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Synthesis and Pesticide Activity of some New Arylic and Pyridylic Oxime Ether Derivatives of Ionone

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Some oxime ether derivatives of α-ionone (4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one) have been synthesized. Reaction of 4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-ketoxime with various chloro and fluoro aromatic and hetero aromatic compounds gave the corresponding oxime ether derivatives *via* aromatic nucleophilic substitution (S_NAr). The structures of these compounds were elucidated by IR, ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectroscopic methods. All the compounds were screened *in vitro* against the common *pistachio psylla*, *Agonoscena pistaciae*, *fifth instar nymphs*. Results showed that compound 3c (LC50 value of 227.76 mg l^{-1}) was much more toxic to *fifth instar nymphs* of common *pistachio psylla* than compound 3a (LC50 = 1539.14 mg l^{-1}) and compound 3f (LC50 = 569.319 mg l^{-1}).

Keywords: Oxime ether, Pesticide, Synthesis, Ultrasonic irradiation, *Agonoscena pistaciae*

INTRODUCTION

The synthesis and study of oxime ether derivatives have attracted considerable interest in recent years due to their anticonvulsant, antimicrobial, antineoplastic, antifungal, antiprotozoan, antienteroviral and antibacterial activities [1-6]. Some oxime ether derivatives have also showed insecticidal, anticholinergic, and acaricidal activities [7-9]. A series of terpenoid juvenile hormone (JH) analogues have been studied and some of them such as methoprene are now in practical use for controlling some pests. A number of oxime ethers of terpenes are also known as insect growth regulators [10]. The significant pesticide activity of some oxime ether motivated us to study the pesticide activity of some new oxime ether derivatives from α-ionone (4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one). The chemical control is a common method in pest management. In this research, some oxime ethers of α-ionone are synthesized and susceptibility of the *fifth instar nymphs* of *Agonoscena pistaciae*, a key pest in pistachio orchards in Iran, to the selected compounds is investigated.

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EXPERIMENTAL

Melting points were determined in open capillary tubes by an Electro thermal IA 9000 melting point apparatus. FT-IR spectra of all the final products were recorded on a Bruker instrument by using the KBr self-supported pellet technique. The ^{13}C NMR, ^{1}H NMR spectra were recorded on a Bruker Avance-300 at 75 or 125, 500, 400 MHz. NMR spectra were obtained in the solution of DMSO-d_6 and $CDCl_3$ using tetramethylsilane (TMS) as internal standard. The ^{19}F NMR spectra were recorded at 470 MHz. In the ^{19}F NMR spectra, upfield shifts were quoted as negative and referenced to $CFCl_3$. Mass spectra were taken by a Micromass Platform II: EI mode (70 eV). Elemental analyses were obtained on an Exeter Analytical CE-440 elemental analyser. Medium pressure (‘flash’) column chromatography was performed using silica (Merck #60). Silica plates (Merck) were used for TLC analysis.

A) General Procedure for Preparation of 4-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-3-buten-2-ket Oxime (2)

To a solution of α-Ionone (4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one) (0.207 ml, 1 mmol) in dry and distilled ethyl alcohol (5 ml) was added hydroxylamine hydrochloride (0.104 g, 1.5 mmol). This reaction mixture was sonicated at 45 kHz and room temperature. After the completion of reaction as indicated by Thin Layer Chromatography (TLC), the reaction mixture was poured into water and extracted with diethyl ether (4 × 15 ml), dried over anhydrous $MgSO_4$, and concentrated in vacuum. An amber colored oily liquid was obtained and purified by column chromatography.

B) General Procedure for Preparation of 4-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-3-buten-2-ket Oxime-NO-aryl Ethers (3a-f)

To a solution of 4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-ketoxime (1 mmol) in THF-dry (25 ml) was added K_2CO_3 (1.5 mmol). The reaction mixture was stirred for another 1 h, which was followed by addition of the appropriate aryl halide (1 mmol). After the completion of reaction as indicated by Thin Layer Chromatography (TLC), the reaction mixture was poured into water and extracted with dichloromethane (4 × 15 ml), dried ($MgSO_4$) and evaporated to give the product purified by column chromatography on silica gel.

(2E,3E)-4-(2,6,6-trimethylcyclohex-2-en-1-yl)but-3-en-2-one *O*-perchloropyridin-4-yl oxime (3a). Dark brown oil, (yield: 98%). IR (KBr, cm^{-1}): 1669.02, 1633.53, 1598.03, 1480, 1086.28, 790, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.4 (d, J_{HH} = 16.4 Hz, 1H, CH), 6.17 (dd, J_{HH} = 16 Hz, 1H, CH), 5.52 (m, 1H, CH), 2.33 (m, 1H, CH), 2.25 (s, 3H, CH_3), 2.05 (m, 3H, CH_3), 1.45 (m, 2H, CH_2), 1.25 (m, 2H, CH_2), 0.94 (s, 3H, CH_3), 0.86 (s, 3H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.9 (Ar-C), 161.9 (C=N), 149.2 (Ar-C), 142 (CH), 141.6 (CH), 126.9 (CH), 125.7 (CH), 122.2 (Ar-C), 54.7 (CH), 31.3 (CH_2), 27.8 (CH_3), 26.8 (CH_3), 23.0 (CH_3), 22.9 (CH_2), 11.8 (CH_3) ppm. UV (λ_{max} (nm)): 570, 450.

4-(((E)-((E)-4-(2,6,6-trimethylcyclohex-2-en-1-yl)but-3-en-2-ylidene)amino)oxy)benzonitrile (3b). Light brown oil, (yield: 89.39%). IR (KBr, cm^{-1}): 2225.32, 1636.51, 1602.04, 1446.6, 1161.57, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (d, J_{HH} = 8.8 Hz, 2H, Ar-H), 7.21 (d, J_{HH} = 9.2 Hz, 2H, Ar-H), 6.15 (d, J_{HH} = 16 H_Z, 1H, CH), 6.21 (d, J_{HH} = 16 Hz, 1H, CH), 5.38 (m, 1H, CH), 2.21 (m, 1H, CH), 2.07 (s, 3H, CH_3), 1.95 (m, 3H, CH_3), 1.37 (m, 2H, CH_2), 1.12 (m, 2H, CH_2), 0.84 (s, 3H, CH_3), 0.76 (s, 3H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.4 (Ar-C), 159.8 (C=N), 144.3 (CH), 133.7 (Ar-C), 132.8 (C-4), 122.3 (CH), 120.5 (CH), 119.2 (CN), 115.1 (Ar-C), 104.9 (Ar-C), 54.7 (CH), 31.4 (CH_2), 27.7 (CH_3), 26.8 (CH_3), 23.1 (CH_3), 22.8 (CH_2), 11.3 (CH_3) ppm. UV (λ_{max} (nm)): 560, 550, 450.

(2E,3E)-4-(2,6,6-trimethylcyclohex-2-en-1-yl)but-3-en-2-one *O*-perfluoropyridin-4-yl oxime (3c). Dark brown oil, (yield: 98%). IR (KBr, cm^{-1}): 1639.48, 1142.48, 1077.45, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.70 (d, J_{HH} = 15.5 Hz, 1H, CH), 6.22 (d, J_{HH} = 15.5 Hz, 1H, CH), 5.31 (m, 1H, CH), 2.35 (m, 1H, CH), 2.23 (s, 3H, CH_3), 2.10 (m, 3H, CH_3), 1.45 (m, 2H, CH_2), 1.25 (m, 2H, CH_2), 0.95 (s, 3H, CH_3), 0.85 (s, 3H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.4 (C=N), 143.1 (CH), 141.6 (Ar-CF), 139.3 (CH), 137.4 (Ar-C), 131.9 (Ar-CF), 132.9 (CH), 124.2 (CH), 121,3 (CH), 55.0 (CH), 32.1 (CH_2), 29.6 (CH_3), 27.0 (CH_3), 23.8 (CH_3), 22.8 (CH_2), 11.3 (CH_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ_F -85.1 (m, 2F), -158.4 (m, 2F) ppm. UV (λ_{max} (nm)): 415, 250.

(2E,3E)-4-(2,6,6-trimethylcyclohex-2-en-1-yl)but-3-en-2-one *O*-(2,4-dinitrophenyl) oxime (3d). Dark brown oil, (yield: 80.17%). IR ($CHCl_3$, cm^{-1}): 1670.61, 1549.40, 1375.68, 1106.26, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.91 (d, J_{HH} = 2.64 Hz, 1H, Ar-H), 8.44 (dd, J_{HH} = 8.44 Hz, 1H, Ar-H), 8.01 (d, J_{HH} = 9.3 Hz, 1H, Ar-H), 7.54 (d, J_{HH} = 6.02 Hz, 1H, CH), 6.25 (dd, J_{HH} = 16.7 Hz, 1H, CH), 5.43 (m, 1H, CH), 2.35 (m, 1H, CH), 2.35 (s, 3H, CH_3), 2.05 (m, 3H, CH_3), 1.47 (m, 2H, CH_2), 1.26 (m, 2H, CH_2), 0.93 (s, 3H, CH_3), 0.86 (s, 3H, CH_3) ppm.^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.7 (C=N), 143.1 (CH), 132.4 (CH), 130.8 (Ar-C), 129.2 (Ar-C), 128.8 (CH), 126 (CH), 122.4 (Ar-C), 122.0 (Ar-C), 117.2 (Ar-C), 54.4 (CH), 31.9 (CH_2), 28.9 (CH_3), 26.8 (CH_3), 23.7 (CH_3), 22.8 (CH_2), 11.4 (CH_3) ppm. UV (λ_{max} (nm)): 560, 555, 550, 545.

2-Fluoro-6-(((E)-((E)-4-(2,6,6-trimethylcyclohex-2-en-1-yl) but-3-en-2-ylidene) amino) oxy) benzonitrile (3e). Light brown oil, (yield: 80.9%). IR ($CHCl_3$, cm^{-1}): 2235.66, 1617.09, 1597.71, 1461.49, 1215.73, 1035.29, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.75 (d, J_{HH} = 9.03 Hz, 1H, Ar-H),

7.50 (dd, J_{HH} = 8.4 Hz, 1H, Ar-H), 7.41 (d, J_{HH} = 8.55 Hz, 1H, Ar-H), 6.85 (d, J_{HH} = 14.32 Hz, 1H, CH), 6.21 (dd, J_{HH} = 15.65 Hz, 1H, CH), 5.54 (m, 1H, CH), 2.34 (m, 1H, CH), 2.06 (s, 3H, CH_3), 1.47 (m, 3H, CH_3), 1.37 (m, 2H, CH_2), 1.26 (m, 2H, CH_2), 0.95 (s, 3H, CH_3), 0.87 (s, 3H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.7 (Ar-C), 165.2 (Ar-C), 161.2 (C=N), 141.4 (CH), 135.1 (CH), 134.97 (Ar-C), 128.8 (CH), 126.7 (CH), 111.1 (CN), 110.3 (Ar-C), 108.8 (Ar-C), 108.5 (Ar-C), 54.8 (CH), 31.3 (CH_2), 27.7 (CH_3), 26.8 (CH_3), 23.7 (CH_3), 22.9 (CH_2), 11.5 (CH_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ -106.39 (d, 1F, $^1J_{CF}$ = 5.7) ppm. UV (λ_{max} (nm)): 560, 555, 550, 545, 540, 535, 445.

2,3,5-Trifluoro-6-(4-(2,6,6-trimethylcyclohex-2-en-1-yl) but-3-en-2-ylidene) amino) oxy) isonicotinonitrile (3f). Dark brown oil, (yield: 80.2%). IR ($CHCl_3$, cm^{-1}): 2399.81, 1670.35, 1215.65, 1076.16, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.61 (d, J_{HH} = 15.82 Hz, 1H, CH), 6.26 (dd, J_{HH} = 15.88 Hz, 1H, CH), 5.40 (m, 1H, CH), 2.36 (m, 1H, CH), 2.26 (s, 3H, CH_3), 2.05 (m, 3H, CH_3), 1.46 (m, 2H, CH_2), 1.26 (m, 2H, CH_2), 0.93 (s, 3H, CH_3), 0.86 (s, 3H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.7 (C=N), 149.1 (Ar-CF), 137.1 (CH), 132.5 (Ar-C), 132.4 (Ar-CF), 131.9 (CH), 129.0 (Ar-CF), 122.6 (Ar-C), 121.4 (CH), 108.8 (Ar-CCN), 106.1 (CN), 54.6 (CH), 31.9 (CH_2), 29.6 (CH_3), 26.9 (CH_3), 23.8 (CH_3), 22.9 (CH_2), 11.2 (CH_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ -86.25 (mp, 1F), -131.73 (mp, 1F), -139.95 (mp, 1F) ppm. UV (λ_{max} (nm)): 560, 555, 550, 545, 535.

RESULTS AND DISCUSSION

In this research, we aimed to synthesize some oxime ether derivatives of α-ionone as potential pesticide agents. α-ionone oxime 2 was obtained by oximation of α-ionone 1 using hydroxylamine hydrochloride in dry and distilled EtOH under ultrasonic irradiation (Scheme 1). After cooling, the reaction mixture was poured into water and extracted with diethyl ether, dried over anhydrous $MgSO_4$, and concentrated in vacuum. In this process an amber colored oily liquid 2 was obtained (Scheme 1).

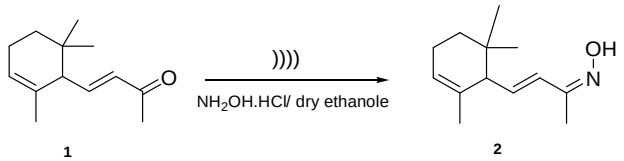
Aromatic nucleophilic substitution reaction of oximes 2 with pentachloropyridine, 4-flouorobenzonitrile, penta-fluoropyridine, 1-chloro-2,4-dinitrobenzene, 2,6-difluoro-benzonitrile, 5-cyano-2,3,4,5-tetrafluoropyridine in dry THF under reflux for appropriate time gave the corresponding new oxime ether derivatives 3a-f which were purified by column chromatography on silica gel (Scheme 2 and Table 1).

The oxime ether derivatives were identified as E-isomer by ^{1}H NMR analysis and their purity was established by thin-layer chromatography (TLC). Oxime ethers were synthesized with different aryl groups attached via oximino group to establish the contribution of the type of the substituted groups on pesticide activity. For this purpose, aromatic and heteroaromatic compounds with different substituents (chloro, fluoro, cyano and nitro) were used to obtain the oxime ethers (Table 1).

The oxime ether derivatives 3a-f were obtained in high yields. The structures of the compounds were confirmed by ^{19}F NMR, ^{1}H NMR, ^{13}C NMR, IR and UV spectroscopic data. Analytical and spectral data were in good agreement with the composition of the compounds. IR spectra of the compounds 3a-f showed a band in the range 1583-1680 cm^{-1} due to C=N stretch. Two bands in the range 1210-1325 and 1120-1150 cm^{-1} were assigned due to the C-O and C-N stretching vibrations of the compounds 3a-f, respectively. ^{1}H NMR spectra of compounds 3a-f showed the signals of the two methyl protons attached to sp^3 carbon as a singlet in the 0.76-0.87 ppm and 0.84-0.95 ppm regions, the signals of two methylene protons as multiples at = 1.12-1.26 and 1.37-1.46 ppm, the signals of the two methyl protons attached to sp^2 carbon as singlets in the 1.95-2.05 ppm and 2.06-2.26 ppm regions and the signal of sp^3 C-H at in the 2.21-2.35 ppm region. The ^{1}H NMR spectra also showed three signals in the regions 5.38-5.52 ppm, 6.00-6.25 ppm and 6.15-7.54 for vinyl protons. Aromatic hydrogens were observed with the expected chemical shift and integral values.

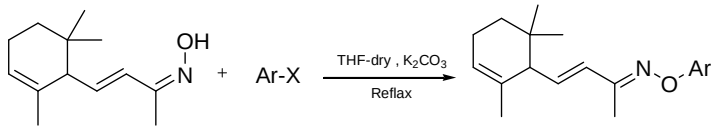
The compounds 3a-f in ^{13}C NMR spectra showed a signal at 156-167 ppm due to the C=N. The CH_2 carbons resonated at 23-32 ppm in all of the compounds. The other carbons resonated at their usual positions.

Identification of 3c, 3e and 3f was also carried out by ^{19}F NMR analysis, in which the resonance attributed to fluorine in compound 3e had a chemical shift of -106.39 ppm. In compound 3f, fluorine located ortho to nitrogen ring has a chemical shift of -86.20 ppm. The corresponding resonance for fluorines located *meta* to ring nitrogen (*ortho* to cyano group) in 3f occurs at -131.74 and -139.95 ppm. Compound



1 2

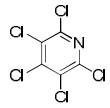
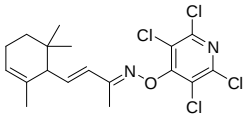
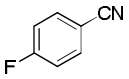
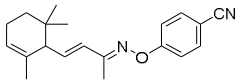
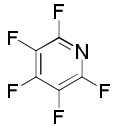
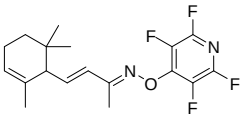
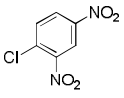
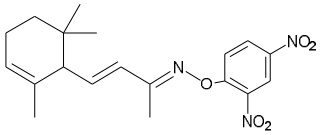
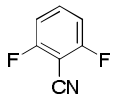
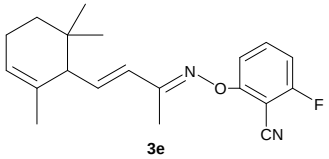
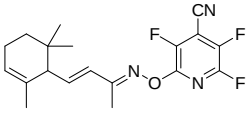
Scheme 2. Synthesis of α-ionone oxime



2 3a-f

Scheme 2. Synthesis of α-ionone oxime ether

Table 1. Reaction of Appropriate Aryl Halide with Ketoxime

Entry	Aryl halide	Product	Yield (%)
1		 **3a**	95
2		 **3b**	90
3		 **3c**	95
4		 **3d**	85
5		 **3e**	85
6		 **3f**	85

3c showed a signal at -88.31 ppm for fluorine atom located *ortho* to ring nitrogen and a signal at -156.42 ppm for fluorine atom located *meta* to nitrogen ring similar to the analogous system [11-13].

PESTICIDE ACTIVITY

To study the susceptibility of the *fifth instar nymphs* of the common *pistachio psylla* to the synthesized compounds, one-day-old *fifth instar nymphs* were transferred into Petri dishes and sprayed with 2 ml of aqueous emulsions of different concentrations of each compound. The spray was applied at 15 mbar using Potter Precision Spray Tower (Burkard Manufacturing Co. Ltd., Rickmansworth Herts, UK). The experiments were carried out with three replications each consisting of twenty nymphs. Treated nymphs were maintained in a climate chamber and reared on fresh leaves. Mortality counts were made after 24 h. Probit analysis was used for the estimation of LC_{50} by POLO-PLUS software.

In the first stage of screening, all the 6 compounds were evaluated against *fifth instar nymphs*. Based on the percentage of mortality, the compounds were ranked and three effective compounds were taken up for further detailed studies.

In the selected compound treatments, mortality of the *nymphs* was proportional to pesticide concentration and increased as concentration of the compound increased. Differences between mortality of the insecticides and control were also significant. Probit analysis revealed that compound 3c (LC_{50} value of 227.76 mg l^{-1}) was much more toxic to the *nymphs* of the common *pistachio psylla* than compound No 3a (LC_{50} = 1539.14 mg l^{-1}) and compound No 3f (LC_{50} = 569.319 mg l^{-1}).

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