Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 8493–8495

TETRAHEDRON LETTERS

Solid phase synthesis of tetrahydro-1,4-benzodiazepin-2-ones

Neal D. Hone,* William Wilson and John C. Reader

Millennium Pharmaceuticals Ltd, Granta Park, Great Abington, Cambridge CB1 6ET, UK

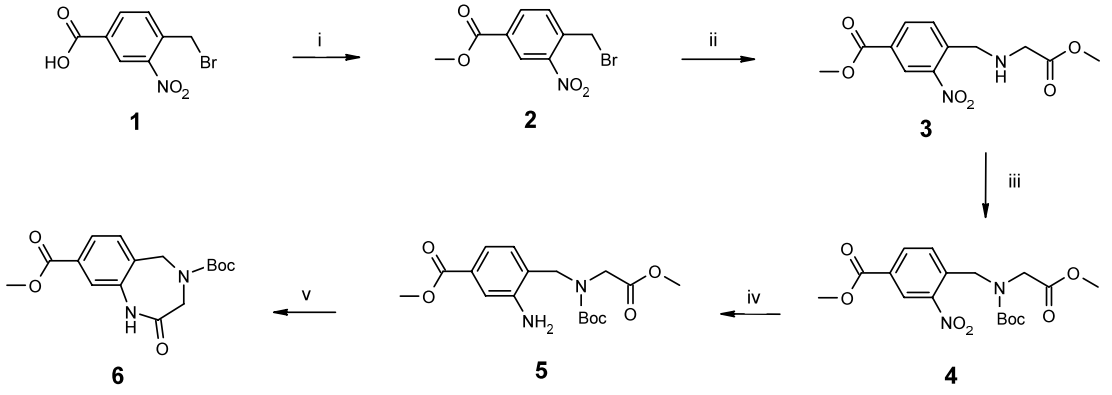
Received 9 July 2003; revised 4 September 2003; accepted 12 September 2003

Abstract—A novel solid phase route to tetrahydro-1,4-benzodiazepin-2-ones is described which involves construction of a core template in solution followed by diverse derivatization on solid phase.

The 1,4-benzodiazepine-2,5-dione template has found widespread therapeutic use across a range of disease states. The closely related 1,4-benzodiazepin-2-one nucleus is less utilised yet has demonstrated anticonvulsant,[1] anti-HIV[2] and anti-coagulant[3] activity. We wished to access a diverse range of these compounds for testing throughout a number of discovery programmes. Two solid phase approaches have been disclosed,[4] and although our initial attempts at multistep solid phase routes showed some promise, products were generally of poor quality. In an alternative approach, the 1,4-benzodiazepin-2-one core was prepared in solution. This was followed by loading onto solid phase and subsequent derivatization, yielding compounds of greatly improved purity.

4-(Bromomethyl)-3-nitrobenzoic acid **1** was treated with methanolic HCl to provide the ester **2** (Scheme 1). Reaction of **2** with glycine methyl ester gave the secondary amine **3** which was Boc protected (**4**) using di-*t*-butyl dicarbonate. Nitro reduction of **4** was achieved through catalytic hydrogenation to give the aniline **5** which was cyclised in boiling toluene to give the 1,4-benzodiazepin-2-one ester **6**. No column chromatography was required throughout the synthesis and the final product crystallised from toluene on addition of ether and cooling in 50% overall yield.

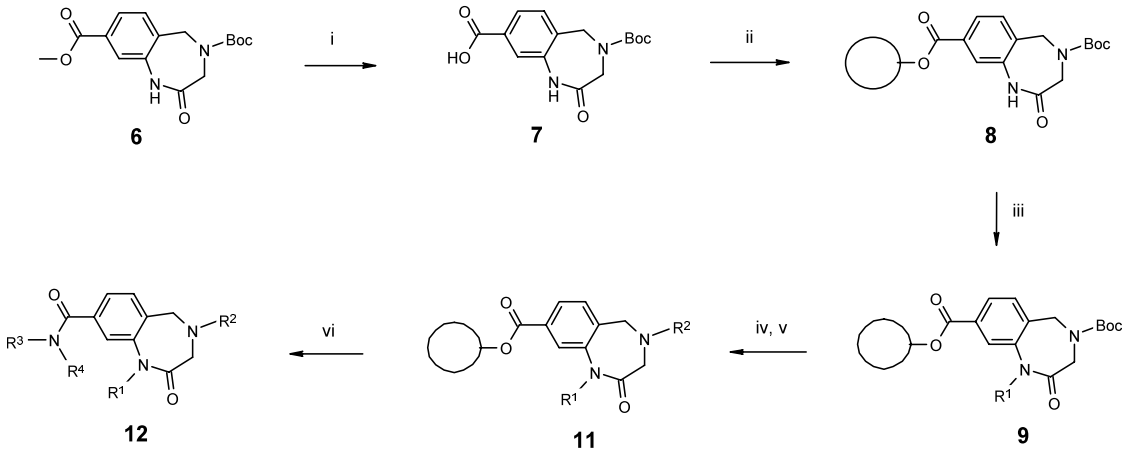
Exposure of **6** to aqueous hydroxide led to degradation of the molecule, but the methyl ester could be successfully cleaved using potassium trimethylsilanolate in



Scheme 1. *Reagents and conditions*: (i) HCl–MeOH, rt, 18 h; (ii) glycine methyl ester hydrochloride (3 equiv.), DIEA (4 equiv.), DMF, rt, 18 h; (iii) Boc-*O*-Boc, DCM, rt, 18 h; (iv) H_2, Pd, rt, 1 atm., 72 h, THF–MeOH (4:1); (v) toluene, Δ, 72 h, then Et_2O rt.

* Corresponding author.

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.09.108



Scheme 2. *Reagents and conditions*: (i) TMSOK (3 equiv.), THF, 40°C, 2 h; (ii) oxime resin, DIC, DMAP (10%); (iii) alkyl halide (5 equiv.), DBU (5 equiv.), DMF, 0–35°C, 20 min; (iv) 50% TFA in DCM, rt, 30 min; (v) electrophile (5 equiv.), DIEA (5 equiv.), DCM, rt, 1 h; (vi) amine (5 equiv.), DCE, 75°C, 18 h.

THF to provide the acid **7** (Scheme 2). This was loaded onto oxime resin[5] using DIC-DMAP, the reaction performed in batches of approximately 40 g. The amide nitrogen of **8** was alkylated using activated alkyl halides[6] and DBU in DMF. This reaction was exothermic and led to product loss from the resin on prolonged treatment. Optimal conditions involved cooling prior to exposure to the alkylating mixture and terminating the reaction after 20 min. The alkylation step was performed on 30 g resin batches. It was observed that alkylations using 100 mg resin required three treatments to achieve reaction completion. The tertiary amides **9** were Boc-deprotected using TFA (30 g resin scale) and the resultant secondary amines **10** derivatized with a range of electrophiles[7] to give **11**. Each resin combination was then cleaved with amine solutions[8] in 1,2-DCE at 75°C overnight to provide 1344 individual compounds **12**.[9] Derivatizations and cleavages were performed using 120 mg resin. Average crude yield was 65% and average crude purity by HPLC-MS was 62% (using diode array detection). All library members were purified by HPLC[10] to an average of 10% yield at 89% average purity.

References

1. Hardy, J.-C.; Bouquerel, J.; Nemecek, P.; Peyronel, J.-F. Pat. Appl. WO 98-FR1638 19980724.
2. Breslin, H. J.; Kukla, M. J.; Kromis, T.; Cullis, H.; De Knaep, F.; Pauwels, R.; Andries, K.; De Clercq, E.; Janssen, M. A. C.; Janssen, P. A. J. *Bioorg. Med. Chem.* **1999**, *7*, 2427–2436.
3. Nakagawa, T.; Tokumasu, M.; Tashiro, M.; Takahashi, M.; Kayahara, T.; Takehana, S.; Kajigaya, Y.; Yoshida, K.; Sakurai, K. Pat. WO 0226732 A1 20020404.
4. (a) Bhalay, G.; Blaney, P.; Palmer, V. H.; Baxter, A. D. *Tetrahedron Lett.* **1997**, *38*, 8375–8378; (b) Wu, Z.; Ercole, F.; FitzGerald, M.; Perera, S.; Riley, P.; Cambell, R.; Pham, Y.; Rea, P.; Sandanayake, S.; Mathieu, M. N.; Bray, A. M.; Ede, N. J. *J. Comb. Chem.* **2003**, *5*, 166–171.
5. Novabiochem 1.3 mmol/g 1% DVB polystyrene.
6. Alkyl halides used were methyl iodide, bromoacetamide, benzyl bromide, 3-methoxybenzyl bromide, 4-chlorobenzyl bromide and 4-cyanobenzyl bromide. The unalkylated amide **8** was also taken through steps iv–vi.
7. Electrophiles used were acetic anhydride, cyclohexanecarbonyl chloride, 3-cyclopentylpropionyl chloride, benzoyl chloride, 4-chlorobenzoyl chloride, 2-fluorobenzoyl chloride, 2-cyanobenzenesulphonyl chloride, 4-cyanobenzoyl chloride, 4-methoxybenzoyl chloride, 2-furoyl chloride, isoxazole-5-carbonyl chloride, 4-methoxybenzenesulphonyl chloride, benzenesulphonyl chloride, 4-chlorobenzenesulphonyl chloride, 3,5-difluorobenzenesulphonyl chloride, ethyl isocyanate, cyclopentyl isocyanate, allyl isocyanate, ethyl chloroformate, benzyl isocyanate, benzyl bromide, 4-chlorobenzyl bromide and 3-methoxybenzyl bromide. The underivatised amine was also taken through step vi.
8. Amines used were ammonia, *n*-propylamine, *N*,*N*-dimethylethylenediamine, ethanolamine, pyrrolidine, morpholine, 2-methoxyethylamine and benzylamine.
9. Typical experimental procedures: Oxime resin loading—The acid **7** (38.74 g, 127 mmol) was dissolved in dry DMF (100 ml) and oxime resin (1.3 mmol/g, 48.6 g, 63 mmol) added. Sufficient dry DCM was then added to attain a thin slurry. DMAP (0.77 g, 6.3 mmol) was added followed by DIC (16.22 g, 129 mmol) and the mixture stirred at room temperature overnight. The resin was then washed with DMF, MeOH, DCM, MeOH, DCM, MeOH and dried in vacuo to provide **8** (65.1 g). Alkylation—resin **8** (1.3 mmol/g, 30 g, 39 mmol) was suspended in sufficient dry DMF to form a thin slurry and the mixture cooled to 0°C using an ice-water bath. DBU (29 ml, 194 mmol) was added, followed by methyl iodide [**caution: Highly toxic, potential carcinogen**] (12.14 ml, 195 mmol), and the mixture stirred at a temperature between 30–40°C, maintained using the ice bath. After 20 min the resin was washed with DMF, MeOH, DCM, MeOH, DCM, MeOH and dried in vacuo to give **9** (R^1 = Me) (30.2 g). Boc deprotection—resin **9** (1.3 mmol/g, 30 g, 39 mmol) was suspended in 50% TFA in DCM and stirred at room temperature for 1 h. The resin was then washed with DCM, MeOH, DCM, MeOH and dried in vacuo to provide resin **10** (26 g). Acylation—resin **10** (1.3 mmol/g,

120 mg, 0.16 mmol) was placed into the well of an ACT Advantage reaction block, swelled with dry DCM (2 ml) and drained. A solution of DIEA (135 μl, 0.78 mmol) in dry DCM (0.5 ml) was added, followed by a solution of 2-furoyl chloride (102 mg, 0.78 mmol) in dry DCM (1 ml) and the suspension vortexed at room temperature for 1 h. The resin was then washed with DCM, MeOH, DCM, MeOH and DCM to provide the resin **11**. Cleavage—the resin **11** was washed with 1,2-DCE then *n*-propylamine (64 μl, 0.78 mmol) in dry 1,2-DCE (1.5 ml) added and the mixture heated to 75°C for 18 h with intermittent vortexing. The mixture was cooled to room temperature and the well vented into a collection vial. The resin was washed with a further 1.5 ml DCM and the washings vented into the collection vial. The contents of the vial were evaporated to dryness using a vacuum centrifuge to provide the 1,4-benzodiazepin-2-one **12** (R^1 = Me, R^2 = 2-furoyl, R^3 = *n*-propyl, R^4 = H) (32 mg, 86% yield based on original resin loading, purity by HPLC using diode array detection = 89%). ^{1}H NMR (400 MHz, $CDCl_3$) 7.75 (1H, s), 7.53 (1H, d, J = 7.8), 7.44 (1H, br s), 7.37–7.25 (1H, m), 7.03 (1H, d, J = 3.5), 6.59 (1H, br s), 6.43 (1H, br s), 4.69 (2H, br s), 4.25 (2H, br s), 3.4–3.31 (5H, m), 1.63–1.52 (2H, m), 0.90 (3H, t, J = 7.4). m/z (ES+) 356 (MH^+).

10. Purification was performed using Gilson preparative systems and Phenomenex Luna 150×21.2 mm C8 columns. Mobile phases were A; 10 mM NH_4OAc in MeOH and B; 10 mM NH_4OAc in water. The gradient was 5% B, 0–3 min; 5–100% B, 3–25 min; 100% B, 25–27 min; 100–5% B, 27–27.5 min.