A Facile Synthesis of [1,2]Oxazinane-3,5-diones

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Received May 17, 1999

4-Acyl substituted [1,2]oxazinane-3,5-diones have been recently known as herbicides, plant growth regulators, and pesticides, and extensively studied by Shy-Fuh Lee.1 The preparation of [1,2]oxazinane-3,5-diones involves the reaction of N-alkyl-O-alkoxycarbonylmethylhydroxylamine and alkyl 3-chloro-3-oxopropionate, followed by the subsequent cyclocondensation and decarboxylation reactions under basic conditions.1 The resulting [1,2]oxazinane-3,5-diones could be converted to 4-acylated derivatives by O-acylation followed by consecutive cyanide catalized rearrangement.2 The diverse synthesis of [1,2]oxazinane-3,5-dione derivatives has not been studied by limited synthetic methods in spite of their biological potentials. Here we wish to report a facile synthesis of [1,2]oxazinane-3,5-diones starting from readily available amines or hydroxylamines in excellent yields.

N-Acetyl-O-benzoylhydroxylamines 2a-d were prepared by the known method3 from amines 1a-d. N,O-Diacetylation of 3a and 3b provided 4a and 4b respectively in quantitative yields. Selective deprotection of the compounds 2a-d and 4a-b by treatment of potassium carbonate in methanol N-acetyl hydroxylamines 5a-f in good yields.

Reaction of the hydroxylamines 5a-f with ethyl 2-bromoisobutyrate (6) in the presence of potassium carbonate in acetone afforded O-alkylated products 7a-f in good yields. Treatment of 7a-f with lithium bis(trimethylsilyl)amide (LiHMDS) in THF at −78 °C gave [1,2]oxazinane-3,5-diones 8a-f in excellent yields. The O-acylation of the compounds 8a and 8b with aromatic or aliphatic acyl chlorides 9a-c, followed by the cyanide catalyzed rearrangement2 provided 4-acyl substituted [1,2]oxazinane-3,5-diones in good yields. All spectroscopic data of compounds 8a-f and 10a-e were satisfactory on 1H NMR, 13C NMR, IR, MS, HRMS and some of these showed good agreement with the data described in the literatures.1

As an extended study, new fused heterocyclic compounds were synthesized from the 4-acyl substituted [1,2]oxazinane-3,5-diones (10, 11). The reaction of 4-acyl [1,2]oxazinane-3,5-diones with phenylhydrazine at reflux in ethanol afforded pyrazolate fused bicyclic ring system, 2,7-dihydro-6-oxa-1,2,5-triaza-inden-4-ones, in good yields. The regiochemistry of cyclocondensation was confirmed by NOE experiments. No NOE enhancements between the protons at phenyl ring of phenylhydrazine moiety and those at two methyl groups on the oxazine ring in 13a and 13b suggested that the only isomers were formed as shown in Scheme 4.

In summary, a variety of [1,2]oxazinane-3,5-diones were...
synthesized from a hydroxylamine or an amine in a few steps in good yields. Their ester derivatives were prepared and the cyanide ion catalyzed rearrangements were performed to yield 4-acyl substituted derivatives in excellent yields. Treatment of 4-acyl substituted \([1,2]\text{oxazinane-3,5-dione}\) with phenylhydrazone afforded 2,7-dihydro-6-oxa-1,2,5-triaza-inden-4-ones in good yields.

**Experimental Section**

Melting points were measured in capillary tubes with a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Schimadzu IR-435 spectrophotometer. \(^1\)H NMR spectra were recorded on a Varian GEMINI-200. \(^13\)C NMR spectra were recorded on a Bruker AM-300. All chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane and coupling constants are given in hertz (Hz). Mass spectra were recorded on a Shimadzu GCMS-OP 1000 mass spectrometer. Chromatographic separations were carried out on silica gel column (Merck silica gel 230-400). Elemental analysis were performed by Organic Chemistry Research Center at Sogang University in Seoul.

A typical procedure for the preparation of 7a

To a solution of \(N\)-acetyl-\(N\)-isopropylhydroxylamine (3.5 g, 29.9 mmol) and ethyl 2-bromoisobutyrate (7.0 g, 35.9 mmol) in acetonitrile (50 mL) at room temperature. The reaction mixture was warmed up to 40 °C and stirred for 8 h. The white solids were filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate (3:1) to give \(N\)-acetyl-\(N\)-isopropylhydroxylamine (7a) as a colorless oil.

**Notes**

Yield: 95%; a colorless oil; \(^1\)H NMR (200 MHz, CDCl\(_3\)) δ 4.22 (q, \(J = 7.11\) Hz, 2H), 2.09 (s, 3H), 1.51 (s, 6H), 1.29 (t, \(J = 7.12\) Hz, 3H).

\(^1\)C NMR (75 MHz, CDCl\(_3\)) δ 172.62, 128.17, 126.721, 84.38, 63.64, 61.34, 50.53; FT-IR (cm\(^{-1}\), neat) 2984.4, 2941.5, 2885.9, 1741.8, 1685.0, 1402.6, 1367.8, 1290.6, 1176.0, 1140.9, 1037.1, 752.5; MS (20 eV) m/z (rel intensity) 232 [(M+1)+, 1.4], 231 (M+, 7.6), 278 (27.3), 271 (16.1), 240 (13.6), 164 (31.2), 140 (35.2), 125 (61.6), 115 (98.86), 87 (87.4); HRMS calcd for \(\text{C}_{12}\text{H}_{22}\text{NO}_4\) 231.1470, found 231.1468.

**A typical procedure for the preparation of 8a**

To a solution of 7a (2.9 g, 12.6 mmol) in dry THF (25 mL) was added LiHMDS (25.2 mL, 25.2 mmol) at –78 °C. The reaction mixture was stirred for 0.5 h and allowed to room temperature. The solvent was removed under reduced pressure and quenched with saturated NH\(_4\)Cl. The reaction mixture was stirred for 0.5 h and allowed to room temperature. The solvent was removed under reduced pressure and quenched with saturated NH\(_4\)Cl. The reaction mixture was stirred for 0.5 h and allowed to room temperature. The solvent was removed under reduced pressure and quenched with saturated NH\(_4\)Cl. The reaction mixture was stirred for 0.5 h and allowed to room temperature.
The preparation of 10a-e: refer to the procedure described in reference 1 and 2.

2-Chloro-benzyl)-6,6-dimethyl-1,2-oxazinane-3,5-dione (8f). Yield: 89%; a pale yellow oil; 1H NMR (200 MHz, CDCl 3 ) δ 8.12-7.37 (m, 5H), 4.27 (h, J = 6.72 Hz, 1H), 1.38 (s, 6H), 1.31 (d, J = 6.72 Hz, 6H); 13C NMR (75 MHz, CDCl 3 ) δ 166.43, 164.25, 128.88, 128.37, 128.04, 127.56, 85.48, 47.28, 46.70, 26.78, 21.87, 21.41, 18.84, 18.70; FT-IR (cm -1 , neat) 2985.0, 2940.0, 1732.0, 1683.8, 1538.7, 1371.5, 1278.6, 1197.9, 768.0; MS (20 eV) m/z (rel intensity) 290 [(M+1)+, 2.4], 289 (M+, 3.9), 231 (5.3), 216 (30.9), 202 (1.2), 188 (2.2), 175 (1.4), 160 (3.2), 138 (7.7), 122 (17.5), 105 (100), 84 (36.4); HRMS calcd for C_{10}H_{17}NO_{3} 289.1314, found 289.1322; Anal. calcd for C_{10}H_{17}NO_{3}: C, 66.42; H, 6.62; N, 4.84; found: C, 66.38; H, 6.50; N, 4.89.

4-(2,4-Dichloro-benzoyl)-5-hydroxy-2-isopropyl-6,6-dimethyl-1,2-oxazin-3-one (10e). Yield: 85%; a light brown oil; 1H NMR (200 MHz, CDCl 3 ) δ 7.67-7.31 (m, 3H), 6.94 (h, J = 6.72 Hz, 1H), 4.38 (s, 6H), 1.66 (h, J = 7.52 Hz, 2H), 1.79-1.60 (m, 2H), 1.40 (s, 6H), 1.26 (d, J = 6.72 Hz, 6H); 13C NMR (75 MHz, CDCl 3 ) δ 190.91, 184.18, 167.80, 136.71, 135.08, 132.67, 129.36, 129.17, 127.06, 84.34, 47.27, 46.08, 26.77, 21.27, 20.99, 16.88; FT-IR (cm -1 , neat) 2985.8, 2941.2, 2255.2, 1689.7, 1591.5, 1546.9, 1470.7, 1178.2, 1103.1, 910.4, 743.6; MS (20 eV) m/z (rel intensity) 358 [(M+1)+, 0.5], 322 (44.4), 280 (13.1), 264 (3.9), 247 (19), 215 (1.6), 190 (13.4), 173 (100.0), 145 (29.3), 109 (24.1); HRMS calcd for C_{10}H_{17}NO_{3}Cl_{2} 357.0534, found 357.0532.

4-Butyl-5-hydroxy-2-isopropyl-6,6-dimethyl-1,2-oxazin-3-one (10c). Yield: 83%; a pale yellow oil; 1H NMR (200 MHz, CDCl 3 ) δ 6.47 (h, J = 6.71 Hz, 1H), 2.94 (t, J = 7.52 Hz, 2H), 1.79-1.60 (m, 2H), 1.40 (s, 6H), 1.26 (d, J = 6.71 Hz, 6H), 1.01 (t, J = 7.52 Hz, 3H); 13C NMR (75 MHz, CDCl 3 ) δ 196.35, 192.28, 169.59, 163.65, 97.97, 83.79, 46.59, 38.33, 21.16, 19.22, 18.56; FT-IR (cm -1 , neat) 2981.4, 2939.1, 2877.3, 1680.4, 1496.8, 1376.0, 1181.0, 1049.0, 910.3; MS (20 eV) m/z (rel intensity) 256 [(M+1)+, 18.9], 255 (M+, 39.7), 238 (5.3), 226 (0.3), 199 (3.9), 182 (83.5), 180 (7.1), 154 (20.8), 126 (7.1), 97 (19.9); HRMS calcd for C_{10}H_{17}NO_{3}Cl_{2} 255.1470, found 255.1467.

4-Butyl-5-hydroxy-2,6,6-trimethyl-1,2-oxazin-3-one (10d). Yield: 76%; a pale yellow oil; 1H NMR (200 MHz, CDCl 3 ) δ 3.25 (s, 3H), 2.92 (t, J = 7.32 Hz, 2H), 1.74-1.60 (m, 2H), 1.41 (s, 6H), 1.00 (t, J = 7.32 Hz, 3H); 13C NMR (75 MHz, CDCl 3 ) δ 196.04, 192.39, 164.09, 102.22, 84.57, 38.68, 38.16, 34.27, 21.16, 19.35, 13.92; FT-IR (cm -1 , neat) 3333.5, 2969.2, 2938.1, 2877.2, 1680.8, 1454.2, 1376.8, 1219.9, 1163.1, 1024.9, 915.7; MS (20 eV) m/z (rel intensity) 228 [(M+1)+, 0.5], 227 (M+, 3.2), 212 (0.6), 181 (1.5), 169 (1.8), 154 (4.5), 126 (9.8), 97 (7.0), 84 (35.1); HRMS calcd for C_{10}H_{18}NO; 227.1175, found 227.1172.

4-(2,4-Dichloro-benzoyl)-5-hydroxy-2,6,6-trimethyl-1,2-oxazin-3-one (10e). Yield: 85%; a light brown oil; 1H NMR (200 MHz, CDCl 3 ) δ 7.45-7.20 (m, 3H), 3.36 (s, 3H), 1.36 (s, 6H); 13C NMR (75 MHz, CDCl 3 ) δ 190.92, 183.49, 169.48, 136.34, 133.96, 132.26, 131.20, 129.34, 127.16, 85.11, 34.53, 26.84, 21.22, 20.96; FT-IR (cm -1 , neat) 3624.1, 3451.0, 3090.9, 2958.2, 2939.2, 1746.1, 1694.1, 1592.4, 1472.0, 1379.7, 1214.9, 1103.9, 825.2; MS (20eV) m/z (rel intensity) 331 [(M+1)+, 0.5], 330 (M+, 2.6), 294 (100.0), 250 (1.4), 236 (37.0), 208 (34.8), 173 (94.0), 145 (29.9), 123 (13.8), 109 (20.1).
A typical procedure for the the preparation of 13b

A mixture of 11 (0.80 g, 2.54 mmol) and phenylhydrazine (0.28 g, 2.54 mmol) in ethanol (25 mL) was refluxed for 4 h. and then concentrated under reduced pressure. The residue was purified by chromatography on silica gel using hexane/ethyl acetate (3 : 1) to give 5-cyclopentyl-7,7-dimethyl-2,3-diphenyl-2,7-dihydro-6-oxa-1,2,5-triaza-inden-4-one (13b) (0.74 g, 75%) as a pale yellow solid. mp 199-200 ºC; 1H NMR (200 MHz, CDCl3) δ 8.17-8.12 (m, 2H), 7.54-7.38 (m, 8H), 4.46-4.32 (m, 1H), 1.81-1.52 (m, 10H), 1.45 (s, 6H); 13C NMR (75 MHz, CDCl3) δ 162.81, 151.29, 150.87, 139.16, 131.35, 129.84, 129.35, 128.95, 128.71, 127.99, 126.99, 108.06, 77.76, 55.42, 29.23, 25.58, 23.97; FT-IR (cm⁻¹, neat) 3070.7, 2991.1, 2934.3, 2852.7, 1657.8, 1503.2, 1477.7, 1459.3, 1210.1, 767.0; MS (20 eV) m/z (rel intensity) 387 [(M+1)+, 0.8], 319 (M+, 5.3), 304 (22.0), 287 (100.0), 271 (9.7), 247 (3.5), 218 (2.1), 184 (0.5), 156 (3.7), 129 (4.3), 104 (11.0); HRMS calcd for C24H25N3O2 387.1946, found 387.1931; Anal. calcd for C24H25N3O2: C, 74.39; H, 6.50; N, 10.84. found: C, 74.33; H, 6.64; N, 10.83.

3-(2,4-Dichloro-phenyl)-5,5,7-trimethyl-2-phenyl-2,7-dihydro-6-oxa-1,2,5-triaza-inden-4-one (13a): Yield: 72%; a pale yellow solid; mp 153-154 ºC; 1H NMR (200 MHz, CDCl3) δ 7.54-7.26 (m, 8H), 3.24 (s, 3H), 1.49 (s, 6H); 13C NMR (75 MHz, CDCl3) δ 163.49, 150.36, 129.54, 129.44, 126.68, 109.41, 78.71, 33.87, 24.00; FT-IR (cm⁻¹, neat) 3070.7, 2985.4, 2936.4, 1673.4, 1596.7, 1503.4, 1365.7, 1105.8, 756.7; MS (20eV) m/z (rel intensity) 402 [(M+1)+, 2.4], 401 (M+, 4.5), 384 (2.3), 366 (80.3), 355 (83.3), 339 (7.2), 321 (49.2), 305 (11.4), 265 (1.2), 242 (1.8), 215 (1.8), 197 (1.5), 178 (5.4), 142 (11.1); HRMS calcd for C20H17N3O2Cl2: 401.0697, found 401.0702; Anal. calcd for C20H17N3O2Cl2: C, 59.71; H, 4.26; N, 10.45. found: C, 59.77; H, 4.24; N, 10.39.

References

