Comments on the Putative Stereoselectivity in Cysteine–Aldehyde Reactions. Selective C(2) Inversion and C(4) Epimerization in Thiazolidine-4-carboxylic Acids

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Abstract: (*R*)- and (*S*)-cysteine react with benzaldehyde and *p*-tolualdehyde nonstereospecifically to produce 1:1 mixtures of C(2) epimeric 2-aryl-1,3-thiazolidine-4-carboxylic acids, **1–3.** N-Acetylation, using acetic anhydride/pyridine at 25 °C or acetic anhydride/water at 100 °C, is accompanied by selective inversion at C(2) of the 2,4-cis and 2,4-trans epimers, respectively. No epimerization occurs at C(4) as evidenced by Raney-Ni desulfurization of both the 2(*R*)- and 2(*S*)-phenyl-3-acetyl-1,3-thiazolidine-4(*R*)-carboxylic acid methyl esters, **12** and **14.** On the other hand, selective epimerization at C(4) takes place when **1, 5,** or **8** are treated with acetic anhydride at 100 °C. Mechanistic proposals, supported by deuterium incorporation measurements and product analyses, are advanced for these epimerization reactions. It is demonstrated that complete stereospecificity in the reaction between (*R*)-cysteine and *p*-tolualdehyde was erroneously implied on the basis of misinterpreted ^{1}H NMR spectra.

The steric course of the reaction between cysteine (and 1,2-aminothiols in general) and aldehydes deserves attention for at least two reasons. First, this reaction has been implicated[2-5] in several biochemical processes; second, an analogous condensation reaction constitutes the first step in the syntheses of important natural products, such as penicillin[6,7] and biotin.[8]

Although the configuration of C(5) in natural penicillins and derivatives [C(2) in simple thiazolidines] has long been established[9] as *R*, and C(5)-epimeric penicillins and norpenicillins[10-12] have been prepared by stereocontrolled syntheses, it is surprising how little attention was paid to the stereochemistry at C(2) in simple thiazolidines. Riemschneider and Hoyer[13] and others[14] who described the synthesis of a great number of 2-substituted thiazolidine-4-carboxylic acids completely neglected this point. Much the same situation prevails with the biologically important reaction between pyridoxal and cysteine and penicillamine.[3-5,15-17] Both C(2) epimers were, however, detected and their configurations assigned by ^{1}H NMR,[18] in the reactions between penicillamine and simple aldehydes as well as in recent syntheses[19] of penicilloic acid derivatives and in some other cases.[20] A great number of 2-substituted thiazolidine-4-carboxylic acids and -benzothiazolines, obtained through reaction of (*R*)-cysteine or *o*-methylaminothiophenol,[21,22] respectively, with monosaccharides, were also separated into C(2) epimers and their configurations were established.[23] The latter studies indicated that these condensation reactions exhibit sometimes remarkable stereoselectivity especially when both the aldehyde (e.g., monosaccharides[21,22] or malonaldehyde derivatives[6,12,19]) and aminothiol (cysteine or penicillamine) components are chiral. *Complete* stereoselectivity, although a priori not excluded, seems, however, unlikely to occur when simple achiral aldehydes react with chiral aminothiols. In a recent paper,[24] however, it was claimed that "the reaction of cysteine with *p*-tolualdehyde gives rise to only *one* configuration of the resulting thiazolidine derivative in which the C(4)-carboxylic acid group is cis to the tolyl group" [i.e. 2(*R*)-*p*-tolyl-1,3-thiazolidine-4(*R*)-carboxylic acid]. Similarly, in another work[8] it was tacitly assumed that the reaction between benzaldehyde and (*R*)-cysteine takes a stereospecific route to give exclusively 2(*R*)-phenyl-1,3-thiazolidine-4(*R*)-carboxylic acid.

In this paper we show that (1) the above reactions in fact are not stereospecific, and (2) the apparent stereospecificity is due entirely to the selective inversions at C(2) during N-acetylation, under specific conditions, of either the 2,4-cis or 2,4-trans epimers of 2-aryl-1,3-thiazolidine-4-carboxylic acids. Epimerization reactions at C(4) of thiazolidine-4-carboxylic acids were also studied in some detail, and mechanisms are proposed for both types of reaction. We demonstrate furthermore that the conclusions of ref 24 were arrived at on the basis of misinterpreted ^{1}H NMR spectra and the claims[24] for "very stable thiazolidine conformers" are unfounded.

Results and Discussion

Acetylation in acetic anhydride–water at 100 °C (method A) of **3**, the reaction product of (*R*)-cysteine and *p*-tolualdehyde, furnishes[24] 2(*R*)-*p*-tolyl-3-acetyl-1,3-thiazolidine-4(*R*)-carboxylic acid (**9**) as the single product. When conducted in pyridine at room temperature (method B), the acetylation of **3** gives another product, **10.** Its ^{1}H NMR spectrum (Table II), albeit characteristically different from that[24] of **9**, is fully consistent with a 2-*p*-tolyl-3-acetyl-1,3-thiazolidine-4-carboxylic acid structure. ^{13}C NMR (Table II) and IR data (see Experimental Section) also support this formulation. On the basis of the significant difference in the optical rotation values for **9** and **10** (Table I) it was concluded that these compounds are epimers either at C(2) or C(4). Analogous results were obtained with 2-phenyl-1,3-thiazolidine-4(*R*)-carboxylic acid (**1**). Compound **5** was isolated as the single product when **1** was subjected to acetylation by method A while method B resulted in the exclusive formation of **8**. The diastereoisomeric relationship of **5** and **8** was proved as follows. **5** and **8** were converted with diazomethane to the respective methyl esters **12** and **14**, then subjected to Raney-Ni desulfurization in boiling ethanol. This treatment in both cases gave the same product, **17,** identified as *N*-acetyl-*N*-benzyl-(*S*)-alanine methyl ester. An authentic sample of the latter was prepared from the known[25] *N*-benzyl-(*S*)-alanine by diazomethane esterification and N-acetylation. This finding clearly shows that the diastereoisomerism is such that **5** and **8** have opposite configurations at C(2). It is seen furthermore that the acetylation by either method leaves the original (*R*) configuration at C(4) unchanged. The absolute configurations at C(2) for **5** and **8** were inferred from comparison with **9**, the stereochemistry of which had been established[24] as 2(*R*),4(*R*) by X-ray analysis. Since **5** and **9** were obtained under identical conditions, it is reasonable to assign the same 2(*R*),4(*R*) stereochemistry to **5** as well. This is further substantiated by the close similarity in optical rotation values (Table I) and ^{1}H and

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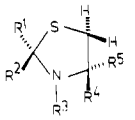
Table I. Physical Properties of 2-Substituted 1,3-Thiazolidine-4-carboxylic Acids[a]



compd	confign	R^1	R^2	R^3	R^4	R^5	mp, °C	$[\alpha]_D$, deg	°C	Yield,[b] %	ref
1	2*R*,4*R* 2*S*,4*R*	Ph	H	H	COOH	H	154–155 dec	−152[c]	23	91	8
2	2*R*,4*S* 2*S*,4*S*	Ph	H	H	H	COOH	159–160 dec	+147[c]	26	92	
3	2*R*,4*R* 2*S*,4*R*	*p*-Tol	H	H	COOH	H	168–169 dec	−120[c]	25	94	42
4	2*R*,4*R* 2*S*,4*R*	Ph	H	H	$COOCH_3$	H	syrup	−91[d]	21	88	
5	2*R*,4*R*	H	Ph	Ac	COOH	H	134–137	+126[d]	21	85	
6	2*S*,4*S*	Ph	H	Ac	H	COOH	133–135	−124[d]	21	80	
7	2*R*,4*S*	H	Ph	Ac	H	COOH	188–189	+315[d]	23	75	
8	2*S*,4*R*	Ph	H	Ac	COOH	H	189–190	−310[d]	21	71	
9	2*R*,4*R*	H	*p*-Tol	Ac	COOH	H	185–187	+131[d]	24	92	42
10	2*S*,4*R*	*p*-Tol	H	Ac	COOH	H	214–216	−286[d]	26	80	
11	2*R*,4*R*	H	Ph	K	COOH	H	132–133	+121[d]	22	91	8
12	2*R*,4*R*	H	Ph	Ac	$COOCH_3$	H	125	+92[e]	25	81	
13	2*S*,4*S*	Ph	H	Ac	H	$COOCH_3$	124–125	−94[e]	25	79	
14	2*S*,4*R*	Ph	H	Ac	$COOCH_3$	H	108–109	−286[e]	26	68	
15	2*R*,4*S*	H	Ph	Ac	H	$COOCH_3$	107–108	+291[e]	25	64	

[a] Abbreviations: Ph = phenyl, *p*-Tol = *p*-tolyl, Ac = $CH_3C{=}O$, K = $CH_3OC{=}O$, dec = decomposition. All optical rotations were measured in 1% solutions (*c* 1). [b] Yields refer to crude reaction products in the case of 1–4, and to pure, recrystallized compounds in the others. [c] In $(CH_3)_2SO$. [d] In methanol. [e] In chloroform.

^{13}C NMR spectral parameters (Table II) of the two compounds, **5** and **9**. In particular, the H(4) and C(2) chemical shifts as well as the $J_{AX} + J_{BX}$ values (Table II) are seen to be practically identical for **5** and **9** while the respective data for **5** and **8** show characteristic differences. By the same reasoning, the stereochemistry of **10** is settled as 2(*S*),4(*R*).

In order to obtain each of the four possible isomers of 2-phenyl-1,3-thiazolidine-4-carboxylic acids, compounds **6** and **7** as well as their methyl esters **13** and **15** were also prepared from (*S*)-cysteine by the procedures outlined above. The corresponding members of the series **5–8** and **12–15** display the expected enantiomeric relationships as can be seen from Table I.

From the foregoing it is clear that at least one of the two procedures (methods A and B) used for the N-acetylation of 2-substituted 1,3-thiazolidine-4-carboxylic acids *must* involve inversion at C(2) with a high degree of stereoselectivity. Therefore the stereochemistry of the parent thiazolidine (such as **1** or **3**) cannot be deduced directly from that of the acylated derivatives (such as **11** or **9**). However, the stereochemistry of **3** and **1** was recently assigned[24,8] on the basis of the X-ray structures of the acetate **9** and the carbamate **11**, respectively, and it was concluded that **3** and **1** were single 2(*R*),4(*R*) epimers. The NMR behavior of **1** and **3** is, however, incompatible with such an assumption. Both substances exhibit two sets of resonances in their room temperature ^1H and ^{13}C NMR spectra (Table II). The ^1H NMR spectrum of **3** was reported[24] to remain unchanged when the sample was heated up to 100 °C in Me_2SO solution. We have confirmed this observation both for **3** and **1** and observed practically no spectral changes up to 140 °C.[26] In ref 24, such a behavior was interpreted in terms of "two very stable conformers" of **3** the interconversion of which is slow on the NMR time scale. Since, up to the decomposition temperature of the compounds, no sizable onset of exchange phenomena (coalescence or even broadening) can be detected in the ^1H NMR spectra, the lower limit of the activation free enthalpy for an assumed interconversion process should be much higher than 63 kJ mol^{-1}, as estimated from the peak separation of the H(2) resonances of **1** at 100 °C. One might speculate about electrostatic interaction between the COO^- and NH_2^+ groups that could contribute to such an unusual stabilization of one of the thiazolidine conformations. It is difficult to imagine, however, why two equally favored conformers should exist and what they are like. In this respect ref 24 gives no clue. Furthermore, the methyl ester **4**, in which no electrostatic interaction between charged groups exists, displays exactly the same NMR behavior as does **1**. It is also difficult to explain, if we follow the reasoning of ref 24, why the high energy barriers between the hypothetical conformers are drastically decreased, with respect to the parent compounds **1–3**, in the N-acetylated thiazolidines **5** and **8**, or in their esters **12** and **14** (vide infra). It is also worth mentioning that the ratio of the two entities in the ^1H NMR spectra of **1–3** is practically solvent independent (Table II) while this is not the case for their N-acetylated derivatives.

Table I reveals that the optical rotation is of diagnostic value in assigning the relative configuration of 2-aryl-1,3-thiazolidine-4-carboxylic acids. In the 4(*R*) series the 2,4-cis isomers show more positive rotation than the 2,4-trans isomers. The opposite holds for the 4(*S*) series, of course. The difference is roughly 1000° in terms of molecular rotation values. Assuming that N-acetylation makes negligible contribution to the molecular rotation of thiazolidine-4-carboxylic acids, a value of $[\alpha]_D$ −138° was calculated for the epimeric mixture **1** in excellent agreement with the measured value $[\alpha]_D$ −142°.

In our opinion the hypothesis of "very stable thiazolidine conformers" is completely incompatible with the above observations. Such an assumption contradicts all experimental and theoretical results obtained with thiazolidines[28] in particular, and with five-membered rings in general.[29] We suggest therefore that compounds **1–3** consist of ~1:1 mixtures of the 2,4-cis and 2,4-trans epimers. This explains satisfactorily the observed NMR behavior, optical rotation values, and chemical reactions of these compounds.

The ^1H NMR spectra of the *N*-acyl derivatives **5–15** also exhibit two sets of signals for the H(2), H(4), acetyl methyl,

Table II. Selected ^1H and ^{13}C NMR Data of 1,3-Thiazolidine Derivatives

compd	solvent	temp, °C	ratio[a]	$J_{AX} + J_{BX}$, Hz[b]	chemical shift, ppm H(2)	H(4)	C(2)	C(4)	C(5)
1	$(CD_3)_2SO$	31	55	12.0	5.70	4.25	71.8	64.8	37.9
			45	15.0	5.49	3.92	71.0	65.4	38.5
	C_5D_5N	31	47	13.0	6.25	4.58			
			53	16.0	5.80	4.32			
	CH_3COOH	31	46	13.8[c]	6.01	4.89[c]			
			54	11.5[c]	5.88	4.32[c]			
4	$(CD_3)_2SO$	30	53	11.5	5.71	4.38			
			47	16.0	5.55	3.85			
	C_5D_5N	30	47	12.5	6.01	4.32			
			53	15.4	5.64	3.90			
	$CDCl_3$	30	44	12.5	5.77	4.16			
			56	16.0	5.52	3.95			
	C_6D_6	30	47	8.5[c]	5.73	3.90[c]			
			53	13.0[c]	5.43	3.75[c]			
5	$(CD_3)_2SO$	31	70		6.32	4.78	65.5	64.3	31.6
			30		6.20	5.12	66.2	64.0	33.6
		100		12.5	6.30	4.99			
8	$(CD_3)_2SO$	31	54	6.5	6.34	5.11	64.3	63.1	30.6
			46	6.0	6.13	5.32	64.5	63.9	32.6
		100		6.5	6.22	5.21			
9	$(CD_3)_2SO$	31	70		6.28	4.77	65.5	64.3	31.6
			30		6.13	5.12	66.0	64.1	33.5
		100		13.0	6.22	4.87			
10	$(CD_3)_2SO$	31	60	6.5	6.29	5.12	64.3	63.2	30.7
			40		6.13	5.30	64.5	64.0	32.7
		100		6.5	6.22	5.20			
12	$(CD_3)_2SO$	30	80	14.5	6.53	4.98			
			20		6.34	5.45			
		100		14.0	6.47	5.18			
	$CDCl_3$	30	91	14.5	6.05	4.96			
			9		6.35	4.8			
		60		14.0	6.07	4.92			
	$(CD_3)_2CO$	30	71	14.5	6.31	4.90			
			29		6.31	5.15			
		50			6.31	4.95			
	$(CD_3)_2SO$	30	68	7.5	6.31	5.21			
			32	7.5	6.15	5.39			
		100		7.5	6.26	5.29			
14	$CDCl_3$	30	87	6.5	5.98	5.16			
			13	6.5	6.17	4.95			
		60		6.5	6.02	5.13			

[a] Epimer ratios in the case of **1** and **4**, and conformer population ratios in the other cases. [b] A = H(5), B = H(5'), X = H(4). [c] These assignments can be interchanged.

and other protons at room temperature. Coalescence of these signals occurs in all cases below 100 °C. The relative intensities of the corresponding resonances show marked solvent dependence (Table II, compounds **12** and **14**[40]). There is little reason to doubt that these phenomena are essentially due to hindered amide rotations.[30] Although in all probability these motions are not completely decoupled from various conformational transitions of the thiazolidine ring,[31] we think that, in contrast to what had been stated in ref 24, there are major difficulties in *not invoking* the *N*-acetyl rotation in these 2-substituted thiazolidines as the main source contributing to the temperature and solvent dependences of the NMR spectra. Indeed, compound **17** (*N*-benzyl-*N*-acetyl-(*S*)-alanine methyl ester), which contains *no thiazolidine ring* but has an *N*-acetyl group, displays an ^1H NMR spectrum whose temperature and solvent dependences are closely analogous to those observed with *N*-acetylthiazolidine methyl esters **12** and **14** (Table II and Experimental Section).

Each of the condensation products of cysteine or its methyl ester with the aldehydes used was shown above to consist of a mixture of C(2) epimeric thiazolidine-4-carboxylic acids. Since acetylation of these mixtures by methods A and B results in the exclusive formation of either the 2,4-cis or the 2,4-trans epimers of 2-substituted *N*-acetyl-1,3-thiazolidine-4-carboxylic acids, respectively, it is apparent that N-acetylation is accompanied in both cases by selective inversion at C(2). Since both reactions take place in heterogeneous systems they are not directly accessible to mechanistic studies by conventional kinetic methods. Therefore, we sought indirect evidence in order to get some insight into the mechanism of these remarkable isomerization reactions. When the mixture **1** of diastereometric 2-phenylthiazolidine-4-carboxylic acids, in which the exchangeable protons had been replaced by deuterons, was subjected to acetylation in D_2O–acetic anhydride at 100 °C (method A) no deuterium incorporation could be observed by ^1H NMR at C(2) or any other position of the thiazolidine ring. This finding eliminates any mechanism involving deprotonation–reprotonation at position 2 of the thiazolidine ring either before or after the acetylation step. A conceivable mechanism which accounts for the absence of deuterium incorporation is depicted in Scheme I.

Base-catalyzed isomerization of thiazolidines through

Scheme I

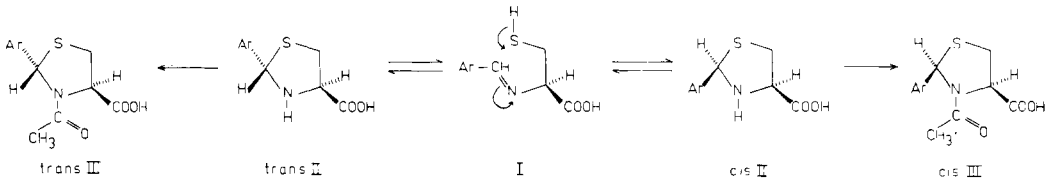
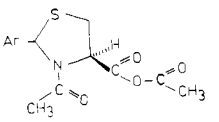


Table III. Epimerization of 3-Acetyl-1,3-thiazolidine-4-carboxylic Acids in Acetic Anhydride

Starting material	mp, °C	products $[\alpha]_D$, deg	structure
5	133-135	+129	**5**
	187-189	+304	**7**
8	188-190	−306	**8**
	132-135	−121	**6**

Schiff-base intermediates (I) is a well-known process.[32,33] If we assume that step *cis*-II → *cis*-III is fast compared with step *trans*-II → *trans*-III, the preferential formation of the cis isomers, *cis*-III, can be rationalized. An analogous mechanism can be invoked to account for the formation of the trans-acetylated products, *trans*-III, by method B. Obviously, in the latter case step *trans*-II → *trans*-III should be much faster than step *cis*-II → *cis*-III. An alternative mechanism[34] which would involve epimerization through ring opening of the acetylated products, *cis*-III or *trans*-III, can be safely ruled out since both **5** and **8** are perfectly stable under the conditions of methods A and B (see Experimental Section). On the other hand, either the cis or the trans acetates, **5** and **8**, were rapidly equilibrated into an approximately 1:1 mixture of the two when heated at 100 °C in pure acetic anhydride for a short time (10 min). Similar treatment of the condensation product of (*R*)-cysteine and benzaldehyde, **1**, resulted in the formation of the above equilibrium mixture of **5** and **8**. When this procedure was repeated using a sample of the condensation product **1** in which the exchangeable protons had been replaced by deuterons, ^1H NMR monitoring of the reaction revealed full deuterium incorporation at C(4) in the reaction products **5** and **8**. No other hydrogens were affected. Finally, neither **12** nor **14** showed any change when kept in acetic anhydride at 100 °C for at least 2 h.

The steric course of this epimerization process could be conveniently determined from optical rotation data of the diastereomers separated after acetic anhydride treatment of either **5** or **8**. These data are summarized in Table III. From the high optical purity of the epimerized products it is evident that inversion of configuration occurred exclusively at C(4). The possibility of simultaneous epimerization at C(2) can be safely excluded since this would have led to partial or complete loss of the optical activity of **7** and **6** (and of **5** and **8**, of course). It is therefore concluded that these reactions take place without opening of the thiazolidine ring. Racemization at α-carbon atoms of *N*-acylamino acid active esters has long been known[35] as the most common side reaction accompanying peptide coupling. Two types of mechanisms were advanced for these base-catalyzed proton exchange reactions. One involves[36] oxazolone-type intermediates formed through nucleophilic attack of the amide carbonyl oxygen on the activated ester carbonyl carbon of the amino acid. Such a mechanism certainly cannot be operative with the thiazolidinecarboxylic acids above since it would involve opening of the thiazolidine ring, which was shown not to occur under the conditions applied. On the other hand, direct proton abstraction-reprotonation at C(4), which was suggested[37] as a racemization mechanism for certain types of peptide coupling reactions, may well account for the epimerizations observed above. Labilization of H(4) and, hence, epimerization at C(4) can easily take place in a mixed anhydride type intermediate as depicted below.



Some support for the intermediacy of the mixed anhydride is provided by the observation that methyl esters **12** and **14** are perfectly stable in acetic anhydride at 100 °C (vide supra). The mixed anhydride of acetic acid with a similar system, 6-methoxycarbonyl-3,4-dihydro-2*H*-1,4-thiazine-3-carboxylic acid, was supposed[38] to occur as an intermediate in the N-acetylation reaction of the latter compound. Mixed anhydrides of 1,3-thiazolidine-4-carboxylic acids were isolated at least in one case.[39] Very recently, it was reported[41] that N-benzoylation is accompanied by more or less extensive racemization at C(4) of certain thiazolidine-4-carboxylic acids.

In conclusion, cysteine reacts with simple aromatic aldehydes nonstereoselectively to produce mixtures of the two C(2) epimers of 2-aryl-1,3-thiazolidine-4-carboxylic acids. These diastereoisomeric mixtures yield, upon N-acetylation under specific conditions, pure 2-4-*cis*- or 2,4-*trans*-2-aryl-3-acetyl-1,3-thiazolidine-4-carboxylic acids. These processes were shown to involve selective inversion at C(2) of the thiazolidine-4-carboxylic acids probably through a ring-opening mechanism involving Schiff-base intermediates. Selective epimerization at C(4) of 2-aryl-3-acetyl-1,3-thiazolidine-4-carboxylic acids was shown to occur without ring opening, presumably via intermediate formation of thiazolidinecarboxylic acid-acetic acid mixed anhydrides. It was demonstrated that misinterpretation of certain NMR results led[24] to incorrect conclusions concerning the stereospecificity of cysteine-aldehyde reactions.

Experimental Section

^1H NMR spectra were recorded at 100 MHz on a JEOL MH-100 instrument and a Varian XL-100 spectrometer was used for the ^{13}C NMR measurements at 25 MHz. Infrared spectra were recorded on Perkin-Elmer Model 283 and Unicam SP 200 G instruments. Melting points were taken on a Boetius micro hot stage.

2-Phenyl-1,3-thiazolidine-4-carboxylic acids (**1** and **2**),[13] 2-*p*-tolyl-1,3-thiazolidine-4-carboxylic acid[42] (**3**), and 2(*R*)-phenyl-3-methoxycarbonyl-1,3-thiazolidine-4(*R*)-carboxylic acid (**11**)[8] were prepared by published procedures.

Methyl 2-Phenyl-1,3-thiazolidine-4(*R*)-carboxylate (4). This substance, consisting of a 1:1 mixture of the two C(2) epimers, was prepared by dissolving 1.71 g (10 mmol) of (*R*)-cysteine methyl ester hydrochloride in 16 mL of methanol. Benzaldehyde (1 mL, 10 mmol) and 0.81 mL (10 mmol) of dry pyridine were added and the reaction mixture was stored overnight at room temperature. Evaporation under reduced pressure yielded a syrup which was partitioned between chloroform and water, and the organic phase was dried ($MgSO_4$) and evaporated to give 1.96 g (88% yield) of colorless oil. Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.16; H, 5.87; S, 14.36. Found: C, 59.60; H, 5.61; S, 14.61.

2,4-Cis Epimers of 2-Aryl-3-acetyl-1,3-thiazolidine-4-carboxylic Acids (5, 6, and 9). These compounds were prepared according to the procedure of Paul and Korytnyk.[42] To 1 mmol of **1**, **2**, or **3**, 0.56 mL of water and 0.50 mL of acetic anhydride were added and the stirred suspensions heated on a steam bath until homogeneous solutions were obtained (usually 5-10 min). ^{1}H NMR spectra, taken immediately after dissolution, of the reaction mixtures (D_2O being used instead of H_2O) indicated exclusive formation of the 2,4-cis epimers, **5**(= **6**) and **9**. The products which crystallized upon cooling were collected by filtration, washed throughly with water, and recrystallized from ethanol-water. One recrystallization was usually sufficient to provide analytically pure samples: IR (KBr) identical for **5** and **6** (2200-3200, 1720, 1660, 1620 cm^{-1}); for **9**, 2200-3300, 1727, 1619 cm^{-1}. Anal. ($C_{12}H_{13}NO_3S$) C, H, S.

2,4-Trans Epimers of 2-Aryl-3-acetyl-1,3-thiazolidine-4-carboxylic Acids (7, 8, and 10). One millimole of either **1**, **2**, or **3** was suspended in 2.5 mL of dry pyridine, 0.3 mL of acetic anhydride added, and the mixture left at room temperature for 1-2 h with occasional shaking. The ^{1}H NMR spectrum of a sample consisting of 60 mg of **1**, 0.5 mL of pyridine-d_5, and 0.1 mL of acetic anhydride-d_6, recorded 10 min after mixing, shows the presence of the 2,4-trans epimer **8** and practically complete absence of either the 2,4-cis epimer **5** or the starting material. Evaporation to dryness under reduced pressure and trituration of the residues with 2 M H_2SO_4 solution yielded solid products which were filtered, washed neutral with water, and recrystallized from ethanol. IR (KBr) identical for **7** and **8** (2210-3200, 1720, 1660, 1600 cm^{-1}); for **10**, 2100-3400, 1730, 1611 cm^{-1}. Anal. ($C_{12}H_{13}NO_3S$) C, H, S.

Methyl 2-Aryl-3-acetyl-1,3-thiazolidine-4-carboxylates (12, 13, 14, and 15). One millimole of either **5**, **6**, **7**, or **8** was dissolved in 5-8 mL of methanol and ethereal diazomethane was added in sufficient amounts. Evaporation to dryness and recrystallization from ethyl acetate-petroleum ether yielded pure products. IR (KBr) identical for **12** and **13** (1755, 1640 cm^{-1}) and for **14** and **15** (1755, 1665 cm^{-1}). Anal. ($C_{13}H_{15}NO_3S$) C, H, S.

Methyl *N*-Benzyl-(*S*)-alaninate (16). *N*-Benzyl-(*S*)-alanine[25] (0.90 g, 5 mmol) was suspended in 8 mL of methanol and stirred with ethereal diazomethane in excess until a homogenous solution was obtained. After evaporation, a mobile, colorless oil was obtained which was purified on a silica gel column using ether as eluant; 0.33 g (34%) of the product was analytically pure, colorless oil, $[\alpha]^{21}_D$ −41.0° (*c* 1.84, methanol). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.60; H, 7.72; N, 7.17. ^{1}H NMR ($CDCl_3$): δ 1.22 (d, 3 H, CH_3), 1.82 (s, 1 H, NH), 3.17 (q, 1 H, CH), 3.50 (s, 3 H, OCH_3), 3.50 (AB q, 2 H, CH_2), 6.90 (m, 5 H, Ph).

Methyl *N*-Benzyl-*N*-acetyl-(*S*)-alaninate (17). A. 16 (0.85 g, 4.35 mmol) was heated in 4 mL of acetic anhydride for 80 min on a steam bath. The reaction mixture was stirred into 80 mL of ice-water, left to stand at room temperature for 3 h, then extracted with ether, and the ethereal solution was dried ($MgSO_4$) and evaporated to give a pale yellow syrup. After purification on a silica gel column using ether as eluant, 0.61 g (58.9%) of a colorless oil was obtained, $[\alpha]^{21}_D$ −62.8° (*c* 1.42, methanol). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 6.39. Found: C, 66.17; H, 7.36; N, 6.56. IR (CCl_4): 3090, 3066, 3030, 2998, 2951, 2858, 1745, 1660 cm^{-1}. ^{1}H NMR (Me_2SO, 30 °C): δ 1.27 (d, 2.25 H, CH_3), 1.31 (d, 0.75 H, CH_3), 2.05 (s, 2.25 H, CH_3CO), 2.15 (s, 0.75 H, CH_3CO), 3.60 (s, 3 H, OCH_3), 4.37 (q, 0.75 H, CH), 4.63 (s, 2 H, CH_2), 4.82 (q, 0.25 H, CH), 7.20 (br s, 1.25 H, Ph), 7.34 (br s, 3.75 H, Ph); (Me_2SO, 100 °C) δ 1.29 (d, 3 H, CH_3), 2.08 (s, 3 H, CH_3CO), 3.60 (s, 3 H, OCH_3), 4.60 (br m, 3 H, CH, CH_2), 7.31 (br s, 5 H, Ph); ($CDCl_3$, 30 °C) 1.35 (d, 3 H, CH_3), 2.08 (s, 2.45 H, CH_3), 2.20 (s, 0.55 H, CH_3), 3.48 (s, 0.55 H, OCH_3), 3.63 (s, 2.45 H, OCH_3), 4.5 (m, 3 H, CH, CH_2), 7.15 (m, 5 H, Ph); ($CDCl_3$, 60 °C) δ 1.35 (d, 3 H, CH_3), 2.08 (br s, 3 H, CH_3CO), 3.61 (br s, 3 H, OCH_3), 7.17 (br s, 5 H, Ph).

B. 12 (0.27 g, 1 mmol) in 15 mL of dry ethanol was refluxed with 6 g of wet Raney Ni (Degussa) for 3.5 h. The product was separated by filtration through a Celite pad which was washed several times with ethanol. The combined filtrates were evaporated to dryness to give a colorless oil in nearly quantitative yield, $[\alpha]^{21}_D$ −57.9 (*c* 1.61, methanol), $[\alpha]^{22}_D$ −43.4° (*c* 1.63, chloroform). This product was identical (NMR, IR, TLC) with the one described under A.

C. Raney-Ni treatment of **14** in the manner described above yielded an oil, $[\alpha]^{21}_D$ −43.9° (*c* 1, chloroform), which proved to be identical (NMR, IR, TLC) with the reaction product described under A.

2-Phenyl-1,3-thiazolidine-4(*R*)-carboxylic Acid-d_2 (1-d_2). 1 (1.05 g, 5 mmol) was dissolved in 10 mL of deuterium oxide (99.9% D) containing 0.45 g (5.5 mmol) of $NaHCO_3$. The solution was lyophilized and the residue dissolved in 5 mL of D_2O and lyophilized again. This procedure was repeated twice more, the residue dissolved in D_2O, and an equivalent amount of 20% DCl in D_2O added. The precipitate was collected by filtration and dried in a vacuum desiccator over phosphorus pentoxide. ^{1}H NMR indicated that 80% of the exchangeable protons had been replaced by deuterons.

Epimerization Studies by ^{1}H NMR. A. Using flame-dried glassware throughout, 50 mg of **1**-d_2 in 0.25 mL of D_2O and 0.25 mL of acetic anhydride-d_6 (Merck) was heated at ~100 °C until a homogenous solution was obtained (ca. 5 min). This was quickly transferred into an NMR tube and the ^{1}H spectrum recorded at 90 °C probe temperature. The whole operation took about 15 min. The expected integrated intensity ratios were obtained for all resonances indicating that no detectable deuterium incorporation had taken place.

B. 1-d_2 (50 mg) was treated with 0.4 mL of acetic anhydride-d_6 as described above. The integrated intensity ratio in the ^{1}H NMR spectrum, recorded at 90 °C probe temperature, was 1:0.25:2 for the H(2), H(4), and H(5,5′) resonances, respectively. This figure shows 75% deuterium incorporation at C(4) which, combined with the isotopic purity of the starting material, is practically equivalent to complete deuteration at C(4).

C. 8 (50 mg) dissolved in 0.25 mL of acetic anhydride-d_6 and 0.25 mL of D_2O was kept at 90 °C for 2 h. No change could be detected by ^{1}H NMR. Treatment of **5** (50 mg) in pyridine-d_5 (0.4 mL) and acetic anhydride-d_6 (0.1 mL) at room temperature overnight led to identical results.

D. 5 (50 mg) was dissolved at 90 °C in 0.4 mL of acetic anhydride and the solution kept at this temperature for 20 min. The ^{1}H NMR spectrum, recorded at 90 °C probe temperature, showed two H(4) resonances, with 4:5 intensity ratio, characteristic of the trans and cis epimers, **8** and **5**, respectively. The same equilibrium mixture was obtained when **8** was subjected to the above treatment. On the other hand, both **12** and **14** remained unchanged, as revealed by ^{1}H NMR, after having been kept in acetic anhydride at 90 °C for 2 h.

Epimerization at C(4) of 5 and 8. A. 5 (1.0 g, 4 mmol) was suspended in 6 mL of acetic anhydride and heated on a steam bath for 20 min. The resulting solution was stirred into 60 mL of ice-water. The initially formed syrupy product slowly solidified (4-5 h) on scratching. After filtration and drying 0.74 g of a white powder was obtained, $[\alpha]^{22}_D$ +205° (*c* 1, methanol). Another 0.22 g ($[\alpha]^{22}_D$ +150°) was obtained by concentrating the mother liquor. Fractional crystallization of the first crop from ethanol yielded 0.21 g of a product, $[\alpha]^{20}_D$ +304° (*c* 1, methanol), which was shown (melting point, mixture melting point, IR) to be identical with **7**. Pure **5** (0.14 g), $[\alpha]^{21}_D$ +129° (*c* 1, methanol) was recovered from the second crop by recrystallization from ethanol-water. No attempt was made to process the epimerized mixture quantitatively.

B. When 1.0 g of **8** was subjected to the treatment described above the first crop of the product (0.41 g), $[\alpha]^{23}_D$ −306° (*c* 1, methanol), was shown (melting point, mixture melting point, IR) to consist of practically pure **8**. The second crop (0.53 g) had $[\alpha]^{23}_D$ −143° (*c* 1.3, methanol) and yielded 0.40 g of pure **6**, $[\alpha]^{22}_D$ −121° (*c* 1, methanol), on recrystallization from ethanol.

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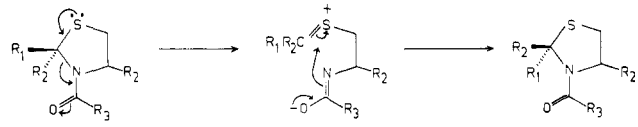

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Use of Polymers as Protecting Groups in Organic Synthesis. Application of Polystyrylboronic Acid to the One-Pot Synthesis of Acylated Carbohydrate Derivatives

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Abstract: The reactions of polystyrylboronic acid with various glycosides show that the polymer is an efficient and very selective protecting group for cis diols. Coupling of the glycosides to the polymer yields the most stable five- or six-membered ring boronate. Examples of diol protection in the formation of selectively acylated glycosides via one-pot reactions include the protection of 2,3-diols in methyl α-L-rhamnopyranoside and methyl α-D-mannopyranoside; 2,4-diols in methyl D-xylopyranosides, methyl β-D-ribopyranoside, and methyl α-D-glucopyranoside; 4,6-diols in methyl α-D-galactopyranoside and methyl α-D-glucopyranoside. In addition, the polymer can be used to protect one of the two 4,6-diol groupings of a disaccharide such as α,α-trehalose. The main advantages of the polymeric protecting group are its selectivity, its insolubility which allows all the reactions to be carried out rapidly and in one pot, and the extreme mildness of the conditions which are required for its use. In addition, the polymer is reusable without regeneration and no loss of activity is observed with repeated use.

Since Merrifield's development of the solid-phase synthesis of polypeptides,[1] functional polymers have been used as supports[2] in a number of other repetitive sequential type syntheses for the preparation of numerous peptides,[3] oligonucleotides,[4] or oligosaccharides.[5] Nonrepetitive syntheses using polymer supports and unprotected polyfunctional molecules have not been studied extensively. In such syntheses, the polymer acts as a protecting group for one of the functionalities of the starting material while reactions are carried out on the other reactive ends of the polymer-protected material. This technique has been applied successfully to the partial functionalization of glycosides[6] and to the monoprotection of other polyfunctional molecules.[7] In all of these cases, however, the polymer did not show any real selectivity. Of the advantages associated with the use of functional polymers in organic synthesis,[8] those related to enhanced purification through simple phase separations have undoubtedly been demonstrated most often and are at the basis of the solid-phase method of synthesis. Another advantage which has often been sought but seldom achieved is one which would make use of the great potential of the functional polymers to be regenerated to their former activity and recycled after use. Our approach to new polymeric protecting groups requires that the functional polymers be fully regenerable since otherwise their high cost

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