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Note

A novel synthesis of spiroisoxazoles *via* 1,3-dipolar cycloaddition of nitrile oxide to 6-arylidene 6,7,8,9-tetrahydrobenzo-cyclohepten-5-one

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Synthesis of a series of spiroisoxazole derivatives have been accomplished in good yield by regioselective 1,3-dipolar cycloaddition of nitrile oxide to 6-arylidene-3-methyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one. The antimicrobial activity of these compounds have been carried out.

Keywords: Benzosuberones, nitrile oxide, 1,3-dipolar cyclo-addition, spiroisoxazoles antimicrobial activity

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1,3-Dipolar cycloaddition of nitrile oxide to an alkene for the synthesis of five membered heterocycles[1] is a classic reaction in organic chemistry. Since the product isoxazolines are useful intermediates in the preparation of bifunctional compounds[2] like β-hydroxy ketones, β-hydroxy nitriles and γ-amino alcohols. Generally, benzonitrile oxide was obtained in two steps, by chlorinating or brominating either *E*- or *Z*-benzaldoxime with NCS (ref. 3) or NBS (ref. 4) and subsequently dehydrohalogenating with base[5]. Occasionally, side reactions occur with the use of triethyl amine, resulting in the formation of adducts with the hydroximoyl halide[6]. Prompted by these observations, we wish to report herein a new simple and efficient method for the direct conversion of aldoximes into their nitrile oxides in one step using NCS and basic alumina instead of triethyl amine, which is inert base towards nitrile oxide.

In an attempt to evaluate the effect of the presence of electron donating/withdrawing groups a direct conjugation with the double bond of the dipolarophile on the regioselectivity in the cycloaddition reactions, the reactions of nitrile oxide with 6-arylidene-3-methyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-ones were studied. 6-Arylidene-3-methyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-ones **2a-h** (ref. 7) obtained by the condensation of 3-methyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*] cyclohepten-5-one **1a,b** (ref. 8) with appropriate aromatic aldehyde in alkaline medium.

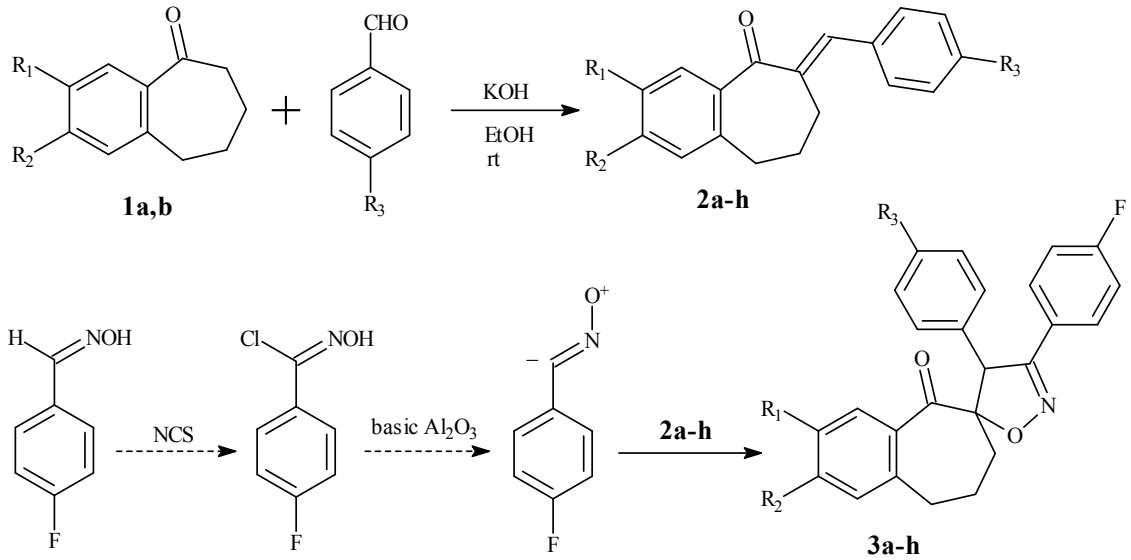
The reaction of 6-arylidene-3-methyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*] cyclohepten-5-one **2a-h** with 4-fluorobenzohydroximoyl chloride in the presence of basic alumina gave the 3′-(4-fluorophenyl)-3-methyl-4′-phenylspiro[6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-6,5′-(4′,5′-dihydroisoxazole)]-5-one **3a-h**. The 4-fluorobenzo hydroximoyl chloride was obtained *in situ* from the reaction of 4-fluoro-benzaldoxime with NCS.

The reaction pathway follows the preliminary formation of 4-fluoro benzohydroximoyl chloride of 4-fluorobenzaldoxime followed by dehydrochlorination to give the 4-fluorobenzonitrile oxide as shown in **Scheme I**. This nitrile oxide on addition to the arylidene double bond of **2a-h** via 1,3-dipolar cycloaddition gave the corresponding spiroisoxazoles **3a-h**.

The structures of each compound **3a-h** have been confirmed by spectroscopic data. The ^{1}H NMR spectrum of compound **3a** exhibited a singlet at δ 5.70 due to benzylic proton and the mass spectrum further confirms the cycloadduct **3a**.

Biological evaluation

All the compounds were screened for their antimicrobial activity at a concentration of 40 μg/well in agar media[9] using doxycyclin in antibacterial and nalidixic acid in antifungal activity as reference compounds. Compounds **3a** (8 mm), **3b** (10 mm), and **3c** (13 mm) showed moderate to good activity in terms of diameter of the zone of inhibition as compared with doxycyclin (16 mm) against gram +ve bacterium *Bacillus suffilis*. Compound **3a** showed moderate activity 11 mm as compared with doxy-cyclin (20 mm) against gram –ve bacterium *E. coli*, while the other compounds not showed the activity against *Bacillus suffilis* and *E. coli*. In the case of antifungal activity all the compounds were found ineffective against the fungus *Trichoderma* species.



a) $R_1 = CH_3$, $R_2 = R_3 = H$
b) $R_1 = R_2 = CH_3$, $R_3 = H$
c) $R_1 = CH_3$, $R_2 = H$, $R_3 = OCH_3$
d) $R_1 = R_2 = CH_3$, $R_3 = OCH_3$
e) $R_1 = CH_3$, $R_2 = H$, $R_3 = Cl$
f) $R_1 = R_2 = CH_3$, $R_3 = Cl$
g) $R_1 = CH_3$, $R_2 = H$, $R_3 = F$
h) $R_1 = R_2 = CH_3$, $R_3 = F$

Scheme I

Experimental Section

Melting points were determined using Gallankamp apparatus and are uncorrected. IR spectra are recorded on a FT-IR 1605 Perkin-Elmer. ^{1}H NMR in $CDCl_3$ on a Varian FT-80A spectrometer with TMS as internal standard. Mass spectra were taken on a VG-micromass 7070H mass spectrometer. TLC was run on silica gel G coated plates and iodine vapour as visualizing agent.

General procedure for the synthesis of 3′-(4-fluorophenyl)-3-methyl-4′-phenyl spiro[6,7,8,9-tetrahydro-5*H*-benzo[*a*]cycloheptene-6,5′-(4′,5′-dihydroisoxazole)]-5-one 3a. A mixture of 6-phenylidene-3-methyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*] cyclohepten-5-one **2a** (0.262 g, 1.0 mmole), 4-fluorobenzaldoxime (0.140 g, 1.0 mmole), NCS (0.200 g, 1.5 mmole) and basic alumina (0.30 g) in dry chloroform (10 mL) was stirred at room temperature for 12 hr. The reaction mixture was filtered and the filtrate was concentrated and purified by column chromatography (60-120 mesh Silica gel) to furnish **3a**, Yield: 0.240 g (60%), liquid, IR (neat): 1690 (C=O), 1609 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.35-2.58 (5H, m, 3-CH_3 & 8-CH_2), 2.62-2.78 (2H, m, 7-CH_2), 2.90-3.10 (2H, m, 9-CH_2), 5.70 (1H, s, 4′-CH), and 7.00-7.60 (12H, m, ArH); MS: *m/z* 399 (M^+). Anal. Found: C, 78.12; H, 5.54; N, 3.47. $C_{26}H_{22}NFO_2$ requires C, 78.19; H, 5.51; N, 3.50%.

3b: Yield 62%, liquid, IR (neat): 1685 (C=O), 1609 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.30 (6H, s, 2 & 3-CH_3), 2.40-2.50 (2H, m, 8-CH_2), 2.60-2.70 (2H, m, 7-CH_2), 2.90-3.10 (2H, m, 9-CH_2), 5.70 (1H, s, 4′-CH), and 6.90-7.60 (11H, m, ArH); MS: *m/z* 413 (M^+). Anal. Found: C, 78.40; H, 5.83; N, 3.40. $C_{27}H_{24}NFO_2$ requires C, 78.45; H, 5.81; N, 3.38%.

3c: Yield 56%, liquid, IR (neat): 1693 (C=O), 1604 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.30-2.50 (5H, m, 3-CH_3 & 8-CH_2), 2.60-2.75 (2H, m, 7-CH_2), 2.90-3.10 (2H, m, 9-CH_2), 3.92 (3H, s, -OCH_3), 5.63 (1H, s, 4′-CH), and 6.70-7.50 (11H, m, ArH); MS: *m/z* 429 (M^+). Anal. Found: C, 75.54; H, 5.55; N, 3.23. $C_{27}H_{24}NFO_3$ requires C, 75.52; H, 5.59; N, 3.26%.

3d: Yield 59%, liquid, IR (neat): 1689 (C=O), 1606 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.30-2.50 (8H, m, 2,3-CH_3 & 8-CH_2), 2.60-2.70 (2H, m, 7-CH_2), 2.90-3.10 (2H, m, 9-CH_2), 3.90 (3H, s, -OCH_3), 5.63 (1H, s, 4′-CH), 6.70-7.50 (10H, m, ArH); MS: *m/z* 443 (M^+). Anal. Found: C, 75.81; H, 5.83; N, 3.10. $C_{28}H_{26}NFO_3$ requires C, 75.84; H, 5.86; N, 3.16%.

3e: Yield 53%, liquid, IR (neat): 1691 (C=O), 1602 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.30-2.50 (5H, m, 3-CH_3 & 8-CH_2), 2.62-2.78 (2H, m, 7-CH_2), 2.90-3.10

(2H, m, 9-CH_2), 5.65 (1H, s, 4′-CH) and 7.00-7.60 (11H, m, ArH); MS: *m/z* 433 (M^+). Anal. Found: C, 71.93; H, 4.80; N, 3.21. $C_{26}H_{21}NClFO_2$ requires C, 72.05; H, 4.84; N, 3.23%.

3f: Yield 55%, liquid, IR (neat): 1685 (C=O), 1604 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): 2.30 (6H, s, 2 & 3-CH_3), 2.38-2.48 (2H, m, 8-CH_2), 2.62-2.70 (2H, m, 7-CH_2), 2.92-3.05 (2H, m, 9-CH_2), 5.68 (1H, s, 4′-CH) and 6.90-7.50 (10H, m, ArH); MS: *m/z* 447 (M^+). Anal. Found: C, 72.43; H, 5.17; N, 3.15. $C_{27}H_{23}NClFO_2$ requires C, 72.48; H, 5.14; N, 3.13%.

3g: Yield 52%, liquid, IR (neat): 1689 (C=O), 1606 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): 2.30-2.50 (5H, m, 3-CH_3 & 8-CH_2), 2.62-2.78 (2H, m, 7-CH_2), 2.90-3.10 (2H, m, 9-CH_2), 5.68 (1H, s, 4′-CH) and 7.00-7.60 (11H, m, ArH); MS: m/z 417 (M^+). Anal. Found: C, 74.94; H, 5.00; N, 3.38. $C_{26}H_{21}NF_2O_2$ requires C, 74.82; H, 5.03; N, 3.35%.

3h: Yield 53%, liquid, IR (neat): 1691 (C=O), 1606 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): 2.30-2.50 (8H, m, 2,3-CH_3 & 8-CH_2), 2.60-2.75 (2H, m, 7-CH_2), 2.90-3.10 (2H, m, 9-CH_2), 5.68 (1H, s, 4′-CH), and 6.90-7.50 (10H, m, ArH); MS: *m/z* 431 (M^+). Anal. Found: C, 75.10; H, 5.35; N, 3.22. $C_{27}H_{23}NF_2O_2$ requires C, 75.17; H, 5.33; N, 3.24%.

In conclusion, a facile and effective procedure is developed to convert hydroximoyl chloride into the corresponding nitrile oxide that in turn affords spiroisoxazoles via 1,3-dipolar cycloaddition. The study further amply indicated that the regiochemistry of the cycloaddition is independent of the electronic nature of the substituent on the arylidene ring of the dipolarophile.

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References

1 (a) Padwa A, *1,3-Dipolar Cycloadition Chemistry,* Wiley-Interscience, New York, Vol.1 & 2, **1984**.
(b) Curran D P, *Advances in Cycloaddition,* JAI press inc, Greenwich, Vol.1, **1988** and Vol.2, **1990**.

2 (a) Panek J S & Beresis R T, *J Am Chem Soc,* 115, **1993**, 7898.
(b) Das N B & Torssel K B G, *Tetrahedron,* 39, **1983**, 2247.

3 (a) Stevens R V, *Tetrahedron,* 32, **1976**, 1599.
(b) Liu K C, Shelton B R & Howe R K, *J Org Chem,* 45, **1980**, 3916.

4 (a) Grundmann C & Richter R, *J Org Chem,* 32, **1967**, 476.
(b) Yamakawa M, Kubota T, Akazawa H & Tanaka I, *Bull Chem Soc Japan,* 41, **1968**, 1046.

5 (a) Huisgen R & Mack W, *Tetrahedron Lett,* 17, **1961**, 583.
(b) Huisgen R, Mack W & Anneser E, *Tetrahedron Lett,* 17, **1961**, 587.
(c) Bast K, Christl M, Huisgen R & Mack W, *Chem Ber,* 106, **1973**, 3312.

6 (a) Caramella P, Corsaro A, Compagnini A & Albini F M, *Tetrahedron Lett,* 24, **1983**, 4377.
(b) Wieland H & Hochtlen A, *Liebigs Ann,* 505, **1933**, 237.
(c) Quilico A, Gaudiano G & Ricca A, *Gazz Chim Ital,* 87, **1957**, 638.
(d) Grundmann C, Mini V, Dean J M & Frommeld H D, *Liebigs Ann,* 687, **1965**, 191.

7 Peesapati V, Anuradha K & Sreelakshmi P, *Synth Commun,* 29, **1999**, 4381.

8 (a) Sen Gupta S G & Parimal Krishna Sen, *Sci Cult,* 28, **1992**, 343.
(b) Somerville L F & Allen C F H, *Org Synth,* 2, **1943**, 81.
(c) Gilmore Jr R C & Horton W J, *J Am Chem Soc,* 73, **1951**, 1411.

9 Kvanagh C, *Anal Microbial,* (Academic Press, New York), **1963**, 249.