Convenient Synthesis of Substituted α-Methylene-δ-valerolactones in Aqueous Medium Using Baylis–Hillman Chemistry

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Abstract: A mild and convenient synthesis of substituted α-methylene-δ-valerolactones was achieved by S$_\text{N}$2 nucleophilic substitution of the acetates of Baylis–Hillman adducts with acetyl acetone followed by one-pot saponification of the ester, reduction of the keto group, and subsequent intramolecular ring closure in aqueous medium.

Key words: Baylis–Hillman, α-methylene-δ-valerolactone, nucleophilic substitution, aqueous medium

The α-methylene-δ-valerolactone moiety is a substructural component of several natural products of biological interest such as vernolepin, vernomenin, pentenalolactone E, teucromiumlactone, and crassin. The importance of α-methylene-δ-valerolactone for the synthesis of α-saturated-δ-valerolactones and C–C bond forming transformations have been widely demonstrated. These considerations possibly led to several elegant approaches towards the synthesis of a variety of α-methylene-δ-valerolactones. The state of the art synthesis of this class of compounds, however, still requires a strategy, which would permit a mild and efficient synthesis of α-methylene-δ-valerolactone. It would be an advantage if the synthesis could be carried out in one pot and without elaborate reaction conditions. In continuation of our studies on the Baylis–Hillman reaction, we believed the reaction could be carried out as a one-pot synthesis.

The ability of the Baylis–Hillman reaction to afford β-hydroxy-α-methylene-ester in a single-step has been efficiently utilized by several groups for the synthesis of a variety of α-alkylidene-lactones. The construction of these lactones have either resulted directly from the Baylis–Hillman products or through acetates and bro-mides obtained from the Baylis–Hillman adducts. In principle, Baylis–Hillman reactions can be utilized for the one-pot synthesis of α-methylene-valerolactones by carrying out S$_\text{N}$2 nucleophilic substitution on the acetates of Baylis–Hillman adducts by acetyl acetone followed by saponification of the ester, reduction of the keto group, and subsequent intramolecular ring closure leading to lactonization.

The Baylis–Hillman adducts 1a–u, generated through methods described in the literature upon acetylation in the presence of pyridine and acetyl chloride yielded acetates 2a–u (Scheme 1). Subsequent S$_\text{N}$2 nucleophilic addition of acetyl acetone to acetates 2a–u in the presence of DABCO in THF–water led to the synthesis of diketo derivatives 3a–u in excellent yields. Initially during optimization studies, through the tandem deacetylation and saponification of the esters 3a, c–e with 15% aqueous KOH or NaOH in methanol furnished monoketo acids 4a, c–e as the major products, minor amounts of diketo acids 5a, e were also formed. The separation of these acids (4 and 5) through column chromatography was tedious and the need arose for a process which could eliminate the formation of compound 5. It was discovered that unlike the reaction in methanol, if the saponification is carried out in aqueous medium the monoketo acid was afforded exclusively. Therefore, saponification with 15% aqueous NaOH at ambient temperature for four to five hours yielded exclusively the acid 4 and the formation of this acid can be expedited if the reaction mixture was refluxed for ten minutes. In a parallel study the monoketo acid 4 was subjected to NaBH$_4$ reduction in the presence of NaOH to yield the hydroxy acid in two hours. Subsequent intramolecular cyclization in the presence of HCl at ambient temperature after 48 hours gave the desired lactone 6 in high yields. At this stage it occurred to us that a one-pot procedure for obtaining α-methylene-δ-valerolactones is possible. Accordingly, we treated the keto ester 3 with aqueous NaOH at reflux for ten minutes, followed by NaBH$_4$ treatment in the same flask. On completion of the reduction, as evidenced by TLC, HCl was added to the reaction mixture and it was then refluxed for one hour. Modification of the reaction process in this fashion expedited the reaction sequence without the need to separate and purify the products at every stage. While this synthetic strategy worked very well for the conversion of a variety of keto esters 3a–u to α-methylene-δ-valerolactones 6a–u (Table 1), the reaction failed to yield the desired product with nitro-substituted phenyl derivative 3i (Table 1, entry 9). The lactones were obtained as diastereoisomeric mixtures as seen in both the HPLC and spectroscopic analysis and therefore separation of the diastereoisomers was attempted. Interestingly, the separation was possible only for products 6f, 6g, 6h, 6j, and 6k where the substituent R was a 2-halophenyl moiety, furan, or a thiophene ring. In all other cases separation of the mixtures was unsuccessful (even with a semi-preparative HPLC system). The relative stereochemistry of products 6 where the diastereoisomers were separated was assigned on the basis of NOE experimen-
ments. It was found conclusively through NOE experiments that the less polar diastereoisomer had the relative stereochemistry between the hydrogen on C-4 and C-6 as syn while in the more polar compound it was anti (Figure 1).

\[ 
\begin{array}{c}
\text{Scheme 1} \quad \text{Reagents and conditions:} \quad \text{a)} \text{AcCl, pyridine, CH}_2\text{Cl}_2, \text{r.t., 2–6 h;} \quad \text{b)} \text{acetyl acetone, DABCO, THF–H}_2\text{O;} \quad \text{c)} 15\% \text{ KOH or NaOH, MeOH, r.t., 4 h;} \quad \text{d)} 15\% \text{ aq NaOH, reflux, 10 min;} \quad \text{e)} \text{NaBH}_4, \text{aq NaOH, r.t., 2 h;} \quad \text{f)} \text{aq HCl, reflux, 1 h.}
\end{array}
\]

Thus, in summary we have described a convenient and practical synthesis of \(\alpha\)-methylene-\(\delta\)-valerolactones in which all reactions were performed in water, an environmentally friendly and benign medium, and in one flask without the need to work up every step. The operational simplicity of this synthetic route will be helpful to elaborate the chemistry and bioactivity of \(\alpha\)-methylene-\(\delta\)-valerolactones, which still remains unexplored.

**Table 1** Structure and Yields\(^a\) of \(\alpha\)-Methylene-\(\delta\)-valerolactones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diketo ester</th>
<th>Lactone</th>
<th>Yield%</th>
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**Figure 1** Structures of the separated diastereoisomers in compound 6g.
Table 1  Structure and Yields* of α-Methylene-δ-valerolactones (continued)

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* The yields reported herein of α-methylene-δ-valerolactones 6 obtained through a one-pot reaction from diketo esters 3.

** Syn and anti isomers were separated.

MPs are uncorrected and were determined in capillary tubes on a hot stage apparatus containing silicon oil. HPLC was carried out on an Agilent 1100 system possessing a DA detector (λmax = 220 nm, 254 nm) using 0–100% MeCN in H2O containing 0.1% TFA in 30 min on a RP-18e column (250 × 4.6 mm) having particle size of 5 μm. IR spectra were recorded using a Perkin Elmer RX FTIR spectrophotometer. 1H NMR and 13C NMR spectra were recorded on either a 300 or a 200 MHz FT spectrometer, using TMS as an internal standard. The FABMS were recorded on JEOL/ SX-102 spectrometers and ESMS were recorded through direct flow injections in Merck M-8000 LCMS system. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar’s Vario EL III microanalyzer. The spectroscopic data for all products obtained as diastereoisomeric mixtures are presented as such, while for compounds 6f, 6g, 6h, 6j, and 6k syn and anti diastereoisomers were separated, the data is presented separately as A and B, respectively. Ratio of syn/anti was ca. 50:50 as evidenced from analytical HPLC and 1H NMR data. Column chromatography was carried out on silica gel.

3a–u: Typical Procedure
To a soln of acetate 2a (8.0g, 34.18 mmol) in THF–H2O (1:1, 30 mL) was added DABCO (4.61 g, 40.97 mmol) and the reaction was allowed to proceed at r.t. As soon as the solution became clear (ca 30 min), acetyl acetone (3.57 mL, 34.18 mmol) in THF was added dropwise with stirring. The reaction was complete in 2 h, after which the reaction mixture was extracted with EtOAc (2 × 100 mL). The organic layers were combined, dried over anhyd Na2SO4, and evaporated to give a residue, which was purified by chromatography (hexane–EtOAc, 70:30).

4-Acetyl-2-methylene-5-oxo-3-phenylhexanoic Acid Methyl Estter (3a)
Yield 6.55 g (83%); white solid; mp 100–102 °C; δ 17.3 min.
IR (KBr): 1694 (2 × C=O), 1724 (CO2CH3) cm–1.
1H NMR (CDCl3, 200 MHz): δ = 1.88 (s, 3 H, COCH3), 2.20 (s, 3 H, COCH3), 3.68 (s, 3 H, CO2CH3), 4.57 [d, 1 H, J = 12.4 Hz, CH(COCH3)2], 4.79 (d, 1 H, J = 12.4 Hz, CHAr), 5.74 (s, 1 H, =CHAr), 6.30 (s, 1 H, 1 H =C/H), 7.25 (s, 5 H, ArH).
13C NMR (CDCl3, 50.32 MHz): δ = 28.8, 31.0, 46.7, 52.5, 73.8, 125.5, 127.8, 128.8, 129.1, 139.0, 141.3, 166.7, 202.9.
MS (FAB+): m/z = 275 (M+ + 1).

4-Acetyl-2-methylene-5-oxo-3-p-tolylhexanoic Acid Methyl Estter (3b)
Yield: 84%; white solid; mp 108–110 °C; δ 18.5 min.
IR (KBr): 1693 (2 × C=O), 1722 (CO2CH3) cm–1.
1H NMR (CDCl3, 200 MHz): δ = 1.93 (s, 3 H, COCH3), 2.19 (s, 3 H, COCH3), 3.68 (s, 3 H, CO2CH3), 4.54 [d, 1 H, J = 12.6 Hz, CH(COCH3)2], 4.75 (d, 1 H, J = 12.4 Hz, CHAr), 5.71 (s, 1 H, =CHAr), 6.26 (s, 1 H, CHH), 7.06 (d, 2 H, J = 8.2 Hz, ArH), 7.13 (d, 2 H, J = 8.2 Hz, ArH).
13C NMR (CDCl3, 50.32 MHz): δ = 21.4, 28.8, 31.0, 46.3, 52.5, 73.8, 125.2, 128.6, 135.9, 137.4, 141.4, 166.8, 203.1.
MS (FAB+): m/z = 289 (M+ + 1).

4-Acetyl-2-methylene-5-oxo-3-(4-trifluoromethylphenyl)hexanoic Acid Methyl Estter (3c)
Yield: 81%; white solid; mp 114–115 °C; δ 19.5 min.
IR (KBr): 1696 (2 × C=O), 1722 (CO2CH3) cm–1.
1H NMR (CDCl3, 200 MHz): δ = 1.94 (s, 3 H, COCH3), 2.19 (s, 3 H, COCH3), 3.70 (s, 3 H, CO2CH3), 4.60 [d, 1 H, J = 12.4 Hz, CH(COCH3)2], 4.87 (d, 1 H, J = 12.4 Hz, CHAr), 5.79 (s, 1 H, =CHAr), 6.34 (s, 1 H, CHH), 7.38 (d, 2 H, J = 8.2 Hz, ArH), 7.54 (d, 2 H, J = 8.2 Hz, ArH).

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1H NMR (CDCl₃, 200 MHz): δ = 2.87, 7.07–7.57 (m, 4 H, ArH).

IR (KBr): 1697 (2 × C=O), 1722 (CO₂CH₃) cm⁻¹.

Yield: 79%; pale yellow oil; tᵣ 17.9 min.

IR (neat): 1720 (br, 2 × C=O, CO₂CH₃) cm⁻¹.


2-(2-Acetyl-2-yl-1-oxobutyl)acrylic Acid Methyl Ester (3j)

Yield: 80%; white solid; mp 50–52 °C; tᵣ 16.1 min.

IR (KBr): 1720 (br, 2 × C=O, CO₂CH₃) cm⁻¹.

4-Acetyl-2-methylene-5-oxo-3-(5-phenylisoxazol-3-yl)hexanoic Acid Methyl Ester (3m)

Yield: 85%; white solid; mp 45–47 °C; Rf 18.9 min.

IR (KBr): 1694 (CO=O), 1725 (CO2CH3) cm–1.

1H NMR (CDCl3, 200 MHz): δ = 2.19 (s, 3 H, COCH3), 2.24 (s, 3 H, COCH3), 3.78 (s, 3 H, CO2CH3), 4.83 [d, 1 H, J = 12.0 Hz, CH(CHOCOCH3)2], 5.10 (d, 1 H, J = 12.0 Hz, HetCH), 5.94 (s, 1 H, =CHH), 6.41 (s, 1 H, =CHH), 6.45 (s, 1 H, HetH), 7.41–7.47 (m, 3 H, ArH), 7.72–7.81 (m, 2 H, ArH).

MS (ES+): m/z = 351.93 (M+ + Na).


2-[2-Acetyl-1-[3-(2-chlorophenyl)isoxazol-5-yl]-3-oxobuty]acrylic Acid Methyl Ester (3o)

Yield: 70%; white solid; mp 136–138 °C; tR 19.6 min.

IR (KBr): 1694 (CO=O), 1725 (CO2CH3) cm–1.

1H NMR (CDCl3, 200 MHz): δ = 2.19 (s, 3 H, COCH3), 2.24 (s, 3 H, COCH3), 3.78 (s, 3 H, CO2CH3), 4.82 [d, 1 H, J = 12.0 Hz, CH(CHOCOCH3)2], 5.06 (d, 1 H, J = 12.0 Hz, HetCH), 5.93 (s, 1 H, =CHH), 6.38 (s, 1 H, =CHH), 6.43 (s, 1 H, HetH), 7.23 (d, 2 H, J = 8.0 Hz, ArH), 7.63 (d, 2 H, J = 8.0 Hz, ArH).

MS (ES+): m/z = 377.73 (M+ + Na).

Anal. Calcd for C19H19ClNO5: C, 63.43; H, 5.96; N, 3.94. Found: C, 67.79; H, 5.98; N, 3.38.

2-[2-Acetyl-3-(3-phenylisoxazol-5-yl)butyl]acrylic Acid Methyl Ester (3q)

Yield: 83%; white solid; mp 108–110 °C; tR 18.5 min.

IR (KBr): 1721 (br, 2 × CO=O, CO2CH3) cm–1.

1H NMR (CDCl3, 200 MHz): δ = 2.20 (s, 3 H, COCH3), 2.24 (s, 3 H, COCH3), 3.78 (s, 3 H, CO2CH3), 4.84 [d, 1 H, J = 11.9 Hz, CH(CHOCOCH3)2], 5.09 (d, 1 H, J = 11.9 Hz, HetCH), 5.95 (s, 1 H, =CHH), 6.43 (s, 1 H, HetH), 7.41–7.47 (m, 3 H, ArH), 7.72–7.81 (m, 2 H, ArH).

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2-Methylene-5-oxo-3-(4-trifluoromethylphenyl)hexanoic Acid

Yield: 88%; white solid; mp 106–108 °C; IR (KBr): 1624 (C=O), 1678 (CO2H) cm–1.

Anal. Calcd for C19H17Cl2NO5: C, 55.63; H, 4.18; N, 3.41. Found: C, 55.86; H, 4.55; N, 3.58.

MS (ES+): m/z = 413.67 (M+ + Na).

6-Methyl-3-methylene-4-phenyltetrahydropyran-2-one (6a)

Pale yellow oil; tR 17.6, 17.9 min.

IR (neat): 1704 (br, C=O, CO2H) cm–1.


6a-e from 4a-e; Typical Procedure

A mixture of keto ester 3b (2.0 g, 69.4 mmol) and 15% aq NaOH (20 mL) was refluxed for 10 min. After cooling to r.t., NaBH4 (0.263 g, 69.4 mmol) was added, and the mixture was stirred at ambient temperature for 2 h. Finally, the reaction mixture was acidified to pH 2.0 by the addition of concd HCl at 0 °C and refluxed for 1 h or stirred for 1 h. On completion, the mixture was extracted with EtOAc (2 × 50 mL) and H2O (100 mL). The organic layers were combined, washed with brine, dried over anhyd Na2SO4, and evaporated to give an oily residue. This residue was purified by column chromatography (hexane–EtOAc, 85:15) to afford 1.18 g (78.7%) of 6b as colorless oil.

6-Methyl-3-methylene-4-phenyltetrahydropyran-2-one (6a)
6-Methylen-3-methylene-4-(4-fluorophenyl)tetrahydropyran-2-one (6c)

Colorless oil; \( t_f = 19.7 \) min.

IR (neat): 1716 (C=O) cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\), 200 MHz): \( \delta = 1.37 \) (d, 3 H, J = 6.2 Hz, CH\(_3\)), 1.44 (d, 3 H, J = 2.6 Hz, CH\(_2\)CH\(_3\)), 2.05–2.14 (m, 2 × 2 H, CH\(_2\)CH\(_2\)CH\(_3\)), 3.78 (d, 1 H, J = 2.1 Hz, CHCH\(_3\)), 4.09 (d, 1 H, J = 4.8 Hz, CHCH\(_3\)), 4.43–4.44 (m, 1 H, CHAr), 4.61–4.64 (m, 1 H, CHAr), 5.24–5.25 (m, 1 H, CH\(_2\)), 5.55–5.56 (m, 1 H, s=CH), 6.58 (d, 1 H, J = 2.7 Hz, =CH), 6.69 (s, 1 H, s=CH), 7.13–7.15 (m, 2 × 2 H, ArH), 7.32–7.34 (m, 2 × 2 H, ArH).

\(^13\)C NMR (CDCl\(_3\), 50.32 MHz): \( \delta = 21.7, 22.1, 37.8, 39.1, 41.8, 44.6, 73.2, 76.0, 129.4, 129.8, 130.9, 131.7, 133.5, 136.3, 138.7, 141.3, 163.5, 168.5.

MS (ES+): \( m/z = 236.93 \) (M\(^+\) + Na).

Anal. Calcd for C\(_{13}\)H\(_{13}\)BrO\(_2\): C, 55.54; H, 4.66. Found: C, 55.58; H, 5.64.

syn-4-(2-Bromophenyl)-6-methyl-3-methylenetetrahydropyran-2-one (6f-A)

White solid; mp 38–40 °C; \( t_f = 19.7 \) min.

IR (KBr): 1720 (C=O) cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\), 200 MHz): \( \delta = 1.37 \) (d, 3 H, J = 6.2 Hz, CH\(_2\)CH\(_3\)), 1.97–2.26 (m, 2 H, CH\(_2\)CH\(_2\)CH\(_3\)), 4.38–4.46 (m, 2 H, CHAr, CH\(_2\)CH\(_2\)CH\(_3\)), 5.59 (s, 1 H, s=CH), 6.72 (s, 1 H, s=CH), 7.09–7.11 (m, 1 H, ArH), 7.21–7.27 (m, 2 H, ArH), 7.39–7.44 (m, 1 H, ArH).

\(^13\)C NMR (CDCl\(_3\), 50.32 MHz): \( \delta = 21.9, 37.6, 41.3, 73.3, 128.0, 128.9, 129.4, 130.2, 134.1, 137.6, 140.3, 166.2.

MS (ES+): \( m/z = 236.93 \) (M\(^+\) + Na).


anti-4-(2-Chlorophenyl)-6-methyl-3-methylenetetrahydropyran-2-one (6g-B)

Colorless oil; \( t_f = 19.1 \) min.

IR (neat): 1716 (C=O) cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\), 200 MHz): \( \delta = 1.45 \) (d, 3 H, J = 6.2 Hz, CH\(_2\)CH\(_3\)), 1.88–2.00 (m, 1 H, CH\(_2\)CH\(_2\)CH\(_3\)), 2.14–2.21 (m, 1 H, CH\(_2\)CH\(_2\)CH\(_3\)), 4.39–4.46 (m, 1 H, CHAr), 4.57–4.66 (m, 1 H, CH\(_2\)CH\(_2\)CH\(_3\)), 5.28 (d, 1 H, J = 2.6 Hz, =CH), 6.59 (s, 1 H, J = 2.8 Hz, =CH), 7.10–7.32 (m, 3 H, ArH), 7.59 (dd, 1 H, J = 2.0, 8.0 Hz, ArH).

\(^13\)C NMR (CDCl\(_3\), 50.32 MHz): \( \delta = 21.6, 37.5, 41.3, 73.3, 128.0, 128.9, 129.4, 130.2, 134.1, 137.6, 140.3, 166.2.

MS (ES+): \( m/z = 236.93 \) (M\(^+\) + Na).


anti-4-(2-Chlorophenyl)-6-methyl-3-methylenetetrahydropyran-2-one (6g-A)

Colorless oil; \( t_f = 19.1 \) min.

IR (neat): 1716 (C=O) cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\), 200 MHz): \( \delta = 1.45 \) (d, 3 H, J = 6.2 Hz, CH\(_2\)CH\(_3\)), 1.92–2.14 (m, 2 H, CH\(_2\)CH\(_2\)CH\(_3\)), 4.38–4.46 (m, 2 H, CHAr, CH\(_2\)CH\(_2\)CH\(_3\)), 5.59 (s, 1 H, s=CH), 6.72 (s, 1 H, s=CH), 7.09–7.11 (m, 1 H, ArH), 7.21–7.27 (m, 2 H, ArH), 7.39–7.44 (m, 1 H, ArH).

\(^13\)C NMR (CDCl\(_3\), 50.32 MHz): \( \delta = 21.9, 37.6, 41.3, 73.3, 128.0, 128.9, 130.2, 134.2, 137.6, 140.3, 166.3.

MS (ES+): \( m/z = 236.93 \) (M\(^+\) + Na).

Anal. Calcd for C\(_{13}\)H\(_{13}\)ClO\(_2\): C, 65.58; H, 5.70. Found: C, 63.57; H, 5.70.
**anti-6-Methyl-3-methylene-4-thiophen-2-yltetrahydropyran-2-one (6k-B)**

Yellow oil; \( t_k = 8.6 \) min (not resolved).

**IR (neat):** 1716 (C=O) cm\(^{-1}\).

**1H NMR (CDCl\(_3\), 200 MHz):** \( \delta = 1.45 \) (d, 3 H, J = 6.4 Hz, CH\(_2\)CH\(_3\)), 1.49 (m, 3 H, CH\(_2\)CH\(_3\)), 2.57–2.64 (m, 1 H, =C=CHCH\(_3\)), 4.32–4.39 (m, 1 H, =C=CHCH\(_3\)), 6.57 (s, 1 H, =CH\(_2\)), 7.49 (m, 1 H, HCHCH\(_3\)), 7.66 (m, 1 H, HCHCH\(_3\)), 8.5–8.50 (m, 2 H, HetH).

**MS (FAB+):** \( m/z = 204 \) (M\(^+\)).

Anal. Calcd for C\(_{12}\)H\(_{14}\)NO\(_2\): C, 70.92; H, 6.45; N, 6.89. Found: C, 70.67; H, 6.75; N, 6.50.

**6-Methyl-3-methylene-4-pyrindin-3-yltetrahydropyran-2-one (6l)**

White solid; mp 114–116 °C; \( t_k = 18.0, 18.4 \) min.

**IR (KBr):** 1711 (C=O) cm\(^{-1}\).

**1H NMR (CDCl\(_3\), 200 MHz):** \( \delta = 1.42–1.49 \) (d, 3 H, J = 6.2 Hz, CH\(_2\)CH\(_3\)), 1.97–2.31 (m, 2 × 2 H, CH\(_2\)CH\(_2\)CH\(_3\)), 4.16–4.27 (m, 2 × 1 H, HetCH), 4.59–4.66 (m, 2 × 1 H, CH\(_2\)CH\(_2\)CH\(_3\)), 5.59 (d, 1 H, J = 2.2 Hz, =CH\(_2\)), 6.57 (s, 1 H, =CH\(_2\)), 6.68 (d, 1 H, J = 2.6 Hz, =CH\(_2\)), 7.47–7.48 (m, 2 × 3 H, ArH), 7.75–7.77 (m, 2 × 2 H, ArH).

**13C NMR (CDCl\(_3\), 75.46 MHz):** \( \delta = 20.3, 20.5, 33.7, 34.0, 35.0, 35.3, 72.5, 74.2, 96.2, 97.5, 124.8, 126.0, 128.0, 129.5, 129.9, 130.4, 132.9, 133.8, 163.8, 164.0, 169.7.

**MS (FAB+):** \( m/z = 270 \).

Anal. Calcd for C\(_{22}\)H\(_{23}\)N\(_4\)O\(_2\): C, 71.36; H, 5.61; N, 5.20. Found: C, 70.99; H, 5.75; N, 4.82.
6-Methyl-3-methylene-4-(5-methyl-3-phenylisoxazol-4-yl)tetrahydropyran-2-one (60)
Yellow oil; \( t_f \) 17.2 min (not resolved).

IR (neat): 1721 cm\(^{-1}\).  
IR (KBr): 1717 cm\(^{-1}\).

\[\text{IR (neat): 1721 (C=O) cm}^{-1}\]

\[\text{IR (KBr): 1717 (C=O) cm}^{-1}\]

\[\text{MS (FAB+): } m/z = 370.13 (M^+ + Na)\]  
Anal. Calcd for C\(_{16}\)H\(_{15}\)NO\(_3\)·H\(_2\)O: C, 66.89; H, 5.96; N, 4.88. Found: C, 55.46; H, 4.34; N, 3.69.

4-[3-(2-Chlorophenyl)-5-methylisoxazol-4-yl]-6-methyl-3-methylenetetrahydropyran-2-one (6p)
White solid; mp 103–105 °C; \( t_f \) 18.2 min (not resolved).

IR (KBr): 1717 cm\(^{-1}\).

\[\text{IR (KBr): 1717 (C=O) cm}^{-1}\]

\[\text{MS (FAB+): } m/z = 326.27 (M^+ + Na)\]  
Anal. Calcd for C\(_{17}\)H\(_{16}\)ClNO\(_3\): C, 66.89; H, 4.91; N, 4.88. Found: C, 66.66; H, 5.10; N, 5.04.

4-[3-(2-Chlorophenyl)isoxazol-5-yl]-6-methyl-3-methylenetetrahydropyran-2-one (6s)
Yellow oil; \( t_f \) 18.3, 18.5 min.

IR (neat): 1720 cm\(^{-1}\).

\[\text{IR (neat): 1720 (C=O) cm}^{-1}\]

\[\text{MS (FAB+): } m/z = 310.20 (M^+ + Na)\]  
Anal. Calcd for C\(_{17}\)H\(_{17}\)NO\(_3\): C, 66.89; H, 4.65; N, 4.61. Found: C, 63.51; H, 5.04; N, 4.33.

\[\text{IR (neat): 1720 (C=O) cm}^{-1}\]

\[\text{MS (FAB+): } m/z = 326.27 (M^+ + Na)\]  
Anal. Calcd for C\(_{17}\)H\(_{16}\)ClNO\(_3\): C, 66.89; H, 4.91; N, 4.88. Found: C, 66.66; H, 5.10; N, 5.04.

\[\text{IR (neat): 1720 (C=O) cm}^{-1}\]

\[\text{MS (FAB+): } m/z = 310.20 (M^+ + Na)\]  
Anal. Calcd for C\(_{17}\)H\(_{17}\)NO\(_3\): C, 66.89; H, 4.65; N, 4.61. Found: C, 63.51; H, 5.04; N, 4.33.
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References

(1) CDRI Communication No. 6732.