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Synthesis Of Spiro[3,4-diaryl-4,5-dihydroisoxazole-5,2′-1′,2′,3′,4-tetrahydro-1′-naphthalenone]

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ABSTRACT: *Synthesis of a series of novel spiro[3,4-diaryl-4,5-dihydroisoxazole-5,2′-1′,2′,3′,4′-tetrahydro-1′-naphthalenone] has been described by the regioselective cycloaddition of nitrile oxides with 2-arylmethylene-1,2,3,4-tetrahydro-1-naphthalenone.*
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INTRODUCTION

1,3-Dipolar cycloaddition reactions offer an excellent route for the construction of isoxazoline derivatives [1]. The isoxazoline derivatives have been extended to many natural product syntheses and also proved to be an efficient precursor for many synthetic intermediates including γ-amino alcohols and β-hydroxy ketones [2]. Spiroisoxazolines display interesting biological properties such as herbicidal properties and plant growth regulatory activities, and they are antitumor agents [3]. Although a plethora of reports are available for the synthesis of isoxazoline derivatives, there appears to be few for spiroisoxazoline derivatives. Further, tetrahydro-1-naphthalenone derivatives have been utilized for the synthesis of benzophenanthridine antitumor alkaloids and ring B of tetracyclins [4,5]. The high synthetic utility and pharmacological importance have prompted us to synthesize some biologically interesting spiroisoxazoline derivatives.

In continuation of our interest in the area of cycloaddition reactions [6–11], herein we report the efficient synthesis of spiroisoxazolines by the regioselective cycloaddition reaction of 2-arylmethylene-tetrahydro-1-naphthalenone with nitrile oxides.

RESULTS AND DISCUSSION

In an attempt to evaluate the effect of electron-donating and electron-withdrawing groups in direct conjugation with the double bond of the dipolarophile on the regioselectivity in the cycloaddition reactions, the reactions of nitrile oxides **2a** or **2b** with 2-arylmethylene-1,2,3,4-tetrahydro-1-naphthalenone **1a–e** have been studied. The dipolarophiles (*E*) 2-arylmethylene-1,2,3,4-tetrahydro-1-naphthalenone **1a–e** prerequisite for the present study were prepared according to the procedure in the literature [8,12]. Reactions of 2-arylmethylene-1,2,3,4-tetrahydro-1-naphthalenone **1a–e** with nitrile oxide **2a** or **2b** (generated *in situ* from the corresponding *N*-benzhydroxyiminoyl chloride in chloroform solution in the presence of triethylamine at room temperature) led to the formation of 1 : 1 adducts as a single product in each case as evidenced by

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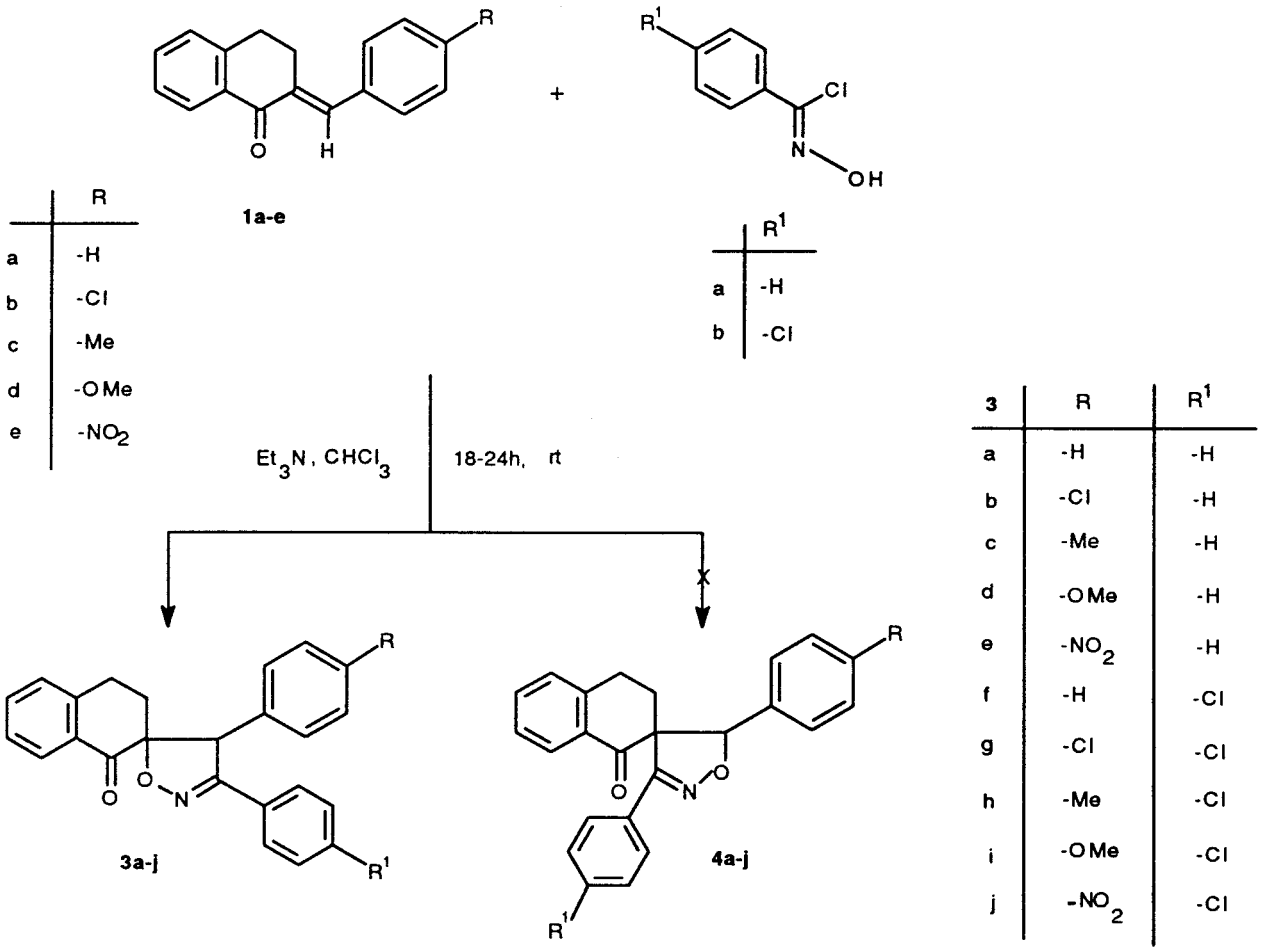

SCHEME 1

thin-layer chromatography (TLC) and mass spectral studies (Scheme 1). The reactions proceeded with good yields (68–84%), affording a series of novel spiro[3,4-diaryl-4,5-dihydroisoxazole-5, 2′-1′,2′,3′,4′-tetrahy-dro-1′-naphthalenone] adducts by the regioselective cycloaddition of the 1,3-dipole across the exocyclic double bond of the 2-arylmethylene-1,2,3,4-tetrahy-dro-1-naphthalenone in each case. The structure of each product **(3a–j)** and the regiochemistry of cycloaddition have been confirmed by spectroscopic data and by X-ray structure analysis of the cycloadduct **3f**. We could not find even a trace of the other regioisomer **(4a–j)** in all the cases that have been studied. The carbonyl absorption in the IR spectrum of the product **3a** appeared at 1682 cm^{-1} showing an increase of 21 cm^{-1} from the starting material at 1661 cm^{-1}, indicating the reduced conjugation of the carbonyl group. The ^1H NMR spectrum of **3a** exhibited multiplets at δ 1.92, 2.62, 2.93, and 3.20 due to four methylene protons, a singlet at δ 5.48 due to the benzylic proton, a multiplet at δ 6.88–7.60, and a doublet at δ 8.13 due to aromatic protons. The spiroheterocyclic structure **3a** was further confirmed by the presence of a signal at δ 88.53 due to the spiro carbon and a peak at δ 159.63, indicating the presence of a C=N–O carbon in the ^{13}C NMR spectrum. These chemical shift values are in good agreement with the values in the literature [10]. The regiochemistry of the cycloadduct **3a** was established by its mass spectrum. The absence of an (M^+-106) peak corresponding to the loss of benzaldehyde and the presence of a base peak at (M^+-160) clearly indicates that the C-terminal of the 1,3-dipole should be at-tached to the 4-position of the dihydroisoxazole ring. The structure and the regiochemistry of cycloaddition were further corroborated by the single crystal X-ray analysis of the compound **3f** (Figure 1).

Identical results were obtained with other derivatives of tetrahydro-1-naphthalenones in the cycloaddition reactions toward nitrile oxides, irrespective of the nature of the substituents present in the dipolarophile.

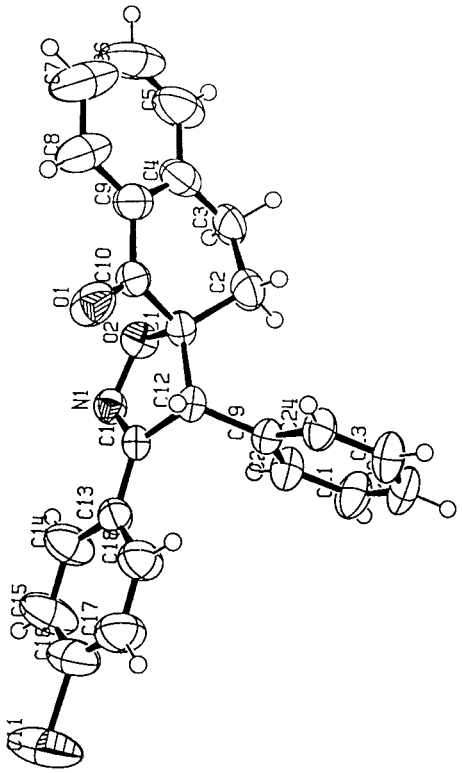

FIGURE 1 ORTEP diagram of structure 3f.

To conclude, efficient syntheses of novel spiroisoxazolines have been demonstrated by the highly regioselective cycloaddition reaction of 2-arylmethylene-1,2,3,4-tetrahydro-1-naphthalenone with nitrile oxides. Apart from the regioselectivity aspect, the spiroisoxazolines prepared should be of interest as precursors for the synthesis of a variety of amino alcohol derivatives that could be readily converted to β-lactams [13], and the regiochemistry of the cycloaddition reaction studied is independent of the electronic nature of the substituent on the arylidene ring of the dipolarophile.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a SHIMADZU FT-IR 8300 instrument. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard on a JEOL FX 90Q at 90 MHz and Bruker DPX200 at 50.3 MHz, respectively. Elemental analyses were carried out on a CEST 1106 instrument. Mass spectra were recorded on a Finnigan MAT-8230 GC-mass spectrometer. Column chromatography was performed on silica gel (100–200 mesh).

The starting materials 2-arylmethylene-tetrahydro-1-naphthalenone [8,12] and *N*-benzhydroxyimi-

TABLE 1 Spiroisoxazolines **3a–j** Prepared

					Analysis Calcd/Found		
Product	*Reaction Time (h)*	*Yield (%)*	*m.p. (°C)*	*Molecular Formula*	*C*	*H*	*N*
3a	24	70	178–179	$C_{24}H_{19}NO_2$	81.55	5.42	3.96
					81.23	5.35	4.02
3b	18	82	111–113	$C_{24}H_{18}NO_2Cl$	74.40	4.69	3.62
					74.12	4.62	3.68
3c	30	68	125–127	$C_{25}H_{21}NO_2$	81.71	5.76	3.81
					81.45	5.64	3.75
3d	36	70	128–130	$C_{25}H_{21}NO_3$	78.30	5.52	3.65
					78.12	5.41	3.70
3e	36	72	140–142	$C_{24}H_{18}N_2O_4$	72.34	4.56	7.03
					71.99	4.52	7.08
3f	24	78	164–166	$C_{24}H_{18}NO_2Cl$	74.40	4.69	3.62
					74.12	4.68	3.60
3g	20	84	119–121	$C_{24}H_{17}NO_2Cl_2$	68.40	4.07	3.33
					68.22	3.95	3.27
3h	30	72	127–129	$C_{25}H_{20}NO_2Cl$	74.79	5.03	3.49
					74.76	4.94	3.55
3i	36	76	130–132	$C_{25}H_{20}NO_3Cl$	71.92	4.83	3.36
					71.72	4.71	3.31
3j	42	70	145–147	$C_{24}H_{17}N_2O_4Cl$	66.65	3.97	6.48
					65.56	3.92	6.54

TABLE 2 Spectral Date for Spiroisoxazolines **3a–j**

Product	*IR (KBr) $V_{c=0}$ (cm^{-1})*	*MS (70 eV m/z) (M^+, $M^+ - 160$)*	*^1H NMR ($CDCl_3$/TMS δ) J (Hz)*
3a	1682	353, 193	1.92 (m, 1H), 2.62 (m, 1H), 2.93 (m, 1H), 3.20 (m, 1H), 5.48 (s, 1H), 6.88–7.6 (m, 13H), 8.13 (d, $J = 7.8$, 1H)
3b	1691	387, 227	1.94 (m, 1H), 2.71 (m, 1H), 2.96 (m, 1H), 3.14 (m, 1H), 5.51 (s, 1H), 6.76–7.72 (m,12H), 8.12 (d, $J = 7.9$, 1H)
3c	1690	367, 207	1.89 (m, 1H), 2.32 (s, 3H), 2.66 (m, 1H), 2.94 (m, 1H),3.21 (m, 1H), 5.53 (s, 1H), 6.79–7.65 (m, 12H), 8.14 (d, $J = 7.8$, 1H)
3d	1693	383, 223	1.97 (m, 1H), 2.71 (m, 1H), 2.88 (m, 1H), 3.09 (m, 1H), 3.74 (s, 3H), 5.48 (s, 1H), 6.87–7.66 (m, 12H), 8.12 (d, $J = 7.8$, 1H)
3e	1689	398, 238	1.93 (m, 1H), 2.66 (m, 1H), 2.84 (m, 1H), 3.05 (m, 1H), 5.65 (s, 1H), 7.01–7.87 (m, 10H), 8.17 (d, $J = 7.8$, 1H), 8.27 (d, $J = 7.9$, 2H)
3f	1683	387, 227	1.95 (m, 1H), 2.61 (m, 1H), 2.91 (m, 1H), 3.10 (m, 1H), 5.48 (s, 1H), 6.81–7.61 (m, 12H), 8.10 (d, $J = 7.8$, 1H)
3g	1690	421, 261	1.85 (m, 1H), 2.67 (m, 1H), 2.96 (m, 1H), 3.30 (m, 1H), 5.42 (s, 1H), 6.94–7.56 (m, 11H), 8.08 (d, $J = 7.8$, 1H)
3h	1693	401, 241	1.92 (m, 1H), 2.33 (s, 3H), 2.64 (m, 1H), 2.95 (m, 1H), 3.11 (m, 1H), 5.50 (s, 1H), 6.82–7.64 (m, 11H), 8.13 (d, $J = 7.9$, 1H)
3i	1691	417, 257	1.93 (m, 1H),2.68 (m, 1H), 2.93 (m, 1H), 3.14 (m, 1H), 3.73 (s, 3H), 5.47 (s, 1H), 6.89–7.64 (m, 11H), 8.14 (d, $J = 7.7$, 1H)
3j	1687	432, 272	1.97 (m, 1H), 2.70 (m, 1H), 2.94 (m, 1H), 3.07 (m, 1H),5.66 (s, 1H), 6.81–7.69 (m, 9H), 8.12 (d, $J = 7.8$, 1H), 8.27 (d, $J = 8.0$, 2H)

TABLE 3 ^{13}C NMR Spectral Data for Spiroisoxazolines **3a–j**

Product	*^{13}C NMR ($CDCl_3$/TMS) ppm*
3a	25.78, 29.01, 55.30, 88.53, 126.73, 127.88, 127.99, 128.66, 128.86, 128.99, 129.49, 129.63, 130.04, 130.33, 133.47, 134.59, 143.32, 159.30, 191.12
3b	25.77, 29.03, 55.27, 88.13, 126.60, 127.54, 127.93, 128.70, 128.82, 128.83, 129.40, 129.63, 129.74, 130.08, 133.30, 134.26, 143.13, 159.28, 191.55
3c	25.70, 26.20, 29.55, 54.39, 88.15, 126.19, 126.95, 128.42, 128.52, 129.59, 130.48, 130.62, 132.84, 133.28, 133.98, 134.96, 136.42, 143.45, 158.19, 192.00
3d	25.46, 29.64, 55.24, 55.54, 89.17, 126.93, 127.12, 128.18, 128.80, 128.92, 129.17, 129.44, 130.51, 134.01, 135.95, 136.77, 143.55, 150.11, 159.08, 191.51
3e	27.20, 28.78, 55.32, 85.15, 113.93, 126.83, 126.95, 128.05, 128.13, 128.39, 131.56, 131.73, 133.07, 133.52, 133.64, 136.65, 143.05, 159.94, 191.84
3f	25.41, 29.69, 54.82, 89.07, 126.83, 126.99, 128.19, 128.65, 128.74, 128.92, 129.45, 130.47, 131.10, 132.65, 134.27, 136.17, 143.45, 158.87, 191.21
3g	25.47, 29.64, 55.66, 88.90, 126.85, 127.55, 127.97, 128.46, 128.56, 128.75, 129.03, 129.22, 129.92, 130.61, 133.87, 134.41, 143.54, 159.96, 191.64
3h	25.27, 27.00, 29.54, 54.06, 88.92, 126.68, 126.84, 128.04, 128.59, 128.77, 129.30, 130.32, 130.95, 132.51, 133.96, 134.12, 136.02, 143.30, 158.72, 191.04
3i	25.36, 29.99, 56.00, 58.64, 88.63, 127.55, 127.96, 128.35, 128.49, 128.76, 128.97, 129.54, 130.02, 130.82, 132.68, 134.21, 143.69, 155.24, 159.63, 191.93
3j	25.16, 29.67, 54.70, 89.14, 126.97, 127.10, 128.14, 128.21, 128.51, 129.39, 129.96, 130.20, 131.56, 133.55, 134.15, 141.57, 143.11, 158.37, 190.45

noyl chloride [14] were prepared according to procedures in the literature.

Reaction of 2-arylmethylene-1,2,3,4-tetrahydro-1-naphthalenone with nitrile oxides: General Procedure

To a solution of 2-arylmethylene-tetrahydro-1-naphthalenone (3 mmol) and the corresponding *N*-benzhydroxyiminoyl chloride (3 mmol) in dry chloroform, triethylamine (3.3 mmol) was added. The reaction mixture was stirred at room temperature until the disappearance of the starting materials, as monitored by TLC, was observed. After the reaction was over, the solution was filtered to remove triethylamine hydrochloride, and the solvent was evaporated under a vacuum. The resulting crude product was purified by column chromatography (hexane/ethylacetate, 9:1) and crystallization from (hexane/ether, 2:1). The reaction time, physical constants, and spectral details for **(3a–j)** are reported in Tables 1, 2, and 3.

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