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Microwave-induced new synthesis of *trans* and *cis* 3-phenylthio-4-carboethoxy β-lactams

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Staudinger cycloaddition of dicarboethoxy-substituted imines with phenylthioacetyl chloride in the presence of N-methylmorpholine under microwave irradiation is investigated toward the synthesis of C-4 dicarboethoxy-substituted β-lactams. One of the ester groups of the products is removed through a decarboethoxylation process by lithium chloride in DMSO under microwave irradiation. This procedure results in the formation of highly functionalized diastereomeric *cis* and trans β-lactams.

Keywords: Microwave, Staudinger [2+2] cycloaddition, Krapcho decarboxylation, β-lactam.

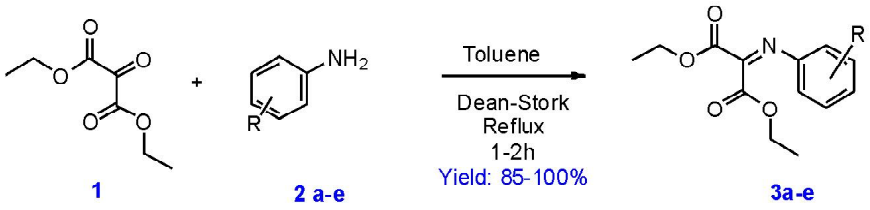
Introduction

Cycloaddition reaction of imines with acid chloride is the most useful procedure for the preparation of β-lactams. Differently substituted β-lactams are accessible by this method. Other methods are not as versatile as this process. But, the stereochemistry of the products is not predictable in many examples from the structure of the reactants. Synthesis of 3-phenylthio substituted β-lactams in *cis* and *trans*-forms starting from diaryl imines and (phenylthio)acetyl chloride in presence of N-methylmorpholine under microwave irradiation is described. One of the ester groups at the C-4 position of the ring is removed following Krapcho-decarboxylation.

Results and discussion

Schiff bases are nitrogen analogue of aldehyde or ketone and typically synthesized by the condensation of primary amine and either aldehyde or ketone. Schiff bases are key intermediates and most widely exploited in organic synthesis for the diverse biologically active molecules. The most remarkable application of Schiff base in ketene-imine [2+2] thermal cycloaddition reaction which was initially developed by Hermann Staudinger in 1907[1]. The discovery of this reaction took place after the isolation of diphenyl ketene in 1905[2]. He reported that ketene reacts with imine to produce 2-azitidinone via [2+2] cycloaddition reaction pathway. After this remarkable discovery of method for access of β-lactam nucleus which constitutes as the central motif of antibiotics[3–5]. This is the century long well know reaction in the synthesis of β-lactam of potential therapeutic drugs[6–9].

Our group demonstrated numerous methods for synthesis of therapeutically active β-lactams[10–15] and many other medicinally relevant molecules[16–18]. In continuation of our research in this area, we report herein a facile synthesis of 3-phenylthio-β-lactams by using Staudinger ketene-imine cycloaddition strategy. The required imine for β-lactam synthesis (**3a-e**) was prepared by refluxing solution of diethyl-2-oxomalonate (1 mmol) (**1**) with numerous aromatic amines (1 mmol) (**2a-e**) in toluene for 1–2 h (Table 1, Scheme 1).



Scheme 1. Synthesis of Schif base (imine).

Table 1. Synthesis of imine derived from diethyl 2-oxomalonate under reflux condition

Entry	Amine [**2**]	Time (h)	Imine [**3**]	Yield[a] (%)
1	**2a** (R = H)	2	**3a** (R = H)	90
2	**2b** (R = Me)	1.5	**3b** (R = Me)	90
3	**2c** (R = OMe)	1.0	**3c** (R = OMe)	100
4	**2d** (R = F)	2.0	**3c** (R = F)	80
5	**2e** (R = Cl)	2.0	**2e** (R = Cl)	85

[a]Crude yield of imine.

Table 2. Microwave induced synthesis of *rac*-diethy 4-oxo-1-phenyl-3-(phenylthio)azetidine-2,2-dicarboxylate (300 W at 25°C)

Entry	Imine [**3a-e**]	Azetidine [**5a-e**]	Temp. (°C)	Time (min)	Yield (%)
1	**3a** (R = H)	**5a** (R = H)	25	8	70
2	**3b** (R = Me)	**5b** (R = Me)	25	5	75
3	**3c** (R = OMe)	**5c** (R = OMe)	25	5	80
4	**3d** (R = F)	**5d** (R = F)	25	10	65
5	**3e** (R = Cl)	**5e** (R = Cl)	25	10	60

In all instances the reaction was very clean and used directly for the β-lactam synthesis without any further purification.

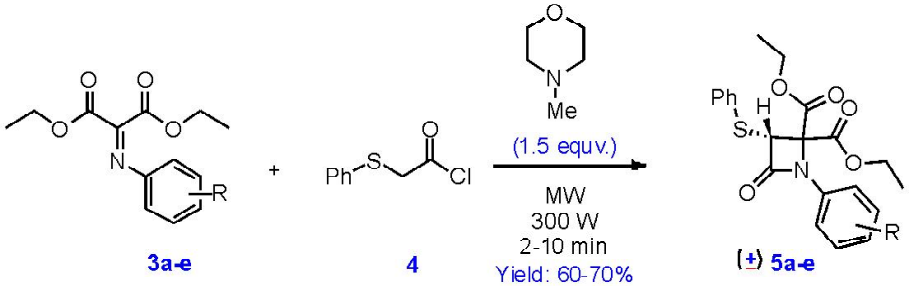
The synthesis of novel *cis* and *trans* 3-pheylthio-β-lactam (**5a-e**) with two diester groups at C-4 position could be achieved via cycloaddition of imine (**3a-e**) and ketene derived from (phenylthio)acetyl chloride (**4**) in presence of N-methyl morpholine under microwave irradiation at room temperature. There was no question of isomer formation since the C-4 position is substituted symmetrically (Table 2, Scheme 2). The structure of the novel β-lactams (**5a-e**) was established by analyzing their ^{1}H and ^{13}C NMR spectra.

It worthy to note that electronically rich imine affords the β-lactam in greater yield with very short reaction time (Table 2, entry 3b-3c) while electron deficient imine took longer time to completion the reaction with moderate yield (Table 2, entry 3d-3e).

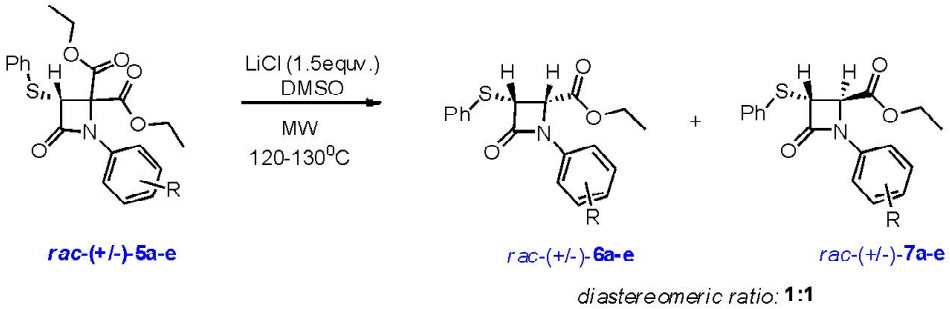
It was found that activated dicarboxyester can be selectively decarboethoxylated by lithium chloride in DMSO at high temperature.

On this basis the β-lactam (**5a-e**) was treated with lithium chloride in DMSO in a microwave oven at 120–130 degree[19–21]. This reaction produced *cis* and *trans* 3-phenylthio-4-carboethoxy-substituted β-lactams **5** and **6** in 1:1 ratio (Scheme 3).

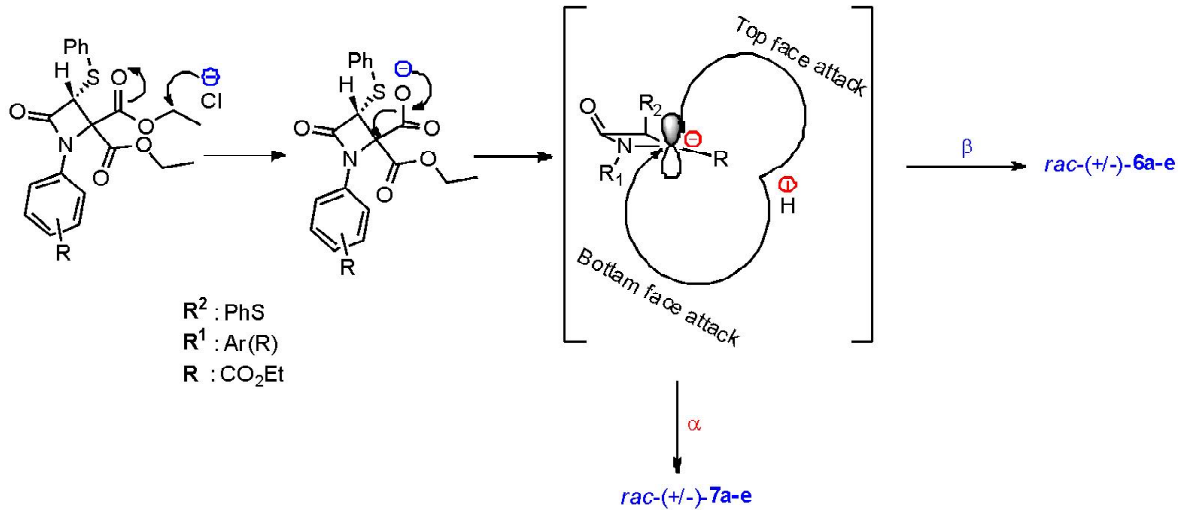
The mechanism of decarboethoxylation can be explained by the attack of a chloride ion to the ester of the β-lactam ring at C-4 position at high temperature. In presence of inorganic salt like LiCl triggered the concerted pathway (SN_2 type



Scheme 2. Synthesis of C-3 phenylthic 4-dicaboethoxy-β-lactams via Staudinger [2+2] cycloaddition reaction.



Scheme 3



Scheme 4

of reaction). Initially the reaction pathway involves nucleophilic substitution at the methylene carbon of the ethyl ester followed by decarboxylation leading to the formation of anionic intermediate that subsequently involves in the facial protonation to afford the *cis/trans* β-lactams (**6a-e**) and (**7a-e**) with 1:1 diastereomeric mixture in good to excellent yield (Scheme 4). However, the chloride ion can attack the two *gem*-esters equally. It is interesting to note that there is no cleavage of the β-lactam ring under this reaction conditions.

All these synthesized β-lactams (*cis/trans*) were purified by column chromatography over silica gel bed using mixture of 20–30% of ethyl acetate in hexane as the eluent. There was no epimerization observed during purification process. The structure of these synthesized β-lactams was determined by the NMR analysis of the purified products.

Conclusions

Preparation of racemic *cis* and *trans* 3-phenylthio β-lactam with a C-4 carboethoxy group is accomplished under microwave irradiation. The work presented herein is interesting since phenylthioacetyl chloride always produces *trans* β-lactam as the sole products in a direct cycloaddition reaction. The notable differences as mentioned in this paper are the preparation of the *cis* isomer with an ester group at the C-4 position. It is therefore, obvious that several chemical transformations can be performed on both *cis* and *trans* phenylthio carboethoxy β-lactam to obtain diverse compounds which are not possible when an aromatic group is present at the C-4 position in the β-lactam ring.

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