# Sterically Controlled Stereoregulation in Aldol Reactions of 3-Aryl-1-alkyl Dihydrothiouracils

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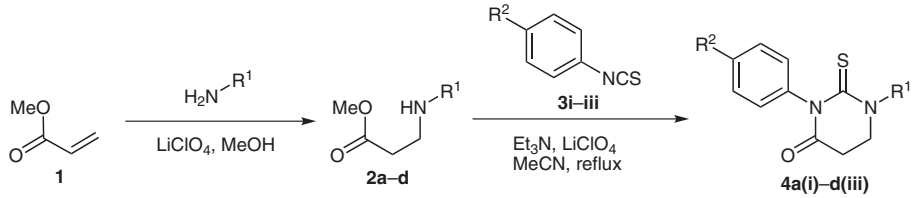
**Abstract:** Aldol reactions of 3-aryl-1-alkyl dihydrothiouracils were investigated with respect to the orientation of the exocyclic group at N1, electronic effects of the aryl substituent at N3 and the steric demands of the electrophile. The reactions highlight the preference for formation of the *anti* aldol diastereomer with increasing steric constraints of the reactants.

**Key words:** aldol reaction, cyclization, aldehyde, dihydrothiouracils, stereoselectivity

With the aim of inducing stereoselectivity in carbon–carbon bond formation, aldol reactions have attained paramount importance.[1] Over the last few decades, stereoselectivity in these reactions have been explored with increased impetus, providing new routes to the desired diastereomers.[2] Numerous reports and theoretical rationalizations on the diastereoselectivity have helped in the total synthesis of several natural products.[3] These studies have demonstrated that analysis of the transitions states, especially of acyclic carbonyl substrates, can allow the stereochemistry of the product to be predicted with reasonable accuracy.[4] In contrast, reactions with cyclic carbonyl compounds seem to be more complex, as observed with lactams, lactones and thiazolidinones,[5] for which the outcome of the reaction largely depends on the conformation adopted by the ring. Since the rotational freedom of $sp^3$ hybridized carbon atoms endows cyclic systems with flexibility, we focused our attention on highly rigid molecules containing $sp^2$ carbon atoms, preferably linked to heteroatoms[6] as this would restrict the conformational variants considerably. Thoughts in this direction led us to consider uracils, which have attained wide recognition in both the chemical and biological realms. The aldol reaction of dihydrouracils for the chain extension of glyceraldehyde has been reported, but the conformational aspects of the heterocycle and the effects of the substituents on the diastereoselectivity have not been investigated. With the limited substrate variation, the scope of the reaction was also not considered.[7] Widely known for its applications in pharmaceutical and agricultural fields,[8] we decided to choose the structurally constrained 1,3-disubstituted dihydrothiouracil, for a detailed investigation. Simultaneously, efforts to functionalize this substrate also stemmed from our interests in developing new biologically active heterocycles,[9] including dihydrothiouracils, as a part of our ongoing cancer research program. This model was expected to help in the understanding of the origin of stereoselectivity arising from steric and conformational control.

This paper discusses the aldol reactions of 3-aryl-1-alkyl dihydrothiouracils, where the steric influence of the electrophile and the conformational effects of the cyclic enolate on diastereoselectivity were examined. A facile synthetic route to 3-aryl-1-alkyl dihydrothiouracils (**4**) involves the condensation of β-amino esters (**2**) with aryl isothiocyanates (**3**). β-Amino esters can be prepared by a conventional aza-Michael addition of amines to methyl acrylate (**1**) through electrophilic activation induced by lithium perchlorate in a polar protic medium.[10] Subsequent condensation with aryl isothiocyanates mediated by a Lewis acid in acetonitrile (Scheme 1) affords 3-aryl-1-alkyl dihydrothiouracils, in short reaction time[9a–c] (Table 1). In general, the reactions afforded the desired products with good yields, however, the reaction with methyl 3-(*tert*-butylamino)propanoate failed, probably because of steric hindrance. Aldol reactions were then performed to examine the reactant parameters on a model reaction of 3-(4-chlorophenyl)-1-alkyl dihydrothiouracil with 4-fluorobenzaldehyde (Table 2). The reaction of the lithium enolate, having an *E* geometry due to structural




**Scheme 1** One-pot synthesis of 3-aryl-1-alkyl dihyrothiouracils

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limitations, afforded a diastereomeric mixture of *syn* and *anti* aldols with poor selectivity, irrespective of which lithium base was employed.

**Table 1** Reactions of β-Amino Esters with Aryl Isothiocyanates

| Entry | $R^1$ | $R^2$ | Time (h) | Yield (%) | Product |
|---|---|---|---|---|---|
| 1 | Et | Cl | 1.0 | 84 | **4a(i)** |
| 2 | *n*-Pr | Cl | 2.5 | 78 | **4b(i)** |
| 3 | *n*-Bu | Cl | 1.5 | 76 | **4c(i)** |
| 4 | *i*-Pr | Cl | 2.5 | 72 | **4d(i)** |
| 5 | *i*-Pr | Br | 2.5 | 80 | **4d(ii)** |
| 6 | *i*-Pr | H | 3.0 | 81 | **4d(iii)** |

**Table 2** Effect of Substituents at N1 and Lithium Bases on Aldol Reactions of 3-(4-Chlorophenyl)-1-alkyl Dihydrothiouracils (Scheme 2, $R^2$ = Cl)

| Entry | $R^1$ | Base | Time (h) | Yield (%) | *anti*:*syn*[a] |
|---|---|---|---|---|---|
| 1 | Et | BuLi | 2.0 | 65 | 56:44 |
| 2 | Et | LDA | 2.5 | 70 | 58:42 |
| 3 | Et | LHMDS | 1.5 | 80 | 56:44 |
| 4 | *n*-Pr | BuLi | 1.5 | 58 | 56:44 |
| 5 | *n*-Pr | LDA | 2.5 | 68 | 55:45 |
| 6 | *n*-Pr | LHMDS | 2.5 | 75 | 56:44 |
| 7 | *n*-Bu | BuLi | 2.5 | 68 | 55:45 |
| 8 | *n*-Bu | LDA | 2.2 | 60 | 56:44 |
| 9 | *n*-Bu | LHMDS | 2.0 | 75 | 57:43 |
| 10 | *i*-Pr | BuLi | 1.5 | 68 | 68:32 |
| 11 | *i*-Pr | LDA | 2.0 | 77 | 68:32 |
| 12 | *i*-Pr | LHMDS | 1.5 | 85 | 72:28 |

[a] Ratio of diastereomers was determined by $^1$H NMR analysis.

From the relatively modest result obtained, LHMDS was chosen for further optimization trials (Scheme 2). Reactions carried out to understand the steric and/or conformational influence exerted by the exocyclic substituent at N1 indicated no significant bearing on the selectivity from a linear expansion of the alkyl chain. This was demonstrated by the observation that no substantial change in diastereoselectivity occurred when the substituent on N1 was varied from ethyl to *n*-propyl and *n*-butyl (Table 2). On the other hand, the results obtained when the *n*-propyl group was changed to an isopropyl group indicated the origin of stereoregulation induced by the steric effects of a simple positional isomerism. With the isopropyl group on N1, the electronic effect of the substituent on N3 was examined. The diastereoselectivity remained unchanged, regardless of the nature of the substituent on the aryl ring (Scheme 3, products **8**–**10**), suggesting that the substituents on the aryl ring at N3 did not make any major contribution to the stereoelectronic effects of the transition state.

To delineate the steric influence of the electrophile, reactions of the dihydrothiouracil **4d(i)** were carried out with various aromatic aldehydes (Scheme 3). It was observed that the reactions with substituted benzaldehydes afforded inseparable diastereomeric mixtures of *syn* and *anti* aldols without appreciable differences in selectivity, with variations of the substituent on the aromatic ring (Scheme 3, products **11**–**14**). To assign the relative configuration, ab initio energy minimization calculations were performed for the *syn* and *anti* aldol diastereomers of **8** using Gaussian B3LYP with basis set 6-31G* (d,p);[11] the dihedral angles were computed for the vicinal protons at C5 and C7 from the optimized structures (Figure 1). A correlation of the dihedral angles and $^1$H NMR spectra of the diastereomeric mixture (see the Supporting Information) indicated that the *syn* diastereomer had a vicinal coupling constant ($J$ = 3.56 Hz) corresponding to a dihedral angle of 67°, and the *anti* diastereomer had a coupling constant ($J$ = 8.04 Hz) consistent with a dihedral angle of 163°. The assumptions drawn on the relative configuration were further confirmed by analysis of aldol diastereomers, which were separated as the corresponding acetate derivatives *syn*-**8′** and *anti*-**8′**.

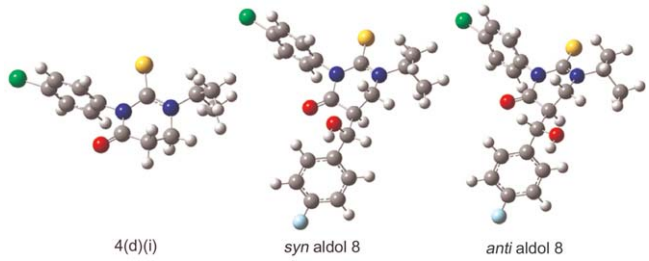
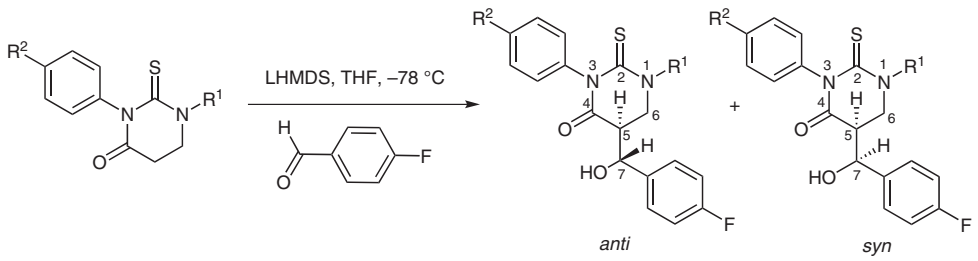
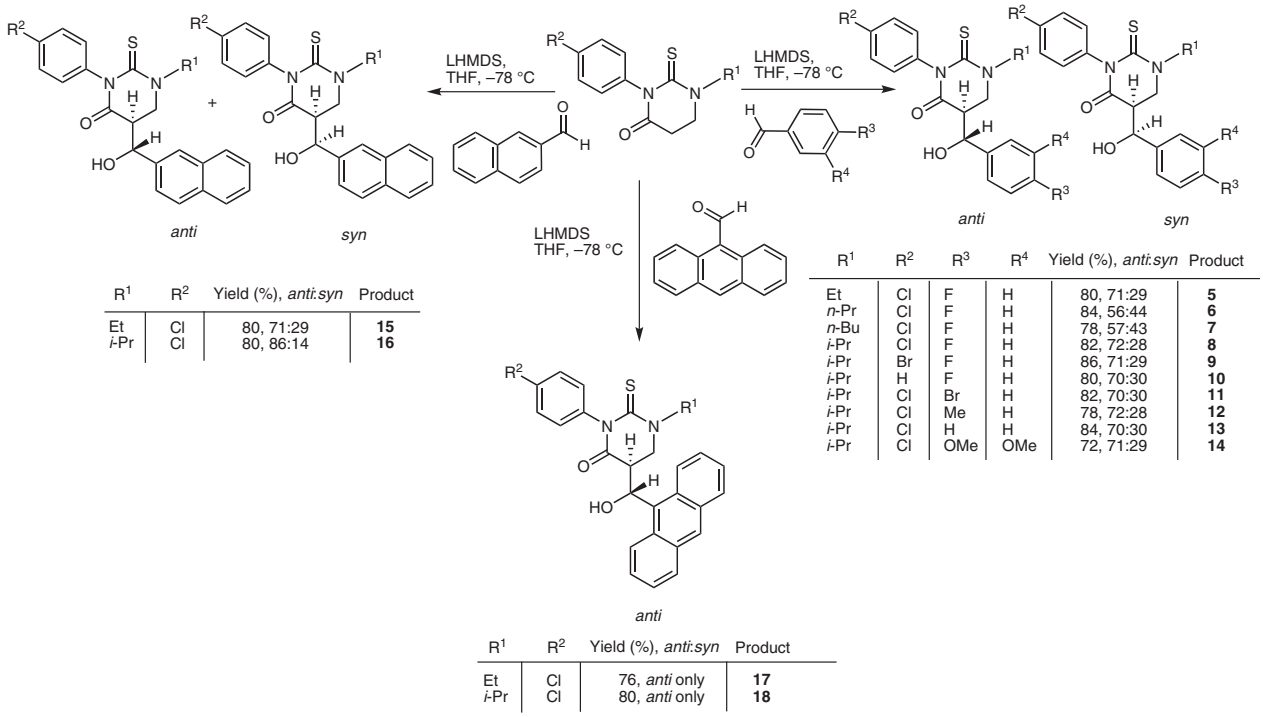



**Figure 1** Energy-optimized structures of **4d(i)**, *syn* aldol **8** and *anti* aldol **8**[11]




**Scheme 2** Aldol reactions of 3-aryl-1-alkyl dihydrothiouracil with 4-fluorobenzaldehyde




| $R^1$ | $R^2$ | Yield (%), *anti*:*syn* | Product |
|---|---|---|---|
| Et | Cl | 80, 71:29 | **15** |
| *i*-Pr | Cl | 80, 86:14 | **16** |

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield (%), *anti*:*syn* | Product |
|---|---|---|---|---|---|
| Et | Cl | F | H | 80, 71:29 | **5** |
| *n*-Pr | Cl | F | H | 84, 56:44 | **6** |
| *n*-Bu | Cl | F | H | 78, 57:43 | **7** |
| *i*-Pr | Cl | F | H | 82, 72:28 | **8** |
| *i*-Pr | Br | F | H | 86, 71:29 | **9** |
| *i*-Pr | H | F | H | 80, 70:30 | **10** |
| *i*-Pr | Cl | Br | H | 82, 70:30 | **11** |
| *i*-Pr | Cl | Me | H | 78, 72:28 | **12** |
| *i*-Pr | Cl | H | H | 84, 70:30 | **13** |
| *i*-Pr | Cl | OMe | OMe | 72, 71:29 | **14** |

| $R^1$ | $R^2$ | Yield (%), *anti*:*syn* | Product |
|---|---|---|---|
| Et | Cl | 76, *anti* only | **17** |
| *i*-Pr | Cl | 80, *anti* only | **18** |

**Scheme 3** Steric effects of electrophiles on aldol reactions with dihydrothiouracils

The $^1$H NMR spectra of the acetate derivatives displayed vicinal coupling constants of $J = 5.12$ and 6.92 Hz, respectively, for the *syn* and *anti* diastereomers (Figure 2). Selectivity towards the *anti* aldol was highly impressive with polyaromatic aldehydes. 2-Naphthaldehyde demonstrated diastereoselectivity (86:14) in favor of the *anti* aldol **16**, whereas 9-anthraldehyde gave the *anti* aldol **18** exclusively. With an ethyl group at N1, the aldol reactions of **4a(i)** with polyaromatic aldehydes gave interesting results. In comparison with **4d(i)**, the selectivity for the reaction of **4a(i)** with 2-naphthaldehyde towards the *anti* aldol **15** was inferior; whereas the reaction with 9-anthraldehyde afforded the *anti* aldol **17** only. This observation augments the fact that the combination of steric effects imparted by the substituent at N1 and the bulky electrophile controls the stereochemical outcome. Reaction of **4d(i)** with a sterically bulky aliphatic aldehyde (e.g., *tert*-butyraldehyde) afforded a mixture of *syn* and *anti* diastereomers, which were inseparable either as the aldol adduct or as its acetate derivative.

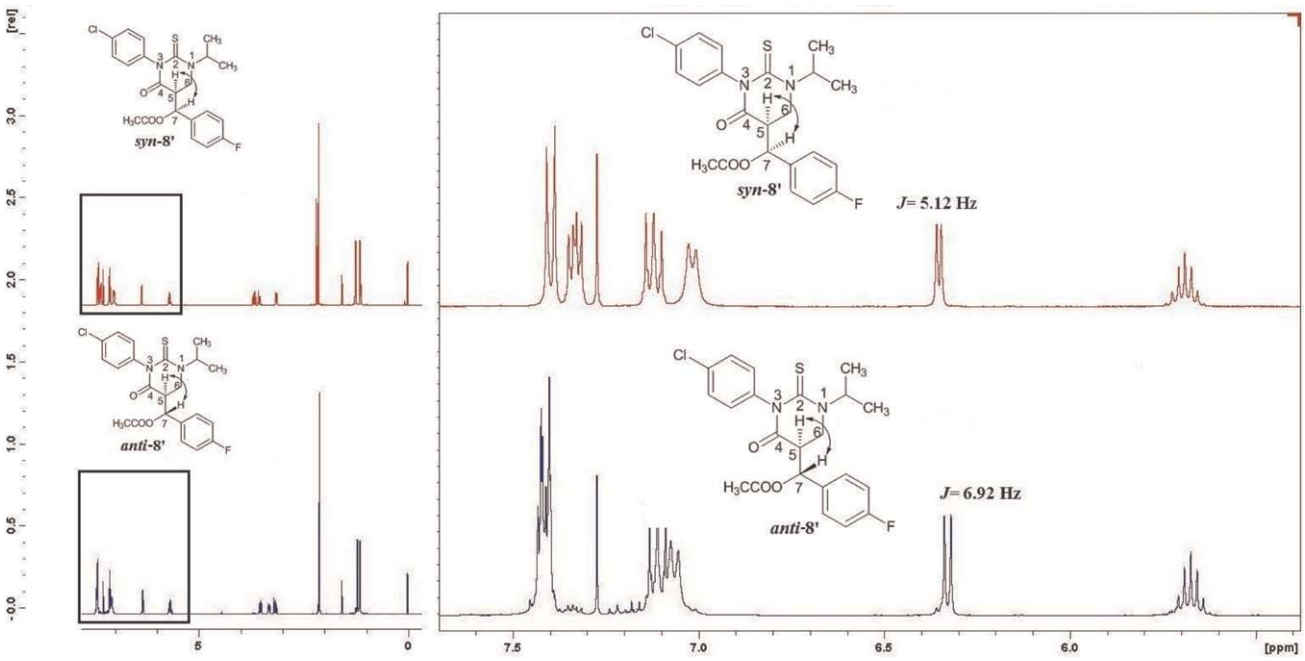



**Figure 2** $^1$H NMR spectra of *syn*-**8′** and *anti*-**8′**

To address the mechanistic issue of kinetic versus thermodynamic pathways, the pure *anti* and *syn* aldols **8**, obtained by hydrolysis of the corresponding acetate derivatives, were subjected to retro-aldol reactions under basic conditions (LHMDS). The *anti* and *syn* diastereomers remained intact, with no traces of the other diastereomer even after several hours of reaction. Retro-aldolization under acidic conditions (HCl) also gave similar results. These observations demonstrate that the reactions proceed by a kinetic mechanism, and not through a thermodynamic pathway.

Based on these results, transition-state models are proposed for the reaction, taking into consideration the geometry of the substrate and the conformation adopted. Structure optimization and energy minimization[11] were performed for **4d(i)**, and the optimized structure is illustrated in Figure 1. In transition state **TS-1**, leading to the formation of the *anti* aldol, the hydrogen atoms at C5 and C7 share a *trans* relationship, whereas they have a *cis* disposition in transition state **TS-2** (Figure 3). As demonstrated by the transition-state models, when $R^Y$ is hydrogen, there is almost equal probability of forming *syn* and *anti* aldols, since a stereofacial discrimination is not possible with the steric and electronic factors remaining equivalent for **TS-1** and **TS-2**. This fact holds experimentally true for unbranched aliphatic substituents at N1, affording poor diastereoselectivity with ethyl, *n*-propyl, and *n*-butyl groups (Scheme 3, products **5**–**7**). However, with the isopropyl group as the substituent at N1, the steric effect imparted by the electrophile favors **TS-1** over **TS-2**, leading to the formation of the *anti* aldol. This can be better understood from the perspective of the 1,2-interaction between the aldehyde substituent and the dihydrothiouracil ring. The 1,2-interaction is prominent in the six-membered cyclic transition state **TS-2** where the substituents at C5 and C7 are disposed in an equatorial–axial manner, while this relation becomes diequatorial in **TS-1**, with a resultant decrease in the torsional strain as the dihedral angle shifts from *gauche* to *anti*. These attributes, arising from steric interactions of the electrophile and the substituent at N1, dictate the stereochemistry of the aldol adduct formed, thereby validating the stereochemical assumptions drawn from the transition-state models.

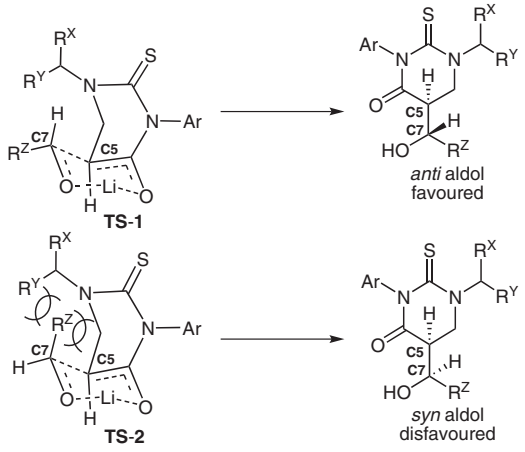



**Figure 3** Transition-state models for *syn* and *anti* aldols

In conclusion, the stereochemical outcome of the aldol reactions of 3-aryl-1-alkyl dihydrothiouracils signifies an enhancement in diastereoselectivity arising from moderate to high steric interactions between the electrophiles and a geometrically constrained heterocyclic enolate, while the electronic effects are regulated.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) (a) Energy calculations were performed using the Gaussian 03 program. Computational calibrations were done on a model compound {(6*S*)-methyl-3-(4-cyano-3-chlorophenyl)--1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one} by energy minimizations using the semi-empirical method MM2, and ab initio calculations by Gaussian B3LYP with basis set 6-31G* (d,p). The outcomes of these independent calculations were perfectly in agreement with the structure of the molecule, as confirmed by single crystal X-ray diffraction analysis, see reference 9b. (b) The present studies involve another molecule of the same template, and the structure was optimized by ab initio calculation using Gaussian B3LYP.