforded an analytically pure sample as white needles: mp 183–185 °C; ^{1}H NMR ($CDCl_3$) δ 11.82 (br s, 1H), 8.66 (dd, 0.9, 4.8, 1H), 7.92 (d, J = 2.4, 1H), 7.85 (dt, J = 1.8, 7.8, 1H), 7.66–7.63 (m, 2H), 7.32 (ddd, J = 1.8, 4.8, 7.8, 1H), 3.86 (br s, 2H), 1.57 (s, 9H); IR 1686, 1640 cm^{-1}; CIMS 344 (MH^+). Anal. Calcd for $C_{18}H_{18}ClN_3O_2$: C, 62.88; H, 5.28; N, 12.22. Found: C, 62.68; H, 5.23; N, 12.16.

4-*tert*-Butyl-7-chloro-9-(2′-furyl)-1*H*-1,4-benzodiazepine-2,5-dione (23). Compound **6f** and 2-furyltrimethylstannane **16**[28,34] were heated at reflux in THF for 22 h. An additional 30 mol % of 2-furylstannane was added followed by heating for 8 h more. Flash chromatography (EtOAc/hexanes, 15–25%) gave recovered **6f** (28%) followed by **23** as a beige solid in 53% yield: mp 164.5–166 °C; ^{1}H NMR ($CDCl_3$) δ 8.38 (br s, 1H), 7.84 (d, J = 2.7, 1H), 7.62 (d, J = 2.4, 1H), 7.59 (d, J = 1.8, 1H), 6.69 (d, J = 3.3, 1H), 6.55 (dd, 1.8, 3.3, 1H), 3.90 (br s, 2H), 1.57 (s, 9H); IR 1687, 1644 cm^{-1}; CIMS 333 (MH^+). Anal. Calcd for $C_{17}H_{17}ClN_2O_3$: C, 61.36; H, 5.15; N, 8.42. Found: C, 61.31; H, 5.07; N, 8.31.

4-*tert*-Butyl-9-(2′-pyridyl)-1*H*-1,4-benzodiazepine-2,5-dione (24). A solution of compound **22** (0.45 g, 1.31 mmol) in 30 mL of EtOH was heated at reflux in the presence of ammonium formate (0.41 g, 6.50 mmol) and 10% Pd–C (0.21 g) for 22 h. After cooling, the catalyst was filtered and the filtrate was concentrated to dryness leaving 0.26 g (68%) of an off-white solid. Recrystallization (EtOH/H_2O) gave an analytically pure sample as white needles: mp 160–162 °C; ^{1}H NMR ($CDCl_3$) δ 11.91 (br s, 1H), 8.65 (d, J = 2.7, 1H), 7.95 (d, J = 7.5, 1H), 7.83 (t, J = 7.5, 1H), 7.68 (t, J = 9, 2H), 7.30–7.24 (m, 2H), 3.86 (br s, 2H), 1.58 (s, 9H); IR 1691, 1637 cm^{-1}; CIMS 310 (MH^+). Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 70.00; H, 6.45; N, 13.38.

JO950925A

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