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Stereochemical Control Factors in the Hantzsch Thiazole Synthesis: A Hammett Substitution Correlation Analysis

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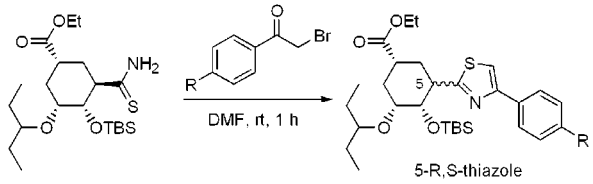
ABSTRACT



It is possible to correlate the distribution of stereochemical products produced during a Hantzsch thiazole synthesis according to the Hammett free-energy equation. This analysis confirms the presumed control of the rate of epimerization during thiazole formation due to stabilization of a cationic transition state intermediate during dehydration of the thiazoline ring system. In the chemical system under study, the stereochemical outcome of the reaction also appears to occur according to a kinetically controlled protonation of a thiazoline tautomer.

In the course of construction of a combinatorial library, it is common to encounter unanticipated reaction products. While systemization of a synthetic procedure is one of the principal concepts of parallel and combinatorial chemistry, it is important to remember that a diversity of reagent structures inherently leads to a diversity of reactivity. In this report, we describe the effect of the diversity set of α-bromoketones on the stereochemical outcome of stereogenic centers adjacent to thiazoles formed via the Hantzsch reaction. Although there have been several reports of epimerization of stereogenic centers adjacent to thiazoles usually derived from amino acid building blocks,[1,2] we have found no quantitative study which might be generalized for application to distinct systems. Significant effort has been expended to reduce[3] and even eliminate epimerization upon thiazole formation either by modification of the Hantzsch conditions[4] or by alternative methods of thiazole synthesis.[5] We wished to understand this phenomenon with a system other than amino acids and in a manner that would guide R group selection to avoid the formation of epimeric products. We report results that show a clear correlation with the Hammett σ constants as part of a linear free-energy relationship. We believe that these results indicate that the stereochemistry of stereogenic centers adjacent to the thiazole C2 position is directly controlled by the rate of carbocation formation during thiazole formation by reaction of thioamide and α-bromoketones. From these results, one can envision strategies to control the stereochemistry at centers adjacent to forming thiazoles.

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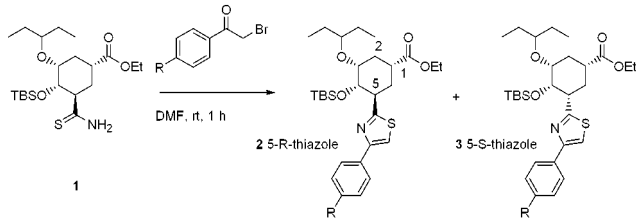
The shikimic acid ring system is an attractive template for the development of combinatorial library chemistry having defined stereochemistry as well as multiple points of diversity attachment.[6] Thiazole formation via the combination of thioamides and α-bromoketones[7,8] are attractive from the point of view of combinatorial chemistry due to the reaction's ease, speed, and tolerance to other function groups and diversity of available reagents.

In part, given the prevalence of the successful application of Hantzsch synthesis of thiazoles[9] and aminothiazoles,[10] we were interested in applying this reaction to a modified shikimic acid template for new lead generation purposes. When several products having unexpected stereochemical configurations were detected during the analysis of products derived from a combinatorial library, a parallel, solution phase model system derived from shikimic acid as starting material was used to study the stereochemical course of the Hantzsch thiazole reaction on this template in which there are significant steric constraints (Scheme 1).

Scheme 1



A MOPAC, semiempirical molecular orbital computational analysis[11] indicated that the β-epimer (5*R*) thiazole conformers (**2**) for this system are thermodynamically more stable than the α-epimer (5*S*) conformers (**3**) by ~2 kcal/mol (Figure 1). Despite this thermodynamic driving force toward the more stable β-epimer, significant quantities of the less stable α-epimer were detected for electron-withdrawing *para* substituents (Table 1). The identity of each reaction product was determined on the basis of ^{1}H NMR analysis of reaction components isolated by flash column chromatography. The

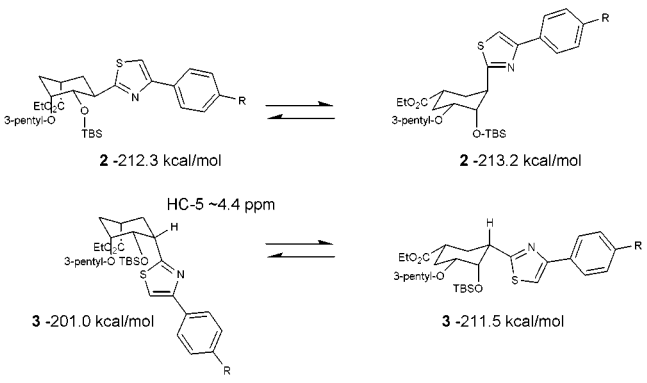


Figure 1. Thiazole epimer conformers and calculated energies.

Table 1. Epimer Product Ratios as a Function of *p*-Substituted α-Bromoketone[a]

R	products ratio (**2**:**3**)	chemical yield, %	σ_p	$\log[(\alpha_R/\beta_R)/(\alpha_H/\beta_H)]$
OCH_3	>20:1	91		
CH_3	20:1	95	−0.17	−0.408
H	7.8:1	84	0	0
F	6.3:1	82	0.06	0.0934
Cl	4.8:1	64	0.23	0.212
OCF_3	2:1	64	0.35	0.592
CF_3	1:1.1	66	0.54	0.933
CN	1:1.5	71	0.66	1.069

[a] Reactions performed in ~45 mM DMF at room temperature with 3.0 equiv of the indicated 2-bromoacetophenone.

chemical shift of HC-5 is particularly diagnostic of the C-5 configuration (HC-5 α ~4.6 ppm, HC-5 β ~4.4 ppm).

An analysis of these results in terms of Hammett σ constants[12] led to the Hammett plot shown in Figure 2. In

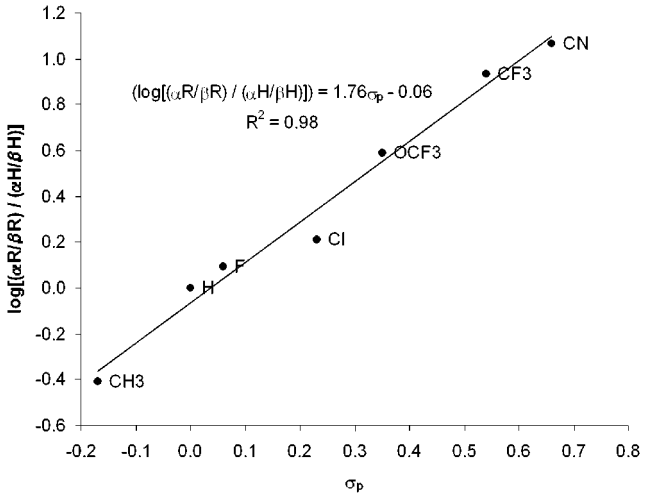


Figure 2. Hammett plot of ρ_p versus $\log[(\alpha_R/\beta_R)/(\alpha_H/\beta_H)]$.

this analysis performed on the basis of the mechanism shown in Figure 3 originally proposed by Holzapfel,[13] it was assumed that the distribution of products resulting from the

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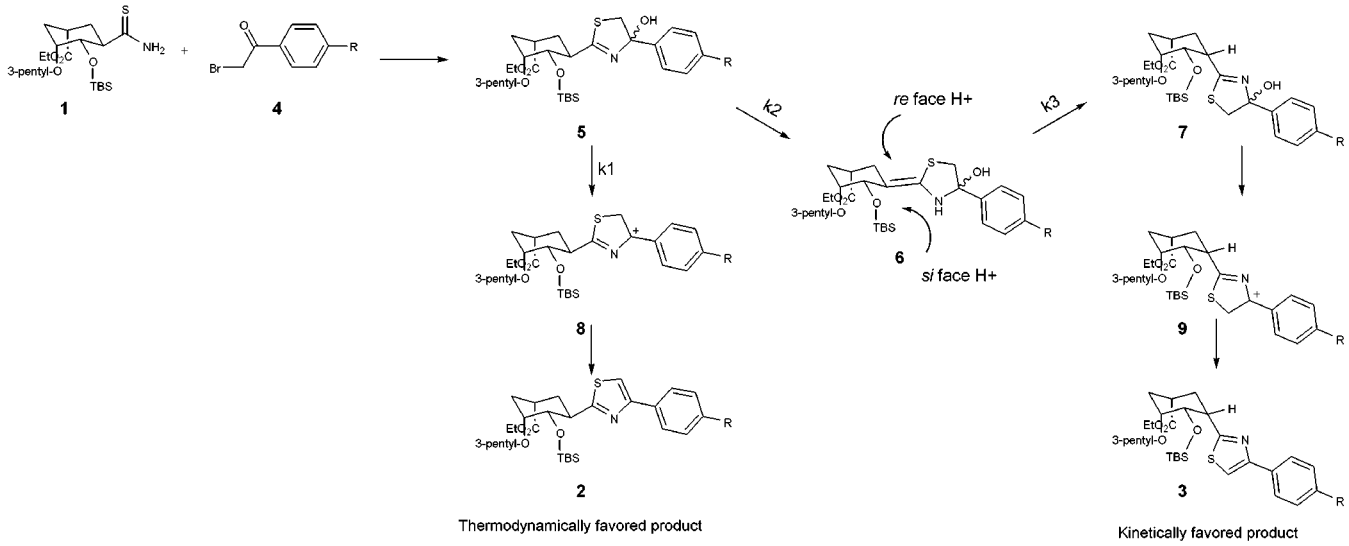

Figure 3. Mechanism and reaction pathways for formation of β- (**2**) and α-epimer (**3**) products.

β-epimer thioamide **1** could be correlated to the rate of formation of intermediate **8**. Thus, the analysis was simplified to the comparison of linear least-squares analysis of Hammett constants versus $\log[(\alpha_R/\beta_R)/(\alpha_H/\beta_H)]$ for α_R/β_R as the ratio of β-product **2** to α-product **3** having the *para*-substituents R for each phenyl ketone.

The Pearson correlation coefficient of $R^2 = 0.98$ in the linear least-squares analysis gives credence to the assumption of the Hammett free-energy relationship in this system. The positive slope of the line is also consistent with the interpretation that electron-withdrawing groups slow the reaction rate of formation of intermediate **8**. As a matter of comparison, the ρ constant derived from the Hammett plot indicates that the rate of intermediate **8** formation is somewhat more sensitive to *para*-substituent effects as compared to the substituent effects on benzoic acid acidities, the classical Hammett analysis comparator ($\rho = 1.76$ vs $\rho = \sim 1$).

Consideration of these data validates the supposition proposed by Holzapfel et al.[13] Apparently, the rate of cation formation predominates for electron-donating substituents, thereby accelerating the dehydration of the thiazoline ring to form thiazole product with retention stereochemistry at C-5 (**1**). However, with increasing electron-withdrawing nature of the phenyl ring substitutions, the rate of the imine−enamine tautomerization (**5** to **6)** becomes competitive with the rate of thiazoline dehydration (**5** to **2**). Holzapfel et al. have shown that imine−enamine tautomerization is likely catalyzed by HBr generated in situ and occurs prior to cation formation; unepimerized product for *p*-methoxy substitution further supports this conclusion. The decrease in overall reaction yield is consistent with a slower product formation via reaction pathways that are open to the formation of other side products.

Acid-catalyzed epimerization of stereogenic centers adjacent to thiazolines via imine−enamine tautomerization has also been reported.[14] This observation in conjunction with the fact that no epimerization is seen with the electron-donating *p*-methoxyphenyl ketone argues against tautomer formation via cation intermediate **8**.

Unlike the results reported for thiazoles derived from amino acid building blocks, in this shikimic acid system protonation of the *re* face of enamine **6** is favored kinetically as the least hindered path of attack. However, this result does not rule out reversion along these reaction pathways after protonation of the C5 position.

To understand the kinetic control of the protonation pathway of this sequence, the α-thioamide (5*S*) **15** was examined for epimerization to β-thiazoles (5*R*) upon cyclization. The α- and β-thioamides are available in four steps from (4*R*,5*S*) epoxide **10**.[15] Of several standard conditions attempted for cyanide opening of epoxide **10**, only Et_2AlCN was found to provide useful quantities of both cyano-alcohol regioisomers (11:1 of 5(*R*)-cyano- to 4(*R*)-cyano-alcohol products).[16] These regioisomers were easily separated by silica gel flash column chromatography. It was necessary to saturate the 1,2 double bond under standard palladium-catalyzed hydrogenation conditions prior to cyano-to-thioamide transformation in order to avoid side reactions of this double bond with the thiolating reagent $(TMS)_2S$.[17] Different ratios of α-thioamide epimers were formed depending upon the commercial source of $(TMS)_2S$ as shown in Scheme 2.

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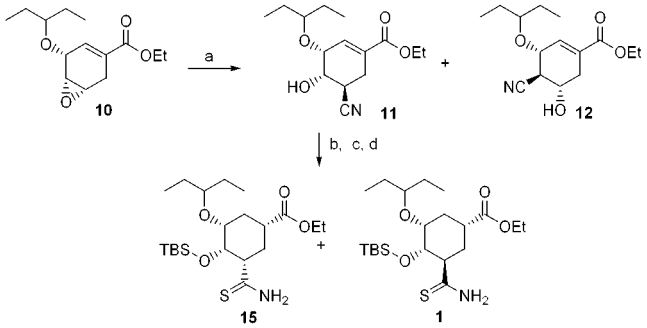
Scheme 2. Preparation of 5(*S*)- and 5(*R*)-Thioamides **1**[a]



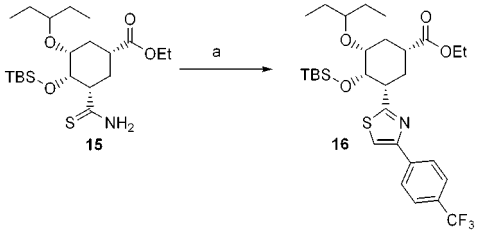
[a] Conditions: (a) Et_2AlCN, toluene, (85% for **11**, 7.5% for **12**); (b) TBDMSCl, imidazole, DMF, 87%; (c) H_2, 50 PSI, 10% Pd/C, CH_3OH, 91%; (d) $(TMS)_2S$, $NaOCH_3$, DMA (73% for **1**, 7% for **15**).

We envision a mechanism involving some small quantity of water to account for the epimerization of the thioimide intermediate en route to formation of the thioamide.

Upon reaction of α-thioamide **15** with a 2-bromo-4′-trifluoromethylacetophenone, only the α-thiazole product **16** was detected (Scheme 3). This result is consistent with *re* face protonation as the only pathway possible for intermediate **6**.

In summary, we have shown a clear correlation of epimerization during thiazole formation with the ease of cation formation. In the system under study, it was possible to isolate various stereochemical control elements. Such mechanistic understanding facilitates increasingly sophisticated library designs.

Scheme 3. Exclusive Formation of α-thiazole (5*S*)[a]



[a] Conditions: (a) 2-bromo-4−4’trifluoromethylacetophenone (3.0 equiv), DMF, 1 h, rt, 65%.

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Note Added after ASAP: This Letter was posted ASAP on 10/16/2001 with an incorrect formula for the α/β epimers in Table 1, Figure 2, and the text. The print and final Web versions (10/19/2001) are correct.

Supporting Information Available: Detailed experimental procedures and spectroscopic data for synthesized compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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