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The synthesis of aryl halomethylated unsaturated iminolactones

Afsaneh Zonouzi[a]*, Hossein Rahmani[b], Mojtaba Biniaz[a], Zakieh Izakian[a] and Seik Weng Ng[c]

[a]*School of Chemistry, University College of Science, University of Tehran, Tehran, Iran*

[b]*Institute of Chemical Technologies, Iranian Research Organisation for Science and Technology (IROST), Tehran, Iran*

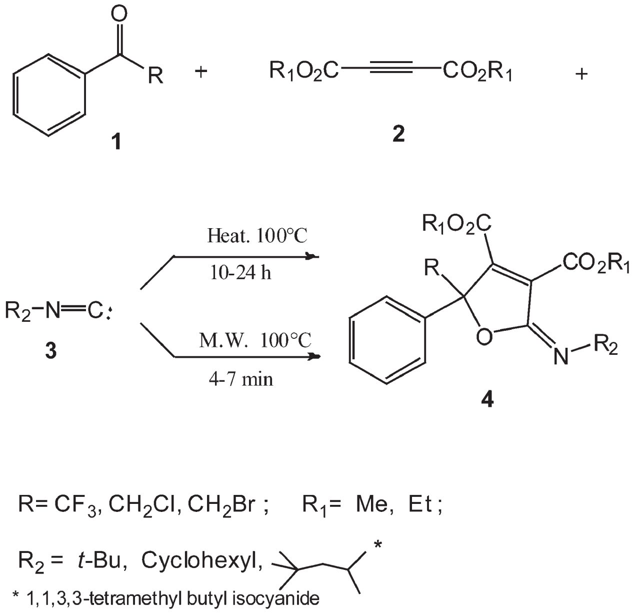
[c]*Department of Chemistry, University of Malaya, 50603 Kuala Lumpur, Malaysia*

Halomethylated iminolactones have been synthesised from alkyl isocyanides, acetylene dicarboxylic acid esters and halogenated acetophenones in solvent free microwave assisted multi-component reactions.

Keywords: one-pot, solvent-free reaction, microwave irradiation, halomethylated iminolactone

The presence of perfluoroalkyl groups in organic molecules leads to the dramatic modification of their physico-chemical properties and biological activities. It may significantly improve metabolic stability and is a powerful tool of modern drug design and drug discovery.[1] Iminolactones are an important class of heterocyclic compounds which can be converted to other heterocyclic compounds or hydrolysed with aqueous hydrochloric acid to produce butenolides (furan-2(5*H*-ones)). They are an important class of natural products with biological activities used in medicine and agriculture.[2] Various synthetic methods have been used to prepare iminolactone derivatives. The synthesis of iminolactones from aldehydes and diketones has been established.[2–6] Nair and coworkers reported in 2000 the one-pot reaction of diketones, dimethyl acetylenedicarboxylate and cyclohexylisocyanide using hot benzene.[7] All of the previous methods used benzene and methylene chloride as solvents.[2–8]

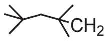
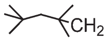
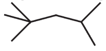
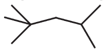
We have already reported multi-component procedures for the synthesis of some heterocyclic compounds.[9–14] We now report a one-pot, solvent-free and multi-component reaction of acetophenone derivatives **1**, acetylenic esters **2** and alkyl isocyanides **3** to afford the halomethylated iminolactones **4** in fairly high yields. Microwave irradiation improved the yields and shortened the reaction times (Scheme 1, Table 1).



Scheme 1

In 2008, Shaabani and coworkers reacted 2-bromo-1-(4-bromophenyl) ethanol, isocyanides and acetylenic esters in CH_2Cl_2[6] to give four derivatives of iminolactons after 12 hours. In our work, we have used solvent free microwave assisted reaction using some different reactants to produce the new iminolactons **4a–p** in short times (4–7 minutes) and higher yields. For comparison purposes we also performed the reaction using

Table 1 Times and yields in the synthesis of halomethylated iminolactones **4** using heat or microwave irradiation

Compd	R	R_1	R_2	Time/h (Δ)	Yield/% (Δ)	Time/min (MW)	Yield/% (MW)
4a	CF_3	Me	Cyclohexyl	10	85	4	98
4b	CF_3	Et	Cyclohexyl	12	80	5	97
4c	CF_3	Me	*t*-Bu	12	75	5	95
4d	CF_3	Et	*t*-Bu	12	70	6	95
4e	CF_3	Me		11	80	5	97
4f	CF_3	Et		12	78	5	96
4g	CH_2Cl	Me	*t*-Bu	20	65	6	87
4h	CH_2C	Et	*t*-Bu	24	62	7	85
4i	CH_2Cl	Me	Cyclohexyl	18	75	5	95
4j	CH_2Cl	Et	Cyclohexyl	20	70	6	93
4k	CH_2Cl	Me		20	65	6	87
4l	CH_2Br	Me	*t*-Bu	18	65	6	85
4m	CH_2Br	Et	*t*-Bu	24	60	7	83
4n	CH_2Br	Me	Cyclohexyl	18	76	5	95
4o	CH_2Br	Et	Cyclohexyl	24	68	6	92
4p	CH_2Br	Me		20	64	7	90

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* Correspondent. E-mail: zonouzi @khayam.ut.ac.ir

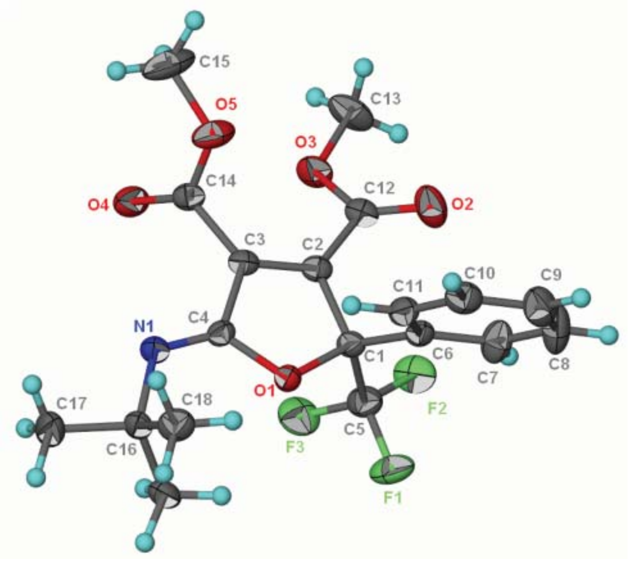


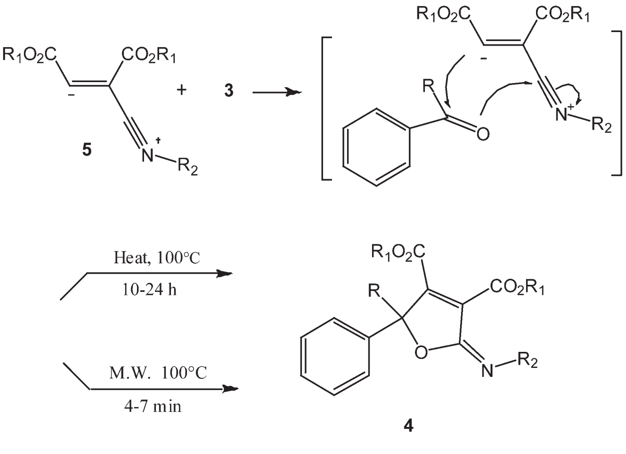
Fig. 1 X-ray crystal structure of **4a**.

conventional heating (oil bath). We kept the quantities of the reactant exactly the same as in the microwave promoted reaction and performed the solvent-free reaction in a 50 mL three-necked flask with a thermometer. The reaction mixtures were heated at 100 °C and the reaction was kept for 10–24 h. Moderate yields (62–85%) of the final products were obtained. Clearly, the microwave irradiation has shortened the reaction time and improved the yield (Table 1). This multi-component reaction can be carried out in hot *p*-xylene with lower yields. For example the product **4g** was obtained in refluxing *p*-xylene (b.p. 138 °C) after 7 days in less than 20% yield.

The highly functionalised iminolactones **4** which are produced in this reaction are stable and were not converted to the other products. For example, they were unchanged by heating with aqueous inorganic acids, probably as a result of steric hindrance by the substituents.

Crystals of **4a** were obtained from a mixture of methanol and acetone. The X-ray crystal structure of **4a** has been reported to confirm its highly functionalised structure (Fig. 1).

A possible mechanism is illustrated in Scheme 2. Addition of alkyl isocyanide to the acetylenic esters generates the 1:1 adduct **5**. Nuleophilic attack of this adduct on the acetophenone derivatives, followed by another attack of negative oxygen to the carbon of the nitrile part of adduct **5** afforded the products **4** (Scheme 2).



Scheme 2

We have already reported the X-ray structure analysis of **4n** which confirmed unambiguously its highly functionalised structure.[15] Structures **4** were assigned on the basis of their elemental analysis, IR, ^{1}H, ^{13}C, ^{19}F NMR and mass spectral data. The mass spectra of compounds **4** displayed molecular ion peaks at appropriate *m/z* values. Initial fragmentation involved the loss of R_1OH and R_2N. ^{1}H NMR and ^{13}C NMR spectra of **4a–p** displayed resonances in agreement with their structures; the partial assignments of these resonances are given in the experimental section. The IR spectra of compounds **4** showed two sharp absorptions for C=O and a medium absorption for C=N. There were also three or four sharp C–O absorptions for compounds **4a–p** (see Experimental).

In conclusion, we have developed a simple and efficient procedure for the synthesis of some new stable highly functionalised halomethylated iminolactones with potential biological activities.

Experimental

Chemicals and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Microwave assisted reactions were carried out in the microwave oven (ETHOS 1600, Milestone) with a power of 600W specially designed for organic synthesis. Column chromatography was performed on silica gel (0.015–0.04 mm, mesh-size) and TLC on precoated plastic sheets (25 $DC_{UV\text{-}254}$) respectively. Melting points were measured on Barnstead Electrothermal melting point apparatus and were not corrected. Elemental analysis for C, H and N were performed using a Thermo Finnigan Flash EA1112 instrument. IR spectra were measured on a Bruker EQUINOX 55 spectrometer as ATR. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were determined in $CDCl_3$ on a Bruker 500 MHzspectrometer and chemical shifts were expressed in ppm downfield from tetramethylsilane. Mass spectra were recorded on a Finnigan-MAT 8430 spectrometer at an ionisation potential of 70 ev.

General procedure

Conventional heating: Acetophenone derivatives **1** (2 mmol) were added at 5 °C to a magnetically stirred mixture of alkyl isocyanide **3** (2 mmol) and acetylenic esters **2** (2 mmol) in a 50 mL three-necked flask with a thermometer, and the reaction mixture was stirred for 10 min and heated at 100 °C for 10–24 h. The precipitated products were washed and recrystallised from methanol as colourless crystals.

Microwave assisted reaction: Magnetically stirred mixture of alkylisocyanide (2 mmol), acetylenic esters (2 mmol) and acetophenone derivatives (2 mmol) was stirred for 10 min and then was placed in an open glass container. Microwave irradiation in a microwave oven at 100 °C for 4–7 min gave the solid products. The white to yellow crystals of **4** were purified by washing and recrystallisation in methanol.

Dimethyl 5-(cyclohexylimino)-2-(trifluoromethyl)-2,5-dihydro-2-phenylfuran-3,4-dicarboxylate (**4a**): White crystals, m.p. 70–71 °C; IR; ν_{max} 3043, 2932, 2756 (C–H), 1740, 1737 (C=O), 1693 (C=N), 1302, 1274 (C–F), 1149, 1090, 1020 (C–O) cm^{-1}; ^{1}H NMR, δ 1.21–1.26, 1.30–1.37, 1.40–1.47, 1.60–1.63, 1.75–1.81 (5m, 10H, CH_2 of cyclohexyl), 3.72 (m, 1H, CH of cyclohexyl), 3.76, 3.92 (2s, 6H, CH_3 of CO_2Me), 7.43–7.44, 7.49–7.54 (2m, 5H, Ph protons); ^{13}C NMR, δ 26.07, 33.53, 33.76 ($^{13}CH_2$ of cyclohexyl), 53.40, 53.60 ($2CH_3$ of CO_2Me), 57.45 (^{13}CH of cyclohexyl), 129.14 ($^{13}CF_3$), 122.15, 124.42, 126.70, 126.91, 127.03, 130.31, 132.16, 139.18, 141.36 (alkene and Ph carbons), 152.67 (^{13}C=N-cyclohexyl), 160.64, 161.71 (2^{13}C=O of $2CO_2Me$); ^{19}F NMR, δ –73.62 (s, CF_3); Ms (EI, 70ev): *m/z* 425 (M^+), 393 ($M^+–CH_3OH$), 296 (M^+-$C_6H_{11}N$, CH_3OH), Anal. Calcd for $C_{21}H_{22}F_3NO_5$; C, 59.29; H, 5.21; N, 3.29. Found: C, 59.27; H, 5.20; N, 3.30%. Crystallographic data for the structure of compound **4a** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC 731528. These data can be obtained free of charge via www.ccdc.com.ac.uk/data_request/cif

Diethyl 5-(cyclohexylimino)-2-(trifluoromethyl)-2,5-dihydro-2-phenylfuran-3, 4-dicarboxylate (**4b**): White crystals, m.p. 69–70 °C; IR; ν_{max} 3068, 2997, 2856 (C–H), 1735, 1721 (C=O), 1693 (C=N), 1342, 1288 (C–F), 1228, 1193, 1118 (C–O) cm^{-1}; ^{1}H NMR, δ 1.24–1.27, 1.39–1.41 (2t, 6H, CH_3 of CO_2Et), 1.3–1.37, 1.46–1.55, 1.64–1.67, 1.79–1.86 (4m, 10H, CH_2 of cyclohexyl), 3.78, 3.83 (m, 1H, CH of cyclohexyl), 4.23–4.27, 4.41–4.45 (2q, 4H, *J* = 7.14 Hz, CH_2 of CO_2Et); 7.47–7.48, 7.60–7.62 (2m, 5H, Ph protons), ^{13}C NMR, δ 14.06, 14.40 ($2^{13}CH_3$ of CO_2Et), 24.95, 26.12, 33.54, 33.76 ($^{13}CH_2$ of cyclohexyl), 57.24 (^{13}CH of cyclohexyl), 62.68, 62.83 ($2^{13}CH_2$ of CO_2Et), 129.01 ($^{13}CF_3$) 122.21, 124.49, 127.00, 130.21, 132.37, 139.15, 141.18 (alkene and Ph carbons), 152.77 (^{13}C=N-cyclohexyl), 160.23, 161.30 ($2^{13}C$=O of $2CO_2Et$); ^{19}F NMR, δ –73.63 (s, CF_3); Ms (EI, 70ev): *m/z* 453 (M^+), 407 (M^+-C_2H_5OH), 310 (M^+–C_2H_5OH, $C_6H_{11}N$), Anal. Calcd for $C_{23}H_{26}F_3NO_5$; C, 60.92; H, 5.78; N, 3.09. Found: C, 60.90; H, 5.78; N, 3.10%.

Dimethyl 5-(tert-butylimino)-2-(trifluoromethyl)-2,5-dihydro-2-phenylfuran-3, 4-dicarboxylate (**4c**): White crystals, m.p. 72–73 °C; IR; ν_{max} 3011, 2961, 2879 (C–H), 1739, 1720 (C=O), 1685 (C=N), 1301, 1274 (C–F), 1173, 1149, 1039, 1009 (C–O) cm^{-1}; ^1H NMR, δ 1.41 (1s, 9H, *t*-Bu protons), 3.80, 3.96 (2s, 6H, $2CH_3$ of CO_2Me), 7.46–7.47, 7.60–7.61 (2m, 5H, Ph protons); ^{13}C NMR, δ 30.03 ($^{13}CH_3$ of *t*-Bu), 53.43, 53.65 ($2^{13}CH_3$ of CO_2Me), 55.93 ($^{13}CMe_3$), 121.93, 123.51, 127.34, 130.97, 132.04, 139.52, 140.18 (alkene and Ph carbons), 129.04 ($^{13}CF_3$), 151.76 (^{13}C=N-cyclohexyl), 160.97, 162.85 ($2^{13}C$=O of $2CO_2Me$); ^{19}F NMR, δ –73.69 (s, CF_3); Ms (EI, 70ev): *m/z* 399 (M^+), 367 (M^+–CH_3OH), 296 (M^+–CH_3OH, *t*-BuN), Anal. Calcd for $C_{19}H_{20}F_3NO_5$; C, 57.14; H, 5.05; N, 3.51. Found: C, 57.13; H, 5.06; N, 3.53%.

Diethyl 5-(tert-butylimino)-2-(trifluoromethyl)-2,5-dihydro-2-phenylfuran-3, 4-dicarboxylate (**4d**): White crystals, m.p. 74–75 °C; IR; ν_{max} 3062, 2955, 2939 (C–H), 1737, 1713 (C=O), 1693 (C=N), 1371, 1340, 1280 (C–F), 1191, 1165, 1014 (C–O) cm^{-1}; ^1H NMR, δ 1.24–1.26, 1.27–1.29 (2t, 6H, CH_3 of CO_2Et), 1.41 (s, 9H, *t*-Bu), 4.22–4.27, 4.40–4.44 (2q, 4H, *J* = 7.01 Hz, CH_2 of CO_2Et), 7.46–7.61 (2m, 5H, Ph protons); ^{13}C NMR, δ 14.06, 14.43 ($2^{13}CH_3$ of CO_2Et), 29.98 ($^{13}CH_3$ of *t*-Bu), 55.83 (^{13}C of *t*-Bu), 62.63, 62.73 ($2^{13}CH_2$ of CO_2Et), 128.99 ($^{13}CF_3$), 122.28, 124.56, 127.03, 130.11, 132.48, 139.87, 140.79 (alkene and Ph carbons), 150.69 (^{13}C=*t*-Bu), 160.22, 161.59 ($2^{13}C$=O of $2CO_2Et$); ^{19}F NMR, δ –73.60 (s, CF_3); Ms (EI, 70ev): *m/z* 427 (M^+), 381 (M^+-C_2H_5OH), 310 (M^+-C_2H_5OH, *t*-BuN), Anal. Calcd for $C_{21}H_{24}F_3NO_5$; C, 59.01; H, 5.66; N, 3.28. Found: C, 59.02; H, 5.65; N, 3.30%.

Dimethyl 5-(2,4-trimethylpenan-2-ylimino)-2-(trifluoromethyl)-2,5-dihydro-2-phenylfuran-3,4- dicarboxylate (**4e**): White crystals, m.p. 76–77 °C; IR; ν_{max} 3062, 2953, 2966 (C–H), 1739, 1725 (C=O), 1697 (C=N), 1284, 1227 (C–F), 1220, 1108, 1028 (C–O) cm^{-1}; ^1H NMR, δ 1.038 (s, 9H, *t*-Bu protons), 1.44–1.46 (2s, 6H, $2CH_3$), 1.69, 1.71 (2s, 2H, CH_2 protons), 3.80, 3.93 (2s, 6H, $2CH_3$ of CO_2Me), 7.46–7.47, 7.61–7.63 (2m, 5H, Ph protons); ^{13}C NMR, δ 29.93, 30.04 ($^{13}CH_3$ of alkyl group), 32.03 ($^{13}CH_3$ of *t*-Bu), 32.34 (^{13}C of *t*-Bu), 53.35, 53.53 ($^{13}CH_3$ of CO_2Me), 55.80 ($^{13}CH_2$), 59.44 ($(CH_3)_2{}^{13}C$–N), 129.04 ($^{13}CF_3$), 122.23, 124.51, 127.03, 130.17, 132.45, 139.25, 141.48 (alkene and Ph carbons), 149.38 (^{13}C=N-alkyl), 160.64, 162.12 ($2^{13}C$=O of CO_2Me); ^{19}F NMR, δ –73.62 (s, CF_3); Ms (EI, 70ev): *m/z* 455 (M^+), 423 (M^+–CH_3OH), 296 (M^+–CH_3OH, $C_8H_{17}N$), Anal. Calcd for $C_{23}H_{28}F_3NO_5$; C, 60.65; H, 6.20; N, 3.80. Found: C, 60.63; H, 6.20; N, 3.10%.

Diethyl 5-(2,4,4-trimethylpentan-2-ylimino-2-(trifluoromethyl)-2,5-dihydro-2-phenylfuran-3,4-dicarboxylate (**4f**): White crystals, m.p. 72–73 °C; IR; ν_{max} 3159, 2954, 2931 (C–H), 1735, 1713 (C=O), 1697 (C=N), 1294, 1253 (C–F), 1217, 1188, 1018 (C–O) cm^{-1}; ^1H NMR, δ 1.037 (s, 9H, *t*-Bu), 1.24–1.27, 1.38–1.41 (2t, 6H, CH_3 of CO_2Et), 1.44, 1.45 (2s, 6H, $2CH_3$), 1.69– 1.71 (2s, 2H, CH_2), 4.22–4.26, 4.37–4.41 (2q, 4H, *J* = 7.11 Hz, CH_2 of CO_2Et), 7.45–7.47, 7.62–7.64 (2m, 5H, Ph protons); ^{13}C NMR, δ 14.06, 14.45 ($2^{13}CH_3$ of CO_2Et) 30.04, 30.13 ($^{13}CH_3$, $^{13}CH_2$ of alkyl group), 32.05 ($^{13}CH_3$ of *t*-Bu), 32.32 (^{13}C of *t*-Bu), 55.78 ($^{13}CH_2$), 59.36 ($(CH_3)_2{}^{13}C$–N), 62.59, 62.68 ($2^{13}CH_2$ of CO_2Et), 128.95 ($^{13}CF_3$), 122.29, 124.57, 127.12, 130.08, 132.64, 139.25, 141.48 (alkene and Ph carbons), 149.38 (^{13}C=N-alkyl), 160.64, 162.12 ($2^{13}C$=O of CO_2Et); ^{19}F NMR, δ –73.63 (s, CF_3); Ms (EI, 70ev): *m/z* 483 (M^+), 437 (M^+-C_2H_5OH), 310 (M^+-C_2H_5OH, $C_8H\ _{17}N$), Anal. Calcd for $C_{25}H_{32}F_3NO_5$; C, 62.10; H, 6.67; N, 2.90. Found: C, 62.10; H, 6.70; N, 2.91%.

Dimethyl 5-(tert-butylimino)-2-(chloromethyl)-2,5-dihydro-2-phenylfuran-3,4-dicarboxylate (**4g**): Light yellow crystals, *m.p.* 69–70°C. IR υ_{max}: 3019, 2958 (C–H), 1751, 1748, 1719 (C=O), 1682 (C=N), 1298, 1255, 1213, 1045 (C–O), 738, 694 (C–Cl) cm^{-1}; ^1H NMR δ 1.42 (s, 9H, *t*-Bu), 3.81, 3.94 (2s, 6H, $2CH_3$ of CO_2Me), 4.25–4.27, 4.67–4.69 (2H, CH_2 of CH_2Cl, d. of d., *J* = 201.71 Hz, *J* = 11.74 Hz), 7.39–7.40, 7.41–7.49 (2m, 5H, Ph protons) ppm; ^{13}C NMR δ 30.02 (CH_3 of *t*-Bu), 48.54 ($^{13}CH_2$ of CH_2Cl), 53.24, 53.33 (CH_3 of $2CO_2Me$), 55.37 ($^{13}CMe_3$), 91.77 (^{13}C–CH_2Cl), 126.20, 129.26, 129.52, 137.22, 139.56, 141.64 (alkene and Ph carbons), 152.66 (^{13}C=N-*t*-Bu), 161.57, 162.78 (^{13}C=O of $2CO_2Me$) ppm; MS: *m/z* (fragment) 379, 381 (M^+, M^++2), 347.379 (M^+, M^++2- CH_3OH), 308, 310 (M^+, M^++2- CH_3OH, C_4H_9N); Anal. Calcd for $C_{19}H_{22}ClNO_5$: C, 60.08; H, 5.84; N, 3.69. Found: C, 60.10; H, 5.82; N, 3.71.

Diethyl 5-(tert-butylimino)-2-(chloromethyl)-2,5-dihydro-2-phenylfuran-3,4-dicarboxylate (**4h**): Light yellow crystals, m.p. 70–71°C. IR υ_{max}: 3010, 2985 (C–H), 1750, 1723 (C=O), 1680 (C=N), 1280, 1251, 1211, 1039 (C–O), 745, 707 (C–Cl) cm^{-1}; ^1H NMR δ 1.30–1.34, 1.39–1.42 (2t, 6H, $2CH_3$ of CO_2Et), 1.49 (s, 9H, *t*-Bu), 4.29–4.31, 4.67–4.69 (2H, d. of d., *J* = 199.53 Hz, *J* = 11.80 Hz, CH_2 of CH_2Cl), 4.52–4.58 (2m, 2H, CH_2 of CO_2Et), 7.40–7.51 (3m, 5H, Ph protons) ppm; ^{13}C NMR δ 14.92, 15.11 ($2CH_3$ of CO_2Et), 29.98 (CH_3 of CO_2t-Bu), 48.58 ($^{13}CH_2$ of CH_2Cl), 6.71 ($^{13}CMe_3$), 61.48, 61.99 ($2^{13}CH_2$ of CO_2Et), 92.07 (^{13}C–CH_2Cl), 126.21, 129.28, 129.53, 137.35, 139.15, 142.61 (alkene and Ph carbons), 159.09 (^{13}C=N-cyclohexyl), 162.17, 163.21 (^{13}C=O of $2CO_2Et$) ppm; MS: *m/z* (fragment) 407, 409 (M^+, M^++2), 361, 363 (M^+, M^++2- C_2H_5OH), 290, 292 (M^+, M^++2- C_2H_5OH, C_4H_9N); Anal. Calcd for $C_{21}H_{26}ClNO_5$: C, 61.84; H, 6.42; N, 3.43. Found: C, 61.83; H, 6.44; N, 3.46%.

Dimethyl 2-(chloromethyl)-5-(cyclohexylimino)-2,5-dihydro-2-phenylfuran-3, 4-dicarboxylate (**4i**): Light yellow crystals, m.p. 70–71°C. IR υ_{max}: 3084, 2935 (C–H), 1753, 1724 (C=O), 1683 (C=N), 1290, 1253, 1205, 1082 (C–O), 792, 736 (C–Cl) cm^{-1}; ^1H NMR δ 1.27–1.48, 1.78–1.88 (4m, 10H, CH_2 of cyclohexyl), 3.74–3.76 (m, 1H, CH of cyclohexyl), 3.80, 3.94 (2s, 6H, $2CH_3$ of CO_2Me), 4.22–4.25, 4.66–4.69 (2H, CH_2 of CH_2Cl, d. of d., *J* = 201.21 Hz, *J* = 11.64 Hz), 7.38–7.46 (2m, 5H, Ph protons,) ppm; ^{13}C NMR δ 25.24, 25.26, 26.19, 33.40, 33.93 ($^{13}CH_2$ of cyclohexyl), 48.43 ($^{13}CH_2$ of CH_2Cl), 57.26 (^{13}CH of cyclohexyl), 91.05 (^{13}C–CH_2Cl), 126.12, 129.33, 129.62, 137.10, 138.18, 142.73 (alkene and Ph carbons), 154.75 (^{13}C=N-cyclohexyl), 161.57, 162.56 (^{13}C=O of $2CO_2Me$) ppm; MS: *m/z* (fragment) 405, 407 (M^+, M^++2), 373, 375 (M^+–CH_3OH), 276, 778 (M^+–CH_3OH, $C_6H_{11}N$); Anal. Calc. for $C_{21}H_{24}ClNO_5$: C, 62.14; H, 5.95; N, 3.45. Found: C, 62.13; H, 5.94; N, 3.46%.

Diethyl 2-(chloromethyl)-5-(cyclohexylimino)-2,5-dihydro-2-phenylfuran-3, 4-dicarboxylate (**4j**): Light yellow crystals, m.p. 72–73°C. IR υ_{max}: 3017, 2982 (C–H), 1749, 1720 (C=O) 1681 (C=N), 1284, 1251, 1199, 1082 (C–O), 771, 734, 702 (C–Cl) cm^{-1}; ^1H NMR δ 1.28–1.37, 1.38–1.41 (2t, 6H, $2CH_3$ of CO_2Et), 1.37–1.91 (4m, 10H, CH_2 of cyclohexyl), 3.76–3.80 (m, 1H, CH of cyclohexyl), 4.27–4.29, 4.66–4.68 (2H, CH_2 of CH_2Cl, d. of d., *J* = 199.14 Hz, *J* = 11.68 Hz), 4.31–4.31 (2m, 2H, CH_2 of CO_2Et), 4.40–4.44 (q, 2H, *J* = 7.05 Hz, CH_2 of CO_2Et), 7.39–7.49 (2m, 5H, Ph protons) ppm; ^{13}C NMR δ 14.20, 14.48 ($2CH_3$ of CO_2Et), 25.17, 26.24, 33.42, 33.94 (CH_2 of cyclohegxyl), 48.52 (CH_2 of CH_2Cl), 57.06 (CH of cyclohegxyl), 62.44, 62.56 ($2CH_2$ of CO_2Et), 90.99 (^{13}C–CH_2Cl), 126.20, 129.24, 129.50, 137.30, 138.17, 142.50 (alkene and Ph carbons), 154.76 (^{13}C=N-cyclohegxyl), 161.23, 162.17 (^{13}C=O of $2CO_2Et$) ppm; MS: *m/z* (fragment) 434 (M^+), 388 (M^+-C_2H_5OH), 291 (M^+-C_2H_5OH, $C_6H_{11}N$); Anal. Calcd for $C_{23}H_{28}ClNO_5$: C, 63.66; H, 6.50; N, 3.23. Found: C, 63.65; H, 6.48; N, 3.25%.

Dimethyl 5-(2,4,4-trimethylpentan-2-ylimino)-2-(chloromethyl)-2,5-dihydro-2-phenylfuran-3,4-dicarboxylate (**4k**): Light yellow crystals, m.p. 73–74°C. IR υ_{max}: 3060, 2982 (C–H), 1748, 1726 (C=O), 1679 (C=N), 1239, 1217, 1028 (C–O), 746, 709 (C–Cl) cm^{-1}; ^1H NMR δ 1.04 (s, 9H, *t*-Bu), 1.43, 1.45 (2s, 6H, $2CH_3$), 2.89 (s, 2H, CH_2), 3.81, 3.94 (2s, 6H, $2CH_3$ of CO_2Me), 4.57–4.59, 4.62–4.64 (2H, d. of d., *J* = 199.76 Hz, *J* = 11.17 Hz, CH_2 of CH_2Cl), 7.39–7.51 (3m, 5H, Ph protons) ppm; ^{13}C NMR δ 29.94, 30.14 ($^{13}CH_3$ of alkyl group), 31.14 ($^{13}CH_2$ of alkyl group), 32.01 ($^{13}CH_3$ of *t*-Bu), 35.39 (^{13}C of *t*-Bu), 51.15, 51.78 ($2^{13}CH_3$ of CO_2Me), 55.80 ($^{13}CH_2$–Cl), 59.44 ($(CH_3)_3$ ^{13}C–N), 92.50 (^{13}C–CH_2Cl), 123.17, 124.51, 126.35, 129.17, 132.54, 139.94, 142.48 (alkene and Ph carbons), 154.09 (^{13}C=N-alkyl), 162.69, 163.25 (^{13}C=O of $2CO_2Me$) ppm; MS: *m/z* (fragment) 477, 479 (M^+, M^++2), 431, 433 (M^+, M^++2-C_2H_5OH), 334, 336 (M^+, M^++2-C_2H_5OH, $C_6H_{11}N$); Anal. Calcd for $C_{23}H_{28}BrNO_5$: C, 57.75; H, 5.90; N, 2.93. Found: C, 57.75; H, 5.87; N, 2.94%.

Dimethyl 5-(tert-butylimino)-2-(bromomethyl)-2,5-dihydro-2-phenylfuran-3,4-dicarboxylate (**4l**): Yellow crystals, m.p. 77–78 °C. IR υ_{max}: 3058, 2990 (C–H), 1756, 1723 (C=O), 1680 (C=N), 1290, 1238, 1219 (C–O), 789, 740(C–Br) cm^{-1}; ^1H NMR δ 1.45 (s, 9H, *t*-Bu), 3.87, 3.99 (2s, 6H, $2CH_3$ of CO_2Me), 4.33–4.35, 4.53–4.55 (2H, d. of d., *J* = 200.12 Hz, *J* =11.01 Hz, CH_2 of CH_2Br), 7.36–7.40 (2m, 5H, Ph protons) ppm; ^{13}C NMR δ 30.16 (CH_3 of *t*-Bu), 37.29 ($^{13}CH_2$

of CH$_2$Br), 50.46(^{13}CMe$_3$), 52.26, 52.68 (2^{13}CH$_3$ of CO$_2$Me), 91.03 (^{13}CH$_2$–Br), 126.24, 129.29, 129.51, 137.63, 138.86, 143.52 (alkene and Ph carbons), 155.70 (^{13}C=N-*t*-Bu), 162.15, 163.28 (^{13}C=O of 2CO$_2$Me) ppm; MS: *m/z* (fragment) 423, 425 (M$^+$, M$^+$+2), 391, 393 (M$^+$, M$^+$+2–CH$_3$OH), 320, 322 (M$^+$, M$^+$+2–CH$_3$OH, C$_4$H$_9$N); Anal. Calcd for C$_{19}$H$_{22}$BrNO$_5$: C, 53.79; H, 5.23; N, 3.30. Found: C, 53.81; H, 5.26; N, 3.33%.

Diethyl 5-(tert-butylimin-o)-2-(bromomethyl)-2,5-dihydro-2-phenylfuran-3,4-dicarboxylate (**4m**): Yellow crystals, m.p. 79–80 °C. IR υ_{max}: 3049, 2993 (C–H), 1753, 1718 (C=O), 1681 (C=N), 1287, 1245, 1209 (C–O), 781, 739 (C–Br) cm^{-1}; ^{1}H NMR δ 1.29–1.33, 1.37–1.41 (2t, 6H, 2CH$_3$ of CO$_2$Et), 1.48 (s, 9H, *t*-Bu), 4.30–4.32, 4.50–4.52 (2H, d. of d., *J* = 199 08 Hz, *J* = 11.05 Hz, CH$_2$ of CH$_2$Br), 7.32–7.37 (3m, 5H, Ph protons) ppm; ^{13}C NMR δ 15.03, 15.98 (2^{13}CH$_3$ of CO$_2$Et), 30.14 (CH$_3$ of *t*-Bu), 38.90 (^{13}CH$_2$ of CH$_2$Br), 53.09 (^{13}CMe$_3$), 60.19, 60.95 (2 ^{13}CH$_2$ of CO$_2$Et), 91.72 (^{13}C–CH$_2$-Br), 126.01, 128.93, 129.60, 137.51, 139.57, 142.12 (alkene and Ph carbons), 157.11 (^{13}C=N-*t*-Bt), 161.83, 162.64 (^{13}C=O of 2CO$_2$Me) ppm; MS: *m/z* (fragment) 451, 453 (M$^+$, M$^+$+2), 405, 407 (M$^+$, M$^+$+2–CH$_3$OH), 334, 336 (M$^+$, M$^+$+2–CH$_3$OH, C$_4$H$_9$N); Anal. Calcd for C$_{21}$H$_{26}$BrNO$_5$: C, 55.76; H, 5.79; N, 3.10. Found: C, 55.78; H, 5.77; N, 3.12%.

Dimethyl 2-(bromomethyl)-5-(cyclohexylimino)-2,5-dihydro-2-phenylfuran-3, 4-dicarboxylate (**4n**): Yellow crystals, m.p. 74–75 °C. IR υ_{max}: 3032, 2944 (C–H), 1758, 1726 (C=O), 1684 (C=C), 1292, 1236, 1205, 1083 (C–O), 792, 736, 698 (C–Br) cm^{-1}; ^{1}H NMR δ 1.27–1.91 (5m, 10H, CH$_2$ of cyclohexyl), 3.74–3.76 (m, 1H, CH of cyclohexyl), 3.81, 3.94 (2s, 6H, 2CH$_3$ of CO$_2$Me), 4.12–4.14, 4.56–4.58 (2H, CH$_2$ of CH$_2$Br, d. of d., *J* = 201.62 Hz, *J* = 11.59 Hz), 7.37–7.47 (2m, 5H, Ph protons) ppm; ^{13}C NMR δ 25.23, 25.27, 26.18, 33.36, 33.95 (CH$_2$ of cyclohexyl), 24.88, 37.23 (^{13}CH$_2$ of CH$_2$Br), 53.32, 53.47 (^{13}CH$_3$ of 2CO$_2$Me), 57.30 (^{13}CH of cyclohexyl), 90.31 (^{13}C–CH$_2$Br), 126.18, 129.33, 129.59, 137.24, 137.95, 143.39 (alkene and Ph carbons), 154.66 (^{13}C=N-cyclohexyl), 161.52, 162.56 (^{13}C=O of 2CO$_2$Me) ppm; MS: *m/z* (fragment) 449, 451 (M$^+$, M$^+$+2), 417, 419 (M$^+$, M$^+$+2–CH$_3$OH), 320, 322 (M$^+$, M$^+$+2–CH$_3$OH, C$_6$H$_{11}$N); Anal. Calcd for C$_{21}$H$_{24}$BrNO$_5$: C, 56.01; H, 5.37; N, 3.11. Found: C, 56.00; H, 5.38; N, 3.13%.

Diethyl 2-(bromomethyl)-5-(cyclohexylimino)-2,5-dihydro-2-phenylfuran-3,4-dicarboxylate (**4o**): Yellow crystals, m.p.76–77 °C. IR υ_{max}: 3060, 2950 (C–H), 1749, 1720 (C=O), 1684 (C=N), 1299, 1257, 1197, 1093 (C–O) cm^{-1}; ^{1}H NMR δ 1.28–1.31, 1.39–1.41 (2t, 6H, 2CH$_3$ of CO$_2$Et), 1.37–1.92 (5m, 10H, CH$_2$ of cyclohexyl), 3.77–3.81 (m, 1H, CH of cyclohexyl), 4.41–4.16, 4.55–4.76 (2H, CH$_2$ of CH$_2$Br, d. of d., *J* = 201.77 Hz, *J* = 11.68 Hz), 4.22–4.31 (m, 2H, CH$_2$ of CO$_2$Et), 4.39–4.44 (q, 2H, CH$_2$ of CO$_2$Et, *J* = 7.33 Hz), 7.38–7.51 (2m, 5H, Ph protons) ppm; ^{13}C NMR δ 14.21, 14.49 (2CH$_3$ of CO$_2$Et), 25.15, 25.18, 16.24, 33.38, 33.96 (^{13}CH$_2$ of cyclohexyl), 37.31 (^{13}CH$_2$ of CH$_2$Br), 62.46, 62.56 (2^{13}CH$_2$ of CO$_2$Et), 90.52 (^{13}C–CH$_2$Br), 126.26, 129.24, 129.48, 137.46, 137.95, 143.15 (alkene and Ph carbons), 154.67 (^{13}C=N-cyclohexyl), 161.17, 162.15 (^{13}C=O of 2CO$_2$Et) ppm; MS: *m/z* (fragment) 477, 479 (M$^+$, M$^+$+2), 431, 433 (M$^+$, M$^+$+2-C$_2$H$_5$OH), 334, 336 (M$^+$, M$^+$+2-C$_2$H$_5$OH, C$_6$H$_{11}$N); Anal. Calcd for C$_{23}$H$_{28}$BrNO$_5$: C, 57.75; H, 5.90; N, 2.93. Found: C, 57.75; H, 5.87; N, 2.94%.

Dimethyl 5-(2,4,4-trimethylpentan-2-ylimino)-2-(bromomethyl)-2,5-dihydro-2-phenylfuran-3,4-dicarboxylate (**4p**): Yellow crystals, m.p. 75–76 °C. IR υ_{max}: 3062, 2975 (C–H), 1745, 1727 (C=O), 1680 (C=N), 1260, 1249, 1225 (C–O), 785, 738 (C–Br) cm^{-1}; ^{1}H NMR δ 1.05 (s, 9H, *t*-Bu), 1.45, 1.47 (2s, 6H, 2CH$_3$), 2.89 (s, 2H, CH$_2$), 3.79, 3.95 (2s, 6H, 2CH$_3$ of CO$_2$Me), 4.35–4.37, 4.42–4.44 (2H, d. of d., *J* = 201.70 Hz, *J* = 11.48 Hz, CH$_2$ of CH$_2$Cl), 7.46–7.54 (3m, 5H, Ph protons) ppm; ^{13}C NMR δ 28.85, 29.70 (^{13}CH$_3$ of alkyl group), 31.35 (^{13}CH$_2$ of alkyl group), 31.91 (^{13}CH$_3$ of *t*-Bu), 36.86 (^{13}C of *t*-Bu), 50.61, 51.57 (2^{13}CH$_3$ of CO$_2$Me), 53.16 (^{13}CH$_2$–Cl), 59.46 ((CH$_3$)$_2$ ^{13}C–N), 90.08 (^{13}C–CH$_2$Br), 124.19, 125.85, 126.16, 129.09, 132.47, 139.43, 141.62 (alkene and Ph carbons), 154.16 (^{13}C=N-alkyl), 162.71, 163.30 (^{13}C=O of 2CO$_2$Me) ppm; MS: *m/z* (fragment) 479, 481 (M$^+$, M$^+$+2), 447, 449 (M$^+$, M$^+$+2–CH$_3$OH), (M$^+$, M$^+$+2-C$_2$H$_5$OH, C$_8$H$_{17}$N); Anal. Calcd for C$_{23}$H$_{30}$BrNO$_5$: C, 57.50; H, 6.29; N, 2.92. Found: C, 57.51; H, 6.27; N, 2.93%.

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