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Stereoselective synthesis of a dialkylhydantoin featuring an asymmetric Strecker reaction on an acyclic dialkyl ketone

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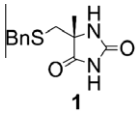
ABSTRACT

A diastereoselective Strecker reaction using (*R*)-(−)-phenylglycinol forms the basis of a concise scalemic route to dialkylhydantoin **1**. The phenylglycinol functionality was exploited in the manipulation of the aminonitrile Strecker product through to the dialkylhydantoin via a short, efficient sequence involving crystalline intermediates.

Imidazolidine-2,4-diones (hydantoins) have featured as the key structural element in a range of compounds designed with pharmaceutical applications in mind.[1] Preparation of achiral and racemic hydantoins generally relies upon the classical Bucherer–Berg construction, whereas direct asymmetric access to chiral hydantoins from acyclic precursors is more challenging.[2] However, there are a number of attractive methods for the stereoselective synthesis of α-amino acid derivatives, such as those based on the Strecker reaction, from which hydantoins may easily be obtained.[3] Diastereoselective Strecker reactions featuring chiral amines,[4] and enantioselective variants employing chiral catalysts[5] have been described, although most utilize aldehydes as substrates. Few reports have appeared concerning dialkyl ketones, from which valuable chiral α,α-dialkylamino acids may be generated.[5,6] As part of a development program for a drug candidate, we required a scalemic route to dialkylhydantoin **1**, and envisioned that an asymmetric Strecker reaction proceeding from known ketosulfide **2** might form the basis of an attractive option. The corresponding benzylimine **3a** was readily prepared (Scheme 1), but the addition of trimethylsilyl cyanide (TMSCN) promoted by a range of chiral catalysts did not exhibit appreciable asymmetric induction.



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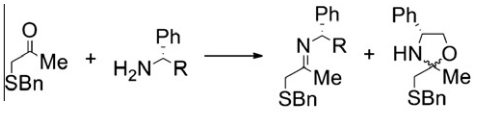
We turned instead to diastereoselective Strecker reactions using α-methylbenzylamine and phenylglycinol. Warmuth has described diastereoselective Strecker reactions of α-methylbenzylamine with cyclic ketones and TMSCN.[7] In contrast with these results, when α-methylbenzylimine **3b** was subjected to TMSCN, the aminonitrile was obtained as a 50:50 mixture of diastereomers.

The use of phenylglycinol as the amine component to engineer a diastereoselective Strecker reaction has been reported by a number of workers.[7–9] Ma has shown that α-arylketones condense with (*R*)-(−)-phenylglycinol to give a mixture of the imine and oxazolidine.[8] Treatment of this mixture with TMSCN followed by hydrolysis gave α-amino esters in varying ratios. Warmuth[7] obtained



2 R = H **3a** **4**
R = Me **3b**
R = CH_2OH **3c**

Scheme 1. Condensation of ketone **2** with amines. Reagents and conditions: 4 Å molecular sieves, toluene, 50 °C, 12 h, quantitative conversion.

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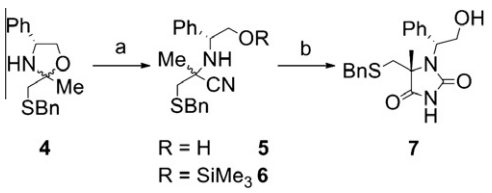
moderate diastereoselectivity in comparison with α-methylbenzylamine. In both these literature cases, condensation of the ketone with phenylglycinol gave a mixture of imine and oxazolidine. In our case, as illustrated in Scheme 1, complete reaction of ketone **2** with (*R*)-(−)-phenylglycinol was attained by stirring an equimolar mixture of the two components at 50 °C in toluene in the presence of 4 Å molecular sieves for 12 h. Analysis by ^{1}H NMR spectroscopy indicated that oxazolidine **4** had been formed as a 50:50 mixture of diastereomers, along with 5% of imine **3c**. The Strecker reaction was attempted upon this mixture in a variety of solvents. In most cases, mixtures of silylated and non-silylated products **6** and **5**, in varying diastereomer ratios, were obtained (Scheme 2). However, we were delighted to observe that in toluene, exclusive formation of **6** took place at 20 °C, albeit at modest conversion (60% after 24 h) and stereoselectivity (80:20). We therefore surveyed a range of metal salt additives, and found that the addition of 10 mol % magnesium bromide diethyl etherate promoted complete conversion in 18 h at −40 °C into a 90:10 mixture of aminonitrile diastereomers. Accordingly, we were able to isolate the major diastereomer [which was eventually assigned as (*R*,*R*)-**6**, *vide infra*] in a 54% overall yield and excellent purity by crystallization from ^{i}hexane–toluene.

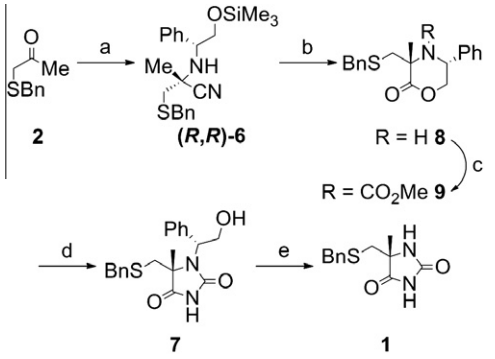
The fragility and sterically hindered nature of **6** limited the options for elaborating this compound to a hydantoin. However, chlorosulfonyl isocyanate[10] successfully engaged the amine at −50 °C in toluene, and following acid-promoted cyclization, hydantoin **7** was isolated in a 30% yield after silica gel chromatography. In the light of the modest selectivity and conversion observed in this direct process, we sought an alternative method of constructing the hydantoin, and found that the addition of a single molar equivalent of water to a solution of **6** saturated with hydrogen chloride afforded lactone **8** (Scheme 3) quantitatively, as a highly crystalline solid. This proved to be a much more robust yet tractable intermediate.

The successful synthesis of lactone **8** also allowed assignment of the relative stereochemistry. Observation of a positive nOe between the methyl and *N*-benzyl protons confirmed that the stereochemistry at the quaternary stereocenter is (*R*). This can be accounted for by kinetic control in the Strecker reaction, assuming coordination of the TMS group to the hydroxy, and activation of the imine by intramolecular hydrogen bonding. Comparison of the two $A_{1,3}$ strain-minimized conformations (Fig. 1) suggests that nucleophilic attack upon **B**, leading to the minor diastereomer, is disfavored by the additional steric encumbrance of the sulfur eclipsing the benzylic proton.

It is plausible that a stabilizing hydrogen bonding interaction with sulfur in **A** is, at least in part, responsible for the favorability of this pathway. We evaluated the relative contributions by carrying out the analogous Strecker reaction on benzyloxyacetone. Were hydrogen bonding the dominant effect, the superior ability of oxygen compared to sulfur in this regard should enhance stereoselectivity. On the other hand, the smaller size of the former should lead to poorer selectivity were that factor to be critical. In the event,



Scheme 2. Strecker reaction of **4** and direct conversion into hydantoin **7**. Reagents and conditions: (a) Me_3SiCN, $Me_3SiOSO_2CF_3$, $MgBr_2.OEt_2$, toluene, −40 °C, 18 h; recrystallization from ^{i}hexane–toluene, 54%; (b) $ClSO_2NCO$, CH_2Cl_2, −50 °C, 2 h; HCl (aq), reflux, 2 h, 30%.



Scheme 3. Summary of route. Reagents and conditions: (a) (*R*)-(−)-phenylglycinol, 4 Å MS, toluene, 50 °C, 12 h; Me_3SiCN, $Me_3SiOSO_2CF_3$, $MgBr_2.OEt_2$, toluene, −40 °C, 18 h; recrystallization from *i*-hexane–toluene, 54%; (b) HCl, CH_2Cl_2, −40 °C, 15 min; H_2O (1 equiv), 12 h, 95%; (c) $ClCO_2Me$, LiH, THF, 40 °C, 48 h, 86%; (d) NH_3 (7 M), MeOH, μW, 150 W, 1 h, 100%; (e) HBr (48% aq), AcOH, reflux, 4 h, 62%.

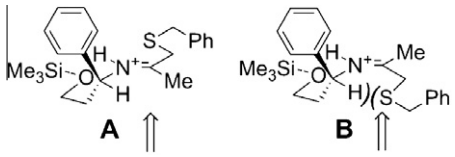


Figure 1. Strecker reaction conformations and nucleophile trajectories.

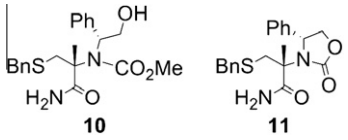


Figure 2. Structure of amide **10** and oxazolidinone **11**.

only a 65:35 ratio of diastereomers was obtained, suggesting that the principal factor is steric. We confirmed that the diastereoselectivity is kinetic and not thermodynamic in origin by re-subjecting the single diastereomer **6** to the reaction conditions, and did not observe any erosion of the stereochemical integrity of the aminonitrile stereocenter.

The secondary amine **8** was reacted with lithium hydride and methyl chloroformate to deliver carbamate **9** (Scheme 3). Ring opening with ammonia took place at room temperature to give amide **10** (Fig. 2), accompanied by approximately 10% of hydantoin **7**. By conducting this reaction in a sealed microwave reactor, we were able to drive this reaction to deliver **7** with complete conversion, as shown in Scheme 3. We did not observe the formation of oxazolidinone **11** (which would arise from attack of the hydroxy group upon the carbamate), consistent with literature reports on related systems.[11] The hydantoin **7** was in turn subjected to refluxing HBr in acetic acid for four hours to afford the target compound **1** in a 62% unoptimized yield.

In summary, and as illustrated in Scheme 3, we have developed a stereocontrolled route to a chiral 5,5-disubstituted hydantoin from (benzylthio)acetone using (*R*)-(−)-phenylglycinol as the source of asymmetric induction in a diastereoselective Strecker reaction. Under optimal reaction conditions, unprecedented levels of stereocontrol derived from the use of phenylglycinol in this context were observed. The phenylglycinol functionality was further exploited in manipulation of the aminonitrile Strecker product **6** through to the target hydantoin **1** via a short, efficient sequence, involving crystalline intermediates.

Acknowledgment

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Supplementary data

Supplementary data (experimental procedures, spectral data and copies of spectra for compounds **1**, **4** and **6–10**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.008. These data include MOL files and InChiKeys of the most important compounds described in this article.

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