Pergamon

Tetrahedron Letters, Vol. 37, No. 25, pp. 4409-4412, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00841-6

Trans -Diastereoselective Synthesis of 3-Phthalimido β-Lactams *via* a two Step-Staudinger Reaction.

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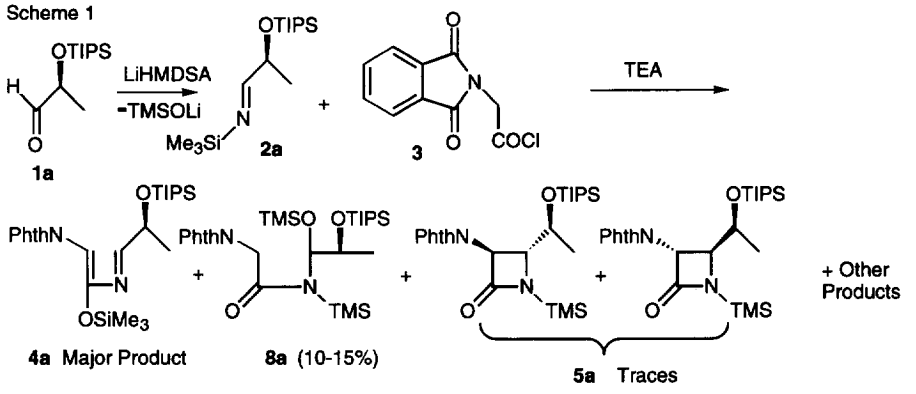
Abstract: New conditions for the Staudinger reaction provide *N*-unsubstituted-3-phthalimido-β-lactams in satisfactory yields with complete trans-selectivity.

In the course of our studies on the synthesis of *N*-unsubstituted azetidin-2-ones starting from *N*-trimethylsilylimines,[1-10] we were interested in finding methods for introducing the phthalimido group on the 3-position of the β-lactam ring, since the resulting azetidin-2-ones are useful intermediates for the preparation of synthetic monobactams, isocephems and carbacephems, as well as penicillins and cephalosporins.

Among a multitude of synthetic methods for the synthesis of azetidin-2-ones, one of the most popular is the [2+2] cycloaddition reaction of imines to ketenes,[11] well known as the Staudinger reaction. Although many studies appeared dealing with synthetic and mechanistic aspects,[12-15] to our acknowledge no studies have appeared on the synthesis of *N-unsubstituted azetidinones*. A paper by Birkofer reported[16] the use of *N*-trimethylsilylimine in the preparation of azetidinones in poor yields unless two equivalents of ketene were used giving rise to the formation of *N*-acyl β-lactams.

Since phthalimido ketene[17,18] has been successfully applied in the Staudinger reaction, we focused our attention on this reaction. As the sample imine we used the *N*-trimethylsilylimine of lactaldehyde **2a**, protected as a triisopropylsilyl (TIPS) ether on the hydroxy functionality.[2] At the beginning of this work we decided to follow the experimental conditions described by Birkofer. Careful ^{1}H and ^{13}C NMR analysis of the crude reaction mixture (Scheme 1) showed that a certain amount of **8a** was formed together with the expected 1-phtalimido-2-trimethylsilyloxy-3-aza-5-triisopropylsilyloxy-1,3-hexadiene **4a**, [19,20] and traces of the β-lactams **5a**. [21] This product distribution prompted us to take a better look at the reaction conditions with the aim of finding procedures to achieve a formal *two-step Staudinger synthesis* of *N*-unsubstituted-β-lactam rings. This letter reports the preliminary results obtained.

Scheme 1



Phth= Phthalimido

Taking into account that **8a** could only arise from the addition of lithium trimethylsilanoate to the diene, the former generated in turn during the preparation of imine (Scheme 1), the first problem we undertook was that of avoiding the formation of **8a** by adding trimethylchlorosilane before the addition of ketene.

The subsequent addition of phthalimidoyl chloride in the presence of TEA resulted in an almost quantitative formation of **4a** as indicated by analyses of ^{1}H- and ^{13}C-NMR spectra. After removing the precipitate of LiCl and Et_3NHCl by filtering under argon, several procedures (use of Lewis acids or TBAF under different reaction conditions), were explored to achieve the ring closure. Unfortunately under such conditions no β-lactam ring was detected in the crude reaction mixture.

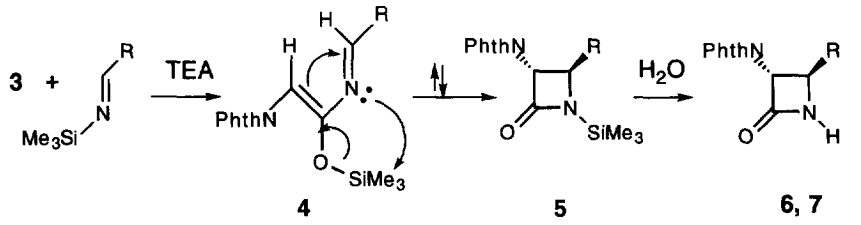
At this point we decided to attempt the ring closure by a retro-silyltropism *via* an intramolecular attack by the lone pair of the iminic nitrogen on the silicon atom (Scheme 2). It was gratifying to obtain the *trans*- β-lactam derivatives **6a** and **7a** in 63% yield and 1/1 facial diastereoselectivity by simply heating-up the diene **4a** at reflux for 6 h in toluene or xylene. No trace of the corresponding *cis*-derivatives was present in the crude reaction mixture. Table 1 reports the results obtained using a variety of imines.

General procedure for the synthesis of azetidin-2-ones **6** and **7:**

To a solution of *N*-trimethylsilyl imine **2** (1 mmol in heptane 5 mL), prepared from the aldehyde **1** (1 mmol) and LiHMDSA (1 mL of 1M solution in THF) in anhydrous heptane, was added in one portion TMSCl (1.1 mmol) at rt. The reaction mixture was stirred for 1 h, cooled at 0 °C and TEA (1 mmol) was added in one portion. The phthalimidoyl chloride dissolved in toluene (5 mL) was added dropwise. Stirring was maintained for 1 h while a copious precipitate occurred. The precipitate was filtered under argon and the resulting pale yellow solution was refluxed for 6 h at 110°C. The crude mixture was diluted with ethyl acetate, poured into saturated NH_4Cl solution and extracted with ethyl acetate. Flash chromatography of the residue yielded the *N*-unsubstituted-3-phthalimido β-lactams in ratio and yields reported in Table 1.

Concerning the mechanism, *E-Z* isomerization of the R-CH=N-$SiMe_3$ moiety and silyl-group transfer are required at some stage of the reaction in order to generated the observed 2-azadiene. One possibility is isomerization through a chloride-induced mechanism, as previously reported by Georg[11, 22-24] followed by silylgroup transfer from the *N*-iminic to the *O*-enolate. (Scheme 2).

Scheme 2



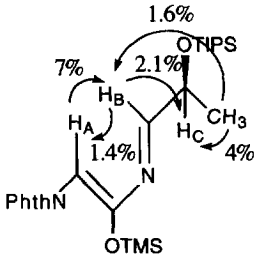


Fig. 1 NOE-Experiments

A series of NOE experiments were performed to establish the stereochemistry of **4a**. Irradiating H_B (Fig. 1) an increment of 1.4% on H_A and 2.1% on H_C is observed whereas upon irradiation of H_A an increment of 7% on H_B is observed. Moreover irradiating the methyl group of the side chain an increment of 1.6% and 4% on H_B and H_A respectively, is observed. All these observations are consistent with a *syn* -(**EE**) conformation as reported in Fig 1 presenting H_A and H_B very close each other. Semiempirical PM3-Calculations[25] showed the reported *syn* (**EE**) conformation more stable than the *anti* - (**EE**) one (-2.4 Kcal/mol), thus supporting a consistent presence of the *syn*-(**EE**) conformation in solution.

Upon heating at reflux temperature of toluene, a concerted retrosilyl tropism and conrotatory ring closure take place. The complete lack of facial diastereoselectivity in the formation of 3-4 bond except for the entry 3, where a sterically demanding group is present on the iminic-C-side chain, may be explained with the lack of any chelation control in our reaction conditions. From this point of view, the use of different solvents (see Entry 1, Table 1) barely affects the simple- and facial-diastereoselectivity of the reaction.

Work is in progress to apply this new methodology to several β-lactam derivatives as well as to improve the facial diastereoselectivity.

Aknowledgement: Financial support was provided by "Progetto Strategico Tecnologie Chimiche Innovative - CNR Rome". M.P. thanks Prof. L.S.Liebeskind of Emory University for the helpful discussion and C.N.R.-Rome for granting a "Short Term Fellow Ship-1995".

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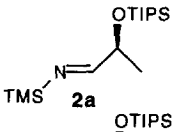
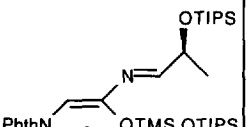
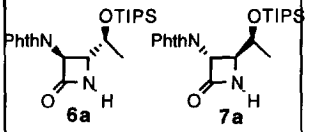
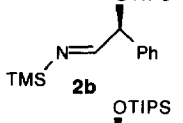
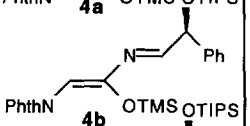
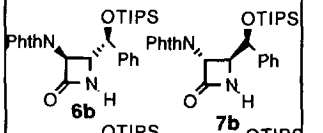
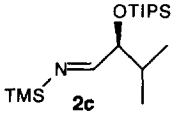
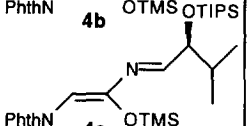
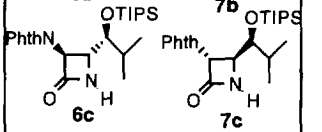
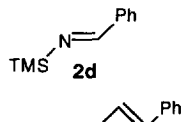
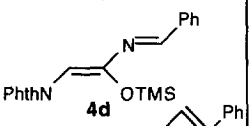
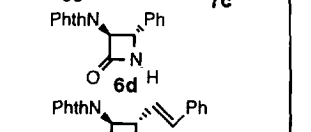
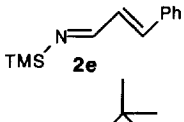
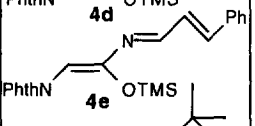
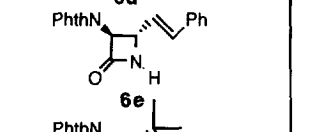
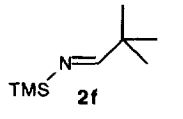
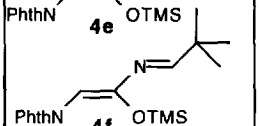
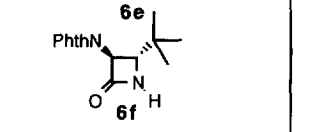
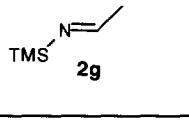
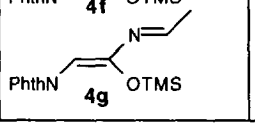
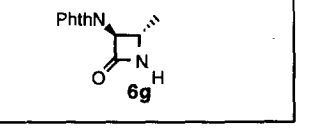
Table 1: Synthesis of β-Lactams 6-7 trough Aza Dienes 4

Entry	Imine	1,3-Azadiene	Solvent	*Syn/Anti*	Y%	Products
1	 **2a**	 **4a**	Toluene	1/1	63	 **6a** **7a**
			DMF	1/1	60	
			CH_3CN	1/1	50	
2	 **2b**	 **4b**	Toluene	1/1	60	 **6b** **7b**
3	 **2c**	 **4c**	Toluene	85/15	40	 **6c** **7c**
4	 **2d**	 **4d**	Toluene		40	 **6d**
5	 **2e**	 **4e**	Toluene		15	 **6e**
6	 **2f**	 **4f**	Xylene		40	 **6f**
7	 **2g**	 **4g**	Toluene		25	 **6g**

*In Entries 4, 5, 6, 7, for the sake of simplicity only one enantiomer has been reported.

(*Received in UK* 29 *February* 1996; *revised* 30 *April* 1996; *accepted* 3 *May* 1996)