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New Compounds

Transformation of the sydnone ring into oxadiazolinones. A convenient one-pot synthesis of 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones from 3-arylsydnones and their antimicrobial activity

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Abstract

3-Arylsydnones (**Ia–u**) have been converted into the corresponding 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones (**IIIa–u**) by a single-step reaction with bromine in acetic anhydride. In the preliminary screening of all these compounds, the halogen-substituted derivatives have shown antimicrobial activities equal to those of the standard drugs used.

Keywords: Sydnone ring; Oxadiazolinones; Antimicrobial activity

1. Introduction

Sydnones are one of the few heterocycles which have gained importance as synthones, as they readily undergo ring transformation to various heterocycles by 1,3-dipolar cycloaddition [1]. Such one-step conversions of sydnones into pyrazole derivatives have been reported from this laboratory [2,3].

2. Chemistry

In continuation of this work, in the present investigation we focused our attention on the synthesis of 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones (**IIIa–u**) from 3-arylsydnones (**Ia–u**). The aim of this work came from the observation that such oxadiazolinones were synthesised with difficulty starting from 3-acetyl-2-phenylcarbazic acid ethylester [4] and 1-phenyl-2-acetylphenylhydrazine [5]. The latter method gave the isomeric 1,2,4-triazolidin-3,5-diones and 1,2,4-triazolidin-5-ones also resulting from the formation of oxadiazolin-2-ones in only 35% yield. (Scheme 1). Instead, the one-pot synthesis of these compounds from sydnones is achieved in 80% yield without the formation of any isomers. Hence, sydnones can be used as versatile starting materials for the preparation of such heterocycles, which are accessible with difficulty. The mechanism of this conversion has been explained in terms of 1,3-dipolar cycloaddition of an acid anhydride to the intermediate product 3-aryl-4-bromosydnone (**II**) [1] (Scheme 2). In this paper we now present the synthesis of the new oxadiazolinones **IIIa–u** and their antimicrobial activity.

The title compounds were prepared from 3-arylsydnones by the reaction of bromine in acetic anhydride. The initial step at 0°C gave the 3-aryl-4-bromosydnones **IIa–u** which were then converted in situ into the oxadiazolinones **IIIa–u** by heating the solution at 60°C. The 3-arylsydnones **Ia–u** and their 4-bromo derivatives **IIa–u** were prepared by literature methods [6,7].

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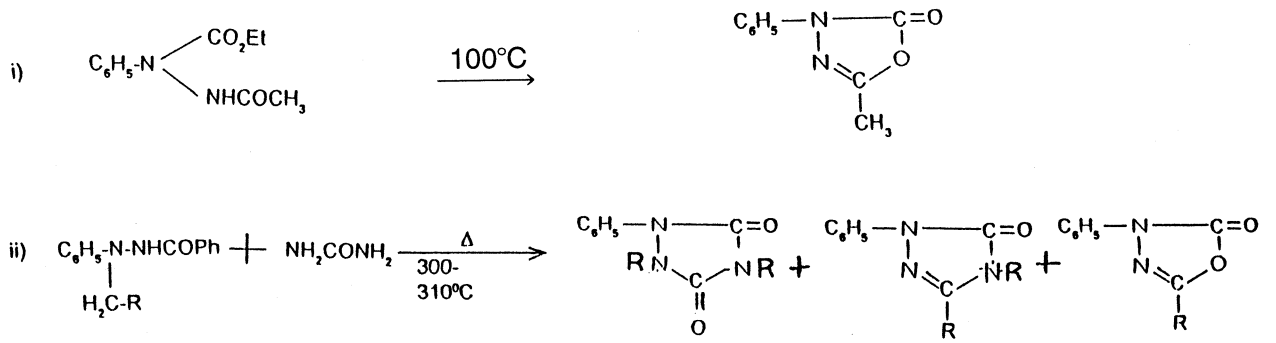


Scheme 1.

3. Spectral characterisation

The IR spectra of these compounds showed bands at 1775 cm^{-1} ν(C=O) and 1630 cm^{-1} ν(C=N). The absence of a band at 3100 cm^{-1}, which is characteristic of the sydnone ring carbonyl group, confirms the transformation. ^1H NMR spectra of all these compounds showed a singlet at δ 2.40 ppm for the CH_3 protons. The protons on the aromatic ring appeared as given below.

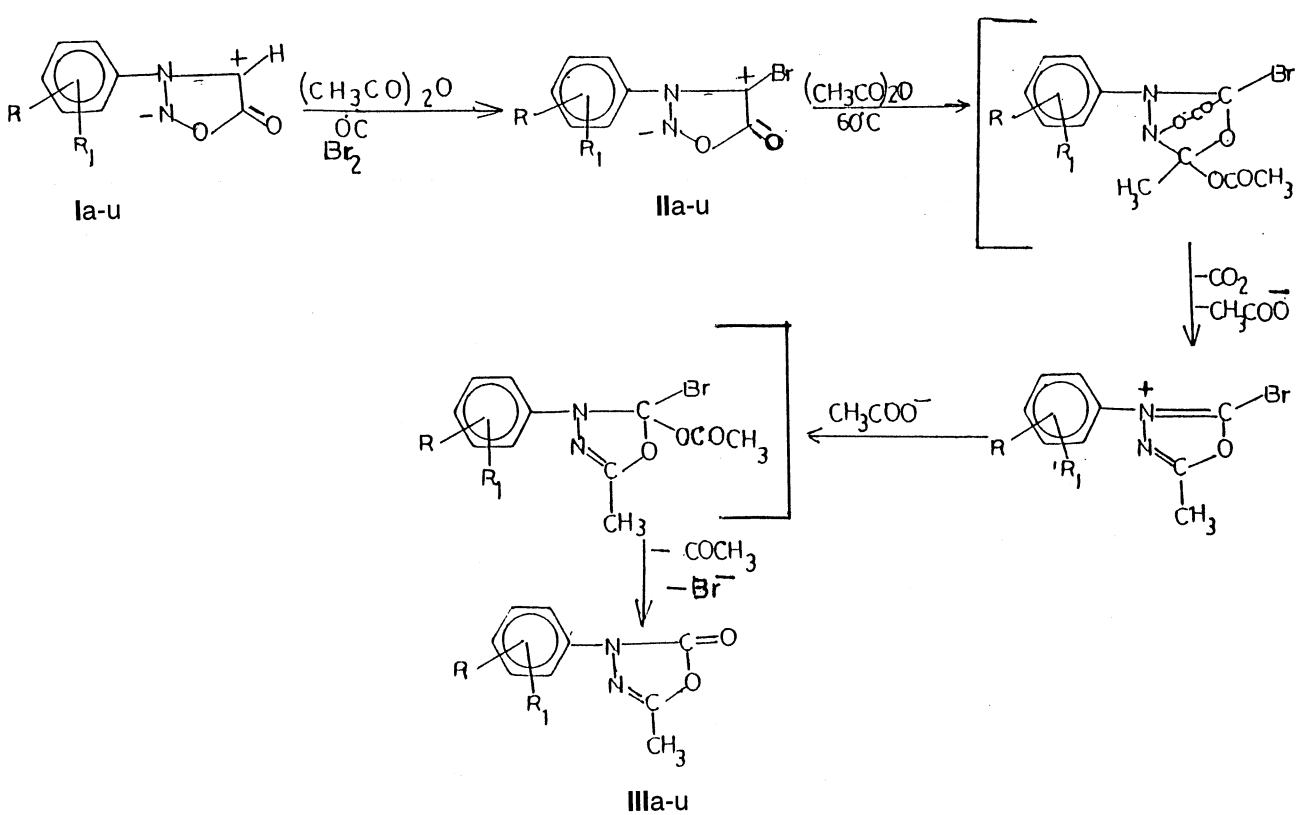
IIIa: One multiplet (5H Ar) at δ 7.20–7.60 ppm.

IIIc (*meta* substituted): One singlet (1H, Ar) and one multiplet (3H, Ar) at δ 7.20–7.60 ppm

IIIb, **e**, **g**, **i**, **j**, **m**, **o** and **p** (*para* substituted): Two doublets (2H each, Ar, AA^1 BB^1) at δ 7.20–7.70 ppm (J 8 Hz).

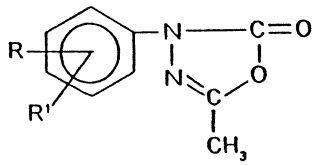
IIId, **f**, **k**, **l** and **n** (*ortho* substituted): One multiplet (4H, Ar) at δ 7.20–7.80 ppm.

IIIq, **r**, **s**, **t** and **u** (disubstituted): One singlet (1H, Ar) at δ 7.15 and two doublets (2H, Ar) at δ 7.20 and 7.70 ppm.



Scheme 2.

Table 1
3-Aryl-5-methyl-1,3,4-oxadiazolin-2-ones



Comp.	R	R^1	Yield (%)	M.p. (°C)
a	H	H	82	95–96
b	H	4-CH_3	80	82–83
c	H	3-CH_3	84	138–39
e	H	2-CH_3	80	121–22
f	H	2-OCH_3	75	139–40
g	H	4-Cl	80	98–99
h	H	3-Cl	82	96–97
i	H	4-Br	85	111–12
j	H	4-NO_2	72	86–87
k	H	2-NO_2	70	80–81
l	H	2-COOH	75	92–93
m	H	4-$COCH_3$	88	138–39
n	H	2-$COCH_3$	85	122–23
o	H	4-$COOCH_3$	86	110–11
p	H	4-$COOCH_2H$	90	107–108
q	3-CH_3	4-CH_3	85	103–04
r	2-CH_3	5-CH_3	80	114–15
s	2-OCH_3	4-Cl	70	83–84
t	4-CH_3	3-Cl	80	92–93
u	4-Cl	3-F	74	101–02

4. Biological evaluation (antimicrobial activity)

All these compounds were screened for their antimicrobial activity against two pathogenic bacteria, viz., *Escherichia coli* and *Pseudomonas pyocyanous* and two cultures viz., *Aspergillis niger* and *Rhizoctonia bataticola*. The standard drugs used were Norfloxacin and Griseofulvin. The tests were carried out by the cup–plate method with 20 μg of the substance in 0.1 ml of dimethylformamide. Dimethylformamide was used as solvent control. The zone of inhibition was measured in mm and was compared with that of the standard drugs. From these qualitative studies it has been observed that the halogen-substituted derivatives exhibit considerable activity. The chloro compounds **IIIg** and **h** show growth inhibition only against *P. pyocyanous* equal to that of Norfloxacin while the bromo derivative **IIIi** shows growth inhibition equal to the standard only against *E. coli*. The antifungal activity of these compounds is more than the standard against both strains. Amongst the bihalogenated derivatives only chloro-fluoro-substituted compound **IIIu** causes growth inhibition equal to the standard against both strains.

5. Experimental

TLC was carried out on silica gel plates using a benzene–ethanol mixture as eluent. The IR spectra were recorded on an IR Nicolet-Impact-410, FTIR spectrometer. ^{1}H NMR spectra were recorded on a Varian EM, 300 MHz, NMR Spectrometer in DMSO-d_6 with TMS as internal standard. The observed elemental analysis results are within 0.4% of the theoretical values.

*5.1. Preparation of 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones. **IIa–u** (general procedure)*

3-Arylsydnone (1.0 g) was suspended in acetic anhydride (5 ml) at 0°C and an ice-cooled solution of bromine (0.5 ml) in acetic anhydride (5 ml) was added with stirring and cooling. 4-Bromosydnone separates after the addition. The reaction mixture was then heated on a water bath, gradually increasing the temperature to 50–60°C for about 30 min. Vigorous evolution of CO_2 was observed. The solution was then diluted with water. The solid obtained was filtered, washed with water and crystallised from ethanol (Table 1).

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