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Triphosgene, an efficient acid activator for the Staudinger reaction

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Abstract

An efficient one-step synthesis of β -lactams by the reaction of imines with acids in the presence of triphosgene and triethylamine has been described. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: triphosgene; Staudinger reaction; azetidiones; ketenes; imines.

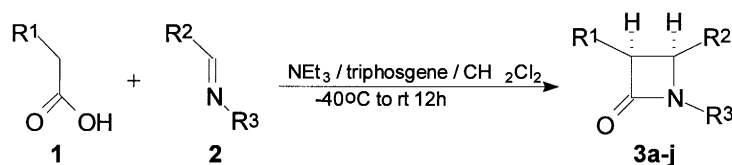
During the last decade, triphosgene [bis(trichloromethyl)carbonate] has become a versatile synthetic auxiliary for the synthesis of some important classes of organic compounds.¹ This white crystalline compound has proven to be safe and advantageous over its gaseous congener, phosgene. As a part of our on-going program on the synthesis and development of methodologies for β -lactam synthesis, we herein report, for the first time, the efficient use of triphosgene as an acid activator in the construction of β -lactams via ketene–imine cycloaddition reactions (Staudinger reaction).

Among the several methods for the synthesis of β -lactams, the cycloaddition of ketenes with imines for the construction of β -lactam rings has found wide acceptance.² This is mainly because of its simplicity, predictability of stereochemical outcome and the proven utility of this method for the synthesis of a large number of monocyclic, bicyclic, tricyclic, and spirocyclic β -lactams.³ The ketenes are usually generated from acid halides (preformed or generated in situ) in the presence of tertiary amines. Alternatively, acid activating reagents² like chloroformates,⁴ trifluoroacetic anhydride,⁵ *p*-TsCl,⁶ phosphorous derived reagents,⁷ the Mukaiyama reagent,⁸ cyanuric chloride,⁹ etc. have been used.

Triphosgene is known to react with acids to produce acid chlorides or anhydrides.¹⁰ We have successfully employed this reagent for one-step cycloaddition reactions of acids and imines to give β -lactams.¹¹ This reaction was found to be very clean and gave excellent yields of β -lactams (Scheme 1). Moreover, this reagent was shown to be better than other acid activators in terms of yield and simplicity of the work-up procedure.

In most of the cases, pure products were isolated by filtration of the reaction mixture through a short silica gel column. Several β -lactams were synthesized in very good yields using this reagent (Table 1). In

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Scheme 1.

all the cases the cycloaddition reaction was found to be stereoselective and only *cis*- β -lactam formation was observed. This method can also be applied for the synthesis of β -lactams derived from Dane salt (see entry 10) and acids which are sensitive to mineral acids or thionyl chloride (see entry 9).

Table 1
Synthesis of β -lactams (**3a–j**) from acids (**1**) and imines (**2**)

Entry No.	R ¹	R ²	R ³	Product ^a	Yield (%) ^{b,c}	M.p. (°C) ^d
1	PhO	Ph	PMP	3a	95 (84) ⁸	185-186
2	PhO	PMP	PMP	3b	82	166-167
3	PhO	Styryl	PMP	3c	93 (58) ⁸	178-180
4	PhO	PMP	Ph	3d	83 (72) ¹²	150 (149-150) ¹²
5	MeO	Ph	PMP	3e	87 (72) ⁸	160-161
6	MeO	PMP	Ph	3f	86	129-130
7	MeO	PMP	PMP	3g	83	114-115
8	PhthN	Styryl	PMP	3h	78 (55) ^{f,7e}	189-190 (192-194) ^{7c}
9		Ph	PMP	3i	65	Thick oil ^e
10		Styryl	PMP	3j	73 ^f	157-158

^a All products were characterized by IR and ¹H NMR spectral analysis, ^b Isolated yield of pure products, ^c The figures in parenthesis represent reported yields, ^d The figures in parenthesis represent reported M.p., ^e Mixture (60:40) of diastereomers, ^f The reaction was carried out at 0°C to room temperature.

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11. Typical procedure: To a solution of acid **1** (1.5 mmol), imine (1 mmol) and triethylamine (6 mmol) in dry CH₂Cl₂ (10 ml), a solution of triphosgene (1 mmol) in dry CH₂Cl₂ (5 ml) was added at -40°C over a period of 20 min and the mixture allowed to warm up to room temperature and stirred for 12 h. The reaction mixture was washed successively with water (20 ml), satd NaHCO₃ (20 ml) and brine (10 ml). The organic layer was dried (Na₂SO₄), filtered through short column of silica gel and the solvent was removed to give the crude product, which was purified either by crystallization or column chromatography to give the β-lactams (**3a-j**) in 65 to 95% yields.
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