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Direct and practical Gilman-Speeter synthesis of 3,4-trisubstituted β-lactams via the Thorpe-Ingold effect

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ABSTRACT

A highly efficient Gilman-Speeter synthesis of 3,4-trisubstituted β-lactams possessing a 4-aryl substituent is described, employing a direct, uncatalyzed Mannich reaction between TMS imines and TMS ketene acetals. The process avoids cryogenic conditions, making it more amenable to process-scale use than related methods for β-lactam synthesis. A Gilman-Speeter diastereoselective version using a sulfinyl imine and leading to homochiral sulfinyl β-aminoester is also presented.

Introduction

The azetidin-2-one (β-lactam) ring provides unique opportunities for the design and synthesis of new derivatives with unprecedented biological profiles. During the last two decades medicinal chemists convincingly demonstrated that structural modifications of monocyclic β-lactams (monobactams) is an effective procedure for the discovery of new and important pharmacological properties different from antibacterial activity [1]. In fact, new β-lactam compounds have been shown to inhibit a wide range of enzymes [2]. The recent discovery that β-lactams can potentially serve as the basis for treatments for neurological disorders including amyotrophic lateral sclerosis (ALS)-also known as Lou Gehrig's disease [3], increases the need for scalable synthetic methods for this heterocycle [4]. The use of β-lactams as useful reactive intermediates leading to biologically active compounds also inspired this work [5]. In connection with our preliminary studies aimed at a novel total synthesis of Ecteinascidin-743 via substituted 1-azetines [6], we became interested in more efficient routes to related β-lactams [7].

Results

Mindful of the pioneering work of Hart on the application of *N*-trimethylsilyl imines to the synthesis of β-lactams employing lithium enolates [8], we reasoned that trimethylsil;yl ketene acetals might be productive partners in this Gilman-Speeter process [9]. It was also thaught that the *in situ* production of one equivalent of trimethylsilyloxy lithium upon formation of the TMS-imine, would obviate the need for catalysis [10].

In practice, when a solution of benzaldehyde in THF was treated with a solution of lithium hexamethyldisilazide in THF at 0 °C, followed by stirring at ambient temperature for 0.5 h, addition of TMS-ketene acetal **1** and heating at THF reflux for 1.5 h, β-lactam **2** was produced as a white solid in 92% yield after extractive isolation and recrystallization (Scheme 1, Ar = Ph, **2a**, Table 1, entry 1).

Although the acid-catalyzed silyl ketene acetal additions to imine-type compounds have been studied in detail [11], none of these methods provides a β-lactam directly thus requiring an extra cyclization step [10]. On the other hand, the direct addition of enolates to *N*-trimethysilyl imines requires costly cryogenic cooling [8], as opposed to the approach presented herein that avoids cryogenic conditions, making it more amenable to process-scale use than related methods for β-lactam formation. It has been found that the reaction proceeds also at ambient temperature, but it takes at least 36 h to complete [12], rendering these reaction conditions unacceptable. In fact, in one experiment in which the TMS-imine of 4-fluorobenzaldehyde was treated with **1** at ambient temperature for 40 h, the corresponding β-aminoester was isolated in good yield suggesting that cyclization to β-lactam is much faster at refluxing THF leading to an excellent yield of β-lactam **2c** (Table 1, entry 3).

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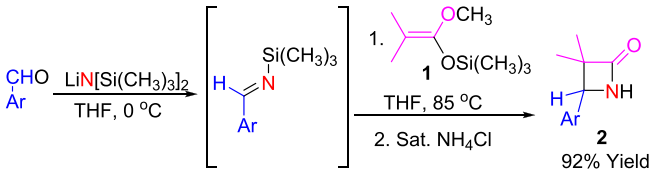
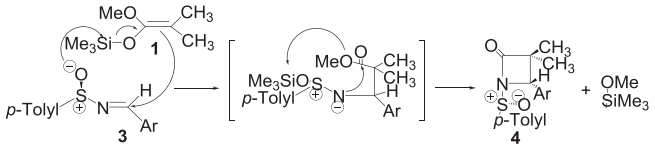
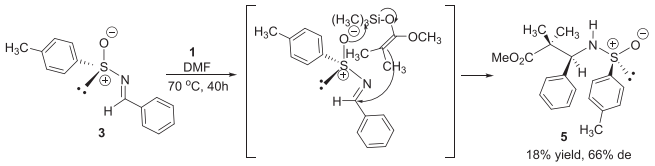


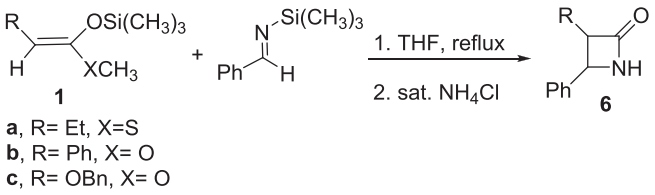
Scheme 1. Synthesis of β-lactam **2** from arylaldehyde and TMS-ketene acetal **1**.



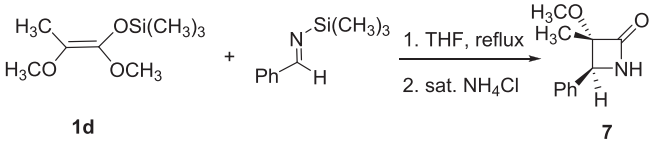
Scheme 2. Projected diastereoselective synthesis of sulfinyl β-lactams employing homochiral sulfinimines.



Scheme 3. Diastereoselective synthesis of β-aminoester **5**.



Scheme 4. Failed β-lactam synthesis with trisubstituted ketene acetals **1a–c**.



Scheme 5. Gilman-Speeter β-lactam synthesis with tetrasubstituted ketene acetal **1d**.

Prior to our success employing *N*-TMS imines and establishing an efficient and convenient as well as economical method not requiring cryogenic cooling, we had been focusing our attention on developing a potential, direct and diastereoselective synthesis of sulfinyl β-lactams using homochiral sulfinimines [13], based on the following premise described in Scheme 2.

Actually, when sulfinimine **3** was treated with TMS-ketene acetal **1** in DMF at 70 °C for 24 h, the corresponding β-amino ester **5** was isolated in 18% yield and 66% de as shown in Scheme 3.

This modest *uncatalyzed* process is interesting given that both Lewis acid-mediated and Lewis base-catalyzed corresponding Mannich reactions have been described [14].

Assignment of the stereochemistry for the major diastereomer was made as previously established by Kawecki.[14a] In fact, the major diastereomer is the same as the major product from both the Lewis acid-mediated and Lewis base-catalyzed reactions [15].

To further explore the scope of this β-lactam synthesis, trisubstituted TMS ketene acetals **1a–c** were prepared in order to determine its stereoselectivity (*cis*/*trans* ratios) [10a,16]. Unfortunately, however, none of these provided the desired β-lactam product **6** upon reaction with benzaldehyde TMS imine in THF (Scheme 4).

At this point, the Thorpe-Ingold or *gem*-dimethyl effect came to mind as a likely explanation of these disparate results [17]. The latter effect (*gem*-Disubstitution effect) refers to the greater facility of synthesis of small or even larger rings that have *gem*-substitution over the less substituted cases [18]. To prove this possibility, tetrasubstituted ketene acetal **1d** was synthesized and reacted with benzaldehde TMS imine [19]. To our satisfaction, β-lactam **7** was obtained in 80% yield, suggesting the full operation of the Thorpe-Ingold effect, as suspected, in this Gilman-Speeter β-lactam synthesis (Scheme 5).

The diastereoselectivity of formation of **1d** was very high as reported [19], and the major *E* isomer led to β-lactam **7** possessing *cis* phenyl and methyl groups as determined by its NOESY 2D-NMR spectrum [20].

Conclusion

In conclusion, we have developed a highly efficient and practical synthesis of unprotected 3,4-Trisubstituted β-lactams amenable to process-scale employment. Furthermore, a diastereoselective Gilman-Speeter reaction of ketene acetal **1** with sulfinimine **3** has been discovered giving rise to useful sulfinyl β-aminoesters. Work is in progress toward the establishment of a catalytic diastereoselective synthesis of sulfinyl β-lactams of type **4** which have been reported to potentially possess very interesting and intriguing biological activities [21].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 1
Data for the one-pot synthesis of β-lactams, see Scheme 1.

Entry (**2**)	Ar	M.P (°C).	Lit. M.P.(°C)[1]	Yield (%)
1 (**a**)	Phenyl	104–105	104–105	92
2 (**b**)	4-Methoxyphenyl	103–104	102–103	90
3 (**c**)	4-Fluorophenyl	102–103		88
4 (**d**)	4-Ethoxy-3-methoxyphenyl	96–97		83
	2-Furyl			
5 (**e**)	2-Bromophenyl	100–101	99–101	75
6 (**f**)	2-Thienyl	127–128		85
7 (**g**)		114–115	113–115	80

1. **a** J. Org. Chem. **1983**, 48, 289–294, **b** Chem. Pharm. Bull. **1993**, 41, 1933–1938, **e** Tetrahedron **1988**, 44, 4157–4172, **g** J. Chem. Soc. Perkin Transl. **1988**, 945–948.

Acknowledgment

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152375.

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