An improved synthesis of 1,3-dihydro-1-methyl-5-phenyl-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-one via *ortho*-directed lithiation of 3-*tert*-butyl and 3-*tert*-butoxycarbonylaminopyridine

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The *ortho*-directed lithiation of 3-*tert*-butyl- or 3-*tert*-butoxycarbonylaminopyridines (**3**) with alkyllithiums and reaction with *N*,*N*-diethylbenzamide followed by acid hydrolysis gave 3-amino-4-benzoylpyridine (**6**) in good yield. Reaction of BTBO with the glycine derivatives **7***a*, *b* and then reaction with **6** afforded 3-alkoxycarbonylaminomethylcarbonylamino-4-benzoylpyridines **8***a*, *b*. Acid-catalyzed hydrolysis and cyclization of **8***a*, *b* yielded **9**, which on methylation gave 1,3-dihydro-1-methyl-5-phenyl-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-one (**10**) in 36% overall yield from **3***a*.

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La lithiation en position *ortho* des *tert*-butyl- ou *tert*-butoxycarbonylamino-3 pyridines (**3**) par les alkyllithiens ou leur réaction avec du *N*,*N*-diéthylbenzamide, suivie d'une hydrolyse acide, conduisent à l'amino-3 benzoyl-4 pyridine (**6**) avec de bons rendements. La réaction du BTBO avec les dérivés **7***a*, *b* de la glycine, suivie d'une réaction avec le composé **6**, conduit aux alkoxycarbonylaminométhylcarbonylamino-3 benzoyl-4 pyridines (**8***a*, *b*). L'hydrolyse acido-catalysée des composés **8***a*, *b*, suivie d'une cyclisation, conduit au composé **9** qui, par méthylation, fournit la dihydro-1,3 méthyl-1 phényl-5 2*H*-pyrido[3,4-*e*] diazépine-1,4 one-2 (**10**), avec un rendement global de 36% à partir du composé **3***a*.

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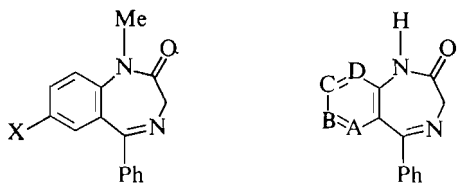
Introduction

The 1,4-benzodiazepin-2-ones **1** are a clinically useful class of compounds that exhibit a wide spectrum of powerful effects on the central nervous system, including anxiolytic, sedative, hypnotic, anticonvulsant, and muscle relaxant properties (1). Although it is known that an electronegative X substituent at C-7 of **1** is required for high potency (1), very few electronically analogous pyrido-1,4-diazepin-2-ones **2** have been investigated. Methods for the synthesis of **2** are often laborious, of narrow applicability, require the relatively inaccessible aminopyridinecarboxylic acid precursors, and provide low overall yields (2). Although **2***c* has been reported, no experimental details were provided (2). An efficient synthesis of **2***c*



1 **2**

a, A = N; B, C, D = CH
b, B = N; A, C, D = CH
c, C = N; A, B, D = CH
d, D = N; A, B, C = CH

and the 4-benzoyl-3-aminopyridine derivatives **4**–**6** and **8** was required for the synthesis of bicyclic and monocyclic reduced pyridyl analogues for other studies in our drug design program. The regioselective *ortho*-directed metallation of 3-substituted pyridines possessing pivaloylamino (3), dialkylaminocarbonyl (4), O-carbamate (5), 4,4-dimethyl-2-oxazolinyl (6), and halogeno (7) substituents is a versatile method for the synthesis of 3,4-disubstituted pyridines. *Ortho*-lithiation of 2- and 4-*tert*-butoxycarbonylaminopyridine has been utilized for the synthesis of 3-substituted-2-aminopyridines (8) and 3-substituted-4-aminopyridines (9), respectively. We now report an improved synthesis of 1,3-dihydro-1-methyl-5-phenyl-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-one (**10**) using *ortho*-directed lithiation of 3-*tert*-butyl- or 3-*tert*-butoxycarbonylaminopyridine (**3**).

Results and discussion

Lithiation of 3-*tert*-butylcarbonylaminopyridine (**3***a*) in THF using *n*-butyllithium and reaction with *N*,*N*-diethylbenzamide yielded 3-*tert*-butylcarbonylamino-4-benzoylpyridine (**4***a*, 70% yield, Scheme 1). Recent reports have suggested that clean metallation of **3***a* is not possible with *n*-butyllithium in THF (3*b*, 10), that specific conditions (THF, Et_2O, TMEDA, 20°C) are required for optimum yields of 50–60% (3*b*), or that C-4 metallation was competitive with nucleophilic attack by the metallation reagent at C-4 (3*a*). Other metallating agents such as lithium diisopropylamide and methyllithium lead neither to *ortho*-lithiation nor nucleophilic addition to the nucleus (3*b*). Alternatively, **4***a* was prepared less efficiently by a multiple step reaction sequence, involving *ortho*-lithiation of **3***a* with *n*-butyllithium, reaction with benzaldehyde, and oxidation of **5***a* with pyridinium dichromate.[2] A similar *ortho*-lithiation of 3-*tert*-butoxycarbonylaminopyridine (**3***b*),[3] using *tert*-butyllithium or *n*-butyllithium, in THF followed by reaction with *N*,*N*-diethylbenzamide as described previously, afforded **4***b* in 65 and 63% yield, respectively. There was no evidence of metallation at any position other than C-4 nor of any nucleophilic addition of the metallating agent to the pyridine ring. The 3-*tert*-butoxycarbonylamino substituent of **3***b* is therefore an example of a single electron-donating substituent that is capable of inducing *ortho*-lithiation of **3***b* by a "coordination-only" mechanism (3*a*). In contrast, reaction of pyridines possessing such electron-attracting substituents as cyano, diethylaminocarbonyl, and oxazolinyl at C-3, with nucleophilic alkyllithium reagents, yielded 1,2-, 1,4-, and (or) 1,6-dihydropyridine products where proton abstraction was superseded by nucleophilic addition to the pyridine ring (6, 12).

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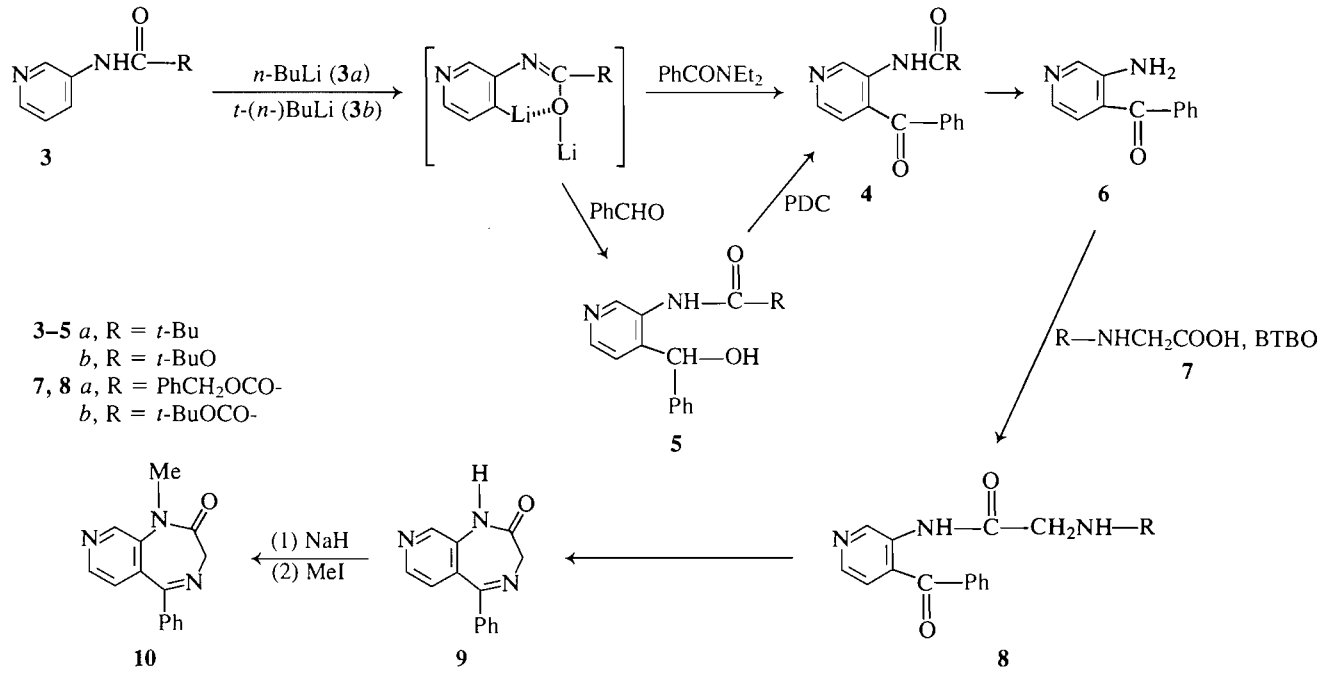
[2]The synthesis of **5***a* has been reported using different reagents and (or) reaction conditions (3*a*, *b*).

[3]1,2,2,2-Tetrachloroethyl *tert*-butyl carbonate has also been reported to be a simple and efficient reagent for the *tert*-butoxycarbonylation of amines and aminoacids, see ref. 11.



SCHEME 1

The reaction of **3***b* with *tert*-butyllithium or *n*-butyllithium, condensation with benzaldehyde to yield **5***b* (68 and 62% yield respectively), and oxidation of **5***b* with pyridinium dichromate also yielded **4***b* (89% yield). Hydrolysis of the 3-*tert*-butylcarbonylamino analog **4***a* using ethanol – hydrochloric acid at reflux afforded 3-amino-4-benzoylpyridine (**6**) in 94% yield, whereas hydrolysis of the 3-*tert*-butoxycarbonylamino derivative **4***b* with trifluoroacetic acid in 1,2-dichloroethane at 25°C yielded **6** in 97% yield. Although the overall yields of **6** prepared from **3***a* and **3***b* are quantitatively similar (**3***a* → **4***a* → **6**, 66% yield, and **3***b* → **4***b* → **6**, 63% yield), the *tert*-butoxycarbonylamino *ortho*-directing substituent may be advantageous for compounds possessing labile substituents or ring systems, due to its more facile conversion to a free amino group.[4]

Activation of *N*-benzyloxycarbonylglycine (**7***a*) with 1,1′-bis-[6-(trifluoromethyl)benzotriazolyl] oxalate (BTBO) (14), followed by condensation with **6**, afforded crystalline **8***a* in 90% yield. A similar reaction of BTBO with *tert*-butoxycarbonylglycine (**7***b*) followed by reaction with **6** yielded crystalline **8***b* in 83% yield.[5] Acid hydrolysis of **8***a* (HBr–CH_3COOH) and **8***b* (CF_3COOH) at 25°C gave the pyridodiazepinone **9** in 82 and 89% yield, respectively. Methylation of **9** using sodium hydride and iodomethane afforded the title compound 1,3-dihydro-1-methyl-5-phenyl-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-one (**10**) in 73% yield.

The synthesis of 3-amino-4-benzoylpyridine, using *ortho*-lithiation methodology, has provided a shorter, simpler, and more efficient method for the synthesis of the pyridodiazepinone **10**. This methodology will be applicable to the construction of structurally related bicyclic nitrogen heterocycles.

Experimental

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined for solutions of deuteriochloroform or deuteriodimethyl sulfoxide with a Bruker AM-300 spectrometer. Infrared spectra were recorded on a Nicolet 5DX FT spectrometer. Mass spectra were measured on a Hewlett Packard 5995A gas chromatograph – mass spectrometer using the direct insertion probe method. Kieselgel silica gel DSF-5 (Camag) was used for preparative thin-layer chromatography (tlc). Silica gel (Baker, 70–200 mesh) was used for column chromatography. Tetrahydrofuran and ether were distilled from sodium-benzophenone immediately before use. *n*-Butyllithium (2.6 *M* solution in hexanes) and *tert*-butyllithium (2.0 *M* solution in pentane) were obtained from the Aldrich Chemical Co. Elemental analyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of Alberta. 3-*tert*-Butylcarbonylaminopyridine (**3***a*) was prepared by the literature procedures (**3***a*, *b*).

*3-*tert*-Butylcarbonylamino-4-benzoylpyridine (**4**a)*

Method 1

A solution of *n*-butyllithium (27 mL, 70 mmol) was added dropwise to a solution of **3***a* (5.12 g, 29 mmol) in 100 mL THF at −78°C with stirring under a nitrogen atmosphere. The temperature was maintained at −78°C for a further 15 min, and then at 0°C for 3 h. The reaction mixture was cooled to −78°C, a solution of *N*,*N*-diethylbenzamide (9.92 g, 52 mmol) in 20 mL THF was added dropwise, and the reaction mixture was allowed to stir at 25°C overnight. The reaction mixture was poured into a mixture of ice (100 g) and 5 *N* HCl (20 mL); this mixture was stirred for 10 min and neutralized with aqueous potassium carbonate prior to extraction with ethyl acetate. The organic extract was washed with brine, dried ($MgSO_4$), and the solvent removed *in vacuo*. Recrystallization from ethyl acetate – hexane (2:1 v/v) afforded **4***a* (5.71 g, 70%): mp 125–126°C; ir (KBr): 3337, 2968, 1688, 1680, 1647 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 10.5 (br s, 1H, NH, exchanges with deuterium oxide), 9.98 (s, 1H, H-2), 8.52 (d, J = 5.8 Hz, 1H, H-6), 7.54–7.88 (m, 5H, phenyl hydrogens), 7.43 (d, J = 5.8 Hz, 1H, H-5), 1.35 (s, 9H, *tert*-butyl); ms, m/z: 282 (M^+). *Anal.*

[4]The *ortho*-functionalization of *N*-(*tert*-butoxycarbonyl)aniline and near quantitative hydrolysis of the *tert*-butoxycarbonylamino group to a free amino group has been reported (13).

[5]BTBO is a superior coupling reagent to dicyclohexylcarbodiimide (DCC) since reactions employing DCC yielded **8** as oils due to the difficulty in removing dicyclohexylurea and *N*-acylurea side products. Compound **8** has been reported as an oil (2*b*).

calcd. for $C_{17}H_{18}N_2O_2$: C 72.32, H 6.43, N 9.92; found: C 72.30, H 6.41, N 10.04.

Method 2

A solution of benzaldehyde (22.3 g, 210 mmol) in THF (35 mL) was added dropwise to a solution of 4-lithio-3-*tert*-butylcarbonylaminopyridine, prepared from reaction of **3***a* (25.1 g, 140 mmol) in 350 mL THF and *n*-butyllithium (135 mL, 351 mmol) as described under Method 1 at −78°C, and the reaction mixture was allowed to stir at 25°C overnight. The reaction mixture was poured into water (200 mL) and the THF fraction was separated. Removal of the solvent *in vacuo* gave a residue that was dissolved in chloroform and washed with water. The chloroform fraction was dried ($MgSO_4$), the solvent was removed *in vacuo*, and the residue was triturated with hexane to yield **5***a*, which was recrystallized from ethyl acetate – hexane (24.1 g, 60%): mp 208–209°C (lit. (3*b*) mp 200–202°C; lit. (3*a*) mp 206–209°C).

A solution of **5***a* (6.79 g, 24 mmol) in 40 mL DMF and pyridinium dichromate (12 g, 32 mmol) was stirred at 25°C for 2 h prior to pouring into water (300 mL). Extraction with ethyl acetate, drying ($MgSO_4$), and removal of the solvent *in vacuo* yielded the product **4***a*, which was purified by silica gel column chromatography using hexane – ethyl acetate (1:1 v/v) as eluant. The product **4***a* (5.6 g, 83%) was identical (mp, ^{1}H nmr) to that of **4***a* described under Method 1.

*3-*tert*-Butoxycarbonylaminopyridine (**3**b)*

A mixture of di-*tert*-butyldicarbonate (41 g, 188 mmol), 3-aminopyridine (17.3 g, 184 mmol), and *tert*-butyl alcohol (200 mL) was heated at 80°C for 2 h. The solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate and washed with 0.5 *M* citric acid (30 mL) and water. The ethyl acetate fraction was dried (Na_2SO_4) and the solvent removed *in vacuo*. The product was purified by silica gel column chromatography, using ethyl acetate – hexane (2:1 v/v) as eluate, and subsequent recrystallization from ethyl acetate – hexane (2:1 v/v) to yield **3***b* (27.1 g, 74%): mp 115–116°C; ir (KBr): 3238, 2976, 1729, 1598, 1548 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 8.56 (d, J = 2.5 Hz, 1H, H-2), 8.35 (dd, J = 1.5 Hz, J = 5 Hz, 1H, H-6), 8.14 (dd, J = 8 Hz, J = 2.5 Hz, 1H, H-4), 7.75 (br s, 1H, NH, exchanges with deuterium oxide), 7.3 (dd, J = 8 Hz, J = 2.5 Hz, 1H, H-5), 1.55 (s, 9H, *tert*-butyl); ms, *m/z*: 194 (M^+). *Anal.* calcd. for $C_{10}H_{14}N_2O_2$: C 61.84, H 7.26, N 14.42; found: C 61.53, H 7.32, N 14.38.

*3-*tert*-Butoxycarbonylamino-4-benzoylpyridine (**4**b)*

Method 1

A solution of *tert*-butyllithium (24.6 mL, 40 mmol) was added dropwise, with stirring, to a solution of **3***b* (3.3 g, 17 mmol) in THF (30 mL) at −78°C under a nitrogen atmosphere. The temperature was maintained at −78°C for a further 15 min and then at −20°C for 3 h. The reaction mixture was cooled to −78°C and a solution of *N*,*N*-diethylbenzamide (5.79 g, 32.7 mmol) in THF (10 mL) was added dropwise. The reaction mixture was allowed to warm to 25°C, poured into a mixture of ice (100 g) and 5 *N* HCl (20 mL), stirred for 10 min, and neutralized with aqueous potassium carbonate. The THF layer was separated and the aqueous fraction was extracted with ethyl acetate. The combined organic fractions were washed with brine, dried (Na_2SO_4), and the solvent was removed *in vacuo*. The product was purified by silica gel column chromatography with hexane – ethyl acetate (1:1 v/v) as eluant prior to recrystallization from the same solvent mixture to yield **4***b* (3.3 g, 65%): mp 123–124°C; ir (KBr): 3353, 2984, 1729, 1655 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 9.75 (s, 1H, H-2), 9.22 (br s, 1H, NH, exchanges with deuterium oxide), 8.44 (d, J = 5.8 Hz, 1H, H-6), 7.52–7.88 (m, 5H, phenyl hydrogens), 7.35 (d, J = 5.8 Hz, 1H, H-5), 1.56 (s, 9H, *tert*-butyl); ms, *m/z*: 298 (M^+). *Anal.* calcd. for $C_{17}H_{18}N_2O_3$: C 68.44, H 6.08, N 9.39; found: C 68.55, H 6.03, N 9.74.

Use of *n*-butyllithium, rather than *tert*-butyllithium as described above, afforded **4***b* in 63% yield.

Method 2

A solution of benzaldehyde (4.15 g, 39 mmol) in THF (10 mL) was added dropwise to a solution of 4-lithio-3-*tert*-butoxycarbonylaminopyridine, prepared from reaction of **3***b* (5.0 g, 26 mmol) in 40 mL THF and *tert*-butyllithium (38 mL, 75 mmol), as described above, at −78°C. The reaction mixture was allowed to warm to 25°C and water (25 mL) was added. Extraction with ethyl acetate, drying (Na_2SO_4), removal of the solvent *in vacuo*, and recrystallization from hexane – ethyl acetate yielded **5***b* (5.26 g, 68%): mp 134–135°C; ir (KBr): 3337 (br), 2976, 1606 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 8.99 (s, 1H, H-2), 8.09 (br s, 1H, NH, exchanges with deuterium oxide), 8.0 (d, J = 5.8 Hz, 1H, H-6), 7.38 (m, 5H, phenyl hydrogens), 7.0 (d, J = 5.8 Hz, 1H, H-5), 6.3 (br s, 1H, OH, exchanges with deuterium oxide), 5.89 (s, 1H, -*CH*—OH), 1.57 (s, 9H, *tert*-butyl); ms, *m/z*: 300 (M^+). *Anal.* calcd. for $C_{17}H_{20}N_2O_3$: C 67.98, H 6.71, N 9.33; found: C 68.13, H 6.70, N 9.36.

Use of *n*-butyllithium, rather than *tert*-butyllithium as described above, afforded **5***b* in 62% yield.

A solution of **5***b* (2.3 g, 7.7 mmol) in DMF (15 mL) and pyridinium dichromate (3.6 g, 9.6 mmol) was stirred at 25°C for 2 h before pouring into water (150 mL). Isolation and purification of the product, as described for **4***a* under Method 2, afforded **4***b* in 89% yield.

*3-Amino-4-benzoylpyridine (**6**)*

Method 1

A solution of 95% ethyl alcohol (10 mL) and 5 *N* HCl (30 mL) was added to **4***a* (1.0 g, 3.5 mmol) and the mixture was heated at reflux for 6 h. After cooling to 0°C the reaction mixture was neutralized with aqueous ammonium hydroxide to yield **6** as yellow crystals (0.6 g, 94%): mp 127–129°C (lit. (2*a*) mp 126–128°C).

Method 2

A solution of trifluoroacetic acid-1,2-dichloroethane (1:12 v/v) (50 mL) was added to **4***b* (1.0 g, 3.4 mmol) and the mixture was stirred at 25°C for 3.5 h. The mixture was neutralized with aqueous potassium carbonate at 0°C, extracted with chloroform, washed with water, dried ($MgSO_4$), and the solvent removed *in vacuo*. Recrystallization from *n*-heptane–chloroform yielded **6** (0.645 g, 97%): mp 126–128°C.

*3-Benzyloxycarbonylaminomethylcarbonylamino-4-benzoylpyridine (**8**a)*

A suspension of BTBO (14) (1.03 g, 2.2 mmol) in acetonitrile (20 mL) was added to a mixture of **7***a* (0.455 g, 2.2 mmol) and pyridine (0.174 g, 2.2 mmol) in acetonitrile (20 mL) at 25°C. The reaction mixture became clear in a few seconds. The mixture was stirred for a further 2 h at 25°C, **6** (0.4 g, 2 mmol) in THF (20 mL) and triethylamine (0.215 g, 2 mmol) were added, and the mixture was allowed to stir at 25°C for an additional 6 h. Removal of the solvent *in vacuo*, dissolution in ethyl acetate (30 mL), and washing with 10% aqueous sodium carbonate and then brine were performed consecutively. The ethyl acetate fraction was dried (Na_2SO_4) and most of the solvent was removed *in vacuo*, at which time hexane was added to afford **8***a* (0.694 g, 90%): mp 88–90°C; ir (KBr): 3385, 3017, 2286, 1704, 1655, 1401 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 10.56 (s, 1H, *NH*CO, exchanges with deuterium oxide), 9.86 (s, 1H, H-2), 8.62 (d, J = 5.8 Hz, 1H, H-6), 7.3–7.84 (m, 11H, phenyl hydrogens, H-5), 5.68 (br t, 1H, *NH*CH_2, exchanges with deuterium oxide), 5.17 (s, 2H, *CH_2*-Ph), 4.06 (d, J = 6.5 Hz, *CH_2*NH); ms, *m/z*: 389 (M^+). *Anal.* calcd. for $C_{22}H_{19}N_3O_4$: C 67.86, H 4.92, N 10.79; found: C 67.70, H 4.92, N 10.73.

*tert-Butoxycarbonylglycine (**7**b)*

Di-*tert*-butyldicarbonate (6.4 g, 29.3 mmol) in DMF (15 mL) was added to a mixture of glycine (2.03 g, 27 mmol) and triethylamine (4.04 g, 39.9 mmol) in water (15 mL) and the reaction was allowed to proceed with stirring at 25°C overnight. Water (200 mL) was added, the mixture was cooled to 0°C, and the pH of the solution was adjusted to 2 with 5 *N* HCl. Extraction with ethyl acetate, washing with brine, drying (Na_2SO_4), and removal of the solvent *in vacuo* gave the product **7***b*. Recrystallization from petroleum ether (bp 30–60°C) – ethyl acetate yielded **7***b* (4.05 g, 87%): mp 88–90°C (lit. (15) mp 87–90°C).[6]

*3-*tert*-Butoxycarbonylaminomethylcarbonylamino-4-benzoylpyridine (**8**b)*

Reaction of BTBO (28.52 g, 62 mmol) in acetonitrile (200 mL) with

[6]This synthesis of **7***b* provides a simple alternative to the preparation from *tert*-butyl *S*-4,6-dimethylpyrimidin-2-ylthiocarbonate and glycine reported in ref. 15.

7*b* (10.9 g, 62 mmol) and pyridine (4.9 g, 62 mmol) in acetonitrile (300 mL) followed by addition of **6** (12.3 g, 62 mmol) and triethylamine (6.27 g, 62 mmol) in THF (200 mL), and completion of the reaction as described for the synthesis of **8***a*, afforded **8***b* (18.4 g, 83%): mp 144–145°C; ir (KBr): 3353, 2976, 2935, 2853, 1704, 1655, 1598, 1565, 1516, 1401 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 10.5 (s, 1H, *NH*CO, exchanges with deuterium oxide), 9.84 (s, 1H, H-2), 8.48 (d, J = 5.8 Hz, 1H, H-6), 7.34–7.84 (m, 6H, phenyl hydrogens, H-5), 5.38 (br t, 1H, *NH*CH_2, exchanges with deuterium oxide), 3.98 (d, J = 6 Hz, 2H, *CH_2*NH), 1.44 (s, 9H, *tert*-butyl); ms, m/z: 355 (M^+). *Anal.* calcd. for $C_{19}H_{21}N_3O_4$: C 64.21, H 5.96, N 11.82; found: C 64.01, H 5.88, N 11.83.

*1,3-Dihydro-5-phenyl-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-one (**9**)*

Method 1

A saturated solution of hydrogen bromide in acetic acid (40 mL) was added to **8***a* (2.15 g, 5.5 mmol) and the mixture was stirred at 25°C for 2 h. Ether (50 mL) and then 10% aqueous methanol (100 mL) were added. Neutralization with aqueous ammonium hydroxide at 0°C, extraction with chloroform, drying the chloroform extract (Na_2SO_4), and removal of the solvent *in vacuo* afforded a residue, which was heated at reflux in toluene (200 mL) and pyridine (2 mL) for 7 h. Removal of the solvent *in vacuo* and addition of hexane yielded **9** (1.31 g, 82%), which was recrystallized from benzene–methanol: mp 258–260°C (lit. (2*a*) mp 258–260°C).

Method 2

A 1 *N* solution of trifluoracetic acid in 1,2-dichloroethane (50 mL) was added to **8***b* (0.227 g, 0.64 mmol) and the resulting solution was stirred at 25°C for 6 h. The solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate (30 mL) and neutralized with aqueous potassium carbonate. The ethyl acetate fraction was washed with brine, dried (Na_2SO_4), and the solvent removed *in vacuo*. Toluene (20 mL) and pyridine (0.5 mL) were added to the residue and the solution was heated at reflux for 7 h. Removal of the solvent *in vacuo* and purification of the residue by preparative tlc, using plates 1.0 mm in thickness, with chloroform–ether–methanol (7:2:1 v/v/v) as development solvent afforded **9**, R_f 0.4 (0.135 g, 89%): mp 258–260°C.

*1,3-Dihydro-1-methyl-5-phenyl-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-one (**10**)*

Sodium hydride (50% dispersion in oil, 0.64 g, 13.2 mmol) was added in aliquots to a solution of **9** (2.95 g, 12.4 mmol) in DMF (20 mL) with stirring at 0°C. Stirring was continued for 25 min, at which time iodomethane (1.76 g, 12.4 mmol) in ether (1 mL) was added. The reaction mixture was stirred for an additional 30 min at 0°C. Addition of water (200 mL), extraction with ethyl acetate, drying ($MgSO_4$), and removal of the solvent *in vacuo* gave a residue. Purification by preparative tlc, using plates 1.0 mm in thickness, with dichloromethane–methanol (11:1 v/v) as development solvent gave **10** (2.28 g, 73%). Recrystallization from ethyl acetate – hexane afforded **10** as white needles: mp 126–127°C; ir (KBr): 3058, 3000, 2992, 1688, 1614 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 8.84 (s, 1H, H-9), 8.52 (d, J = 5.8 Hz, 1H, H-7), 7.45–7.69 (m, 5H, phenyl hydrogens), 7.27 (d, J = 5.8 Hz, 1H, H-6), 4.97 (d, J_{gem} = 12 Hz, 1H, NCH′CO), 3.82 (d, J_{gem} = 12 Hz, 1H, NCH″CO), 3.52 (s, 3H, N-CH_3); ms, m/z: 251 (M^+). *Anal.* calcd. for $C_{15}H_{13}N_3O$: C 71.70, H 5.21, N 16.72; found: C 71.53, H 5.20, N 16.71.

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