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Short Communication

Synthesis and antimicrobial activity of 1,4-diaryl-2-azetidinones

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Abstract

Cycloaddition of substituted 4,4-benzylidene–anilines to in situ prepared dichloroketenes in the presence of dichloroacetyl chloride and triethylamine affords a variety of 2-azetidinones. All the compounds were characterized by IR and ^{1}H NMR. Their antimicrobial activity, against Gram(+) and Gram(−) bacteria and fungi, was tested.

Keywords: Cycloaddition; β-Lactam; Penicillin

1. Introduction

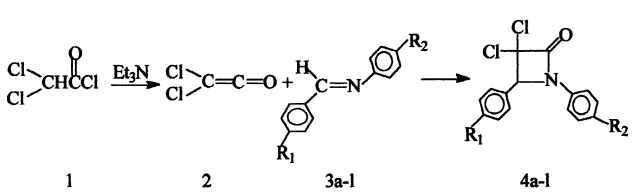
Many compounds containing the β-lactam ring possess various interesting biological properties [1]. The synthesis of 2-azetidinone continues to be a very active research area because of the importance of this structural unit in penicillin and related antibiotics [2–8]. Selectivity (activity) can be influenced decisively by substituents, which are attached to the p-position of the rings [9,10].

In this paper, we report the synthesis and characterization of a number of substituted 1,4-diarylazetidinones and their antimicrobial activity.

2. Chemistry

The ketene–imine cycloaddition reaction is one of the most widely used methods, constructing the β-lactam skeleton present in the different families of β-lactam antibiotics [11,12]. The Staudinger reaction is now widely employed in the preparation of β-lactams because it provides direct access to these compounds from simple precursors [13]. Numerous β-lactams have been prepared by the reaction of acid chloride and imine in the presence of a tertiary amine [14–17].

In the present paper, we report the synthesis and characterization of a number of substituted 1,4-diaryl-2-azetidinones. 1,4-Diaryl-2-azetidinones were prepared by the method of Scheme 1. Imines with various substituents in the benzene rings were prepared and used in this study as illustrated in Table 1.



1 2 3a-l 4a-l

Compound	R_1	R_2	Compound	R_1	R_2
a	H	H	f	CH_3	H
b	H	OCH_3	g	Cl	H
c	H	CH_3	h	NO_2	H
d	H	Cl	i	NO_2	OCH_3
e	OCH_3	H	l	OCH_3	Cl

Scheme 1.

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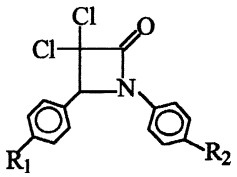
Table 1
Physical and spectral data of compounds **1**–**10**



Compound	R_1	R_2	Formula	m.p (°C)	$\nu_{C=O}$ (cm^{-1})	δ_H (ppm)
1	H	H	$C_{15}H_{11}NOCl_2$	164	1771	5.55
2	H	OCH_3	$C_{16}H_{13}NO_2Cl_2$	106	1780	5.49
3	H	CH_3	$C_{16}H_{13}NOCl_2$	142	1778	5.51
4	H	Cl	$C_{15}H_{10}NOCl_3$	135	1790	5.53
5	OCH_3	H	$C_{16}H_{13}NO_2Cl_2$	128	1778	5.49
6	CH_3	H	$C_{16}H_{13}NOCl_2$	136	1780	5.51
7	Cl	H	$C_{15}H_{10}NOCl_3$	154	1771	5.52
8	NO_2	H	$C_{15}H_{10}N_2O_3Cl_2$	136	1775	5.65
9	NO_2	OCH_3	$C_{16}H_{12}N_2O_4Cl_2$	126	1773	5.61
10	OCH_3	Cl	$C_{16}HH_{12}NO_2Cl_3$	126	1771	5.47

Cycloaddition reaction between imines and dichloroketene has been studied at room temperature (r.t.). The structures of β-lactams were determined by IR, ^{1}H NMR and X-ray spectra. In the IR spectra, stretching frequencies of carbonyl groups are changed between 1770 and 1788 cm^{-1} due to the effect of the substituents in the rings. According to X-ray results, the C–N bond lengths of the compounds **4a**, **4b**, **4d** and **4g** are 1.362(6), 1.357(4), 1.367(4) and 1.374(1), respectively [18–21]. The phenyl rings are nearly perpendicular to one another [66.3 (**4a**), 66.6 (**4b**), 79.4 (**4d**), 62.15 (**4g**)].

3. Experimental

3.1. Chemistry

^{1}H NMR spectra have been recorded on a Bruker DPX-400 MHz spectrometer employing $CDCl_3$ as the solvent with TMS as the internal standard. The IR spectra were obtained on a Hitachi 270-30 spectrometer as KBr pellets. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. Benzene and triethylamine were dried over sodium and freshly distilled before use.

3.1.1. General procedure for the synthesis of 4-4′-disubstituted benzylidene–anilines

The 4,4′-disubstituted benzylidene–anilines, necessary to the present work, were prepared by refluxing equimolecular amounts of 4-substituted benzaldehydes and 4′-substitute anilines in dry benzene. The reaction was over in about 2 h. The solvent was removed by evaporation in vacuo and the residue was crystallized from ethanol or petroleum ether [22].

3.1.2. General procedure for the preparation of β-lactams (*4a–1*)

A solution of an imine (**3a**–**l**) (0.001 mol) and triethylamine (0.002 mol) in 50 ml benzene was stirred for 15 min. Dichloroacetyl chloride (**1**) (0.002 mol) was added dropwise to the solution and the mixture was stirred at r.t. for 1 h. The triethylamine salts were filtered. The mixture was washed with 5% HCl and water and dried over sodium sulfate. The products were fractionally crystallized from ethanol or petroleum ether. Some physical properties and spectral findings of **1**–**10** are given in Table 1.

3.2. Microbiological studies

3.2.1. Microorganisms

Compounds (**4a**–**l**) were subjected to an antimicrobial screening procedure against Gram(+) and Gram(−) strains of *Staphylococcus aureus* ATCC 25923 (S.a), *Bacillus subtilis* ATCC 6633 (B.s), *Escherichia coli* ATCC 35218 (E.c), *Pseudomonas aeruginosa* ATCC 10145 (P.a) and towards *Candida albicans* ATCC 10231 (C.a), *Candida glabrata* ATCC 66032 (C.g). The microorganism used in this study was obtained from Karadeniz Technical University.

3.2.2. Medium

Mueller Hinton Broth (Oxoid) medium was used for diluting the microorganism suspension and two fold-dilution of the compounds. Sabouraud liquid medium (Oxoid) was used for yeast-like fungi for the same purpose.

Table 2
Antibacterial and antifungal activity of compounds **1**–**10** and the standard drugs (MIC in μg/ml) [a]

Compound	R_1	R_2	S.a	B.s	E.a	P.a	C.a	C.g
1	H	H	>250	>250	250	125	125	125
2	H	OCH_3	>250	>250	250	125	125	125
3	H	CH_3	>250	>250	250	125	125	125
4	H	Cl	>250	>250	250	125	125	125
5	OCH_3	H	>250	>250	250	125	125	125
6	CH_3	H	>250	>250	250	125	125	125
7	Cl	H	>250	>250	250	125	125	125
8	NO_2	H	>250	>250	250	125	125	125
9	NO_2	OCH_3	>250	>250	250	125	125	125
10	OCH_3	Cl	>250	>250	250	125	125	125
Ampicillin	–	–	0.1	0.1	62.5	62.5	–	–
Griseofulvin	–	–	–	–	–	–	62.5	62.5

[a] Microorganisms selected are as follows: S.a, *Staphylococcus aureus*; B.s, *Bacillus subtilis*; E.c, *Escherichia coli*; P.a, *Pseudomonas aeruginosa*; C.a, *Candida albicans*; C.g, *Candida glabrata*.

3.2.3. Equipment

Falcon® 96-well microplates were used for the microdilution method. A Brinkmann transferpette® was used for two fold-dilution of the compounds in the wells.

3.2.4. Method

The microdilution method was employed for antibacterial and antifungal activity tests [23,24]. For the antifungal activity test, 0.1 ml Sabouraud liquid medium and for the antibacterial activity test 0.1 ml Mueller Hinton medium were placed into each well of the microplates. 0.1 ml of the compound solution in DMSO at 1000 μg/ml concentration was added into the first raws of microplates; ampicillin anhydrate and griseofulvin were used as control agents under the same conditions. Double dilutions of the compounds and standard 250, 125, 0.1 μg/ml were made by dispensing the solutions to the remaining wells. 0.1 ml microorganism suspensions, at 10^6 cfu/ml (colony forming unit/ml) concentration, were inoculated into all the wells. The sealed microplates were incubated at 36°C for 24 and 36 h in the humid chamber. The lowest concentration of the compound that completely inhibits macroscopic growth was controlled and MIC (minimum inhibitory concentration) reported. MIC values of the two derivatives, ampicillin anhydride and griseofulvin as standards and ten compounds have been shown as μg/ml in Table 2.

4. Results and discussions

Compounds **1**–**10** were evaluated for their in vitro antimicrobial activity against some Gram(+) and Gram(−) bacteria and fungi (Table 2). Their antibacterial and antifungal activity was determined as MIC values. The activity of the compounds **1**–**10**, reported in Table 2, showed that, in contrast with the well-known activity of β-lactam antibiotics, the inhibitory effect is significant against fungi and Gram(−) bacteria. The activity of compounds **1**–**10** was particularly interesting against *Pseudomonas aeruginosa*. The unexpected activity of all compounds against fungi is not affected by substituents.

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