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Solid-Phase Synthesis of 1,5-Benzodiazepin-2-ones

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Abstract: A solid-phase synthesis of polysubstituted 1,5-benzodiazepin-2-ones is described. Resin-bound 4-fluoro-3-nitrobenzoic acid was reacted with different β-amino acids, followed by nitro group reduction and formation of the seven-membered ring. Subsequent alkylations at N(5) and N(1) afforded the title compounds in high purities and yields.

The growing application of combinatorial chemistry methodologies in drug discovery is reflected in the rapidly increasing number of reaction types and synthetic strategies which have been successfully implemented as solid-phase protocols enabling the generation of large compound collections. Of particular interest with regard to generating and maximizing diversity are synthetic strategies which provide access to multiple, structurally diverse compound classes starting from a common fundamental building block. An example of such a multiparous building block is 4-fluoro-3-nitrobenzoic acid, **1**. Several recent reports describing the use of **1** in solid-phase syntheses of quinoxalin-2-ones,[1] benzimidazolones[2] and 2-alkylthio-benzimidazoles[3] have prompted us to disclose the results of our studies, which include solid-phase syntheses of various benzo-fused heterocycles, such as 1,5-benzodiazepin-2-ones, from **1**.[4]

Given their impressive record as therapeutic agents, it is not surprising that benzodiazepines were among the first classes of small molecules to be synthesized on solid support.[5] The main synthetic interest, however, has so far focused on 1,4-benzodiazepin-2-ones[6] and 1,4-benzodiazepin-2,4-diones,[7] with 1,5-benzodiazepin-2-ones having received little attention.[8] It therefore seemed appealing to us to explore the possibility of assembling 1,5-benzodiazepin-2-ones from resin-bound **1** and β-amino acids, **4**, *via* the strategy outlined in Scheme 1. ArgoGel-Rink-resin, following Fmoc-deprotection, was allowed to react with 4 eq. of **1**, 4 eq. of HATU, and 8 eq. of DIEA in DMF. The resulting intermediate **3** is poised to undergo S_NAr-type reactions, in which fluorine can be substituted by sulfur- and/or nitrogen-nucleophiles, such as, *e.g.*, the β-amino group of **4**. The initial attempts to effect the fluorine displacement were based on literature procedures describing S_NAr-reactions on solid-support,[1-3,9,10] which typically use DMF or NMP as solvents and, occasionally,[1,10] DIEA as an auxiliary base. It was soon realized, however, that these non-aqueous conditions would restrict us to using β-amino acid esters as nucleophiles (of which only few are commercially available), for the free β-amino acids, due to their poor solubility, either completely failed to react or afforded product mixtures. As we had previously observed in the synthesis of 3,4-disubstituted quinoxalin-2-ones from **3** and free α-amino acids,[4] a 1:1 mixture of 0.5M aqueous $NaHCO_3$ and acetone again proved to be the ideal solvent system for S_NAr -type reactions between resin **3** and free β-amino acids.[11] More than 40 examples of both aliphatic and aromatic β-amino acids were found to furnish the desired *o*-nitro-anilines **5**, about 80% of which were successfully carried on to eventually afford the final products **10** (see Table 1 for a selection of structures). In general, the anthranilic acids required slightly harsher conditions than most aliphatic β-amino acids for the displacement to go to completion. Subsequent reduction of the nitro group of **5** with 2M $SnCl_2 \cdot 2H_2O$ in DMF afforded the corresponding di-anilines **6**, along with varying amounts of the cyclic intermediates **7**, depending on the nature of the substituents derived from the β-amino acids (R_1). The partial formation of the seven-membered ring was then driven to completion using diethyl cyanophosphonate (DECP) and DIEA in DMF.[11]

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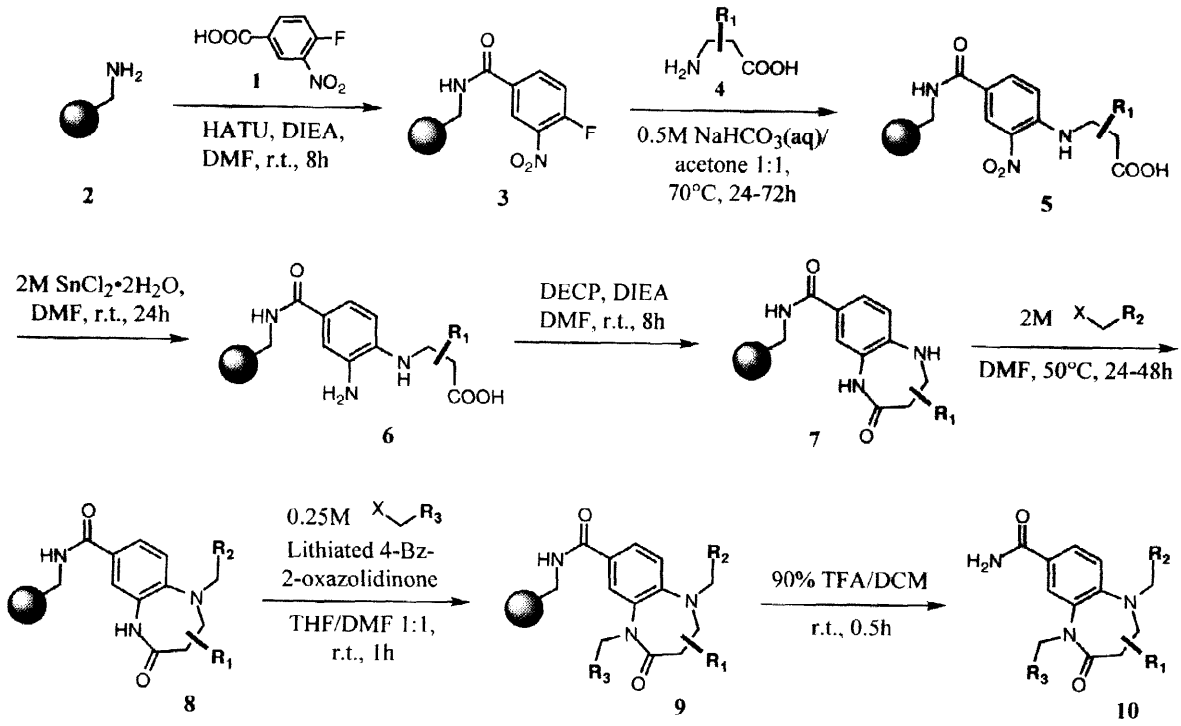
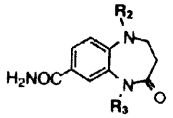
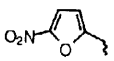
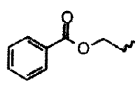
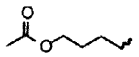
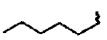
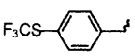
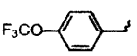
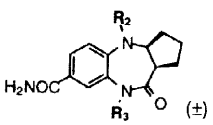
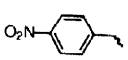
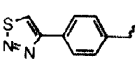
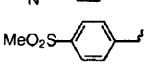
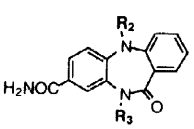
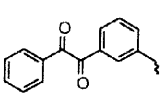
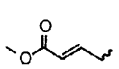
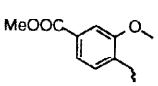
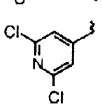
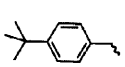
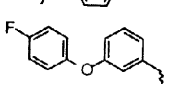
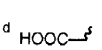
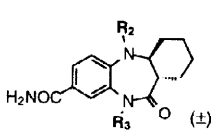
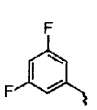
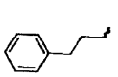
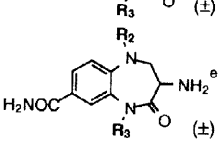
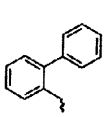
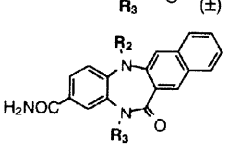
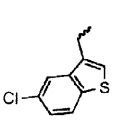


Scheme 1

Among the numerous conceivable ways of elaborating N(5) of the cyclic intermediates **7**, we focused on acylation with solutions of acid chlorides and DIEA in DMF, and alkylation with concentrated solutions of alkyl halides in DMF.[11] While both approaches delivered the desired products in high purities and yields, only the latter was initially pursued for library generation, because the compounds produced were considered more attractive in terms of their stability towards potential degradation *in vivo*. The group of alkyl halides having passed the quality criterion of producing N(5)-substituted benzodiazepines **8** with > 85% purity by HPLC encompasses over 40 benzyl bromides, allyl bromide, bromoacetic acid esters, as well as methyl and ethyl iodide. Other alkyl iodides, along with benzyl chlorides and α-bromo-acetophenones, however, did not exhibit satisfactory results. Table 1 displays a selection of R_2-groups present in the products **10**. The final alkylation involving N(1) of **8** was accomplished using alkyl halides and lithiated 4-benzyl-2-oxazolidinone as a base.[5,6b] As can be seen from Table 1, the same set of alkyl halides used for N(5)-alkylation was also found suitable for N(1)-alkylation, with the notable expansion to include other alkyl iodides beyond methyl and ethyl iodide. From the spectroscopic data of the final products **10**, and in agreement with literature data,[5,6b] no evidence was found for C- and/or O-alkylation.

At every stage of the synthetic sequence, an aliquot of resin was subjected to TFA-cleavage to liberate the products for the purpose of analysis. After thorough evaporation of the solvent and gravimetric estimation of the crude yields, the residues were routinely analyzed by HPLC (UV-detection at 220/280 nm) and ESI-MS. Larger amounts of selected products and key intermediates were purified by preparative RP-HPLC, weighed again,[12] and analyzed by ESI-MS and ^{1}H-NMR (representative analytical data collected for a complete set of intermediates derived from a given β-amino acid, *e.g.*, in the case of *cis*-2-amino-1-cyclopentane-carboxylic acid, for the corresponding *o*-nitro-aniline **5a**, for the 1,5-unsubstituted, the 5-monosubstituted and the 1,5-disubstituted 1,5-benzodiazepin-2-ones, **16**, **17**, and **18**, respectively, are tabulated below).[13]

Table 1. Representative Examples of 1,5-Benzodiazepin-2-ones of the General Structure **10**

Entry	*Core structure* (R_1)	*N(5)-Substituents* (R_2)	*N(1)-Substituents* (R_3)	*Yields*[a,b] *(Purity*[c]*)*
11			H	>90[a] (93)
12				>90[a] (87)
13				>90[a] (95)
14				56[b] (>95)
15				>80[a] (90)
16	 (±)	H	H	69[b] (>95)
17			H	62[b] (>95)
18				67[b] (>95)
19				>80[a] (80)
20				56[b] (>95)
21			H	>90[a] (87)
22				>80[a] (85)
23				>90[a] (90)
24				66[b] (>95)
25			[d] 	>80[a] (89)
26	 (±)			57[b] (>95)
27	 (±)		H	>90[a] (93)
28				>90[a] (87)

[a] Crude yields as determined from gravimetric analysis of the dried residues obtained from TFA-cleavage of 10-20 mg of resin [b] Yields of isolated, RP-HPLC-purified compounds, derived from cleavage of 100-200 mg of resin [c] Determined by analytical RP-HPLC (UV-detection at 220nm) [d] from *tert*-Butyl bromoacetate [e] from N-α-Boc-α,β-diaminopropionic acid

In summary we have enabled a versatile, high-yielding solid-phase route to polysubstituted 1,5-benzodiazepin-2-ones. In addition, the compatibility of this synthetic approach with the chemical encoding strategy developed at Affymax[14] has been demonstrated, setting the stage for the construction of large (> 30k member) encoded libraries. In subsequent experiments, the synthetic strategy outlined in Scheme 1 has been extended to provide syntheses of 1,5-benzothiazepin-4-ones and 4-alkoxy-1,4-thiazin-3-ones by using suitably protected forms of cysteine and α-mercapto acids, respectively, in nucleophilic aromatic substitution reactions of **3**. The results of these studies will be reported in detail in the near future.

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8. A solid-phase synthesis of structurally related, pyridine-based tricyclics, *via* a different synthetic strategy, has been reported by Woolard, F.X.; Paetsch, J.; Ellman, J.A. *J. Org. Chem.* **1997**, *67*, 6102-6103. Researchers at R.W. Johnson P.R.I. have been exploring related approaches towards 1,5-benzodiazepin-2-ones (Jung Lee, personal communication, 1998)
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11. General procedure for S_NAr-reactions in aqueous medium: (aliphatic β-amino acids) To 300mg-aliquots of resin **3** was added 12 ml of a hot 0.17M solution of **4** in acetone/0.5M $NaHCO_3$(aq) 1:1, and the mixtures were agitated at 70-75°C for 24h. After removal of the supernatant, the resin portions were washed with 5% HOAc(aq) (5x), H_2O (3x), MeOH (3x), DCM (3x), DMF (3x) and Et_2O (3x), and dried *in vacuo*; (anthranilic acids) The same protocol was used, but the reactions were allowed to proceed for 3 days at 75-80°C. General procedure for the cyclisation reaction: To 300mg-portions of resin **6** was added 4 ml of a 0.2M solution of DIEA in DMF at room temperature, followed by addition of 0.8 mmol DECP. After a reaction time of 8h, the supernatants were removed, the resin batches were washed with DMF (5x), MeOH (2x), DCM (3x), Et_2O (2x), and dried *in vacuo*. General procedure for N(5)-alkylation: To 150 mg of resin **7** was added 2 ml of a 2M solution of the alkyl halide in DMF, and the reaction was allowed to proceed at 55-60°C for 3.5 days. After removal of the supernatant, the resin was extensively washed with DMF (5x), DCM (3x), MeOH (3x), DCM (2x), DMF (3x), DCM (3x), and dried *in vacuo*.
12. The difference between the values obtained for crude and isolated yields are due to the presence of PEG residues in the crude samples (resin "bleeding"), as well as to losses encountered during RP-HPLC purification of the compounds.
13. **5a**: ^{1}H-NMR (300MHz, DMSO-d_6) δ 1.5-1.8 (3H, m), 1.9 (2H, m), 2.05 (1H, m), 3.05 (1H, q, J = 7.8), 4.35 (1H, quin, J = 7.2), 7.17 (1H, d, J = 9.1), 7.25 (1H, broad), 7.95 (1H, dd, J = 9.1, 2.1), 7.96 (1H, broad), 8.52 (1H, d, J = 7.6), 8.58 (1H, d, J = 2.1), 12.2-12.6 (1H, broad); MS(ESI) m/z = 294.2 (MH^+). **16**: ^{1}H-NMR (300MHz, DMSO-d_6) δ 1.4-1.6 (3H, m), 1.6-1.7 (1H, m), 1.8-1.9 (1H, m), 2.05-2.15 (1H, m), 2.8 (1H, m), 3.85 (1H, q, J = 7.9), 6.98 (1H, d, J = 8.1), 7.2 (1H, broad), 7.38 (1H, d, J = 2.1), 7.42 (1H, dd, J = 8.1, 2.1), 7.7 (1H, broad), 9.58 (1H, s); MS(ESI) m/z = 246.2 (MH^+). **17**: ^{1}H-NMR (300MHz, DMSO-d_6) δ 1.6-1.9 (4H, m), 2.1-2.2 (1H, m), 2.2-2.3 (1H, m), 2.8-2.9 (1H, m), 4.0 (1H, m), 4.46 (1H, d, J = 15.6), 4.54 (1H, d, J = 15.3), 7.2-7.4 (7H, m), 7.57 (1H, dd, J = 8.1, 1.8), 7.55 (1H, s), 7.9 (1H, broad), 9.73 (1H, s); MS(ESI) m/z = 336.1 (MH^+). **18**: ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.5-1.7 (3H, m), 1.9-2.0 (1H, m), 2.1-2.3 (2H, m), 2.81 (1H, m), 3.6 (1H, m), 4.26 (1H, d, J = 15.0), 4.32 (1H, d, J = 15.4), 4.97 (1H, d, J = 15.8), 5.50 (1H, d, J = 15.8), 6.9-7.1 (5H, m), 7.21 (1H, d, J = 8.4), 7.30 (1H, broad), 7.50 (1H, dd, J = 8.4, 1.8), 7.59 (2H, d, J = 8.4), 7.83 (1H, d, J = 1.8), 7.88 (1H, broad), 8.14 (2H, d, J = 8.4); MS(ESI) m/z = 471.2 (MH^+).
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