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Combinatorial Solid-Phase Synthesis of Structurally Complex Thiazolylhydantoines[**]

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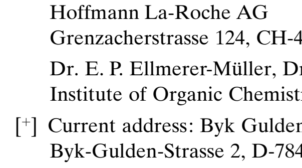
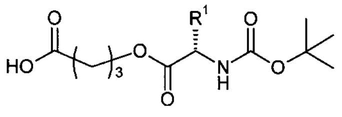
Andreas Takó, Najib Maslouh, and Willi Bannwarth

In the past few years combinatorial chemistry[1] and the related solid-phase synthesis[2] of nonpeptide substance libraries have become established as valuable tools in pharmaceutical research for the discovery and optimization of lead compounds. We have developed a synthetic strategy that allows efficient construction by solid-phase synthesis of libraries of structurally complex thiazolylhydantoines of the general formula **1**. At the same time, exploitation of an intrinsic purification principle has led to products with excellent purity after nine synthetic steps and subsequent removal of the target from the polymer support.



1

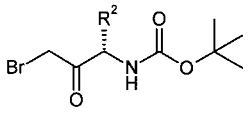
Derivatives **2a–c**,[3] prepared from amino acids with *N*-butoxycarbonyl (Boc) protecting group, served as building blocks for the synthesis of a representative substance library (note the strategic importance of the ester functionality for detachment of the target compounds from the polymer support). Other key components were α-bromoketones **3a–c**[4] derived from *N*-Boc-protected amino acids, carboxylic acids **4a**, **b**, and allyl isocyanate (**5**), which can be seen as a representative of isocyanates in general.



2a $R^1 = CH_2C_6H_5$

2b $R^1 = CH_2\text{-cyclo-}C_6H_{11}$

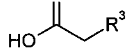
2c $R^1 = CH_2C(O)N(CH_2CH_2)_2O$



3a $R^2 = H$

3b $R^2 = CH_3$

3c $R^2 = CH_2CH(CH_3)_2$



4a $R^3 = 4\text{-}FC_6H_4$

4b $R^3 = H_3CC_6H_4O$

5

In a first reaction step, building blocks **2a–c** were linked through their free acid functionalities to a benzhydrylamine resin modified with 6-aminohexanoic acid. 1,1,3,3-Tetramethyl-*O*-(2-oxo-1,2-dihydropyridin-1-yl)uronium tetrafluoroborate (TPTU)[5] served as the coupling reagent to give derivatives **7a–c**. After cleavage of the Boc protecting group, free amines **8a–c** were transformed by reaction with allyloxycarbonyl isothiocyanate (**9**)[6] into the thiourea derivatives **10a–c**, which contain the allyloxycarbonyl (Alloc) protecting group. Pd^0 catalyzed removal of the Alloc group[7] yielded thioureas **11a–c** as starting materials for the subsequent construction of 2-aminothiazole templates (Scheme 1).

2-Aminothiazoles **12aa–12cc** were obtained by the reaction of aliquot portions of resins **11a–c** with α-bromoketones **3a–c**. Free amines **13aa–13cc** were isolated after removal of the Boc protecting group. Once again, aliquots of resins **13aa–13cc** were coupled through their amino groups with carboxylic acids **4a**, **b** to give amides **14aaa–14ccb**. Preliminary experiments in solution had shown that coupling with carboxylic acids takes place exclusively at the primary amino group. Under the chosen reaction conditions the amino group attached to the heterocycle does not react with carboxylic acids. Reaction of compounds **14aaa–14ccb** with allylisocyanate (**5**) led finally to urea derivatives **15aaa–15ccb**, which were removed from the polymeric supports by a base-induced cyclization reaction specific to the ester function (the importance of which was alluded to earlier)[8] to give the

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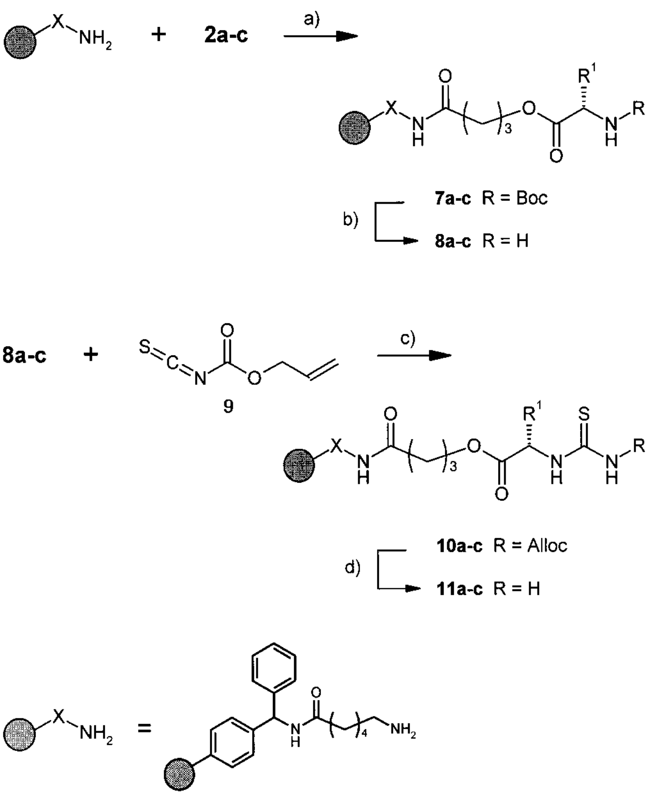


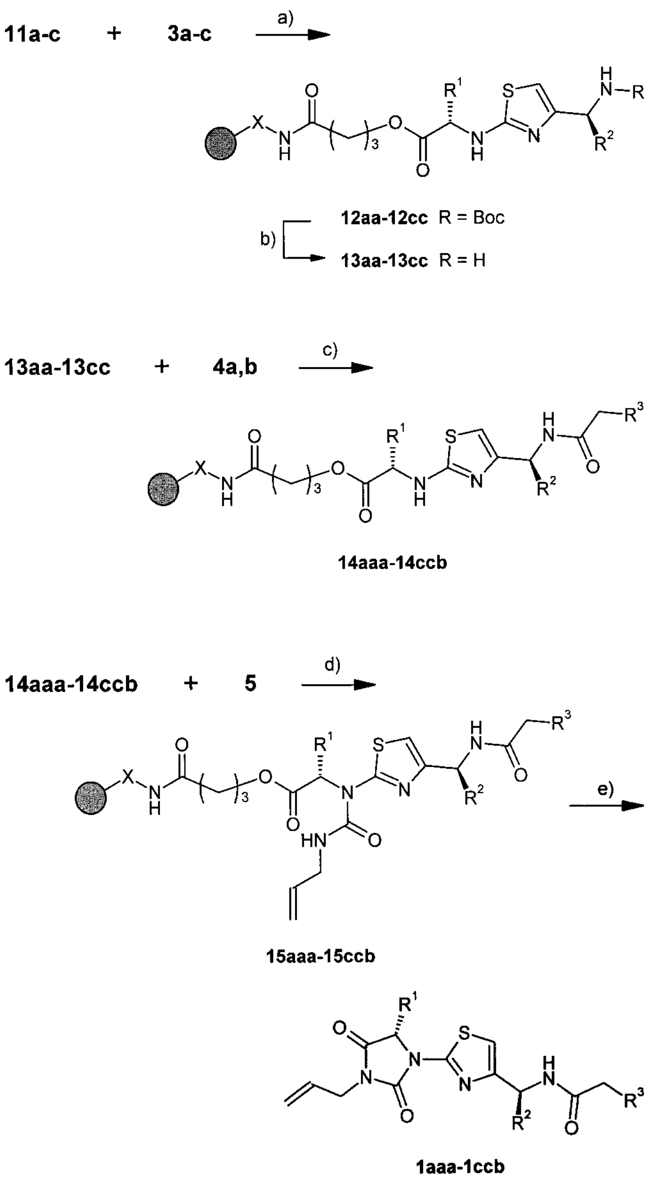
Scheme 1. a) TPTU, *i*PrNEt$_2$, DMF, 15 min; b) trifluoroacetic acid (TFA)/CH$_2$Cl$_2$ 1/2, 30 min; c) toluene, 60 min; d) Me$_2$NSiMe$_3$, CF$_3$COOSiMe$_3$, [Pd(PPh$_3$)$_4$], CH$_2$Cl$_2$, 6 h.[6]

desired hydantoines **1aaa**–**1ccb**[9] (Scheme 2). All compounds were tested for purity and identity by HPLC and MS (Table 1).

Table 1. Yields and physical data for **1aaa**–**1ccb**.

Compound	Building blocks	Yield[a]	m/z $[M+H^+]$	R_t(HPLC) [min] (intensity)[b]
1aaa	**2a**,**3a**,**4a**	130	479	4.26 (96.0)
1aab	**2a**,**3a**,**4b**	137	491	5.03 (90.0)
1aba	**2a**,**3b**,**4a**	69	505	4.78 (99.7)
1abb	**2a**,**3b**,**4b**	165	493	5.59 (98.7)
1aca	**2a**,**3c**,**4a**	111	535	6.02 (99.8)
1acb	**2a**,**3c**,**4b**	88	547	6.76 (96.5)
1baa	**2b**,**3a**,**4a**	80	485	5.57 (98.6)
1bab	**2b**,**3a**,**4b**	122	497	6.26 (97.2)
1bba	**2b**,**3b**,**4a**	113	499	6.03 (99.3)
1bbb	**2b**,**3b**,**4b**	117	511	6.81 (95.1)
1bca	**2b**,**3c**,**4a**	105	541	7.16 (94.1) 7.42 (5.8)
1bcb	**2b**,**3c**,**4b**	121	553	8.19 (82.8) 8.52 (6.1)
1caa	**2c**,**3a**,**4a**	134	516	2.14 (97.9)
1cab	**2c**,**3a**,**4b**	142	528	2.67 (82.1)
1cba	**2c**,**3b**,**4a**	91	530	2.44 (99.0)
1cbb	**2c**,**3b**,**4b**	191	542	3.19 (94.8)
1cca	**2c**,**3c**,**4a**	140	572	3.85 (96.4)
1ccb	**2c**,**3c**,**4b**	166	584	4.68 (97.9)

[a] Yields are based on milligrams of product per gram of resin. [b] Retention time R_t; relative intensity is indicated in parentheses in area percent; diastereomers arise in the case of **1bca** and **1bcb** due to partial racemization of the amino acid building blocks.



Scheme 2. a) Dioxane, 60 °C, 16 h; b) TFA/CH$_2$Cl$_2$ 1/2, 30 min; c) TPTU, *i*PrNEt$_2$, DMF, 15 min; d) dioxane, 70 °C, 16 h; e) dioxane/Et$_3$N 95/5, 60 °C, 6 h.

The high purity of the desired products, especially after a nine-step solid-phase synthesis, can be understood in the context of an intrinsic purification principle that accompanies the process. Thus, after the final reaction with isocyanates, only molecules that have taken part in the prior construction of 2-aminothiazole templates will be detached from the resin.

We have therefore demonstrated that, with careful choice of the reaction sequence, a multistep solid-phase synthesis can be an appropriate tool for the preparation of structurally complex, high-quality substance libraries.

Experimental Section

HPLC: LiChroCART 125-4, Lichrospher, RP-select B; solvent system: CH$_3$CN/H$_2$O 1/1 (1 min), CH$_3$CN/H$_2$O 1/1 → 3/1 (4 min), CH$_3$CN/H$_2$O 3/1 (3 min); flow rate 1 mL min^{-1}.

1433-7851/98/3710-1403 $ 17.50+.50/0

2a–c: Prepared by esterification of benzyl 4-hydroxybutyrate[3] with appropriate *N*-Boc-protected amino acids (*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC), 4-dimethylaminopyridine (DMAP), CH_2Cl_2) followed by hydrogenolysis of the benzyl ester (H_2, 10% Pd on C, EtOH).

Modified benzhydrylamine resin: Benzhydrylamine resin (0.9 mol $-NH_2$ per gram) was coupled with Fmoc-6-aminohexanoic acid (TPTU, *i*$PrNEt_2$, DMF; Fmoc = 9-fluorenylmethoxycarbonyl), and the Fmoc protecting group was subsequently cleaved (20% piperidine in DMF). Excess reagents were used in all solid-phase reactions ($1.2-1.5\,\text{mmol}\,g^{-1}$). After the reactions were complete, the resins were repeatedly washed with DMF, *i*PrOH, and Et_2O. Solutions of product obtained after detachment of the resins were filtered through a minimal amount of neutral alumina (activity grade 3) and evaporated to dryness under reduced pressure.

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Structural Diversity in the Solid-State Structures of the Rubidium and Cesium Salts of 2,6-Dimesitylphenylphosphane[**]

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*Dedicated to Professor Wolfgang A. Herrmann
on the occasion of his 50th birthday*

We recently focused our interest on the heavier alkali metal derivatives of primary and secondary phosphanes with the general formula MPR_2 and MPRH, respectively. In light of numerous reports on lithium derivatives[1] and a few examples of sodium[2] and potassium[2c, 3] derivatives of MPR_2 and MPRH species, the dearth of structural data available on derivatives of rubidium and cesium is surprising. Recently, the solid-state structure of a sterically congested cesium silyl(fluorosilyl)phosphanide aggregate was reported.[2d] Heavier alkali metal phosphides are important because of their enhanced reactivity over their lithium counterparts, and also with respect to the structural diversity of their solid-state structures. We presented earlier a preliminary[3] and a full report[4] on the molecular structures of $[MP(H)Mes^*]_x$ species ($M = K-Cs$; $Mes^*PH_2 = 2,4,6\text{-}t Bu_3C_6H_2PH_2$, "supermesitylphosphane"[5]) as well as several different base adducts of these compounds. We also reported crystal structure determinations of three different base adducts of an asymmetrically substituted potassium phosphide, KP(*t*Bu)Ph.[6] All of these alkali metal derivatives exhibit infinitely extended, one-dimensional polymeric M–P ladder-type arrangements in the solid state.

Motivated by our recent findings, we have now extended our studies to heavier alkali metal derivatives of other sterically demanding primary phosphanes. We decided to employ the 2,6-dimesitylphenyl (Dmp) substituent,[7] since earlier work has suggested that this ligand is even more bulky than the Mes* ligand.[8] However, recent studies have indicated that the steric relationship between Dmp and Mes* is not as simple as once thought.[9] The preparation of the corresponding phosphane, $DmpPH_2$, was described recently.[10]

Reaction of equimolar amounts of rubidium or cesium metal with $DmpPH_2$ in THF at room temperature produced the yellow-orange RbP(H)Dmp and yellow CsP(H)Dmp complexes, respectively. Even in the presence of excess alkali

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