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Synthesis of N^1-alkyl-1,4-diazepin-5-ones via Schmidt ring expansion chemistry

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Abstract

Reaction of 4-piperidone with alkyl bromides gave the corresponding *N*-alkyl-4-piperidones, and treatment of these with hydrazoic acid resulted in the Schmidt reaction to give the corresponding N^1-alkyl-1,4-diazepin-5-ones in good overall yields.

Keywords: N^1-Alkyl-1,4-diazepin-5-ones; *N*-alkyl-4-piperidones; ring expansion; Schmidt reaction.

Introduction

We have previously reported (Parker et al., 2002; Huddleston et al., 2004) on our rationale for the design of pyrimido[4,5-*e*][1,4]diazepine-based folates (**1**) as potential antitumor agents via inhibition of the enzyme glycinamide ribonucleotide formyltransferase (Baldwin et al., 1991; Taylor et al., 1997; Read et al., 1999). One of our synthetic strategies to these targets relies on the preparation of the diazepinone derivatives **2** (Scheme 1). We had envisioned preparing these derivatives via straightforward alkylation of tetrahydro-1,4-diazepin-5-one (**3**) with appropriate alkyl halides.

Results and discussion

We attempted to prepare **3** following literature procedures as outlined in Scheme 2. Thus, reaction of methyl acrylate with ethylenediamine gave the 1,4-conjugate addition product **6** in quantitative crude yield (Plenio et al., 2001). However, attempts to cyclize this material gave a mixture of products from which it was difficult to isolate the desired cyclic product **3** in good yield. The problem was that **3** is very water soluble and even with continuous extraction procedures, it was not possible to obtain better than 10% yield of pure product after column chromatography. We therefore investigated an alternative method to the synthesis of **3** which relied on the Schmidt ring expansion reaction of 4-piperidone (**7**) with hydrazoic acid, generated from the treatment of sodium azide with sulfuric acid (Groves et al., 1997). Although this method did give the desired diazepinone **3**, it was obtained in low yield. The water solubility of **3** was once again a factor in the poor isolated yield.

We reasoned that alkylating 4-piperidone first followed by the ring expansion chemistry with hydrazoic acid may be a better strategy since the *N*-alkyl diazepineone derivatives (**2**) would be more hydrophobic than **3** and, consequently, they should extract into organic solvents more easily than **3**. With this in mind, we treated 4-piperidone with the alkyl bromides **8a–c** and potassium carbonate in N,N-dimethylformamide (DMF) and obtained the corresponding *N*-alkylated 4-piperidones **9a–c** in very good yields (Scheme 3). We were gratified to find that ring expansion of these *N*-alkyl-4-piperidones with hydrazoic acid did, indeed, give the corresponding diazepinones **2a–c** in very good isolated yields after purification by column chromatography. We are currently investigating the conversion of these intermediates to our targets.

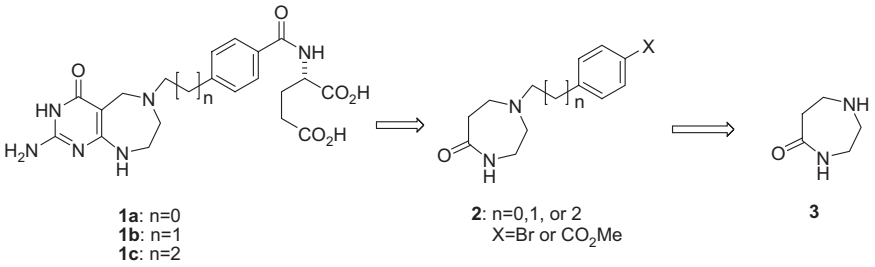
Experimental

Melting points were determined in open capillary tubes using a MELT-TEMP apparatus and are uncorrected. All ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on a Varian 400 spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from internal tetramethylsilane. Column chromatography was performed on Merck silica gel 60 (240–400) mesh, and silica gel plates were used for TLC determinations. Elemental analyses were determined by Atlantic Microlab Inc. (Norcross, GA, USA) and were within ±0.4% of the theoretical values.

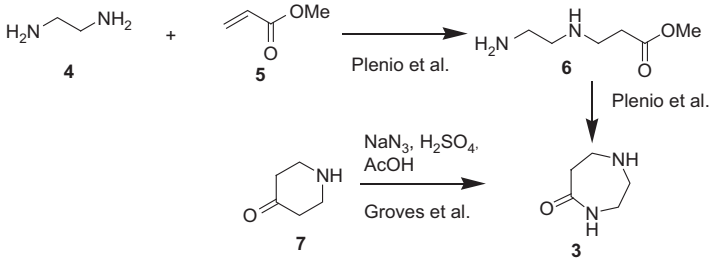
General procedure for alkylation of 4-piperidone (7) with alkyl halides 8a–c

To a mixture of 3.4 g (22 mmol) of 4-piperidone monohydrate hydrochloride, the alkyl bromide **8a**, **b** or **c** (21 mmol), anhydrous DMF (10 ml) and anhydrous potassium carbonate (22 mmol) were added. The mixture was stirred for 24 h and water (100 ml) was added. The mixture was extracted with ethyl acetate (3×50 ml) and organic layers were combined, washed with brine (50 ml), and dried over anhydrous sodium sulfate. The mixture was filtered and the solvent was removed by rotary evaporation under reduced pressure. The residue was purified by column chromatography on silica gel using 1%–2% methanol in chloroform to give the desired product.

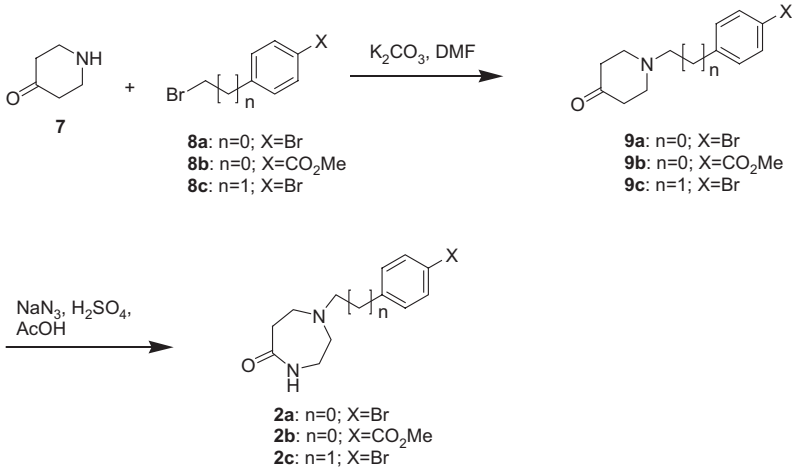
1-(4-Bromobenzyl)piperidin-4-one (9a, Rowbottom et al., 2007) A colorless solid was obtained in 84% yield; mp 59–60°C; ^{1}H NMR ($CDCl_3$): δ 2.45 (t, *J*=6.1 Hz, 4H), 2.73 (t, *J*=6.1 Hz, 4H), 3.57 (s, 2H), 7.25 (d, *J*=8.3 Hz, 2H), 7.46 (d, *J*=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.5, 53.1, 61.4, 121.5, 130.7, 131.7, 137.0, 209.2.



Scheme 1 General strategy to pyrimido[4,5-e] [1,4]diazepine-based folates (1).



Scheme 2 Synthesis of tetrahydro-1,4-diazepin-5-one (3).



Scheme 3 Synthesis of N^1-alkyl-1,4-diazepin-5-ones via the Schmidt reaction.

Methyl 4-[(4-oxopiperidin-1-yl)methyl]benzoate (9b, Arniz et al., 2007) A colorless solid was obtained in 88% yield; mp 63–65°C; ^{1}H NMR ($CDCl_3$): δ 2.47 (t, *J*=5.9 Hz, 4H), 2.76 (t, *J*=5.9 Hz, 4H), 3.68 (s, 2H), 3.92 (s, 3H), 7.45 (d, *J*=8 Hz, 2H), 8.02 (d, *J*=8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 41.4, 52.3, 53.2, 61.8, 128.9, 129.9, 143.8, 167.1, 209.1.

1-(4-Bromophenethyl)piperidin-4-one (9c, Schnatterer et al., 2009) A colorless solid was obtained in 85% yield; mp 67–68°C; ^{1}H NMR ($CDCl_3$): δ 2.47 (t, *J*=6.3 Hz, 4H), 2.67–2.72 (m, 2H), 2.78–2.83 (m, 6H), 7.1 (d, *J*=8.1 Hz, 2H), 7.42 (d, *J*=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 33.5, 41.2, 53.1, 58.9, 120.0, 130.4, 131.5, 138.9, 208.9.

General procedure for the ring expansion of *N*-alkyl-4-piperidones 9a–c with hydrazoic acid

The *N*-alkyl 4-piperidone **9a**, **b** or **c** (5 mmol) was added to a mixture of glacial acetic acid (3 ml) and concentrated sulfuric acid (1.5 ml) and the mixture was cooled in an ice-water bath. Sodium azide (5 mmol) was added in small portions over a 20 min period to the stirred mixture. The mixture was left stirring for 12 h. The mixture was cooled in an ice-water bath, and a saturated solution of sodium hydroxide was added dropwise until the pH was 7–8. The mixture was extracted with dichloromethane (3×50 ml) and the combined organic layers were washed with water (50 ml) and dried over anhydrous sodium sulfate. The mixture was filtered and the solvent was

removed by rotary evaporation under reduced pressure. The residue was purified by column chromatography on silica gel using 2%–3% methanol in chloroform to give the ring expanded product.

1-(4-Bromobenzyl)-1,4-diazepin-5-one (2a) A colorless solid was obtained in 83% yield; mp 170°C; ^{1}H NMR ($CDCl_3$): δ 2.57–2.61 (m, 6H), 3.28–3.29 (m, 2H), 3.54 (s, 2H), 6.51 (br s, exchangeable with D_2O, 1H), 7.21 (d, *J*=8.1 Hz, 2H), 7.45 (d, *J*=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 38.2, 42.0, 50.8, 57.2, 62.6, 121.2, 130.7, 131.7, 137.5, 178.1. Analysis: calcd. for $C_{12}H_{15}BrN_2O$: C, 50.90; H, 5.34; N, 9.89, Br, 28.22. Found: C, 50.98; H, 5.29; N, 9.80; Br, 27.99.

Methyl 4-[(5-oxo-1,4-diazepin-1-yl)methyl]benzoate (2b) A colorless solid was obtained in 85% yield; mp 148–149°C; ^{1}H NMR ($CDCl_3$): δ 2.59–2.64 (m, 6H), 3.19–3.40 (m, 2H), 3.65 (s, 2H), 3.92 (s, 3H), 6.52 (br s, exchangeable with D_2O, IH), 7.41 (d, *J*=8.5 Hz, 2H), 8.0 (d, *J*=8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 38.2, 43.0, 50.9, 52.3, 57.3, 62.9, 128.9, 129.4, 129.9, 143.9, 167.1, 178.1. Analysis: calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.10; H, 6.95; N, 10.61.

1-(4-Bromophenethyl)-1,4-diazepin-5-one (2c) A colorless solid was obtained in 82% yield; mp 147–148°C; ^{1}H NMR ($CDCl_3$): δ 2.62–2.73 (m, 10H), 3.29–3.32 (m, 2H), 6.38 (br s, exchangeable with D_2O, 1H), 7.07 (d, *J*=8.3 Hz, 2H), 7.40 (d, *J*=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 32.9, 37.9, 42.8, 50.5, 57.1, 50.2, 119.9, 130.4, 131.4, 139.0, 177.8. Analysis: calcd. for $C_{13}H_{17}BrN_2O$: C, 52.54; H, 5.77; N, 9.43; Br, 26.89. Found: C, 52.66; H, 5.80; N, 9.34; Br, 26.75.

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