Canadian Chemical Transactions

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 3 | Page 353-364

Research Article

DOI:10.13179/canchemtrans.2014.02.03.0115

Environmental Friendly Ultrasound Promoted Synthesis of Some Novel *N*-Thiocarbamoyl Piperidone Oxime Esters

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Received: *April 4, 2014* ***Revised:*** *May 18, 2014* ***Accepted:*** *May 18, 2014* ***Published:*** *May 19, 2014*

Abstract: Substituted *N*-thiocarbamoylpiperidone oxime esters were synthesized by the reaction of various piperidone oxime esters with substituted isothiocyanates. Reactions were carried out under ultrasonic and by conventional methods; it was found that ultrasound irradiations reduce the reaction time compared with conventional method. In addition to improvement in reaction time, the products were obtained in high yields and their structures were determined by FT-IR, NMR (^{1}H and ^{13}C) and mass spectrometry.

Keywords: *N*-Substituted Piperidones; Thiourea; Thiophosgene; Isothiocyanates; Sonication

1. INTRODUCTION

The piperidine ring is a ubiquitous structural feature of many natural alkaloids and drug candidates. The syntheses of N-substituted piperidones have been incorporated due to its importance as a synthetic building block in medicinal chemistry which expands considerable number of pharmacological agents. Some of N-substituted piperidone derivatives have demonstrated fascinating potential applications including anti-HIV, cytotoxins, 5α-reductase inhibitors, CARM1 inhibitors, anti-proliferative, antioxidant and antimicrobial activities [1-8].

In addition, piperidone oxime ethers and esters have received considerable attention over the past years because of their wide range of biological activities. In particular, oxime esters with free radical (nitrogen centered iminyl ($R_2C=N^{\cdot}$) radicals) molecular frameworks are used for the development of pharmaceutical agents for diverse applications [6,8,9].

Thiourea derivatives are valuable building blocks for the synthesis of five- and six-membered heterocycle and often display a wide range of biological activities [10]. Thiourea derivatives represent one of the most promising classes of anticancer agents with a wide range of activities against various leukemia and solid tumors [11]. Schwartz reported for the first time a potent and selective histamine H3 antagonist, which enhances the activity of histaminergic neurons by blocking auto receptors, leading to greater release of histamine [12]. Structural studies of active thiourea derivatives have shown that these compounds contain a central hydrophilic part and two hydrophobic moieties forming a butterfly-like

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conformation. This conformation is a part of structure of anti-HIV agent, which is useful in the treatment of AIDS [13]. A large variety of thiourea derivatives have been used as M1 receptor, RNAi therapy, MCH-R1 antagonists, and NPY Y2 receptor [14-17]. Recently, thiourea derivatives have been used in organocatalysis [18].

An easiest and most general method for making symmetrical disubstituted thioureas is the treatment of 2 equivalents of primary and/or secondary amines with thiophosgene [19]. However, this method is hazardous due to the toxic properties of thophosgene. Hence, alternative methods have been developed for the synthesis of thiourea derivatives with isothiocyanate which is a highly unsaturated organic compound [20]. Reactivity of alkyl and aryl isocyanates/isothiocyanates with various nucleophilic compounds has been widely studied due to the interest in the resulting products [21].

In recent years, green chemistry protocols are incorporated for the synthesis of organic molecules due to their advantages that include mild conditions, reduction of waste, improved yields and decrease of reaction time compared with classical methods which required drastic reaction conditions and prolonged reaction time. Ultrasound irradiation has been considered as a clean and useful protocol in organic synthesis in the past few decades [22]. We report in this paper an efficient and clean procedure to synthesis few *N*-thiocarbamoylpiperidone oxime esters under sonication in DCM solvent.

2. EXPERIMENTAL DETAILS

2.1 Materials and Methods

All the reagents and solvents purchased were reagent grade and were used without further purifications. Completion of reactions was monitored by TLC on silica gel coated aluminum sheet (Type 60 GF254, Merck). The melting points were measured in open capillaries and are uncorrected. FT-IR spectra were recorded on an AVATAR-300 FT-IR spectrometer (Thermo Nicolet) using KBr (pellet form).

The spectral features are reported in wave number (cm^{-1}). ^{1}H-NMR and ^{13}C-NMR were recorded on Bruker 400 MHz and 100MHz spectrometer. ^{1}H-NMR and ^{13}C-NMR chemical shifts values are reported in parts per million (ppm) from tetramethylsilane (TMS) with solvent resonance as the integral standard ($CDCl_3$). Peak multiplicities are designated by: s-singlet, bs-broad singlet, d-doublet, dd-double doublet, t-triplet, q-quartet, m-multiplet and *J*-coupling constant in Hz. The ultrasonic assisted reactions were carried out in a ‘‘Spectralab model UMC 20 Ultrasonic cleaner’’ with a frequency of 50 kHz and a nominal power 250 W.

2.2 General Procedure for Synthesis of *N*-thiocarbamoylpiperidin-4-one oxime esters (14-24)

To a solution of 3-isopropyl-2,6-diphenylpiperidin-4-one *O*-benzoyl oxime (0.6 g, 1.5 mmol) in dry DCM (5 mL), pyridine (1.5 eq) and allylisothiocyanate (0.17 g, 1.75 mmol) were added drop wise over 5 min in 50 mL Erlenmeyer flask. The reaction mixture was subjected to ultrasound irradiation for 1 h at 30 ˚C and the progress of the reaction was monitored by TLC. Upon completion of the reaction, the reaction mixture was slowly poured into crushed ice to get the crude product as a precipitate. Then it was subjected to recrystallisation from absolute ethanol to get pure *N*-allylthiocarbamoylpiperidin-4-one oxime esters **14** with a good yield (0.62 g, 82 %). The same procedure was followed for other compounds (**15-24**) of this series.

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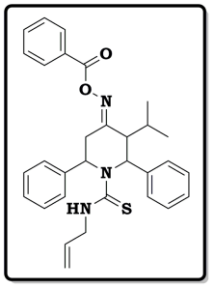
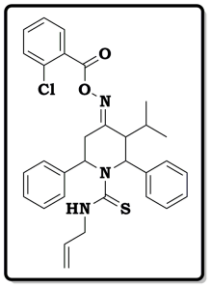
2.2.1 (*E*)-*N*-allyl-4-((benzoyloxy)imino)-3-isopropyl-2,6-diphenylpiperidine-1-carbothioamide (14)



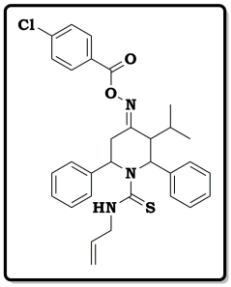
Colorless solid, mp: 165-168°C. IR (cm^{-1}): 3424 (N-H), 3057-2871 (C-H), 1709 (C=O), 1589 (C=N), 1523 (C=C), 1084 (C=S), 876 (N-O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, 2H, *J* = 7.2 Hz), 7.75 (d, 2H, *J* = 7.2 Hz), 7.52 (t, 1H, *J* = 6.8, 13.6 Hz), 7.24-7.42 (m, 11H), 5.64 (s, 1H, **H2**), 5.49 (m, 1H, **H10**), 4.90 (t, 2H, *cis***H11, H6**), 4.72 (d, 1H, *J* = 17.2 Hz, *trans***H11**), 4.25 (d, 1H, *J* = 15.6 Hz, **H9x**), 4.01 (d, 1H, *J* = 15.6 Hz, **H9y**), 3.43 (d, 1H, *J* = 9.2 Hz, $\mathbf{H5_{eq}}$), 3.21 (dd, 1H, *J* = 3.6, 18.8 Hz, **H3**), 2.49 (dd, 1H, *J* = 12, 18.4 Hz, $\mathbf{H5_{ax}}$), 1.92 (unresolved m, 1H, C**H**), 1.32 (d,3H, *J* = 5.6 Hz, C$\mathbf{H_3}$), 1. 24 (d, 3H, *J* = 6 Hz, C$\mathbf{H_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 58.11(**C2**), 49.51 (**C3**), 163.51 (**C4**), 33.88 (**C5**), 59.38 (**C6**), 29.61 (**C**H), 22.65, 21.52 (**C**H_3), 49.32 (**C9**), 164.73 (**C=O**), 185.32 (**C=S**), 134.60 (**C10**), 116.93 (**C11**), 140.92, 140.78, 133.42, 132.89, 130.60, 130.00, 129.63, 128.93, 128.83, 128.74, 128.55, 127.54, 127.01, 126.02 (aryl carbons). Elemental Analysis for $C_{31}H_{33}N_3O_2S$, Found (Calcd): C 72.08 (72.79), H 6.42 (6.45), N 6.42 (6.45), S 6.20 (6.26).

2.2.2(*E*)-*N*-allyl-4-(((2-chlorobenzoyl)oxy)imino)-3-isopropyl-2,6-diphenylpiperidine-1-carbothioamide (15)



Colorless solid, mp: 176-178°C. IR (cm^{-1}): 3397 (N-H), 3052-2871 (C-H), 1764 (C=O), 1589 (C=N), 1512 (C=C), 1095 (C=S), 876 (N-O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (t, 3H), 7.21-7.43 (m, 12H), 5.63 (s, 1H, **H2**), 5.51 (unresolved m, 1H, **H10**), 4.92 (t, 2H, *cis***H11, H6**), 4.71 (d, 1H, *J* = 17.2 Hz, *trans***H11**), 4.24 (d, 1H, *J* = 14.4 Hz, **H9x**), 4.02 (d, 1H, *J* = 14.8 Hz, **H9y**), 3.41 (d, 1H, *J* = 8 Hz, $\mathbf{H5_{eq}}$), 3.23 (unresolved dd, 1H, *J* = 18 Hz, **H3**), 2.45 (dd, 1H, *J* = 12.4, 18 Hz, $\mathbf{H5_{ax}}$), 1.93 (unresolved m, 1H, C**H**), 1.32 (d, 3H, *J* = 4 Hz, C$\mathbf{H_3}$), 1. 24 (d, 3H, *J* = 4.8Hz,C$\mathbf{H_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 58.01 (**C2**), 49.49 (**C3**), 163.22 (**C4**), 34.28 (**C5**), 59.28 (**C6**), 29.62 (**C**H), 22.62, 21.54 (**C**H_3), 49.24 (**C9**), 165.27 (**C=O**), 185.24 (**C=S**), 133.27 (**C10**), 116.90 (**C11**), 140.91, 140.65, 132.89, 132.85, 131.47, 130.93, 129.94, 129.31, 128.78, 128.72, 128.01, 127.56, 126.99, 126.78, 125.89 (aryl carbons). LC-MS: *m/z* calcd 545.19; *m/z* found: 546.50 (M^+H^+). Elemental Analysis for $C_{31}H_{32}N_3O_2S$, Found (Calcd): C 68.02 (68.25), H 5.80 (5.87), N 7.72 (7.70), S 5.86 (5.87).

2.2.3(*E*)-*N*-allyl-4-(((4-chlorobenzoyl)oxy)imino)-3-isopropyl-2,6-diphenylpiperidine-1-carbothioamide (16)



Colorless solid, mp: 173-175°C. IR (cm^{-1}): 3419 (N-H), 3052-2876 (C-H), 1758 (C=O), 1605 (C=N), 1528(C=C), 1068 (C=S), 854 (N-O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 (d, 2H, *J* = 7.6 Hz), 7.74 (d, 2H, *J* = 6.8 Hz), 7.26-7.42 (m, 11H), 5.64 (s, 1H, **H2**), 5.51 (unresolved m, 1H, **H10**), 4.90 (t, 2H, *cis***H11, H6**), 4.72 (d, 1H, *J* = 17.2 Hz, *trans***H11**), 4.24 (d, 1H, *J* = 15.2 Hz, **H9x**), 4.01 (d, 1H, *J* = 15.6 Hz, **H9y**), 3.42 (d, 1H, *J* = 8.8 Hz, $\mathbf{H5_{eq}}$), 3.18 (dd, 1H, *J* = 15.6 Hz, **H3**), 2.48 (dd, 1H, *J* = 12, 18 Hz, $\mathbf{H5_{ax}}$), 1.92 (unresolved m, 1H, C**H**), 1.32 (d, 3H, *J* = 5.2 Hz, C$\mathbf{H_3}$), 1. 23 (d, 3H, *J* = 5.6 Hz, C$\mathbf{H_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 58.05 (**C2**), 49.52 (**C3**), 162.71 (**C4**), 33.91 (**C5**), 59.36 (**C6**), 29.58 (**C**H), 22.65, 21.51 (**C**H_3), 49.33 (**C9**), 165.02 (**C=O**), 185.33 (**C=S**), 139.33 (**C10**), 116.96 (**C11**), 140.85, 140.73, 132.86, 131.01, 130.03, 128.93, 128.89, 128.76, 127.58, 127.16, 126.97, 126.00 (aryl carbons). Elemental Analysis for $C_{31}H_{32}ClN_3O_2S$, Found (Calcd): C 68.21 (68.25), H 5.86 (5.87), N 7.68 (7.70), S 5.86 (5.87).

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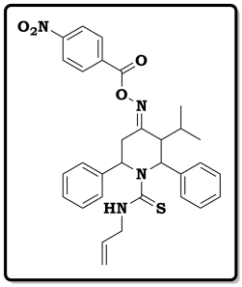
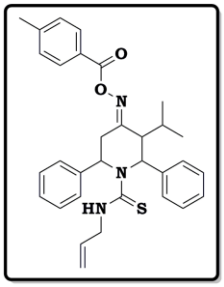
2.2.4(*E*)-*N*-allyl-3-isopropyl-4-(((4-nitrobenzoyl)oxy)imino)-2,6-diphenylpiperidine-1-carbothioamide (17)



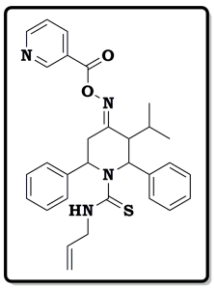
Colorless solid, mp: 180-182°C. IR (cm^{-1}): 3380 (N-H), 3052-2871 (C-H), 1758 (C=O), 1605 (C=N), 1517 (C=C), 1057 (C=S), 882 (N-O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (d, 2H, *J* = 8.8 Hz), 8.09 (d, 2H, *J* = 8 Hz), 7.75 (d, 2H, *J* = 7.6 Hz), 7.26-7.43 (m, 9H), 5.67 (s, 1H, **H2**), 5.47 (m, 1H, **H10**), 4.93 (d, 2H, *cis***H11, H6**), 4.72 (d, 1H, *J* = 17.2 Hz, *trans***H11**), 4.25 (t, 1H, **H9x**), 4.01 (t, 1H, **H9y**), 3.43 (d, 1H, *J* = 8.8 Hz, **H5$_{eq}$**), 3.20 (dd, 1H, *J* = 4.8, 18.8 Hz, **H3**), 2.51 (dd, 1H, *J* = 12, 18.8 Hz, **H5$_{ax}$**), 1.92 (m, 1H, C**H**), 1.33 (d, 3H, *J* = 6 Hz, C**H$_3$**), 1. 24 (t, 3H, *J* = 6.4 Hz, C**H$_3$**). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 57.93 (**C2**), 49.51 (**C3**), 161.71 (**C4**), 34.00 (**C5**), 59.33 (**C6**), 29.52 (**C**H), 22.67, 21.51 (**C**H$_3$), 49.43 (**C9**), 165.91 (**C=O**), 185.35 (**C=S**), 134.25 (**C10**), 116.98 (**C11**), 150.65, 140.77, 140.62, 132.82, 130.79, 130.07, 128.98, 128.79, 127.64, 126.93, 125.99, 123.69 (aryl carbons). LC–MS: *m/z* calcd: 556.21; *m/z* found: 557.25(M^+H^+). Elemental Analysis for $C_{31}H_{32}N_4O_4S$, Found (Calcd): C 66.87 (66.90), H 5.74 (5.75), N 10.02 (10.07), S 5.72 (5.75).

2.2.5(*E*)-*N*-allyl-3-isopropyl-4-(((4-methylbenzoyl)oxy)imino)-2,6-diphenylpiperidine-1-carbothioamide (18)



Colorless solid, mp: 161-162°C. IR (cm^{-1}): 3408 (N-H), 3063-2871 (C-H), 1747 (C=O), 1605 (C=N), 1523 (C=C), 1013 (C=S), 838 (N-O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 (dd, 4H), 7.17-7.42 (m, 11H), 5.65 (s, 1H, **H2**), 5.51 (unresolved m, 1H,**H10**),4.92(t,2H,*cis***H11, H6**), 4.72(d, 1H, *J* = 16.8 Hz, *trans***H11**), 4.25 (d, 1H, *J* = 14 Hz, **H9x**), 4.02 (d, 1H, *J* = 14.4 Hz, **H9y**), 3.42 (d, 1H, *J* = 7.6 Hz, **H5$_{eq}$**), 3.21 (unresolved dd, 1H, *J* = 17.6 Hz, **H3**), 2.49 (dd, 1H, *J* = 13.2, 16.8 Hz, **H5$_{ax}$**), 2.36 (s, 3H, *p*-C**H$_3$**), 1.92 (bra s, 1H, C**H**), 1.32 (unresolved d, 3H, C**H$_3$**), 1. 24 (t, 3H, *J* = 3.2 Hz, C**H$_3$**). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 58.12 (**C2**), 49.50 (**C3**), 163.59 (**C4**), 33.86 (**C5**), 59.38 (**C6**), 29.62 (**C**H), 21.73, 21.52 **C**H$_3$), 22.64 (*p*-**C**H$_3$), 49.29 (**C9**), 164.51 (**C=O**), 185.30 (**C=S**), 132.90 (**C10**), 116.92 (**C11**), 144.25, 140.95, 140.80, 129.98, 129.66, 129.26, 128.81, 128.73, 127.53, 127.02, 126.01, 125.92 (aryl carbons). Elemental Analysis for $C_{32}H_{35}N_3O_2S$, Found (Calcd): C 73.09 (73.14), H 6.65 (6.66), N 7.98 (8.0), S 6.08 (6.09).

2.2.6 (*E*)-*N*-allyl-3-isopropyl-4-((nicotinoyloxy)imino)-2,6-diphenylpiperidine-1-carbothioamide (19)



Colorless solid, mp: 183-185°C. IR (cm^{-1}): 3402 (N-H), 3063-2865 (C-H), 1747 (C=O), 1600 (C=N), 1517 (C=C), 1112 (C=S), 870 (N-O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.08 (s, 1H), 8.74 (s, 1H), 8.25 (s, 1H), 7.75 (s, 2H), 7.25-7.45 (m, 11H), 5.67 (s, 1H, **H2**), 5.20 (br s, 1H, **H10**), 4.92 (unresolved t, 2H, *cis***H11, H6**), 4.72 (d, 1H, *J* = 16 Hz, *trans***H11**), 4.25 (unresolved d, 1H, **H9x**), 4.04 (unresolved d, 1H, **H9y**), 3.44 (br s, 1H, **H5$_{eq}$**), 3.22 (d, 1H, *J* = 17.6 Hz, **H3**), 2.50 (t, 1H, **H5$_{ax}$**), 1.93 (br s, 1H, C**H**), 1.33 (s, 3H, C**H$_3$**), 1. 25 (s, 3H, C**H$_3$**). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 58.00 (**C2**), 49.50 (**C3**), 162.20 (**C4**), 34.03 (**C5**), 59.31 (**C6**), 29.54 (**C**H), 22.67, 21.53 **C**H$_3$), 49.36 (**C9**), 165.53 (**C=O**), 185.33 (**C=S**), 137.33 (**C10**), 116.95 (**C11**), 153.79, 150.51, 140.80, 140.58, 132.83, 130.10, 128.97, 128.77, 127.60, 126.93, 125.92, 124.98, 123.58 (aryl carbons). Elemental Analysis for $C_{30}H_{32}N_4O_2S$, Found (Calcd): C 70.30 (70.31), H 6.24 (6.25), N 10.90 (10.93), S 6.24 (6.25).

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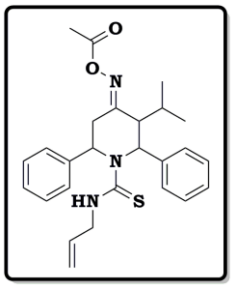
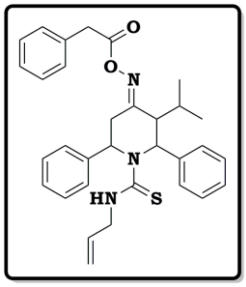
2.2.7 (*E*)-4-(acetoxyimino)-*N*-allyl-3-isopropyl-2,6-diphenylpiperidine-1-carbothioamide (20)



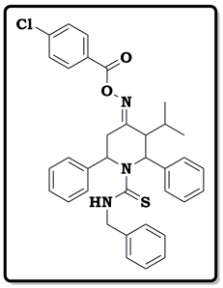
Colorless solid, mp: 156-158°C. IR (cm^{-1}): 3402 (N-H), 3090-2876 (C-H), 1736 (C=O), 1589 (C=N), 1517 (C=C), 1095 (C=S), 871 (N-O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 (d, 2H, *J* = 7.6 Hz), 7.21-7.40 (m, 9H), 5.63 (s, 1H, **H2**), 5.46 (m, 1H, **H10**), 4.91 (d, 1H, *J* = 10.4 Hz, *cis***H11**), 4.79 (dd, 1H, *J* = 4.4, 12 Hz, **H6**), 4.70 (d, 1H, *J* = 16.2 Hz, *trans***H11**), 4.24 (d, 1H, *J* = 15.6 Hz, **H9x**), 4.00 (d, 1H, *J* = 15.6 Hz, **H9y**), 3.31 (d, 1H, *J* = 8.8 Hz, **H5$_{eq}$**), 3.11 (dd, 1H, *J* = 4.4, 18.8 Hz, **H3**), 2.32 (dd, 1H, *J* = 12.4, 18.8 Hz, **H5$_{ax}$**), 2.11 (s, 3H, C**H**$_3$), 1.86 (m, 1H, C**H**), 1.29 (d, 3H, *J* = 6 Hz, C**H**$_3$), 1. 17 (d, 3H, *J* = 6.4 Hz, C**H**$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 58.08 (**C2**), 49.47 (**C3**), 163.61 (**C4**), 33.96 (**C5**), 59.32 (**C6**), 29.52 (**C**H), 22.62, 21.50 **C**H$_3$), 49.18 (**C9**), 19.68 C**H**$_3$), 168.34 (**C=O**), 185.29 (**C=S**), 132.87 (**C10**), 116.87 (**C11**), 140.92, 140.78, 129.97, 128.83, 128.68, 127.51, 126.94, 125.89 (aryl carbons). LC–MS: *m/z* calcd: 449.21; *m/z* found: 450.25 (M^+H^+). Elemental Analysis for $C_{26}H_{31}N_3O_2S$, Found (Calcd): C 69.46 (69.48), H 6.88 (6.90), N 9.32 (9.35), S 7.09 (7.12).

2.2.8 (*E*)-*N*-allyl-3-isopropyl-2,6-diphenyl-4-((2-phenylacetoxy)imino)piperidine-1-carbothioamide (21)



Colorless solid, mp: 184-187°C. IR (cm^{-1}): 3413 (N-H), 3068-2920 (C-H), 1726 (C=O), 1589 (C=N), 1523 (C=C), 1073 (C=S), 865 (N-O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, 2H, *J* = 6.8 Hz), 7.14-7.36 (m, 14H), 5.60 (s, 1H, **H2**), 5.50 (m, 1H, **H10**), 4.91 (d, 1H, *J* = 10 Hz, *cis***H11**), 4.78 (unresolved dd, 1H, *J* = 8 Hz, **H6**), 4.69 (d, 1H, *J* = 17.2 Hz, *trans***H11**), 4.22 (d, 1H, *J* = 15.6 Hz, **H9x**), 4.00 (d, 1H, *J* = 15.2 Hz, **H9y**), 3.68 (s, 1H, C**H**$_2$), 3.28 (d, 1H, *J* = 9.2 Hz, **H5$_{eq}$**), 2.94 (unresolved dd, 1H, *J* = 2.8, 19.2 Hz, **H3**), 2.25 (dd, 1H, *J* = 12.4, 18.4 Hz, **H5$_{ax}$**), 1.85 (unresolved m, 1H, C**H**), 1.27 (d, 3H, *J* = 5.2 Hz, C**H**$_3$), 1. 14 (t, 3H, *J* = 6 Hz, C**H**$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 57.94 (**C2**), 49.46 (**C3**), 164.56 (**C4**), 33.73 (**C5**), 59.24 (**C6**), 39.99 (**C**H$_2$), 29.53 (**C**H), 22.57, 21.47 (**C**H$_3$), 49.13 (**C9**), 168.60 (**C=O**), 185.22 (**C**=S), 133.23 (**C10**), 116.87 (**C11**), 140.89, 140.63, 132.90, 129.88, 129.40, 129.26, 128.77, 128.69, 128.58, 127.50, 127.25, 126.94, 125.85 (aryl carbons). Elemental Analysis for $C_{32}H_{35}N_3O_2S$, Found (Calcd): C 73.10 (73.14), H 6.65 (6.66), N 7.97 (8.0), S 6.07 (6.09).

2.2.9(*E*)-*N*-benzyl-4-(((4-chlorobenzoyl)oxy)imino)-3-isopropyl-2,6-diphenylpiperidine-1-carbothioamide (22)



Colorless solid, mp: 179-181°C. IR (cm^{-1}): 3416 (N-H), 3063-2860 (C-H), 1764 (C=O), 1599 (C=N), 1515 (C=C), 1075 (C=S), 854 (N-O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (d, 2H, *J* = 8 Hz), 7.78 (d, 2H, *J* = 7.6 Hz), 7.16-7.45 (m, 14H), 6.71 (d, 2H, *J* = 6.8 Hz), 5.78 (s, 1H, **H2**), 4.71 (m, 2H, **H9x**, **H6**), 4.49 (d, 1H, *J* = 14 Hz, **H9y**), 3.43 (d, 1H, *J* = 8.8 Hz, **H5$_{eq}$**), 3.14 (dd, 1H, *J* = 4, 18.8 Hz, **H3**), 2.45 (dd, 1H, *J* = 12.4, 18.8 Hz, **H5$_{ax}$**), 1.91 (m, 1H, C**H**), 1.34 (d, 3H, *J* = 5.6 Hz, C**H**$_3$), 1.23 (d, 3H, *J* = 6 Hz, C**H**$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): 58.00 (**C2**), 49.35 (**C3**), 162.69 (**C4**), 34.01 (**C5**), 59.39 (**C6**), 29.58 (**C**H), 22.71, 21.55 **C**H$_3$), 51.70 (**C9**), 164.97 (**C=O**), 184.97 (**C**=S), 140.91, 140.75, 139.91, 136.72, 131.01, 130.11, 129.01, 128.93, 128.78, 128.66, 128.42, 127.73, 127.65, 127.59, 127.15, 126.99, 126.87, 125.93 (aryl carbons). Elemental Analysis for $C_{35}H_{34}ClN_3O_2S$, Found (Calcd): C 70.56 (70.58), H 5.68 (5.71), N 7.04 (7.05), S 5.35 (5.37).

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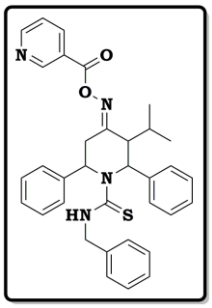
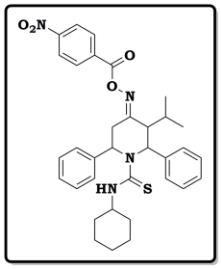
2.2.10 (*E*)-*N*-benzyl-3-isopropyl-4-((nicotinoyloxy)imino)-2,6-diphenylpiperidine-1-carbothioamide (23)



Colorless solid, mp: 187-189°C. IR (cm^{-1}): 3410 (N-H), 3075-2840 (C-H), 1755 (C=O), 1595 (C=N), 1523 (C=C), 1060 (C=S), 870 (N-O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.05 (s, 1H), 8.72 (s, 1H), 8.22 (d, 2H, *J* = 7.6 Hz), 7.78 (d, 2H, *J* = 7.2 Hz), 7.14-7.47 (m, 13H), 6.70 (d, 2H, *J* = 6.8 Hz), 5.80 (s, 1H, **H2**), 4.71 (m, 2H, **H9x**, **H6**), 4.49 (d, 1H, *J*=14Hz, **H9y**), 3.44(d, 1H, *J* = 9.2 Hz, **H5$_{eq}$**), 3.17 (dd, 1H, *J* = 4, 18.8 Hz, **H3**), 2.46 (dd, 1H, *J* = 12.4, 18.8 Hz, **H5$_{ax}$**), 1.91 (m, 1H, C**H**), 1.35 (d, 3H, *J* = 5.6 Hz, C**H$_3$**), 1.23 (d, 3H, *J* = 6.4 Hz, C**H$_3$**). ^{13}C NMR ($CDCl_3$, 100 MHz): 57.95 (**C2**), 49.39 (**C3**), 162.18 (**C4**), 34.11 (**C5**), 59.34 (**C6**), 29.55 (**C**H), 22.72, 21.56 (**C**H$_3$), 51.70 (**C9**), 165.48 (**C=O**), 184.99 (**C**=S), 153.77, 150.49, 140.85, 140.62, 137.32, 136.70, 130.18, 129.00, 128.86, 128.78, 128.65, 128.41, 127.71, 127.64, 127.62, 126.96, 126.86, 125.85, 124.97, 123.55 (aryl carbons). Elemental Analysis for $C_{34}H_{34}N_4O_2S$, Found (Calcd): C 72.58 (72.59), H 6.01 (6.04), N 9.94 (9.96), S 5.68 (5.69).

2.2.11(*E*)-*N*-cyclohexyl-3-isopropyl-4-(((4-nitrobenzoyl)oxy)imino)-2,6-diphenylpiperidine-1-carbothioamide (24)



Colorless solid, mp: 182-184°C. IR (cm^{-1}): 3395 (N-H), 3057-2865 (C-H), 1740 (C=O), 1603 (C=N), 1516 (C=C), 1084 (C=S), 831 (N-O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (d, 2H, *J* = 8 Hz), 8.09 (d, 2H, *J* = 8.4 Hz), 7.76 (d, 2H, *J* = 7.2 Hz), 7.26-7.42 (m, 8H), 5.52 (d, 1H, *J* = 6.4 Hz, N**H**), 4.83 (d, 1H, *J* = 9.2 Hz, **H2**), 4.19 (d, 1H, *J* = 4 Hz, **H6**), 3.43 (d, 1H, *J* = 8.8 Hz, **H5$_{eq}$**), 3.18 (dd, 1H, *J* = 18.8 Hz, **H3**), 2.48 (dd, 1H, *J* = 12.4, 18.8 Hz, **H5$_{ax}$**), 1.90 (m, 1H, C**H**), 2.02-0.45 (m, 11H), 1.32 (d, 3H, *J* = 6 Hz, C**H$_3$**), 1.24 (d, 3H, *J* = 6.4 Hz, C**H$_3$**). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 57.90 (**C2**), 49.45 (**C3**), 161.72 (**C4**), 34.07 (**C5**), 58.82 (**C6**), 29.67 (**C**H), 22.50, 21.55 (**C**H$_3$), 166.03 (**C=O**), 183.74 (**C**=S), 55.09, 32.75, 31.52, 25.39, 24.45, 24.35 (cyclohexyl carbons), 150.68, 141.04, 140.89, 134.26, 130.79, 130.03, 128.95, 128.75, 127.53, 126.95, 125.97, 123.70 (aryl carbons). Elemental Analysis for $C_{34}H_{38}N_4O_4S$, Found (Calcd): C 68.20 (68.22), H 6.34 (6.35), N 9.34 (9.36), S 5.34 (5.35).

3. RESULTS AND DISCUSSION

3.1 Synthesis of *N*-thiocarbamoylpiperidin-4-one oxime esters

In the present work, four consecutive steps were adopted for the synthesis of *N*-thiocarbamoylpiperidone oxime esters (Scheme 1). The key intermediate of compound 3-alkyl-2,6-diphenylpiperidin-4-one **1** was synthesized [23] by Mannich condensation of respective ketone, aldehyde and ammonium acetate in 1:2:1 molar ratio, followed by oximation [24] of **1** using hydroxylamine hydrochloride in the presence of sodium acetate trihydrate in absolute ethanol. The obtained piperidone oxime **2** was treated with aromatic acids and $POCl_3$/pyridine [8].

In the final step of this investigation, we planned to synthesize *N*-thiocarbamoylpiperidone oxime esters from various piperidone oxime esters and substituted isothiocyanates. The optimization of this protocol was evaluated by the reaction of piperidone oxime ester 3 with allylisothiocyanate in the presence of various solvents in pyridine as base under sonication.

The ultrasonic assisted reactions were carried out with a frequency of 50 kHz and nominal power of 250 W at 30 ˚C. The screening of various solvents and base revealed that DCM/pyridine (Entry 3) was the most efficient for the transformation of secondary amine into thiourea

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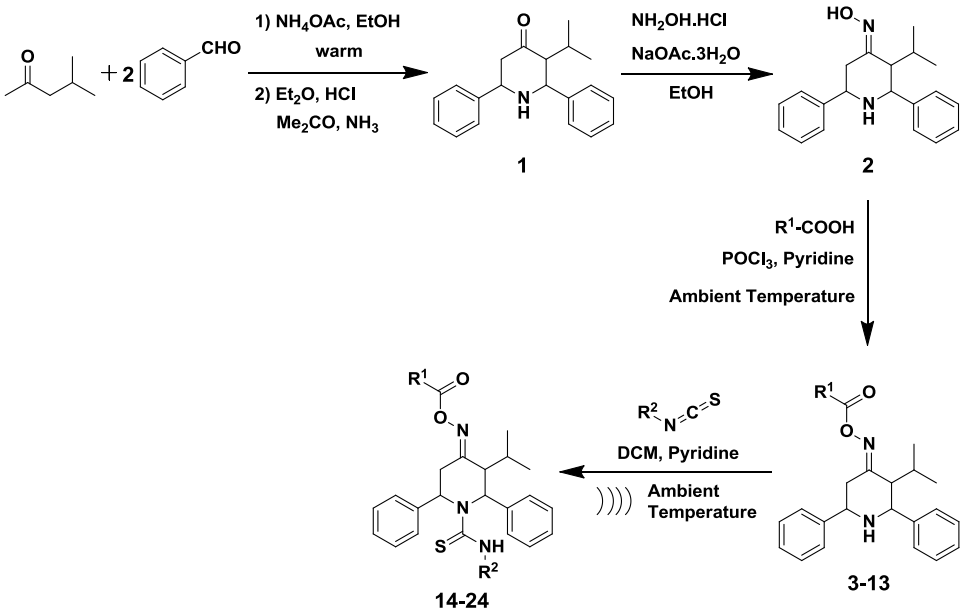
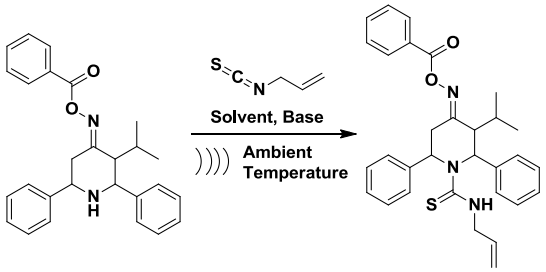
derivative. The results obtained from ultrasound irradiation are summarized in Table 1. It was found that, when employing 1 equiv of oxime ester 3 with 1.2 equiv of allylisothiocyanate without base in DCM, the product was not obtained (Entry 7) and the starting oxime ester **3** was fully recovered. At the same time, with pyridine as base, a significant change occurred in benzene, acetonitrile and DMF (Entries 1, 4 and 5), while toluene and ethanol led to the desired product in poor yields (Entries 2 and 6).



Scheme 1. Synthesis of *N*-thiocarbamoylpiperidin-4-one oxime esters.

Table 1. Optimization of the reaction conditions for synthesis of *N*-thiocarbamoylpiperidone oxime esters.



Entry	Solvent	Base(1.5 eq)	Time (h)	Yield (%)*
1	Benzene	Pyridine	2.5	40
2	Toluene	Pyridine	3	35
3	**DCM**	**Pyridine**	**1**	**82**
4	Acetonitrile	Pyridine	2	56
5	DMF	Pyridine	2	45
6	Ethanol	Pyridine	4	25
7	DCM	-	4	-

*= isolated yield

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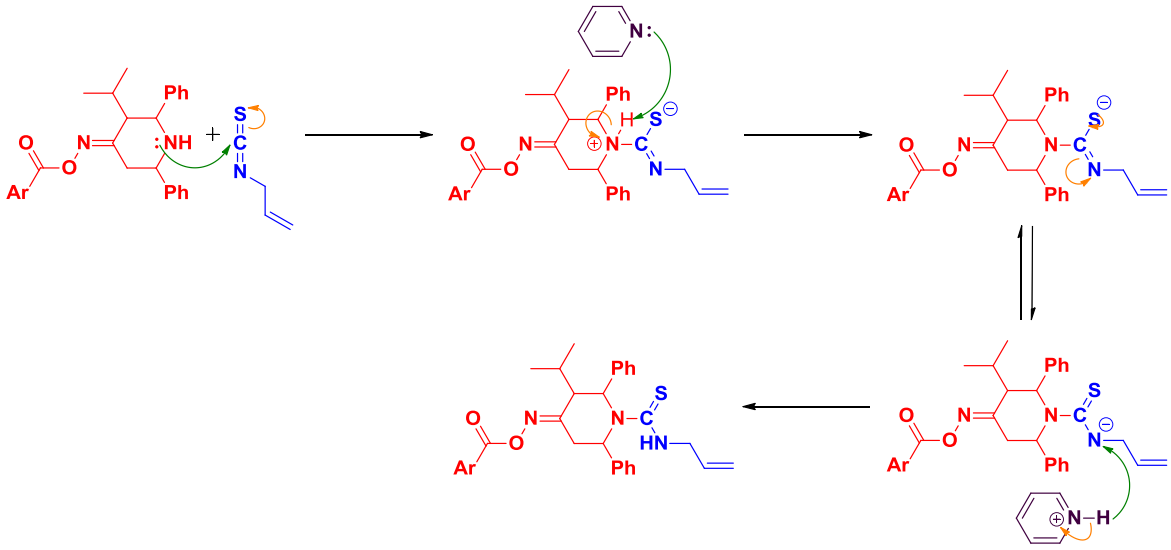
To study the scope and limitation of this protocol compared with conventional method, first an attempt was made by conventional method with piperidone oxime ester **3** and allylisothiocyanate in DCM/pyridine at 80 ˚C. It gave 51 % of product which is moderated while the reaction carried out under ultrasound irradiation. The results obtained were in good agreement with all the other substrates of piperidone oxime esters and isothiocyanate in high yields of product with shorter reaction time compared with classical method. It is found that 2˚amine with electron withdrawing group gives excellent results that are summarized in Table 2. The final products were well characterized using Elemental analysis, FT-IR, ^{1}H, ^{13}C-NMR and Mass spectrometry.

Table 2. Substrate scope of piperidin-4-one oxime ester and substituted isothiocyanate

Entry	Compound	R^1	R^2	Yield (%)	
				Conv.	US.
1	14	C_6H_5	allylisothiocyanate	51	82
2	15	*o*-Cl-C_6H_4	allylisothiocyanate	42	83
3	16	*p*-Cl-C_6H_4	allylisothiocyanate	45	86
4	17	*p*-NO_2-C_6H_4	allylisothiocyanate	65	90
5	18	*p*-Me-C_6H_4	allylisothiocyanate	27	78
6	19	3-C_6H_4N	allylisothiocyanate	39	80
7	20	CH_3	allylisothiocyanate	20	76
8	21	$PhCH_2$	allylisothiocyanate	37	80
9	22	*p*-Cl-C_6H_4	benzylisothiocyanate	48	85
10	23	3-C_6H_4N	benzylisothiocyanate	36	79
11	24	*p*-NO_2-C_6H_4	cyclohexylisothiocyanate	53	89

*= isolated yield



Scheme 2. The proposed mechanism for the formation of thiourea

A proposed reaction mechanism for the formation of thiourea is shown in Scheme 2. The correct order of addition of the reagents was found to be essential in order to obtain clean products. This gave us an indication of the mechanism of the reaction. The nucleophilic attack of piperidone oxime ester on

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allylisothiocyanate leads to the formation of an intermediate. During the consecutive steps, deprotonation and protonation of the intermediate results in the formation of the final product thiourea.

3.2 NMR Spectral Analysis of Compound 14

In the ^{1}H-NMR spectral analysis, we have chosen compound **14** as the representative for the spectral assignments. The numbering of carbon atoms in compound **14** is shown in Figure 1. The protons are numbered accordingly. The aromatic protons of two phenyl groups in piperidine ring and *O*-benzoyl group obviously appeared as multiplets in the up field region 7.24-7.94 ppm with 15 protons integral and NH proton of allylthiocarbamoyl moiety merged along with the aromatic protons. In the allylic system, one multiplet and four doublets appeared in the downfield region at 5.49, 4.95, 4.72, 4.25 and 4.01 ppm, respectively. The multiplet is assigned to vinylic proton, first two doublets with coupling constants of 10.4 Hz, 17.2 Hz are assigned to *cis* and *trans* protons of the vinylic part and the latter two doublets are due to diastereotopic methylene protons. The benzylic protons at C2 and C6 appeared as broad singlet and unresolved doublet of doublet at 5.56 and 4.90 ppm. The remarkable deshielding of ring protons (benzylic protons) in *N*-allylthiocarbamoylpiperidone oxime ester compared to that of parent piperidone oxime ester [8] is due to the $A^{1,3}$-strain between ring nitrogen substituted and the phenyl group at C2 and C6 positions of the piperidine ring. The H2 proton appeared as single, due to absence of coupling between C2-H and C3-H bonds which indicated that the dihedral angle between H2 and H3 bonds is decreased (~90˚). It confirmed C2-C3 linkage resulting in twist boat conformation [25]. The doublet at 3.43 ppm (J = 9.2 Hz) with one proton integral is assigned for $H5_{eq}$. The two doublet of doublet at 3.21 ppm (J = 18.8, 3.6 Hz) and 2.49 ppm (J = 18.4, 12 Hz) are assigned for $H3_{ax}$ and latter one for $H5_{ax}$.The methine proton and protons belonging to methyl group of isopropyl moiety appeared as a multiplet at 1.92 ppm and two doublet at 1.32 ppm and 1.24 ppm, respectively.

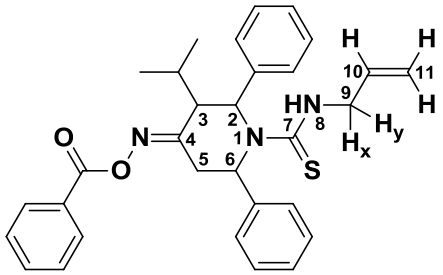

Figure 1. Numbering of atoms in Compound **14**

In the ^{13}C-NMR analysis of compound **14**, the aromatic carbons resonates in the regions of 126.02-133.42 ppm and the signal due to *ipso* carbons of the two phenyl rings and *O*-benzoyl group observed at 140.92, 140.78 and 133.42 ppm, respectively. The imino carbon, *O*-benzoyl carbonyl carbon and thiocarbonyl carbons appeared in the downfield region at 163.51, 164.73 and 185.32 ppm, respectively. The signals observed at 134.60, 116.93 and 49.32 ppm correspond to C10, C11 and C9 carbons of the allyl moiety. In the up field region, isopropyl group, methine and two methyl carbons appeared at 29.61, 22.65 and 21.52 ppm, while the piperidine ring carbons C2, C3, C5 and C6 absorbed at 59.38, 49.51, 33.88 and 58.11 ppm, respectively.

The C5 carbon signal (33.88 ppm) is more shielded compared to C3 carbon (49.51 ppm) due to the $A^{1,3}$ interaction between the N-O and C5-H bonds. Hence, it was concluded that *O*-benzoyl group is *syn* to C5 carbon [25].

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4. CONCLUSIONS

In conclusion, we have described in this paper a new methodology for the synthesis of various *N*-thiocarbamoylpiperidone oxime ester derivatives by ultrasound irradiation. This methodology has many advantages over conventional method that include high yields, simple work-up, short reaction times, no side reactions and no expensive column chromatography. The present method is practically convenient, economic and environmental friendly process for the synthesis of *N*-thiocarbamoyl derivatives.

SUPPORTING INFORMATION

^{1}H NMR and ^{13}C NMR spectra of all the compounds and LC-MS of compounds 15, 17 and 20 can be found *via* the Supplementary Content section of this article's online.

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ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
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The authors declare no conflict of interest

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