The Regiospecific Synthesis of Some New 3,5-Disubstituted Isoxazoles

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The compounds with isoxazole moiety have many pharmacological, biological and industrial applications, specifically their antiviral activity. In this research work, seven new compounds of 3,5-disubstituted isoxazoles were synthesized. Propargyl alcohol (**1**) reacted with benzoyl chloride to give propargylphenylcarboxylate (**2**). Then, the aldehydes (**3a-3g**) were converted to the related oximes (**4a-4g**) and nitrileoxides *in situ* by NaOCl, consequently. Reaction of compound **2** with nitrileoxides in a [3+2] cycloaddition reaction gave regiospecifically isoxazoles (**5a-5g**). ^{1}H NMR, ^{13}C NMR, FT-IR, and elemental analyses confirmed the structure of the synthesized compounds.

Keywords: Isoxazoles; Propargyl alcohol; [3+2] cycloaddition.

INTRODUCTION

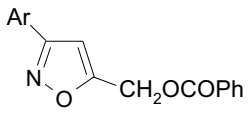
Isoxazoles are a large group of compounds, a number of which display interesting medicinal or agricultural activity or have some other industrial utility.[1] Various pharmacologically important isoxazoles with antibacterial, antiviral, antiinflammatory, antidiabetic, antifungal, antiparkinson, antihypertensive and antitumor activity have already been reported.[2] Isoxazoles are unique in their chemical behavior, not only among heterocyclic compounds in general, but also among related azoles. This is because isoxazoles possess the typical properties of the aromatic system, which are in fact rather pronounced in these derivatives, together with high lability of the ring under certain conditions, particularly at the nitrogen-oxygen bond.[2] They were first synthesized in 1903.[3] The preparation of several isoxazoles with antipicornavirus activity has also been achieved by G. D. Diana et al.[4,5] Recently, we synthesized new analogues of isoxazoles and studied their electrochemical behaviours.[6,7] This work describes the synthesis of some new members of the isoxazole family with a structure which has two substitutions in the 3 and 5 positions.

RESULTS AND DISCUSSION

Several methods exist for the synthesis of isoxazole rings. The most important and the most used method is the [3+2] cycloaddition reaction. In this approach, the isoxazole ring was obtained by using an alkyne and a nitriloxide, which are produced by oxidation of oximes. In this method, the isoxazole ring was obtained regiospecifically (Scheme V). Therefore, for the synthesis of the isoxazole ring, propargyl alcohol was protected by benzoyl chloride as a suitable protecting group to produce propargylphenyl carboxylate (**2**) in high yield (Scheme II).[8,9] If the hydroxyl group of propargyl alcohol is not protected, it will oxidize in the next step. Then, the aldehydes (**3a-3g**) are converted to the oximes (**4a-4g**) in high yield by $NH_2OH.HCl$ in pyridine as a solvent (Scheme III). The obtained data of oximes are listed in Table 1.

In the next step, the obtained oximes (**4a-4g**) were converted to the related nitrileloxids *in situ* with NaOCl. Then, reaction of nitrileoxides with propargylphenyl carboxylate (**2**) by a [3+2] cycloaddition reaction gave the related isoxazoles (**5a-5g**) in high yields (Scheme IV).[10] The

Scheme I



Scheme II

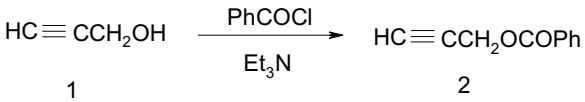


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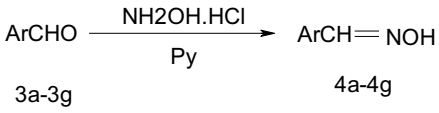
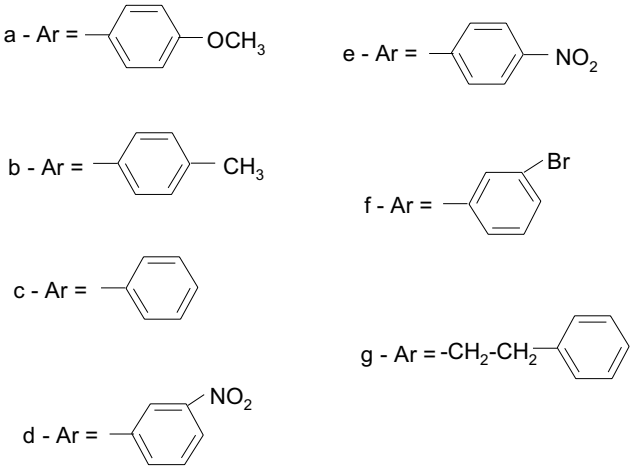
Table 1. Characterization of synthesized Ar-CH = NOH

Entry	Ar	Yield (%)	m.p. (°C)	FT-IR (cm^{-1})
4b	4-methylphenyl	87	74	3600-3000, 2950, 1650, 1550, 1280, 1200, 1100, 950, 865-810, 700
4c	phenyl	80	liquid	3500-2500, 1600, 1575, 1490, 1410, 1270, 1170, 1150, 920
4d	3-nitrophenyl	90	122	3500-3200, 1615-1530, 1345, 1300, 1100, 935, 835, 800, 750, 700.
4e	4-nitrophenyl	96	130	3500-3200, 1600, 1530, 1345, 1100, 840, 745
4f	3-bromophenyl	91.5	80	3100-2300, 1620, 1585, 1535, 1475, 1415, 1310, 1200, 106, 970, 900.
4g	2-phenylethyl	89	74	3400-2400, 1600, 1490, 1420, 1300, 1065, 900, 750, 690.

Scheme III





synthesized isoxazoles were purified by preprative T.L.C. and characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and elemental analyses.

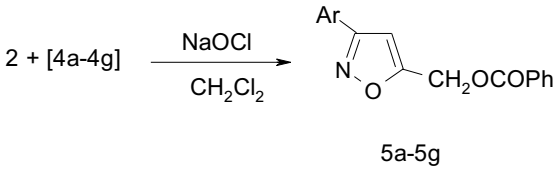
EXPERIMENTAL

Instruments and materials

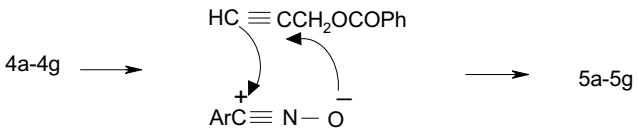
Melting points were determined using an Electrothermal 9100 apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker (400 MHz) in $CDCl_3$. FT-IR spectra were recorded on a Shimadzu IR-408 spectrophotometer. Elemental analyses were performed by a Heraus CHN-O-RAPID instrument.

All chemicals were regeant grade materials purchased from Merck and used without further purification.

Scheme IV



Scheme V



Preparation of propargylphenylcarboxilate (2)

To a mixture of propargyl alcohol (**1**) (9.97 g, 0.18 mol), Et_3N (20.6 g, 0.20 mol) and benzene (50 mL) was slowly added PhCOCl (25.0 g, 0.18 mol) at 0-5 °C. The mixture was stirred at room temperature for 2 h, filtered and evaporated. The residue was distilled at reduced pressure (12 mmHg/37 °C) to give 25.5 g (94%) of **2** as colorless oil. FT-IR (neat, cm^{-1}) 3450, 3300, 3100, 2950, 1730 (C=O), 1600, 1450, 1260, 1100.

Preparation of 4-methoxybenzaldoxime (4a)[11]

A solution of 4-methoxy benzaldehyde (11.15 g, 0.08 mol), hydroxylamine hydrochloride (25.25 g, 0.36 mol), and pyridine (25 mL) was refluxed for 2 h and the solvent evaporated. The reaction mixture was dissolved in water and the aqueous layer extracted with ethylacetate (EtOAc) 2 times. The organic layer was dried with Na_2SO_4, filtered and evaporated. Recrystallization of solid residue from EtOAc and petroleum ether gave 8.93 g (80%) of **4a**. m.p. 60 °C; FT-IR (KBr, cm^{-1}) 3200, 1610, 1570, 960, ^{1}H NMR

($CDCl_3$, ppm) 3.65 (s, 3H, CH_3), 6.7 (d, J = 11 Hz, 2H, Ar-H), 7.35 (d, J = 11 Hz, 2H, Ar-H), 8.0 (s, 1H, CH), 9.0 (s, 1H, OH).

Preparation of compounds (4b-4g)

These compounds were prepared with the described method for **4a** and data are listed in Table 1.

Preparation of 3-(4-methoxyphenyl)-5-[methyl(phenylcarboxylate)]isoxazole (5a)

To a mixture of 4-methoxybenzaldoxime (**4a**) (11.36 g, 0.08 mol) and **2** (8.24 g, 0.11 mol) in CH_2Cl_2 (125 mL) was added dropwise NaOCl (150 mL, 20%) and stirred at room temperature for 48 h. The organic phase was separated, dried and the solvent removed in vacuum. The residue was purified by column chromatography on silica gel 100 (eluent CH_2Cl_2 - petroleum ether 4:1 (v/v); R_f = 0.5) to give **5a** (78%) as a white solid. m.p. 109 °C; FT-IR (KBr cm^{-1}): 3100, 3000, 2900, 1720 (C=O), 1605, 1525, 1420, 1300, 1250, 1160, 1085, 1020, 900, 810, 700; ^{1}H NMR ($CDCl_3$, ppm) 3.9 (s, 3H, CH_3), 5.5 (s, 2H, CH_2), 6.7 (s, 1H, isoxazole-H), 7-8.1 (m, 9H, Ar-H); ^{13}C NMR ($CDCl_3$, ppm) 55.7, 57.3, 104.5, 114.7, 121.6, 128, 128.6, 128.9, 129.2, 130.3, 133.9, 163.1, 166, 167.4; Anal. Calc. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53; Found: C, 69.59; H, 4.85; N, 4.37.

Preparation of 3-(4-methylphenyl)-5-[methyl(phenylcarboxylate)]isoxazole (5b)

This compound was prepared with the described method for **4a**. Yield 82%; m.p. 73 °C; FT-IR (KBr, cm^{-1}): 3100, 2900, 1720, 1600, 1445, 1425, 1260, 1310, 1185, 1100, 1060, 910, 810, 700; ^{1}H NMR ($CDCl_3$, ppm) 2.42 (s, 3H, CH_3), 5.5 (s, 2H, CH_2), 6.7 (s, 1H, isoxazole-H), 7.25-8.15 (m, 9H, Ar-H); ^{13}C NMR ($CDCl_3$, ppm) δ: 21.8, 57.3, 102.6, 127.1, 128.9, 129.5, 130, 130.2, 132, 133.9, 140.7, 164, 166, 167.4; Anal. Calc. for $C_{18}H_{15}NO_3$: C, 93.71; H, 5.15; N, 4.78; Found: C, 73.41; H, 5.14; N, 4.78.

Preparation of 5-isoxazolemethanol, 3-phenyl, 5-benzoate (5c)[12]

This compound was prepared with the described method for **4a**, Yield 85%; m.p. 76 °C; FT-IR (KBr, cm^{-1}): 3100, 2950, 1720, 1605, 1440, 1400, 1360, 1266, 1100, 900. ^{1}H NMR ($CDCl_3$, ppm) 5.50 (s, 2H, CH_2), 6.72 (s, 1H, isoxazole-H), 7.25-8.15 (m, 10H, Ar-H); ^{13}C NMR ($CDCl_3$, ppm) 57.3, 102.7, 108, 119, 127.2, 128.9, 129.3, 130.2, 130.5, 133.9, 148, 163, 170.3; Anal. Calc. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02; Found: C, 73.14; H, 4.65; N, 4.94.

Preparation of 3-(3-nitrophenyl)-5-[methyl(phenylcarboxylate)]isoxazole (5d)

This compound was prepared with the described method for **4a**, Yield 75%, m.p. 71 °C; FT-IR (KBr, cm^{-1}) 3050, 2090, 1720, 1610, 1525, 1445, 1345, 1260, 1100, 800, 700. ^{1}H NMR ($CDCl_3$, ppm) 5.6 (s, 2H, CH_2), 6.81 (s, 1H, isoxazole-H), 7.45-8.55 (m, 9H, Ar-H); ^{13}C NMR ($CDCl_3$, ppm) 57.2, 102.5, 105, 122.3, 125.1, 128.9, 129.2, 130, 130.3, 132.9, 134, 150, 155, 160, 169; Anal. Calc. for $C_{17}H_{12}N_2O_5$: C, 62.96; H, 3.73; N, 8.64; Found: C, 62.52; H, 3.58; N, 8.60.

Preparation of 3-(4-nitrophenyl)-5-[methyl(phenylcarboxylate)]isoxazole (5e)

This compound was prepared with the described method for **4a**, Yield 63%, m.p. 136 °C; FT-IR (KBr, cm^{-1}): 3100, 2950, 1725, 1590, 1510, 1425, 1345, 1310, 1260, 1100, 850, 700; ^{1}H NMR ($CDCl_3$, ppm) 5.55 (s, 2H, CH_2), 6.8 (s, 1H, isoxazole-H), 7.3-8.4 (m, 9H, Ar-H); ^{13}C NMR ($CDCl_3$, ppm) 57.4, 102.8, 114, 124.6, 127.1, 128.9, 130.2, 134, 135, 145, 157.5, 163, 167; Anal. Calc. for $C_{17}H_{12}N_2O_5$: C, 62.9; H, 2.73; N, 8.64; Found: C, 62.54; H, 3.61; N, 8.86.

Preparation of 3-(3-bromophenyl)-5-[methyl(phenylcarboxylate)]isoxazole (5f)

This compound was prepared with the described method for **4a**, Yield 56%, m.p. 50 °C. FT-IR (KBr, cm^{-1}), 3050, 2950, 1720, 1600, 1560, 1440, 1250, 1100, 700; ^{1}H NMR ($CDCl_3$, ppm) 5.5 (s, 2H, CH_2), 6.7 (s, 1H, isoxazole-H), 7.3-8.1 (m, 9H, Ar-H); ^{13}C NMR ($CDCl_3$, ppm) 57.2, 102.6, 108.2, 123.4, 125.8, 128.9, 129.5, 130.3, 130.9, 131.1, 133.5, 133.9, 161.8, 166.2, 168.1; Anal. Calc. for $C_{17}H_{12}NO_3Br$: C, 57.01; H, 3.38; N, 3.91; Found: C, 56.35; H, 3.31; N, 3.75.

Preparation of 3-(2-phenylethyl)-5-[methylphenylcarboxylate)]isoxazole (5g)

This compound was prepared with the described method for **4a**, Yield 71% as viscous oil. FT-IR (neat, cm^{-1}) 3050, 2900, 1720, 1600, 1580, 1490, 1430, 1100, 700. ^{1}H NMR ($CDCl_3$, ppm) 3 (s, 4H, CH_2-CH_2), 5.4 (s, 2H, CH_2), 6.2 (s, 1H, isoxazole-H), 7.2-8.15 (m, 10H, Ar-H); ^{13}C NMR ($CDCl_3$, ppm) 28.4, 34.8, 57.3, 104.5, 126.8, 128.8, 128.9, 129, 129.5, 130, 140.8, 163.9, 166.3, 166.8; Anal. Calc. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 5.60; Found: C, 74.14; H, 5.76; N, 5.39.

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REFERENCES

1. Lang, S.-A.; Lin, Y. Isoxazoles and Their Benzo Derivatives. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A.-R.; Ress, C.-W., Eds.; Pergamon Press: New York, 1984; Vol. 6, pp 127-145.
2. Kochetkov, N.-K.; Sokolov, S.-D. Recent Development in Isoxazole Chemistr. In *Advances Heterocyclic Chemistry*; Katritzky, A.-R., Ed.; Academic Press: New York, 1963; Vol. 2, pp 365-397.
3. Acheson, R.-M. *An Introduction to Chemistry of Heterocyclic Compounds*; John Wiley & Sons: New York, 1963; pp 1-15.
4. Diana, G.-D.; Mckinlay, M.-A.; Brsson, C.-J.; Zalag, E.-S.; Mirallco, J.-V.; Salvador, U.-J**.** *J. Med. Chem.* **1985**, *28*, 748.
5. Diana, G.-D.; Mckinlay, M.-A.; Otto, M.-J.; Akullian, V.; Oglesby, C. *J. Med. Chem.* **1985**, *28*, 1906.
6. Mirzaei, Y.-R.; Bavili-Tabrizi, S.; Hashemi-Gohare, M.; Zare-Neivizi, H.; Edjlali, L. *Org. Prep. Proced. Int.* **2003**, *35*, 207.
7. Edjlali, L.; Golabi, S.-M.; Rastgar-Mirzaei, Y. *Bull. Electrochem*. **2000**, *16*, 354.
8. Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S. *Synthesis* **1979**, 618.
9. Sankyo Co, Ltd. Jpn, *Chem. Abstr.* **1981**, *94*, 1397 81q.
10. Theobald, H. (ABSFA- G.), *Chem. Abstr.* **1979**, *91*, 140372 b.
11. Thomas, B.; Prathapan, S.; Sugunan, S. *Micropor. Mesopor. Mater.* **2005**, *79*, 21.
12. Mugnaini, E.; Grunanger, P. *Heterocyclic Syntheses with Propargyl Alcohol and Butynediol. II*; Oxford: New York, 1953.