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Solid-Phase Synthesis of "Small" Organic Molecules Based on Thiazolidine Scaffold

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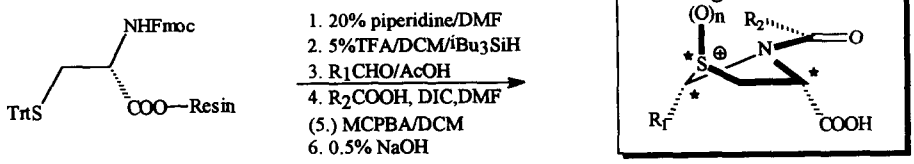
Abstract: 2-Substituted thiazolidine-4-carboxylic acids were obtained by reaction of aldehydes with unprotected (R)-cysteine attached to the polymeric support via an ester bond. Subsequent transformation into N-acyl derivatives followed by alkaline hydrolysis provided almost exclusively the corresponding (2R,4R)-stereoisomer. A convenient solid phase synthesis of substituted thiazolidines, including an evaluation of aldehydes, conditions for N-acylation and S-oxidation as well as the stability of thiazolidines to reagents used in solid phase synthesis are described.

The increasing interest in combinatorial solid phase synthesis of non-peptide compounds has recently started a "diversity sprint" and intensified efforts to develop general solid phase technologies in order to speed up the process of finding new families of biologically active compounds.[1] While great strides are being made in achieving practical solid phase "organic" synthesis in a number of reactions,[2] approaches for generating molecular diversity on structurally defined scaffolding domains still remain a major challenge.[3] One of the strengths of the scaffolding approach is the ability to vary the conformational rigidity of such a template along with the length and flexibility of defined tethers which serve to connect different functional groups with the template base, thus enhancing the chances for definition of steric and stereoelectronic requirements for observed ligand-target interaction.

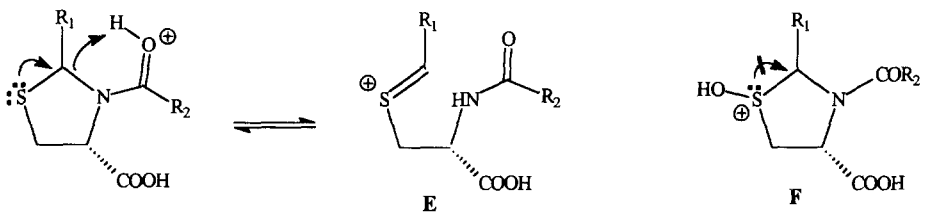
The reaction of β-mercaptoalkylamines with aldehydes and ketones has represented a valuable and general method for the synthesis of thiazolidines for over forty years.[4] Derivatives of the thiazolidine skeleton exhibit significant antimicrobial,[4c] antihypertensive,[5] and antitumor activity.[6] Furthermore, thiazolidines have found use as secondary structure disrupting building blocks in peptide synthesis.[7] In contrast to carbocyclic rings, detailed structural studies indicate that thiazolidine derivatives exist in preferred conformations, since the introduction of heteroatoms, especially those of sulfur and sp^2-hybridized nitrogen in N-acyl derivatives, increases the relatively high potential energy barrier for cyclopentane-like pseudorotation.[8] Due to the promising architecture of the thiazolidine skeleton and the variety of directions in which it can be elaborated, we decided to investigate the scope and generality of its solid phase synthesis. As a starting point, we selected representative aldehydes and acylating agents for the "solution" synthesis of model compounds. The models **A-D** were used to evaluate (i) the efficiency of thiazolidine formation on solid phase, (ii) conditions for



Scheme 1

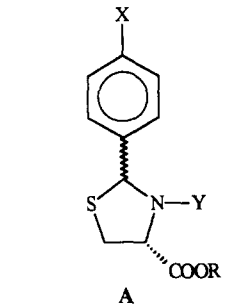
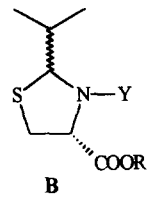
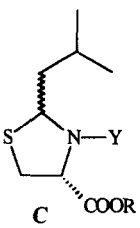
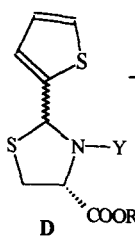
R_1, R_2: alkyl, aryl; n = 0,1

N-acylation, and (iii) the stability of N-acyl thiazolidines to reagents used for deprotection of acid/base labile side chain protecting groups as well as the final multiple release from the solid support.[9] Furthermore, since thiazolidine formation gives rise to a new chiral center at the C-2 position, the question of diastereoselection can be addressed as well. Mechanistic studies to date on the thiazolidine formation and following N-acylation have provided considerable data concerning the intermediates involved and the stereoselectivity observed in both steps.[5,10] Scheme 1 shows the key synthetic strategy that allows the solid phase construction of substituted thiazolidines in a general fashion. The results of experiments describing yields and the diastereomer ratio (dr%) for "solution" (Soln.) and solid phase (SP) syntheses of compounds **1-30** are given in Table I. The thiazolidine ring formation was nearly quantitative for all aldehydes studied and the diastereomeric ratio (2R,4R):(2S,4R) ranged between 70:30 and 40:60.[11] Detailed examination of the data reveals that trends in the stereoselectivity and yields for acylations parallel both the nature of acylating agent, the aldehyde, and strength of the base employed. It is noteworthy that strongly electron-withdrawing substituents in the para position of the aromatic ring caused a dramatic decrease in the rate of acylation. On the other hand, thiazolidines possessing aliphatic or aromatic electron-donating substituents could be acylated easily under mild conditions. In all cases, RP-HPLC, TLC, and ^{1}H NMR analysis showed preferential formation of the (2R,4R) N-acyl product. Assignment of the absolute stereochemistry at the C-2 stereocenter was based on analogy of thiazolidine analogues whose stereochemistry had been established by X-ray crystallography and NMR studies.[5,8] Of additional note was the observation that acylation of carboxyl protected thiazolidines could be accomplished in high stereoselectivity using either pyridine or DIEA. These results are strikingly different from the reported acylation-selectivity in the presence of a free carboxyl group which was drastically dependent on the strength of the base used.[5,10] Furthermore, we observed that N-acyl thiazolidines, particularly **6** and **7**, suffer from lability in nonaqueous acidic conditions (60-100%TFA/DCM). The origin of the acid sensitivity could be attributed to the stabilization of positive charge in the sulfonium ring *seco* intermediate **E** by the electron-rich aromatic ring. From these experiments it became clear that any synthetic strategy should avoid exposure to a strongly acidic environment once the thiazolidine ring is formed. On the other hand, all N-acyl thiazolidines



proved chemically stable under basic conditions (0.5% NaOH, amines). Thus, acid instability of the thiazolidine skeleton represents serious limitations for their use in combinatorial chemistry since some building blocks usually contain acid labile protection. To overcome this problem, we speculated that sulfur oxidation might enhance the acid stability of thiazolidines since the ring opening of the sulfonium intermediate **F** would be prevented by the higher oxidation state of the sulfur atom. To this end, we examined the stabilities of prepared sulfoxide and sulfone derivatives **8,9** under the same acidic conditions as described above. As a result, both recovered thiazolidine derivatives were found to be unchanged by ^{1}H NMR and TLC analysis. Surprisingly, while solid phase oxidation of the thiazolidine **6** using MCPBA/DCM (1h, 5°C) gave analytically pure sulfoxide **8**, oxidations using H_2O_2/AcOH (4h, reflux), 10% Na_2WO_4-H_2O_2/H_2O/dioxane, and $Pr_4N^+RuO_4^-$/NMMO/CH_3CN (the latter two reagents: RT, 8h) gave only a small amount (ca. 10%) of desired the sulfone **9**. The reason for the failure of further oxidation of the sulfoxide remains unclear at this time. While exploring the base-stability of thiazolidines, we noticed that treatment of any N-acyl thiazolidine with 0.5% NaOH in D_2O/MeOD (80:20) led to nearly complete (>95%) incorporation of deuterium at the C-4 stereocenter. The

Table 1 Synthesis of 2-Substituted Thiazolidine-4-Carboxylic Acid Derivatives

General Structure	Compd. No.		Substituents X	Y	R	Base (in DMF)	Yield (%)[a] Soln.	SP	dr (%)[b] Soln.	SP
 A	A	1	NO_2	H	Me		86		43	
		2		Ac	H	DIEA[c]		0		
		3		Ac	Me	DIEA[c]	22		>97	
	A	4	OMe	H	H		80		46	
		5		H	Me		92		66	
		6		Ac	H	DIEA	79	68	>97	>97
		6		Ac	H	Py	91	90	64	>97
		7		Ac	Me	Py	71		>97	
		8[d]		Ac	H	DIEA	67	94	>97[e]	>97[e]
		9[f]		Ac	H	DIEA	94	<10	>97	>97
		10		MeNHCO	H			69[g]		~83[h]
		11		MeNHCO	Me		70		83	
	A	12	H	Ac	H			61		>97
		13		Ac	Me	Py	92		>97	
		14		Bz[i]	H	Py		81		>97
		15		Bz[i]	Me	Py	88		>97	
 B	B	16		H	H		85		40	
		17		H	Me		97		66	
		18		Ac	H	DIEA	52		64	
		18		Ac	H	Py	58	40	29	>95
		19		Ac	Me	DIEA	83		>95	
		19		Ac	Me	Py	64		>95	
		20		Bz[i]	H	Py		79		>97
		21		Bz[i]	Me	Py	66		>97	
		22		PhNHCO	H			58[g]		~65[h]
		23		PhNHCO	Me		89		65	
 C	C									
		24		H	H		72		47	
		25		H	Me		91		70	
		26		Ac	H	Py		75		>95
		27		Ac	Me	Py	74		>95	
 D	D									
		28		H	Me		78		51	
		29		Ac	H	Py		63		>97
		30		Ac	Me	Py	83		>97	

[a] Isolated yield after extractive workup (HPLC purity >97%). [b] Diastereoisomer ratio dr(%)=100x(2R,4R)/[(2R,4R)+(2S,4R)]. [c] In the presence of 5mol% of DMAP. [d] Sulfoxide. [e] Absolute stereochemistry of isolated pure diastereoisomer was assigned to be (1R,2R,4R); see note 12. [f] Sulfone. [g] Methyl- and phenylisocyanates were used for acylation of **10,11** and **22,23**, respectively; quantitative conversion to the corresponding hydantoin was observed under alkaline conditions. [h] Ratio for (2RS,4RS) mixture of two enantiomers; enantiomer composition was determined by ^1H NMR using $Eu(tfc)_3$ chiral shift reagent. [i] Benzoylchloride was used for acylation.

stereochemical course of ester hydrolysis and hydantoin formation proved especially interesting. On the basis of product analysis, both processes were found to be highly diastereoselective, affording the (2RS, 4RS) mixture of both enantiomers in a ratio dependent on the stereochemistry at the C-2 center. Since no such asymmetric induction was observed for the diastereomeric mixture of the corresponding acids, one possible explanation for the "chirality self-reproduction" at the C-4 stereocenter is the intermediacy of the rigid bicyclic tautomer of 5(4H)-oxazolone and hydantoin structure, respectively.[14] A representative example is the preparation of N-acetyl-2-(4'-methoxyphenyl)thiazolidine carboxylic acid **6**. Commercially available Fmoc-Cys(Trt)-OH was attached directly to TentaGel S OH resin (ester bond; DIC/HOBt/NMI, 18h) and both protecting groups were simultaneously removed by treatment with a) 20% piperidine/DMF (20min) and b) 10% TFA/5%$^{i}Bu_3SiH$/DCM (3x30min). Reaction with p-anisaldehyde in a mixture of toluene/CH_3CN/AcOH (45:45:10) provided 2-(4-methoxyphenyl)thiazolidine carboxylic acid (not isolated) which after reaction with 5 equiv. of Ac_2O/Py in DMF and final hydrolytic cleavage from the resin (0.5% NaOH) afforded pure **6** in 90% yield.

In conclusion, the methodology presented herein provides a simple and direct route to the combinatorial solid phase synthesis of thiazolidine derivatives. Routine oxidation of the sulfide group enables access to a variety of acid stable sulfoxide analogues. Apparently, additional thiazolidine structural motifs could be suggested but would, of course, require additional refinements in the specific chemistry and choice of building blocks intended to employ for randomization.

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12. The ^{1}H NMR assignment of absolute R-configuration of sulfur of **8** was based on the reported data[13] and suggests the coordination of MCPBA from the less hindered face.
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