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Synthesis of 2-azetidinones from 2-diazo-1, 2-diarylethanones and *N*-(2-thienylidene)imines as possible antimicrobial agents

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Abstract

An equimolar reaction of 2-diazo-1, 2-diarylethanones with *N*-(2-thienylidene)imines affords 1-substituted-3, 3-diaryl-4-(2-thienyl)-2-azetidinones in excellent yields. The products have been characterized on the basis of satisfactory analytical and spectral (IR, ^{1}H and ^{13}C NMR, MS) data. The mechanism of formation of the products is shown. The antimicrobial activity of the compounds against some Gram(+) and Gram(–) bacteria, and fungi is reported.

Keywords: 2-Azetidinones; Diazoketones; Diarylketenes; Cycloaddition; Antibacterial; Antifungal

1. Introduction

2-Azetidinones, commonly known as β-lactams, are well-known heterocyclic compounds among organic chemists. The activity of the famous antibiotics such as penicillin, cephalosporin and carbapenem are attributed to the presence of 2-azetidinone ring in them. The β-lactams also serve as synthons for some biologically important class of organic compounds such as β-amino acids. Due to this, the investigation of synthesis, chemistry and biology of these compounds continue to appeal the synthetic and medicinal organic chemists [1]. Recently some other types of biological activity besides the antibacterial activity have been reported in compounds containing 2-azetidinone ring [2,3]. Some examples include antifungal, antitubercular, antitumor, cholesterol absorption inhibition and enzyme inhibition activity. The biological activity is observed to depend on the substituents especially at nitrogen of the 2-azetidinone ring. Recent years have seen a resurgence of interest in monocyclic azetidinones due to their cholesterol absorption and enzyme inhibition activity [4,5].

The most common method for the synthesis of 2-azetidinones is the Staudinger ketene-imine cycloaddition [1]. It involves the reaction of imines with acid chloride in the presence of a tertiary base (Scheme 1). This reaction, however, depends, on many factors including temperature, which often needs to be optimized [6]. Our group has been investigating the reactions of α-diazoketones through ketenes and carbenoids with organic compounds containing nitrogen atom in different structural environments in order to develop new methodology for synthesis of heterocyclic compounds [7,8]. These reactions are simple to carry out, versatile and do not require the use of any acidic or basic reagent.

The present paper reports the synthesis, characterization data and antimicrobial screening results of 1-substituted-3, 3-diaryl-4-(2-thienyl)-2-azetidinones from the reaction of 2-diazo-1, 2-diarylethanones with *N*-(2-thienylidene)imines. To the best of our knowledge, all the compounds are new.

2. Experimental

2.1. Chemistry

Melting points have been recorded on a Stuart Scientific melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin–Elmer-781 IR spectrophotometer using KBr disc of the sample. The NMR and mass spectra were recorded on a Bruker™ 300 MHz spectrometer in a $CDCl_3$ solution and on a Mat SSQ 7000 spectrometer using dichloromethane as a solvent, respectively.

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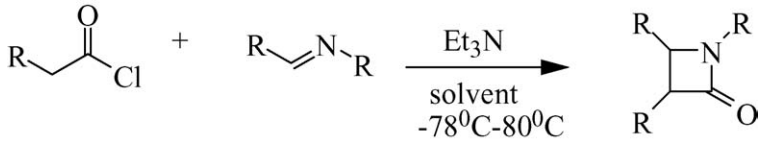
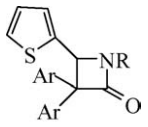


Scheme 1.

Benzil, 4,4′-dimethylbenzil, hydrazine hydrate, thiophene-2-carboxaldehyde and amines were Aldrich products. Acetonitrile was dried by refluxing on phosphorus pentaoxide.

2-Diazo-1, 2-diarylethanones were prepared by oxidation of the benzil monohydrazones [9]. The latter compound was synthesized by the condensation of benzils with hydrazine hydrate by reported method [10]. *N*-(2-Thienylidene)imines were prepared by refluxing thiophene-2-carboxaldehyde with an equimolar amount of appropriate amine in dry benzene according to the method reported by Jones and Heads [11].

Table 1
Physical data of the 2-azetidinones **3a–j**



3a-j

Compounds	Ar	R	Mol. Formula[a]	m. p. (°C)	Yield (%)[b]
3a	4-MePh	Ph	$C_{27}H_{23}NOS$	180	79
3b	4-MePh	4-MePh	$C_{28}H_{25}NOS$	159	81
3c	4-MePh	4-MeOPh	$C_{28}H_{25}NO_2S$	146	86
3d	4-MePh	4-EtOPh	$C_{29}H_{27}NO_2S$	150	90
3e	4-MePh	4-ClPh	$C_{27}H_{22}NOSCl$	126	61
3f	4-MePh	4-NO_2Ph	$C_{27}H_{22}N_2O_3S$	246	67
3g	4-MePh	$CHPh_2$	$C_{34}H_{29}NOS$	140	65
3h	Ph	4-MeOPh	$C_{26}H_{21}NO_2S$	128	83
3i	Ph	4-EtOPh	$C_{27}H_{23}NO_2S$	120	87
3j	Ph	4-NO_2Ph	$C_{25}H_{18}N_2O_3S$	100	60

[a] The elemental analysis for C, H and N were within ± 0.4 from theoretical value.
[b] Yield of pure isolated product.

2.2. General procedure for the synthesis of 2-azetidinones (3a–j)

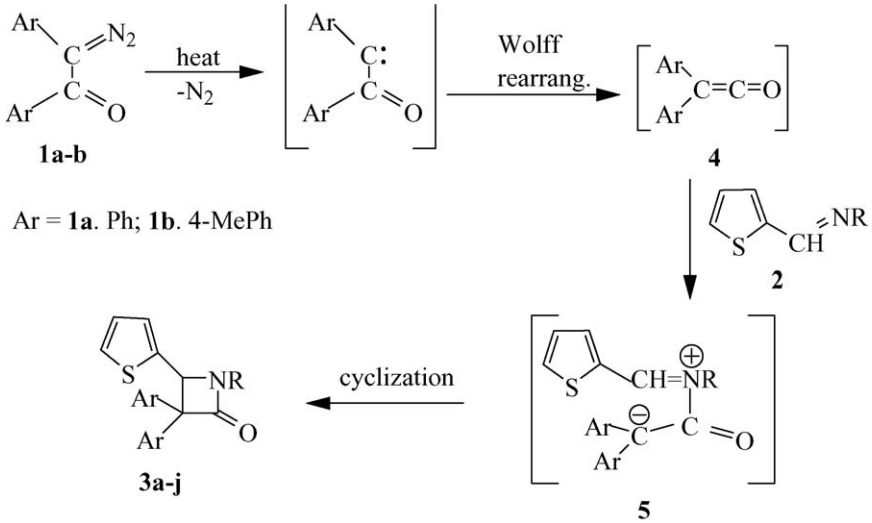
A solution of equimolar amounts (10 mmol of each) of the α-diazoketones (**1a–b**) and imines (**2**) in acetonitrile (60 ml) was refluxed for 4 h under continuous stream of nitrogen. The solvent was removed under reduced pressure and the residual matter crystallized with ethanol to afford white crystalline product. The products obtained in this way were pure enough for elemental and spectral analysis. The physical and spectral data of the products **3a–j** are shown in Tables 1 and 2, respectively.

2.3. Microbiology

The compounds were screened in vitro for their antibacterial activity against some Gram(+) and Gram(–) strains of *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Escherichia coli*, and fungi *Candida albicans*, *Cochliobolus sativus* and *Macrophomina phaseolina*. The antibacterial and antifungal activity (MIC) of the compounds and references were determined by the Mueller–Hinton agar dilution method [12]. The results of the screening are shown in Table 3.

3. Results and discussions

An equimolar reaction of the diazoketones **1a–b** with imines **2** in acetonitrile afforded white crystalline products char-



Scheme 2.