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Heterocyclic synthesis using nitrilimines: Part 10. Synthesis of some new 1,3,4,6-tetrasubstituted 1,2,4,5-tetrazines

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Abstract: A new series of 1,3,4,6-tetrasubstituted 1,2,4,5-tetrazines were synthesized from the cycloaddition reaction of methylhydrazones of alkanal and cycloalkanal with appropriate hydrazonoyl halides.

Keywords: Nitrilimine, cycloaddition, methylhydrazones, 1,2,4,5-tetrazines.

1. Introduction

Nitrilimines are useful reactive intermediates in azaheterocyclic synthesis. They undergo two main cyclization reactions: 1,3-dipolar cycloaddition reactions with multiple bonds and cyclocondensation reactions with nucleophilic substrates containing suitably located electrophilic centers leading to various heterocyclic compounds.[1-6] 1,2,4,5-Tetrazines represent an important class of heterocyclic compounds that find many practical and synthetic applications.[7] They are generally prepared from hydrazine derivatives or from nitrilimines. The reaction of nitrilimines with hydrazones has been reported to give the corresponding tetrazines. Methylhydrazones of aliphatic aldehydes and ketones give directly the 1,2,3,4-tetrahydro-s-tetrazines.[2,8,9] However, those of simple hydrazones give the acyclic products which undergo oxidative cyclization upon refluxing with active charcoal to yield the corresponding dihydro-s-tetrazines or amidrazones.[2,10,11] In continuation of our work concerning the utility of nitrilimines in the synthesis of heterocyclic compounds, we investigated the reaction of

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C-aroyl-N-arylnitrilimines **2** with methylhydrazones **3** in an attempt to synthesize new 1,2,4,5-tetrazine derivatives in anticipation of expected interesting biological activities.

2. Experimental

Melting points were determined in open capillaries on Electrothermal Melting Temperature apparatus and are uncorrected. The IR spectra were obtained by using Satellite 3000 Mid infrared FTIR spectrometer in KBr pellets. The ^{1}H NMR and ^{13}C spectra were recorded on a Bruker AM 300 MHz spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as internal reference. All chemical shifts (δ) were reported in ppm from internal TMS. Elemental analysis was performed at Cairo University, A.R.E. and the results agreed with the calculated values within experimental errors. The hydrazonoyl halides **1**[12-15] and methylhydrazones **3**[9,16] were prepared according to known literature procedures.

2.1 General procedure for synthesis of compounds (4a-o):

Triethylamine (0.05 mol) in tetrahydrofuran (THF) (10 ml) was dropwise added to a stirred solution of appropriate hydrazonoyl halides **1** (0.01 mol) and the respective alkanal methylhydrazones **3** (0.02 mol) in THF (70-100 ml) at room temperature. Stirring was continued overnight, the solvent was then evaporated in vacuo. The residue was washed several times with water to get rid the triethylamine salt. The resulting crude solid was collected and recrystallized from ethanol or methanol to afford the desired products **4a-o**.
The following compounds were synthesized using this method:

1,3-Dimethyl-6-(2-naphthoyl)-4-phenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (4a):

Yield: 78%; M.p. 156-158 °C; ^{1}H NMR ($CDCl_3$) (δ/ppm): 8.55-7.05 (m, 12H, Ar-H), 4.85 (m, 1H, CH), 4.24 (d, 1H, NH, *J*=3 Hz), 3.20 (s, 3H, NCH_3), 1.38 (d, 3H, CH_3, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) (δ/ppm): 184.5 (C=O), 141.8, 136.4, 135.6, 132.7, 132.4, 132.0, 131.8, 130.0, 128.6, 128.0, 127.7, 126.7, 125.4, 120.5, 115.5, 68.7 (C-3), 42.6 (NCH_3), 20.2 (CH_3); IR (ν/cm^{-1}): 3269 (NH), 1645 (C=O), 1619 (C=N); Analysis (% Calculated/found) for $C_{21}H_{20}N_4O$ (Mw 344.42) C: 73.23/73.10, H: 5.85/5.80, N: 16.27/16.40.

3-Ethyl-1-methyl-6-(2-naphthoyl)-4-phenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (4b):

Yield: 71%; M.p. 163-165 °C; ^{1}H NMR ($CDCl_3$) (δ/ppm): 8.50-7.04 (m, 12H, Ar-H), 4.82 (m, 1H, CH), 4.22 (d, 1H, NH, *J*=3 Hz), 3.24 (s, 3H, NCH_3), 1.63 (m, 2H, CH_2), 1.06 (t, 3H, CH_3, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) (δ/ppm): 184.3 (C=O), 141.3, 136.6, 135.6, 132.7, 132.4, 132.0, 131.8, 130.0, 128.6, 128.0, 127.7, 126.7, 125.4, 120.5, 115.3, 68.9 (C-3), 42.6 (NCH_3), 24.9 (CH_2), 6.7 (CH_3); IR (ν/cm^{-1}): 3265 (NH), 1647 (C=O), 1615 (C=N); Analysis (% Calculated/found) for $C_{22}H_{22}N_4O$ (Mw 358.45) C: 73.72/73.90, H: 6.19/6.05, N: 15.63/15.50.

4-(4-Chlorophenyl)-3-n-hexyl-1-methyl-6-(2-naphthoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (4c):

Yield: 76%; M.p. 152-154 °C; ^{1}H NMR ($CDCl_3$) (δ/ppm): 8.52-7.05 (m, 11H, Ar-H), 4.65 (m, 1H, CH), 4.24 (d, 1H, NH, *J*=3 Hz), 3.18 (s, 3H, NCH_3), 1.82-0.60 (m, 13H, n-Hexyl protons); ^{13}C NMR ($CDCl_3$) (δ/ppm): 184.1 (C=O), 141.6, 136.5, 135.6, 132.7, 132.4, 132.0, 131.8, 130.0, 128.6, 128.0, 127.7, 126.7, 125.4, 120.5, 115.7, 68.9 (C-3), 42.6 (NCH_3), 24.6, 19.7, 13.6, 7.8, 4.7, 4.3 (n-hexyl

carbons); IR (ν/cm^{-1}): 3273 (NH), 1645 (C=O), 1617 (C=N); Analysis (% Calculated/found) for $C_{26}H_{29}ClN_4O$ (Mw 449.00) C: 69.55/69.80, H: 6.51/6.70, N: 12.48/12.30.

4-(4-Chlorophenyl)-3-cyclohexyl-1-methyl-6-(2-naphthoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (4d):

Yield: 74%; M.p. 146-148 °C; ^{1}H NMR ($CDCl_3$) (δ/ppm): 8.46-7.12 (m, 11H, Ar-H), 4.67 (m, 1H, CH), 4.30 (d, 1H, NH, *J*=3 Hz), 3.20 (s, 3H, NCH_3), 1.90-1.20 (m, 11H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$) (δ/ppm): 184.2 (C=O), 141.7, 136.7, 135.6, 132.7, 132.4, 132.0, 131.8, 130.0, 128.6, 128.0, 127.7, 126.7, 125.4, 120.5, 115.5, 70.4 (C-3), 42.9 (NCH_3), 40.2, 27.6, 25.3, 24.1 (cyclohexyl carbons); IR (ν/cm^{-1}): 3274 (NH), 1650 (C=O), 1620 (C=N); Analysis (% Calculated/found) for $C_{26}H_{27}ClN_4O$ (Mw 446.98) C: 69.87/70.10, H: 6.09/5.90, N: 12.53/12.40.

1,3-Dimethyl-4-(4-methylphenyl)-6-(2-naphthoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (4e):

Yield: 71%; M.p. 136-138 °C; ^{1}H NMR ($CDCl_3$) (δ/ppm): 8.44-7.02 (m, 11H, Ar-H), 4.65 (m, 1H, CH), 4.26 (d, 1H, NH, *J*=3 Hz), 3.23 (s, 3H, NCH_3), 1.39 (d, 3H, CH_3, *J*=7 Hz), 2.71 (s, 3H, $ArCH_3$); ^{13}C NMR ($CDCl_3$) (δ/ppm): 184.6 (C=O), 141.2, 136.5, 135.6, 132.7, 132.4, 132.0, 131.8, 130.0, 128.6, 128.0, 127.7, 126.7, 125.4, 120.5, 115.1, 69.8 (C-3), 42.4 (NCH_3), 20.7 (CH_3), 20.3 (CH_3); IR (ν/cm^{-1}): 3270 (NH), 1645 (C=O), 1612 (C=N); Analysis (% Calculated/found) for $C_{22}H_{22}N_4O$ (Mw 358.45) C: 73.72/73.50, H: 6.19/6.10, N: 15.63/15.80.

3-Ethyl-1-methyl-4-(4-methylphenyl)-6-(2-naphthoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (4f):

Yield: 75%; M.p. 129-131 °C; ^{1}H NMR ($CDCl_3$) (δ/ppm): 8.50-7.05 (m, 11H, Ar-H), 4.72 (m, 1H, CH), 4.22 (d, 1H, NH, *J*=3 Hz), 3.26 (s, 3H, NCH_3), 2.72 (s, 3H, Ar-CH_3), 1.62 (m, 2H, CH_2), 1.05 (t, 3H, CH_3, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) (δ/ppm): 184.5 (C=O), 141.1, 136.8, 135.6, 132.7, 132.4, 132.0, 131.8, 130.0, 128.6, 128.0, 127.7, 126.7, 125.4, 120.5, 115.1, 68.9 (C-3), 42.3 (NCH_3), 26.2 (CH_2), 20.7 (Ar-CH_3), 6.5 (CH_3); IR (ν/cm^{-1}): 3266 (NH), 1648 (C=O), 1616 (C=N); Analysis (% Calculated/found) for $C_{23}H_{24}N_4O$ (Mw 372.47) C: 74.17/73.80, H: 6.49/6.60, N: 15.04/14.80.

6-Benzoyl-4-(4-chlorophenyl)-1,3-dimethyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (4g):

Yield: 83%; M.p. 191-193 °C; ^{1}H NMR ($CDCl_3$) (δ/ppm): 8.10-7.12 (m, 9H, Ar-H), 4.82 (m, 1H, CH), 4.30 (d, 1H, NH, *J*=3 Hz), 3.21 (s, 3H, NCH_3), 1.36 (d, 3H, CH_3, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) (δ/ppm): 183.8 (C=O), 142.4, 135.9, 135.5, 132.7, 130.8, 130.3, 128.5, 127.9, 126.1, 70.7 (C-3), 42.3 (NCH_3), 19.8 (CH_3); IR (ν/cm^{-1}): 3277 (NH), 1660 (C=O), 1625 (C=N); Analysis (% Calculated/found) for $C_{17}H_{17}ClN_4O$ (Mw 328.80) C: 62.10/61.80, H: 5.21/5.05, N: 17.04/16.80.

6-Benzoyl-4-(4-chlorophenyl)-3-ethyl-1-methyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (4h):

Yield: 80%; M.p. 155-157 °C; ^{1}H NMR ($CDCl_3$) (δ/ppm): 8.15-7.15 (m, 9H, Ar-H), 4.61 (m, 1H, CH), 4.28 (d, 1H, NH, *J*=3 Hz), 3.24 (s, 3H, NCH_3), 1.60 (m, 2H, CH_2), 1.03 (t, 3H, CH_3, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) (δ/ppm): 183.9 (C=O), 142.3, 136.4, 135.5, 132.7, 130.8, 130.3, 128.5, 127.9, 126.2, 70.2 (C-3), 42.8 (NCH_3), 26.2 (CH_2), 6.6 (CH_3); IR (ν/cm^{-1}): 3275 (NH), 1655 (C=O), 1622 (C=N); Analysis (% Calculated/found) for $C_{18}H_{19}ClN_4O$ (Mw 342.83) C: 63.06/63.30, H: 5.59/5.70, N: 16.34/16.20.

6-Benzoyl-4-(4-chlorophenyl)-3-cyclohexyl-1-methyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (4i):

Yield: 81%; M.p. 140-142 °C; ^{1}H NMR ($CDCl_3$) (δ/ppm): 8.20-7.18 (m, 9H, Ar-H), 4.58 (m, 1H, CH), 4.33 (d, 1H, NH, *J*=3 Hz), 3.23 (s, 3H, NCH_3), 1.90-1.20 (m, 11H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$) (δ/ppm): 184.0 (C=O), 142.4, 136.3, 135.5, 132.7, 130.8, 130.3, 128.5, 127.9, 126.1, 42.9 (NCH_3), 40.2, 27.3, 25.4, 24.2 (Cyclohexyl carbons), 7.4 (C-3); IR (ν/cm^{-1}): 3279 (NH), 1655 (C=O), 1620 (C=N); Analysis (% Calculated/found) for $C_{22}H_{25}ClN_4O$ (Mw 396.92) C: 66.57/66.30, H: 6.35/6.50, N: 14.12/14.05.

4-(4-Chlorophenyl)-1,3-dimethyl-6-(2-furoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (4j):

Yield: 77%; M.p. 116-118 °C; ^{1}H NMR ($CDCl_3$) (δ/ppm): 8.22-7.20 (m, 7H, Ar-H), 4.68 (m, 1H, CH), 4.26 (d, 1H, NH, *J*=3 Hz), 3.25 (s, 3H, NCH_3), 1.40 (d, 3H, CH_3, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) (δ/ppm): 173.3 (C=O), 141.9, 137.3, 135.2, 135.0, 129.1, 128.2, 128.0, 120.8, 115.6, 70.5 (C-3), 42.2 (NCH_3), 20.4 (CH_3); IR (ν/cm^{-1}): 3280 (NH), 1665 (C=O), Analysis (% Calculated/found) for $C_{15}H_{15}ClN_4O_2$ (Mw 318.77) C: 56.52/56.60, H: 4.74/4.80, N: 17.58/17.50.

4-(4-Chlorophenyl)-3-ethyl-6-(2-furoyl)-1-methyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (4k):

Yield: 79%; M.p. 131-132 °C; ^{1}H NMR ($CDCl_3$) (δ/ppm): 8.30-7.22 (m, 7H, Ar-H), 4.63 (m, 1H, CH), 4.20 (d, 1H, NH, *J*=3 Hz), 3.30 (s, 3H, NCH_3), 1.64 (m, 2H, CH_2), 1.06 (t, 3H, CH_3, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) (δ/ppm): 173.5 (C=O), 141.8, 137.4, 134.8, 134.6, 128.9, 127.9, 127.7, 120.1, 115.8, 70.4 (C-3), 42.1 (NCH_3), 26.3 (CH_2), 6.7 (CH_3); IR (ν/cm^{-1}): 3276 (NH), 1650 (C=O), 1615 (C=N); Analysis (% Calculated/found) for $C_{16}H_{17}ClN_4O_2$ (Mw 332.79) C: 57.75/57.90, H: 5.15/5.00, N: 16.84/16.70.

4-(4-Chlorophenyl)-3-cyclohexyl-6-(2-furoyl)-1-methyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (4l):

Yield: 76%; M.p. 127-129 °C; ^{1}H NMR ($CDCl_3$) (δ/ppm): 8.25-7.15 (m, 7H, Ar-H), 4.55 (m, 1H, CH), 4.32 (d, 1H, NH, *J*=3 Hz), 3.31 (s, 3H, NCH_3), 1.90-1.20 (m, 11H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$) (δ/ppm): 173.6 (C=O), 142.1, 140.2, 137.3, 135.5, 135.1, 129.3, 128.5, 128.3, 115.6, 71.8 (C-3), 42.2 (NCH_3), 40.9, 27.7, 25.3, 24.2 (Cyclohexyl carbons); IR (ν/cm^{-1}): 3277 (NH), 1655 (C=O), 1610 (C=N); Analysis (% Calculated/found) for $C_{20}H_{23}ClN_4O_2$ (Mw 386.88) C: 62.09/62.30, H: 5.99/6.10, N: 14.48/14.60.

4-(4-Chlorophenyl)-1,3-dimethyl-6-(2-thenoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (4m):

Yield: 75%; M.p. 166-168 °C; ^{1}H NMR ($CDCl_3$) (δ/ppm): 8.30-7.19 (m, 7H, Ar-H), 4.67 (m, 1H, CH), 4.27 (d, 1H, NH, *J*=3 Hz), 3.33 (s, 3H, NCH_3), 1.40 (d, 3H, CH_3, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) (δ/ppm): 174.2 (C=O), 140.9, 136.9, 135.4, 134.9, 128.9, 128.1, 127.9, 120.6, 114.9, 70.5 (C-3), 42.2 (NCH_3), 20.4 (CH_3); IR (ν/cm^{-1}): 3267 (NH), 1665 (C=O), 1620 (C=N); Analysis (% Calculated/found) for $C_{15}H_{15}ClN_4OS$ (Mw 334.83) C: 53.81/53.60, H: 4.52/4.80, N: 16.73/16.80.

4-(4-Chlorophenyl)-3-ethyl-1-methyl-6-(2-thenoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (4n):

Yield: 72%; M.p. 137-139 °C; ^{1}H NMR ($CDCl_3$) (δ/ppm): 8.25-7.16 (m, 7H, Ar-H), 4.64 (m, 1H, CH), 4.24 (d, 1H, NH, *J*=3 Hz), 3.31 (s, 3H, NCH_3), 1.64 (m, 2H, CH_2), 1.06 (t, 3H, CH_3, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) (δ/ppm): 174.3 (C=O), 141.0, 136.9, 135.1, 134.6. 129.0, 128.3, 127.7, 120.9, 115.1, 70.4 (C-3), 42.1 (NCH_3), 26.3 (CH_2), 6.7 (CH_3); IR (ν/cm^{-1}): 3266 (NH), 1660 (C=O), 1617 (C=N); Analysis (% Calculated/found) for $C_{16}H_{17}ClN_4OS$ (Mw 348.86) C: 55.09/54.80, H: 4.91/5.10, N: 16.06/15.80.

4-(4-Chlorophenyl)-3-cyclohexyl-1-methyl-6-(2-thenoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (4o):

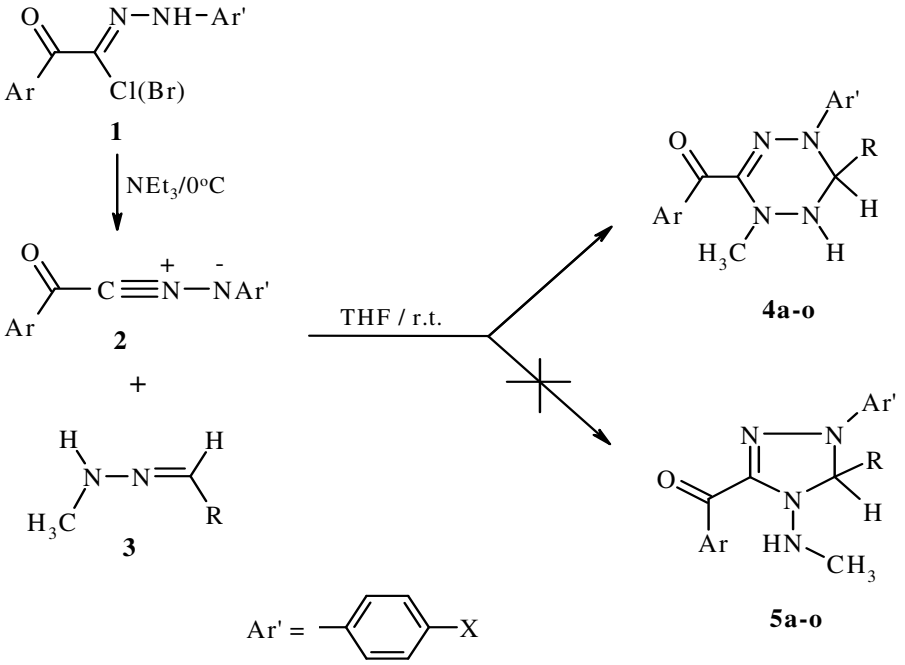
Yield: 70%; M.p. 143-145 °C; ^{1}H NMR ($CDCl_3$) (δ/ppm): 8.30-7.20 (m, 7H, Ar-H), 4.58 (m, 1H, CH), 4.34 (d, 1H, NH, *J*=3 Hz), 3.32 (s, 3H, NCH_3), 1.90-1.20 (m, 11H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$) (δ/ppm): 174.4 (C=O), 141.2, 137.4, 135.9, 135.4, 129.2, 128.4, 128.1, 120.8, 115.1, 71.6 (C-3), 42.2 (NCH_3), 40.9, 27.5, 25.7, 24.2 (Cyclohexyl carbons); IR (ν/cm^{-1}): 3265(NH), 1665 (C=O), 1615 (C=N); Analysis (% Calculated/found) for $C_{20}H_{23}ClN_4OS$
(Mw 402.95) C: 59.62/59.40, H: 5.75/5.80, N: 13.90/13.80.

3. Results and Discussion

The C-benzoyl, C-2-furoyl-, C-2-thenoyl-, C-2-naphthoyl and C-phenylaminocarbonyl-N-arylnitrilimines (**2**) were generated in situ from the reaction of hydrazonoyl halides (**1**) by reaction with triethylamine. The nitrilimines were not isolated, but immediately reacted with the alkanal and cycloalkanal methylhydrazones (**3**) affording the corresponding 1,2,3,4-tetrahydro-1,2,4,5-tetrazines (**4a-o**) in good yields (Scheme 1). No cycloaddition to C=N occurred to get substituted 4-methylamino-1,2,4-triazoles (**5**). It is worth mentioned that, the reaction of nitrilimines with hydrazones containing electron withdrawing groups (-COMe, -COOMe and -COPh) found to give directly 1,2,4-triazoles via cycloaddition to C=N due to the weak nucleophilicity of the nitrogen atom carrying the electron withdrawing groups.[17,18]

3.1 Spectroscopic data analysis:

The structures of the title compounds **4a-o** were confirmed by elemental analysis and their spectral data. The IR spectra of the obtained compounds showed strong absorption band in the 3280-3250 cm^{-1} region corresponding to NH of the ring. The absorption bands of the aroyl carbonyl groups appear in the 1660-1640 cm^{-1} region. In the ^{1}H NMR spectra, the signal of N-H proton of tetrazine ring recorded between 4.5-4.2 ppm and the N-methyl protons appear as singlet in the range of 3.4-3.1 ppm. The ^{13}C NMR spectra show the expected resonance signals of the different carbons, especially the signal of C-3 of tetrazine ring around 70 ppm. This assignment is in good agreement with literature data for carbon flanked by tow nitrogens and azomethine carbon in six-membered heterocycles.[9,19]



Entry	Ar	R	X
a	2-Naphthyl	$-CH_3$	H
b	2-Naphthyl	$-CH_2CH_3$	H
c	2-Naphthyl	$-(CH_2)_5CH_3$	Cl
d	2-Naphthyl	-cyclohexyl	Cl
e	2-Naphthyl	$-CH_3$	Me
f	2-Naphthyl	$-CH_2CH_3$	Me
g	Ph	$-CH_3$	Cl
h	Ph	$-CH_2CH_3$	Cl
i	Ph	-cyclohexyl	Cl
j	2-Furyl	$-CH_3$	Cl
k	2-Furyl	$-CH_2CH_3$	Cl
l	2-Furyl	-cyclohexyl	Cl
m	2-Thienyl	$-CH_3$	Cl
n	2-Thienyl	$-CH_2CH_3$	Cl
o	2-Thienyl	-cyclohexyl	Cl

Scheme 1: Synthetic path way for compounds **4a-o**.

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