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# Reversal of stereochemistry in a two-step Staudinger reaction by changing the backbone protecting group. Synthesis of NH-*trans*-3-benzoyloxy-4-aryl-azetidinones

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**Abstract**

Changing the protecting group in the glyoxylic acid derived ketene from benzyloxy to benzoyloxy provides a simple way of switching the diastereoselectivity of the substituents on the final β-lactam ring from *cis* to *trans*.


*Keywords:* stereocontrol; azetidinones; *N*-silyl imides; Staudinger reaction.

The [2+2] cycloaddition of an imine and a ketene (the Staudinger reaction) is a traditional method for the construction of a β-lactam ring.[1] The stereochemical outcome of the reaction depends on the structures of the imine and the ketene precursor, the sequence of addition of the reagents, the nature of the solvent and the base used to produce the ketene from an acyl chloride. The requirement that the ketene be generated in situ raises the possibility that species such as the acid chloride, the tertiary amine, the amine hydrochloride salt and *N*-acylammonium, or *N*-acyliminium species may also play a role in the reaction.[2] To partially overcome these problems, a rather general route to *trans* β-lactams[3] starting from a *N*-trialkylsilyl imine[4] and an acyl chloride proceeding through the formation of a stable azadiene intermediate,[5] which resembles the zwitterionic intermediate invoked in the classical Staudinger reaction,[6] has been reported. In a more recent paper,[7] the stereoselective synthesis of *cis*-3-benzyloxy-4-phenyl-azetidin-2-one and related compounds, which are valuable intermediates in the synthesis of aryl-isoserine side chains of the potent anticancer agent Taxol,[8] has been described. With this information in hand, more systematic studies of the stereochemical aspects of this novel two-step Staudinger reaction have been undertaken. In this paper, a simple method for switching the stereochemistry at C-3 and C-4 of the 3-hydroxy-4-aryl-β-lactam ring[9] from *cis* to *trans* by simply changing the protecting group of the glyoxylic acid derived ketene from benzyloxy to benzoyloxy (Scheme 1) is outlined.

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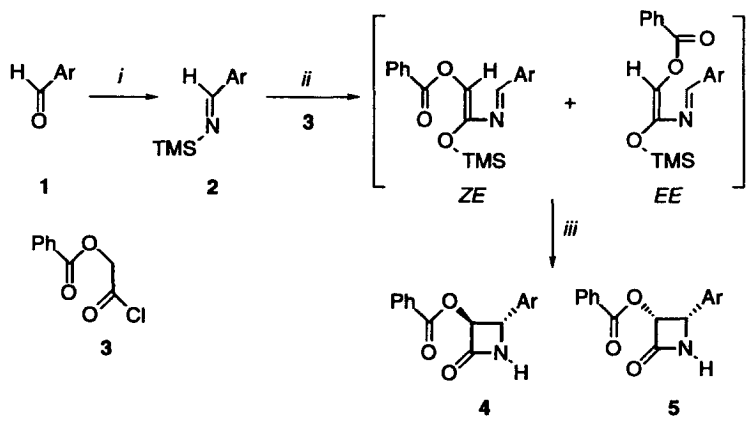

Scheme 1. Reagents and conditions: (i) LiHMDS, TMSCl, hexane; (ii) $NEt_3$, **3**, toluene; (iii) Toluene reflux **1a**, **2a**, **4a**, **5a**: Ar=Ph; **1b**, **2b**, **4b**, **5b**: Ar=*p*-Cl-Ph; **1c**, **2c**, **4c**, **5c**: Ar=*p*-MeO-Ph; **1d**, **2d**, **4d**, **5d**: Ar=2-Naphthyl; **1e**, **2e**, **4e**, **5e**: Ar=2-MeO-1-Naphthyl; **1f**, **2f**, **4f**, **5f**: Ar=2-Thienyl; **1g**, **2g**, **4g**, **5g**: Ar=*N*-Boc-indol-3-yl; **1h**, **2h**, **4h**, **5h**: Ar=*o*-$NO_2$-Ph; **1i**, **2i**, **4i**, **5i**: Ar=*m*-$NO_2$-Ph; **1j**, **2j**, **4j**, **5j**: Ar=*p*-$NO_2$-Ph; **1k**, **2k**, **4k**, **5k**: Ar=2-Pyridyl; **1l**, **2l**, **4l**, **5l**: Ar=3-Pyridyl; **1m**, **2m**, **4m**, **5m**: Ar=4-Pyridyl

## 1. Synthesis of *trans*-3-benzoyloxy-4-phenyl-azetidin-2-one 4a as a typical example

TMSCl (1.2 mmol) was added in one portion to a solution of *N*-trimethylsilylimine **2** (1 mmol) obtained from the corresponding aldehyde **1a** and LiHMDS, according to the reported procedure,[4] in hexane (5 ml) and the reaction mixture stirred for 1 h at rt. A white precipitate formed. The solution was cooled at 0°C and triethylamine (2 mmol) was added in one portion. Benzoyloxyacetyl chloride **3** (1.2 mmol)[10] in toluene (3 ml) was added dropwise and stirring was maintained for 1 h during which time a copious precipitate appeared. The precipitate was filtered under argon, the solvent completely removed in vacuo, toluene (10 ml) was added and the resulting pale yellow solution was stirred overnight at reflux. The crude mixture was poured into a saturated $NaHCO_3$ solution and extracted with ethyl acetate. Flash chromatography of the residue yielded the *N*-unsubstituted-3-benzoyloxy-4-phenyl-β-lactam **4a** in 50% yield (Scheme 1 and Table 1).

As shown in Table 1, the relative stereochemistry of the substituents on the β-lactam ring is predominantly *trans*[11] (entries 1–8 and 12) using the benzoyloxy protecting group of the hydroxy functionality of the glyoxylic acid. It must be stressed that an exclusive *cis*-diastereoselectivity was obtained with a benzyloxy group on the glyoxylic acid.[7,12] The difference between the benzyloxy- and the benzoyloxy-derivative is the presence of an ethereal versus an ester oxygen, therefore, assuming that there is a conrotatory ring closure of the azadiene, it can be postulated that the formation of the *trans*-azetidinone **4** proceeds through a (*Z,E*)-azadiene (Scheme 1).

However, a lack of *trans* diastereoselectivity is observed when an imine bearing an electron withdrawing group or a heteroatom in the aromatic ring is used (Table 1, entries 9, 10, 11 and 13).

In these cases the formation of a diastereomeric mixture of *cis–trans* azetidinones may be ascribed to an enhanced electropositivity of the imino carbon caused by the presence of a powerful electron withdrawing group. This effect seems to balance, at least partially, the poorer electron donating ability of the alkoxy oxygen of the ester compared with that of the simple ether.[7] As a result, the competitive formation of the (*E,E*)-azadiene, and therefore of the *cis*-β-lactam ring, takes place (Scheme 1). Surprisingly, the *trans*-azetidinone **4h** is the sole β-lactam ring arising from the silylimine **2h**. This behaviour may be explained, in an over simplification, as a dominance of steric effects on electronic

Table 1
Synthesis of azetidin-2-ones **4** and **5**

| Entry | Ar | Aldehyde **1** | β-Lactams **4, 5** | Ratio **4 / 5** | Yields (%)[a,b] |
|---|---|---|---|---|---|
| 1 | Ph | **1a** | **4a / 5a** | >98/2 | 50 |
| 2 | p-Cl-Ph | **1b** | **4b / 5b** | >98/2 | 45 |
| 3 | p-MeO-Ph | **1c** | **4c / 5c** | >98/2 | 45 |
| 4 | 2-Naphthyl | **1d** | **4d / 5d** | >98/2 | 13 |
| 5 | 2-MeO-1-Naphtyl | **1e** | **4e / 5e** | >98/2 | 25 |
| 6 | 2-Thienyl | **1f** | **4f / 5f** | >98/2 | 40 |
| 7 | *N*-Boc-Indol-3-yl[c] | **1g** | **4g / 5g** | >98/2 | 30 |
| 8 | o-$NO_2$-Ph | **1h** | **4h / 5h** | >98/2 | 61 |
| 9 | m-$NO_2$-Ph | **1i** | **4i / 5i** | 5/95 | 22 |
| 10 | p-$NO_2$-Ph | **1j** | **4j / 5j** | 30/70 | 45 |
| 11 | 2-Pyridyl | **1k** | **4k / 5k** | 53/47 | 36 |
| 12 | 3-Pyridyl | **1l** | **4l / 5l** | >98/2 | 38 |
| 13 | 4-Pyridyl | **1m** | **4m / 5m** | 39/61 | 50 |

[a] Overall yields and diastereomeric ratios are for pure isolated products (racemic mixtures) and are based on the starting aldehyde from which the imine was obtained.

[b] The values of diastereomeric ratios found by HPLC and $^1$H NMR analysis of the crude reaction mixtures are identical with those obtained upon isolation of the products by flash chromatography. The *trans* and *cis* stereochemistry was assigned from the H-3-H-4 coupling constant ($J_{trans}$ 1.2-2.2 Hz; $J_{cis}$ 4.0-6.0 Hz).

[c] No β-lactam product was detected when unprotected *NH*-3-formyl-indole was used.

effects in the formation of the intermediate azadiene. Nevertheless, it can be seen that these explanations lack the full characterisation of the intermediate azadienes as well as high level theoretical calculations to provide support for these hypotheses. Several points need further clarification, in particular, if these differences in stereochemical outcome arise from the involvement of several distinct reaction pathways, for example through a different geometry of attack of the imine on the ketene which could lead to different diastereomers through an internal or external transition state.[13] Alternatively, an isomerization could take place at some stage in the process. Work is in progress to answer these questions and will be reported in due course.

The preliminary results presented in this paper demonstrate that changing the nature of the protecting groups used in this chemistry is sufficient to invert the stereoselectivity without major modifications to the reactants and without addition of extra reactants.

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