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Reversible Thiazolidine Exchange: A New Reaction Suitable for Dynamic Combinatorial Chemistry

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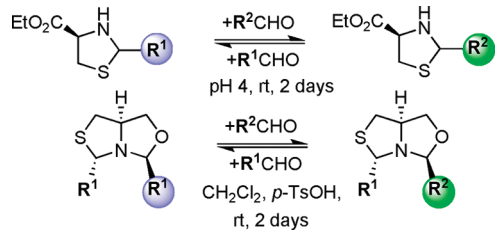
ABSTRACT



New dynamic combinatorial libraries (DCLs) were generated using the reversible aminothiol exchange reaction of thiazolidines and aromatic aldehydes. The reaction proceeded in aqueous buffered media at pH 4 and room temperature to generate thermodynamically controlled mixtures of heterocycles. The synthesis of an enantiomerically pure thiazolidinyloxazolidine is also reported. The oxazolidine moiety could be exchanged in CH_2Cl_2 in the presence of catalytic *p*-TsOH.

Dynamic combinatorial chemistry (DCC) has considerable potential in the discovery of small molecule ligands for artificial receptors and large biomolecules. DCC is largely based on the use of reversible reactions to generate compound mixtures—dynamic combinatorial libraries (DCLs)—that are in thermodynamic equilibrium. The composition of the library is determined by the properties of each of the library members under the particular conditions of the experiment; this equilibrium is likely to respond to the presence of a template or another change in the environment.[1]

The covalent reversible reactions usable in DCC are relatively rare compared to the irreversible processes favored in traditional synthetic chemistry, and most of the former involve carbonyl compounds, imines, and acetals.

Four different types of substrates have previously been used to generate DCLs from carbonyl compounds by acetal exchange (Figure 1): (a) diols in the presence of catalytic

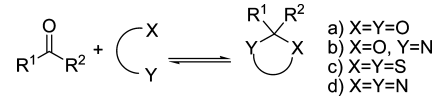


Figure 1. Cyclic acetal formations suitable for DCL.

TfOH,[2] H_2SO_4,[3] or *p*-TsOH;[4] (b) aminoalcohols, leading to mixtures of imines, oxazinanes, and oxazolines;[5] (c) thiols in the presence of catalytic $Zn(OTf)_2$[6a] or $Hf(OTf)_4$;[6b] and (d) diamines in aqueous buffered media at pH 4, conditions described by our group for the formation of pyrazolotriazinone heterocycles.[7]

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(1) For reviews, see: (a) Ladame, S. *Org. Biomol. Chem.* **2008**, *6*, 219–226. (b) Ludlow, R. F.; Otto, S. *Chem. Soc. Rev.* **2008**, *37*, 101–108. (c) Lehn, J.-M. *Chem. Soc. Rev.* **2007**, *36*, 151–160. (d) Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M.; Otto, S. *Chem. Rev.* **2006**, *106*, 3652–3711.

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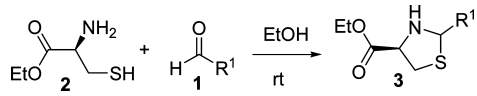
The acid-catalyzed transacetylation of thiazolidines and related compounds attracted our closer attention as a possible extension of the latter heterocycle formation process.

Thiazolidines **3** were selected as simple models to identify equilibration conditions for DCL formation. In spite of a literature report on the reversible formation of thiazolidines under basic conditions,[8] this transformation has not been previously reported as useful for DCC. 4-Carboxyl ethyl-2-arylthiazolidines can be readily obtained by condensation of aldehydes (**1**) and cysteine ethyl ester (**2**) in EtOH at room temperature (Scheme 1).

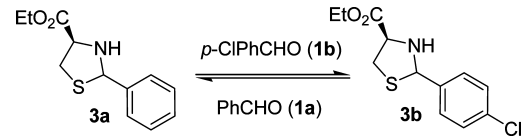
Scheme 1. Thiazolidine Formation from Cysteine



The discovery of new reversible reactions compatible with an aqueous environment is an important objective for the use of biomolecules as templates in DCLs. We screened different aqueous conditions, with variations in pH and reaction time, in order to establish optimal thermodynamic exchange conditions for the thiazolidine exchange. The reaction of **3a** with equimolar amounts of *p*-Cl-benzaldehyde (**1b**) at room temperature was used as a reference (Table 1).

Thermodynamic equilibration of a mixture of **3a** and **1b** occurred at pH 4 over 24 to 48 h at room temperature.[9] After 3 d, heterocycles **3a** and **3b** were stable in the aqueous environment and thiazolidines (90−98%) and ester **2** (2−10%) were recovered (entries 1, 2, and 3). Equilibration at pH 5 was slower, but after 3 d, the ratio indicated that equilibrium was reached (entries 4, 5, and 6). Equilibration at pH 6 was not complete after 3 d at rt (entries 7, 8, and 9). Equilibration at pH 7 did not proceed during 3 d at rt (entry 10) and the presence of ester **2** was not detected. The method of choice for blocking further equilibration is a simple raise of pH to 7; since we did not observe any further equilibration at this pH, the yields of recovered products were quantitative.

Table 1. Optimization of Thiazolidine Exchange Reaction of **3a**



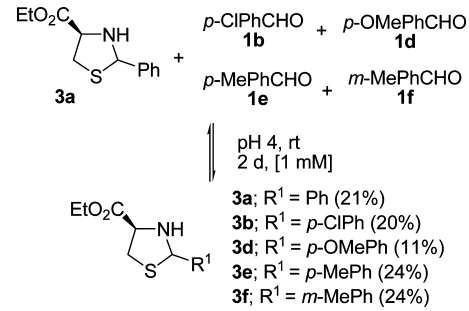
entry	reaction conditions[a]	time (h)	**3a**/**3b** ratio[b]	**2** (%)[c]
1	pH 4, rt	24	45/55	3
2	pH 4, rt	48	44/56	2
3	pH 4, rt	72	46/54	10
4	pH 5, rt	24	71/29	5
5	pH 5, rt	48	68/32	10
6	pH 5, rt	72	52/48	9
7	pH 6, rt	24	96/4	0
8	pH 6, rt	48	97/3	0
9	pH 6, rt	72	90/10	0
10	pH 7, rt	72	98/2	0
11	pH 4, 35 °C	24	45/55	18[d]
12	pH 4, 35 °C	48	35/65	16[e]

[a] Starting concentration of each component was 1 mM; the reaction mixture was stirred in a buffered acetate solution at pH 4 and pH 5, and in a phosphate solution at pH 6 and pH 7. [b] Ratio was determined by ^{1}H NMR. [c] Mass balance was quantitative. [d] Total yield **3a** + **3b** (64%). [e] Total yield **3a** + **3b** (49%).

When the temperature was increased to 35 °C at pH 4, the equilibration occurred faster, but significant amounts of cysteine ester **2** were observed. The total recovered yield for thiazolidines was 64 and 49% after 1 and 2 d, respectively (Table 1, entries 11 and 12). The mass balance was decreasing, probably due to ester hydrolysis in compound **2**.

Thiazolidines **3a** and **3b** have different stabilities depending on pH; at pH 4−5 thiazolidine hydrolysis occurs to an acceptable extent (2−10%) at rt over 3 d. Temperature seems to play an important role in these systems; higher temper-

Scheme 2. Exchange Reaction between Thiazolidines **3a** and Aldehydes **1b**,**1d**−**f**[a]



[a] Yields in parentheses reflect the equilibrium distribution. The ratio was determined by ^{1}H NMR and confirmed by preparative isolation.

(2) (a) Cacciapaglia, R.; Di Stefano, S.; Mandolini, L. *J. Am. Chem. Soc.* **2005**, *127*, 13666–13671. (b) Fuchs, B.; Nelson, A.; Star, A.; Stoddart, J. F.; Vidal, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 4220–4224. (c) Cacciapaglia, R.; Di Stefano, S.; Mandolini, L.; Mencarelli, P.; Ugozzoli, F. *Eur. J. Org. Chem.* **2008**, 186–195.

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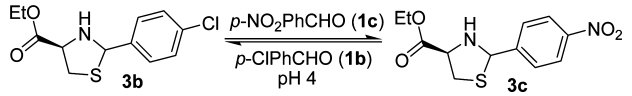
(9) Typical procedure: A solution of compound **3a** (20.8 mg, 0.09 mmol) and *p*-Cl-benzaldehyde (12.3 mg, 0.09 mmol) in a mixture of acetate buffer at pH 4 (63 mL) and MeOH (27 mL) was stirred at rt for 2 d. The pH was raised to 7 by adding a saturated solution of $NaHCO_3$, and the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo (temperature should never exceed 22 °C). The residue was analyzed by ^{1}H NMR to determine the ratio and products were confirmed by preparative isolation of **3a** + **3b** (26 mg, 98% yield).

atures accelerate the exchange process but under concomitant hydrolysis of the thiazolidine and the cysteine ethyl ester.

We also probed the reversibility of the system by starting from products **3b** and **3c** at pH 4 (Table 2). If equilibration

Table 2. Thiazolidine Exchange Processes Starting with **3b** or **3c**



entry	reaction conditions[a]	time (h)	**3b/3c** ratio[b]	**2** (%)
1	**3b**, **1c**	48	25/75	4
2	**3c**, **1b**	48	24/76	3

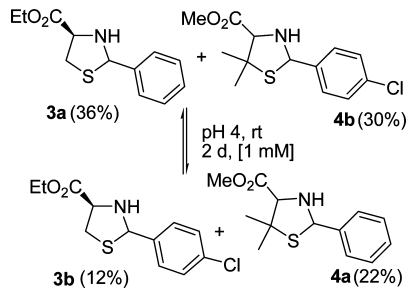
[a] Starting concentration of each component was 1 mM, the reaction mixture was stirred at rt in a buffered acetate solution at pH 4. [b] Ratio was determined by ^{1}H NMR and confirmed by preparative isolation.

was reached, the distribution pattern should be identical. At pH 4, equilibration required 48 h at rt, providing a comparable product ratio as observed for the inverse process (entries 1 and 2, Table 2).

Thiazolidine **3a** was allowed to equilibrate with aldehydes **1b** and **1d**−**f**; the starting concentrations of the mixture components were kept at 1 mM each. The distribution of the corresponding heterocycles varied slightly for thiazolidines **3a**,**b**,**e** and **f** (20−24%) except for **3d** (11%) after 2 d. Thiazolidine **3d** bearing an EDG on the benzene ring has the lowest stability in the acidic medium. The mass balance indicated a 93% yield of thiazolidines and 7% of ester **2** after 4 d, and the distribution remained unchanged. Even though some formation of compound **2** was observed, thiazolidines are stable in the acid media (pH 4) for 4 d. This stability enables this DCL for the observation of template effects.

We also studied the possibility for direct side-chain metathesis of thiazolidines. An equimolecular mixture of **3a** and **4b**, which differ by their substitution at 2, 4 and 5-positions of the heterocycles, was equilibrated during 2 d at pH 4 and rt (Scheme 3). As expected, a mixture of four

Scheme 3. Metathesis of Thiazolidines[a]

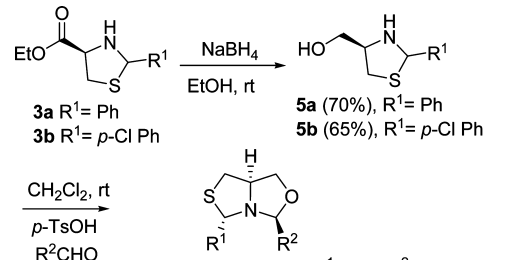


[a] Yields in parentheses reflect the equilibrium distribution. The ratio was determined by ^{1}H NMR and confirmed by preparative isolation.

products (the original starting materials and two crossover derivatives) was formed. Small amounts of penicillamine methyl ester (3%) and cysteine ethyl ester (7%) were also detected, but 90% of the thiazolidine products was recovered after 3 d.

As a means to increase diversity in the side chains at the 4-position of the heterocycles, the ester moiety of thiazolidines **3a**−**b** was converted to the alcohol by reduction with $NaBH_4$. When the aminoalcohols **5a**−**b** were individually treated with aldehydes **1a**−**b** in acid media (*p*-TsOH), the fused thiazolidine−oxazolidines **6** were formed. This class of compounds represents a new example of a bicyclic DCC scaffold (Scheme 4).[10] Even though aminoalcohols **5** were

Scheme 4. Synthesis of Fused Thiazolidine−Oxazolidine Heterocycles



used as a 1:1 mixture of diastereomers, only *anti*-**6** was formed. The relative configuration was confirmed by NOE experiments. This result is not completely unexpected due to the fact that thiazolidines undergo facile ring-opening and closure reactions.[11]

We hypothesize that this reaction proceeds by a thermodynamic equilibration, with *anti*-**6** being the more stable fused heterocycle.

Thiazolidinyloxazolidine heterocycles present interesting opportunities for exchange processes: products include thiazolidine $\mathbf{5_R}$, oxazolidine $\mathbf{8_R}$, the fused heterocycles at the thiazolidine or the oxazolidine site $\mathbf{6_{RR}}$, and also the imine isomers $\mathbf{9_R}$,[12] as shown in Scheme 5.

When bicycle **6aa** [10 mM] in CH_2Cl_2 was equilibrated at rt with an equimolar amount of aldehyde **1b** in the

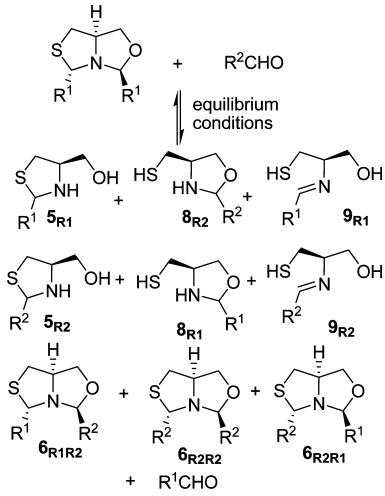
(10) Related fused thiazolidine-oxazolidinones and thiazolidine-oxazolidines were obtained when aminoalcohol **5a** was treated with phosgene. González, A.; Lavilla, R.; Piniella, J. F.; Alvarez-Larena, A. *Tetrahedron* **1995**, *51*, 3015–3024.

(11) (a) Deroose, F. D.; De Clercq, P. J. *J. Org. Chem.* **1995**, *60*, 321–330, and ref 8b.

(12) In ref 5a, Fuchs and coworkers report traces of imine in a DCL constructed from aminoalcohols.

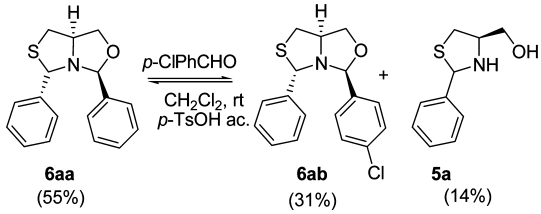
(13) Typical procedure: A mixture of compound **6aa** (100 mg, 0.36 mmol) and *p*-Cl-benzaldehyde (50 mg, 0.36 mmol) in CH_2Cl_2 (35.5 mL) and *p*-toluenesulfonic acid (10 mg, 0.13 mmol) was stirred at rt for 2 d. The reaction mixture was poured into water, the pH was adjusted to pH 7, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were dried and filtered, and the solvent was removed under reduced pressure. The residue was analyzed by ^{1}H NMR to determine the product ratio, and the products were confirmed by preparative isolation.

Scheme 5. Potential Library of Thiazolidine−Oxazolidine Heterocycles



presence of catalytic *p*-TsOH, only the mixture of the exchanged products **6aa** and **6ab** and free aminoalcohol **5a** was obtained (Scheme 6).[13] To identify the products, it was

Scheme 6. Exchange Reaction of Bicycle **6aa**[a]



[a] Ratio was established by ^{1}H NMR.

necessary to perform a chiral-HPLC (Chiralcel-OD) analysis of the possible products **6ba** and **6ab**, because they have almost identical signals in the ^{1}H NMR spectra. The chromatographic analysis indicated that the exchange was limited to the N−C−O linkage, forming **6ab**. Alternative species like imines **9a**, **9b** or oxazolidines **8a**, **8b** were not detected in the ^{1}H NMR spectra or the HPLC traces.

We also performed an experiment in absence of *p*-TsOH in $CDCl_3$ with compound **6aa** and aldehyde **1b** at a 10 mM concentration, and we found no evidence of exchange or decomposition after 3 d. This observation is indicative that the products are stable and that the exchange requires acid catalysis.

It is important to point out that conditions for the synthesis and exchange of these bicycles are quite similar, that is, CH_2Cl_2 and *p*-TsOH. In the acidic media, the diasteromeric mixture of alcohol **5** is in a fast equilibration by ring-opening and closing. During this equilibration only the acetal N−C bond of thiazolidine would be broken and the R^1 side chain remains linked to the sulfur atom, probably via a sulfenium cation. This mechanism explains that we did not observe the formation of $\mathbf{6_{R2R1}}$ in the synthesis of $\mathbf{6_{R1R2}}$ and also why the exchange occcurred only at the oxazolidine site.

In summary, we explored a new exchange reaction between thiazolidines and carbonyl compounds. The thermodynamic exchange proceeds in an acidic aqueous environment (pH 4) and represents a new reversible reaction useful for DCC methodologies. A structural diversification of the core scaffolds can be accomplished by modifications at the 2, 4 and 5-positions of the heterocycles. The thiazolidines **3a**−**f** are stable in buffered media over 4 d, and these conditions are suitable for the generation of DCLs as well as for the direct screening of these libraries. Moreover, the exchange reaction can be stopped by raising the pH to 7, thus providing a convenient way to analyze the compound distribution patterns. As an important extension of this work, we also present the synthesis of fused thiazolidine-oxazolidine heterocycles such as *anti*-**6**, representing a new compound class. These bicycles are stable under neutral or basic conditions but can be equilibrated at the oxazolidine moiety in CH_2Cl_2 in the presence of catalytic *p*-TsOH.

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Supporting Information Available: Experimental procedures, ^{1}H NMR and HPLC of DCLs, and spectral data for compounds **4b**, **5b, 6aa, 6ab, 6ba,** and **6bb**. This material is available free of charge via the Internet at http://pubs.acs.org.

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