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Short communication

Synthesis and antimicrobial activity of new 1-alkyl/cyclohexyl-3,3-diaryl-1′-methylspiro[azetidine-2,3′-indoline]-2′,4-diones

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Abstract

The paper describes the synthesis of new 1-alkyl/cyclohexyl-3,3-diaryl-1′-methylspiro[azetidine-2,3′-indoline]-2′,4-diones from the reactions of the 2-diazo-1,2-diarylethanones with 1-methyl-3-(alkyl/cyclohexylimino)indolin-2-ones under thermal condition. The compounds, characterized by satisfactory analytical and spectral (IR, ^{1}H NMR and ^{13}C NMR) data, have been screened for their antibacterial and antifungal activities.

Keywords: Spiroazetidinones; Diarylketenes; 3-Iminoindolin-2-ones; Cycloaddition; Antimicrobial activity

1. Introduction

The 2-azetidinones, commonly known as β-lactams, are among the most useful azaheterocyclic compounds from both synthetic and medicinal chemistry points of views. Most of the researches up to early 90s focused on synthesis of 2-azetidinones and study of their antibacterial property [1–3]. Later researches have shown some other useful biological activities of such compounds, e.g. cholesterol absorption inhibition, enzymes inhibition, hypoglycemic, and anticancer activity [4,5]. Ezetimibe, a monocyclic 2-azetidinone, is now in clinical use as a cholesterol absorption inhibitor [6]. Recent years have shown extensive investigation on use of 2-azetidinones as synthons for diverse types of biologically important compounds such as β-aminoacids, γ-aminoalcohols, azetidines, pyrimidones, etc. [7–11]. However, most of these studies are undertaken either on monocyclic or fused bicyclic 2-azetidinones. It is due to the fact that the first 2-azetidinone-containing antibiotics penicillin and cephalosporin had fused bicyclic skeletons whereas monobactams and nocardicins, observed in late 70s and early 80s to have antibacterial activity, had monocyclic 2-azetidinone ring. The spiro-fused 2-azetidinones constitute a scarce class of compounds. There are only a few reports in the literature on the synthesis, reactivity and biological activity of such 2-azetidinones [12–27]. The diverse types of biological activities associated with indoline-2,3-dione (isatin) derivatives and their interesting chemistry [28–31] prompted us to synthesize 2-azetidinones spiro-fused to 1-methylindolin-2-one ring and study its antimicrobial activity. Accordingly, the present paper reports the synthesis and antimicrobial activity of 10 new 1-alkyl/cyclohexyl-3,3-diaryl-1′-methylspiro[azetidine-2,3′-indoline]-2′,4-diones from the reactions of 1-methyl-3-(alkyl/cyclohexylimino)indolin-2-ones with three 2-diazo-1,2-diarylethanones – 2-diazo-1,2-diphenylethanone, 2-diazo-1,2-bis(4-methylphenyl)ethanone and 2-diazo-1,2-bis(4-methoxyphenyl)ethanone.

There are several methods reported in the literature for the synthesis of 2-azetidinones [9,10]. However, the Staudinger ketene–imine cycloaddition reaction is one of the most common methods to synthesize 2-azetidinones [32]. It involves reaction of an imine with acid chloride in the presence of a tertiary base, usually triethylamine at temperatures ranging from −78 °C to reflux temperature in various solvents such as dichloromethane, acetonitrile, toluene, etc. (Scheme 1). In the present study, diarylketenes are generated *in situ* by thermal decomposition of α-diazoketones because their reactions appeared versatile, simpler to carry out requiring

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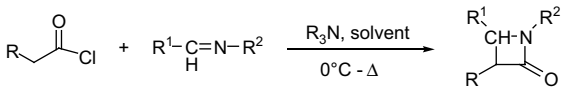

Scheme 1. The Staudinger method for the preparation of 2-azetidinones.

no temperature control, no acid or base treatment and also no water work-up.

2. Results and discussion

2.1. Chemistry

An equimolar reaction of 2-diazo-1,2-diphenylethanone (**1a**) with 1-methyl-3-(isopropylimino)indolin-2-one (**2a**) in dry benzene afforded a white crystalline compound characterized as 1-isopropyl-1′-methyl-3,3-diphenylspiro[azetidine-2,3′-indoline]-2′,4-dione (**3a**) on the basis of satisfactory analytical and spectral data (see Section 4).

Similar reactions of 2-diazo-1,2-diphenylethanone (**1a**) with 1-methyl-3-(*N*-substituted imino)indolin-2-ones (**2b–d**) also afforded spiro(azetidin-2,3′-indoline)-2′,4-diones (**3b–d**) in good yields (Table 1). The reactions of 2-diazo-1,2-bis(4-methylphenyl)ethanone (**1b**) and of 2-diazo-1,2-bis(4-methoxyphenyl)ethanone (**1c**) were carried out in a similar manner with 1-methyl-3-(alkylimino)indolin-2-ones **2a–d** and with **2a** and **b**, respectively, which yielded new spiro(azetidin-2,3′-indoline)-2′,4-diones (**3e–h**) and (**3i,j**), respectively, in good to excellent yields (Table 1) which have been characterized on the basis of satisfactory analytical and spectral data discussed briefly in the succeeding paragraph.

The IR spectra of compounds **3a–j** showed two strong absorption bands – one at around 1745–1760 and the other at around 1720–1730 cm^{-1} corresponding to two lactam carbonyl groups. The ^{13}C NMR spectra showed the two carbonyl carbons at around δ 173 and 169 ppm. In the IR and ^{13}C spectra of the products **3a–j**, the disappearance of the band at around 1640 cm^{-1} corresponding to azomethine linkage and of signal at around δ 155 ppm corresponding to azomethine carbon, respectively, in substrates **2a–d** confirmed the reaction at azomethine linkage of the substrates forming spiro[azetidine-2,3′-indoline]-2′,4-diones. It is noteworthy to mention that the ^1H NMR spectra of spiro-compounds **3c** and **g** with α-phenylmethyl group on azetidinone ring nitrogen showed the signals in sets of two (approximately in the ratio of 9:1) indicating two spatial arrangement of the groups in these compounds. The *N*-methyl and methine signals for minor configuration appeared slightly downfield than the signals for these protons in major configurations whereas the signal for methyl proton [CH(Me)Ph] appeared slightly upfield. The mass spectra of the products recorded showed the quasimolecular ions formed by addition of sodium $(M + Na)^+$.

Table 1
Physical data of the spiro[azetidin-2,3′-indoline]-2′,4-diones **3a–j**

Compound number	Ar	R	Molecular formula	M.p. (°C)	Yield (%)
3a	Ph	$CHMe_2$	$C_{26}H_{24}N_2O_2$	200–202	69
3b	Ph	$CHPh_2$	$C_{36}H_{28}N_2O_2$	236–237	74
3c	Ph	CH(Me)Ph	$C_{31}H_{26}N_2O_2$	162–165	60
3d	Ph	Cyclohexyl	$C_{29}H_{28}N_2O_2$	155–158	50
3e	4-MeC_6H_4	$CHMe_2$	$C_{28}H_{28}N_2O_2$	258–260	72
3f	4-MeC_6H_4	$CHPh_2$	$C_{38}H_{32}N_2O_2$	194–195	78
3g	4-MeC_6H_4	CH(Me)Ph	$C_{33}H_{30}N_2O_2$	214–216	68
3h	4-MeC_6H_4	Cyclohexyl	$C_{31}H_{32}N_2O_2$	180–182	52
3i	4-$MeOC_6H_4$	$CHMe_2$	$C_{28}H_{28}N_2O_4$	255–258	77
3j	4-$MeOC_6H_4$	$CHPh_2$	$C_{38}H_{32}N_2O_4$	204–206	80

The mechanism of formation of the product, which is similar to the one proposed earlier for such reactions [28], is shown in Scheme 2. Thermal decomposition of the 2-diazoketones leads to the formation of α-ketocarbenes with extrusion of nitrogen. The α-ketocarbenes are known to undergo the Wolff rearrangement leading to *in situ* generation of ketenes [33]. The reaction of imines with ketenes may lead to the formation of a *zwitterionic* intermediate, which cyclizes to give the product 2-azetidinones.

2.2. Pharmacology

All the synthesized compounds were screened for their antibacterial and antifungal activities (Table 2). The concentrations ranging from 1.0 to 100.0 μg mL^{-1} of the test compound were used for the screening. The bacterial strains used were Gram-(+) *Bacillus subtilis*, *Staphylococcus aureus* and Gram-(−) *Escherichia coli* and *Pseudomonas aeruginosa*. The antifungal screening was done on *Candida albicans* and on *Saccharomyces cerevisiae*. Of the 10 compounds screened against bacterial strains, four compounds showed activity on *E. coli* (**3d**: MIC = 100 μg mL^{-1}, **3e**: MIC = 10 μg mL^{-1}, **3h**: MIC = 100 μg mL^{-1}, **3j**: MIC = 50 μg mL^{-1}) whereas only one compound showed activity on *P. aeruginosa* (**3e**: MIC = 50 μg mL^{-1}). None of the compounds showed activity on Gram-(+) strains up to the maximum concentration of 100 μg mL^{-1} used in the study. These results are in agreement with previous studies on monocyclic 2-azetidinones which reported higher activity of such 2-azetidinones against Gram-(−) bacteria in comparison to that against Gram-(+) bacteria [34–36]. Although none of the compounds showed activity up to 100 μg mL^{-1} against *C. albicans* six compounds (**3a**: MIC = 50 μg mL^{-1}, **3b**. MIC = 10 μg mL^{-1}, **3e**: MIC = μg mL^{-1}, 50, **3f**: MIC = 100 μg mL^{-1}, **3i**: MIC = 50 μg mL^{-1}, **3j**: MIC = 50 μg mL^{-1}) have been observed active on *S. cerevisiae*. Only compound **3e** with two 4-methylphenyl groups and an isopropyl group on 2-azetidinone ring carbon and nitrogen, respectively, showed activity against three organisms out of five studied.

3. Conclusions

In conclusion, the paper reports the synthesis of spiro-compounds containing 2-azetidinone and 1-methylindolin-2-one rings from the reactions of 1-methyl-3-(alkylimino) indolin-2-ones with three diarylketenes – diphenylketene,