Communications

An Expedient and High-Yielding Method for the Solid-Phase Synthesis of Diverse 1,4-Benzodiazepine-2,5-diones

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The goal of rapid identification of novel therapeutic agents has inspired intensive effort toward the synthesis of libraries of nonpolymeric organic compounds. The development of general, high-yielding, solid-phase methods is a crucial step in the generation of such libraries. The well-documented clinical value of 1,4-benzodiazepines[1] has led to the development of solid-support chemistry to generate libraries of 1,4-benzodiazepin-2-ones **1** (Figure 1).[2] Our group has reported chemistry which was designed to introduce a great deal of diversity at the R^2, R^3, and R^4 sites, while providing access to a more limited repertoire of functionality at the R^1 position.

The 1,4-benzodiazepine-2,5-diones **2** have been reported as anticonvulsants,[3] mimetics of the RGD tripeptide,[4] and synthetic precursors to benzodiazepine receptor antagonists.[5] Herein we report a general and high-yielding solid-phase synthesis of 1,4-benzodiazepine-2,5-diones (**2**).[6] This strategy complements our previous reports in that it allows for direct introduction of a variety of functionality (R^1) on the aromatic core of **2** from the over 40 commercially available anthranilic acids (2-aminobenzoic acids) or related heterocyclic structures.

Our synthetic strategy toward structures **2** involves incorporation of three commercially available components: In addition to the over 40 anthranilic acids (R^1), there are more than 50 α-amino esters (R^3) available with the appropriate side-chain protection and over 100 alkylating agents (R^2). Rapid library construction depends upon the direct incorporation of these components in their commercially available form. Therefore, to expedite library generation, we required that incorporation of the anthranilic acid derivatives be accomplished without prior protection of either its aniline or carboxylic acid functionality.

1 2

Figure 1.

Our synthetic design was predicated on our own model studies,[7] as well as literature examples,[3,8] which indicate that lactamization to provide the 1,4-benzodiazepine-2,5-diones would be the most general and high-yielding method for effecting ring closure. In order to achieve efficient lactamization, the acyclic precursor must contain a tertiary and not a secondary amide. Along these lines, chloromethylpolystyrene (Merrifield resin) was derivatized according to Scheme 1 by alkylation with the sodium salt of 4-hydroxy-2,6-dimethoxybenzaldehyde (**3**) to provide the resin-bound aldehyde **4**.[9,10] The synthesis of 1,4-benzodiazepine-2,5-diones is then initiated by first loading an α-amino ester onto the support by reductive amination employing $NaBH(OAc)_3$ in DMF with 1% HOAc.[11] Racemization is not observed if the imine resulting from condensation of the α-amino ester and aldehyde **4** is reduced immediately upon its formation. If racemic material is desired, racemization may be accomplished by equilibrating α-amino esters with aldehyde **4** in the presence of i-Pr_2EtN for 3 h prior to the addition of $NaBH(OAc)_3$ (vide infra).

Acylation of the resulting secondary amine **5** with a commercially available unprotected anthranilic acid then provides the support-bound tertiary amide **6**. This acylation step required considerable optimization. For example, even the highly activated 7-azabenzotriazole-based reagents, such as HATU[12] (recently developed by Carpino), gave poor conversion. Carbodiimides were the only coupling agents found to effect this transformation efficiently. Furthermore, good yields of acylated material were obtained only when the carbodiimides were employed in conjunction with the hydrochloride salt of a tertiary amine. EDC (1-ethyl-3-(3-(dimethylamino)-propyl)carbodiimide·HCl) proved to be the most convenient activating agent since the tertiary amine hydrochloride is present in the carbodiimide structure. To ensure that complete acylation occurs, the resin is subjected twice to this coupling procedure.[13]

Solution studies[7] indicated that base-catalyzed lactamization would be the most general way of producing the support-bound cyclic product (**8**, R^2 = H). Ideally, cy-

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(10) A monomethoxy analog of the dimethoxy linker described herein was initially employed. However, treatment with TFA resulted in release of the linker from the support still covalently bound to the benzodiazepine.

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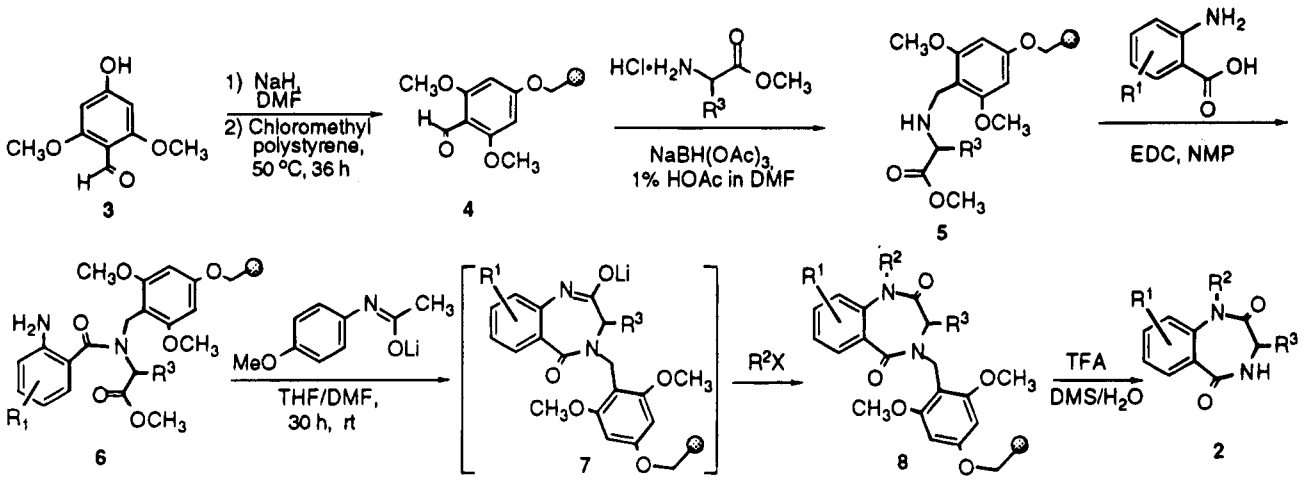
(13) When coupling nitro-containing anthranilic acids, an additional subjection may be necessary. Anthranilic acids with electron-releasing functionality ortho or para to the aniline produce significant amounts of dimer or oligomer upon subjection to these coupling conditions.

0022-3263/95/1960-5742$09.00/0

Scheme 1



clization would be accomplished under conditions sufficiently basic to provide the anilide anion **7** for subsequent alkylation to introduce the R^2 components of compounds **8** in the same reaction step. The lithium salt of either acetanilide or *p*-methoxyacetanilide proved optimal for effecting these transformations.[14] Treatment of **6** with either of these lithium salts in DMF/THF (1:1) for 30 h followed by addition of an appropriate alkylating agent provides a fully derivatized, support-bound benzodiazepine **8**. Complete cyclization and alkylation (>95%) are observed in this reaction sequence as determined after cleavage of benzodiazepines **2** from support. Finally, additional diversity may also be introduced onto the benzodiazepine through the Suzuki cross-coupling reaction. This reaction is one of the most versatile methods for carbon-carbon bond formation on solid support[15] due to the high reaction yields, commercial availability of aromatic and heteroaromatic boronic acids, and ready access to alkylboranes by in situ hydroboration methods. Cleavage of benzodiazepine products from support is accomplished by treatment with TFA/Me_2S/H_2O (90:5:5). Good yields are obtained for a range of different derivatives including benzodiazepines incorporating amino acids with side chain functionality such as tyrosine and lysine, compounds **2h** and **2i** in Table 1, respectively. Application of the Suzuki reaction is exemplified by compound **2g** in Table 1, where a cross-coupling reaction was carried out with *p*-methoxybenzeneboronic acid and the support-bound benzodiazepine **8c**. As an additional example, a Suzuki cross-coupling reaction was performed using *B*-hexyl-9-BBN to provide compound **2h** in good yield.

Racemization is not observed (<1%) during the acylation and cyclization reaction sequence as determined by chiral HPLC[16] analysis of benzodiazepine derivative **2j** (R^2 = H), which was prepared from (*S*)-leucine methyl ester. In addition, significant racemization is not observed (≤3%) in the fully-derivatized, alkylated product (supporting information). We also did not observe racemization (<1%) in **2k** which incorporates the more racemization-prone phenylalanine.[17]

Table 1

entry	compd	R^1	R^2	R^3	yield[a] (%)
1	**2a**	8-Cl	Et	$CH_2CH(CH_3)_2$	75
2[b]	**2b**	7-Cl	allyl	$CH_2C_6H_5$	89
3	**2c**	7-Br	Et	$CH_2CH(CH_3)_2$	71
4	**2d**	8-NO_2	Et	$CH_2CH(CH_3)_2$	92
5	**2e**	6-F	CH_2CONH_2	$CH_2C_6H_5$	62
6	**2f**	8-OMe	*c*-$C_3H_5CH_2$	$CH_2CH(CH_3)_2$	79
7[c]	**2g**	7-(*p*-$MeOC_6H_4$)	Et	$CH_2CH(CH_3)_2$	62
8[c]	**2h**	8-$CH_3(CH_2)_5$	*p*-$PhC_6H_4CH_2$	$CH_2C_6H_4OH$	77
9	**2i**	7-Cl	allyl	$(CH_2)_4NH_2$	63
10[b,d]	**2j**	8-Cl	H	$CH_2CH(CH_3)_2$	89
11[b,d]	**2k**	7-Cl	H	$CH_2C_6H_5$	89

[a] Yields of purified materials are based on the loading levels of leucine and phenylalanine ester-derived resins. These resins were acetylated with Ac_2O/pyr/DMAP and the resulting products cleaved from support and quantitated after flash chromatography. [b] Product prepared by racemization-free procedure described in text. All others were prepared by equilibration of α-amino ester and aldehyde **4** before addition of reductant. [c] This is a Suzuki cross-coupling product. [d] In the alkylation step, acetic acid was substituted in place of an alkylating agent. Less than 1% racemization was observed by chiral HPLC as described in the text. A racemic sample was also prepared as a reference.

A straightforward, solid-phase method has been described to prepare 1,4-benzodiazepine-2,5-diones directly from three commercially available components: anthranilic acids, α-amino esters, and alkylating agents. The synthesis sequence is compatible with a diverse range of functionality; all steps in this sequence proceed at room temperature and generate benzodiazepines in good yield with minimal racemization. We are continuing to investigate the further functionalization of support-bound benzodiazepines **8**.

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Supporting Information Available: Complete procedures and compound characterization (9 pages).

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(14) These bases are sufficiently mild that overalkylation of amide, carbamate, and ester functionality should not occur. See compounds **2e** and **2i**, Table 1.

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