A Novel Synthesis of 3-Aryl-5-tert-butyl-4-oxazolin-2-ones

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An efficient synthetic method for 3-aryl-5-tert-butyl-4-oxazolin-2-ones (6) is described. The reaction of ethyl N-arylcarbamates (10) with 1-bromo-3,3-dimethyl-2-butane (9a) or 1-bromo-3-ethyl-3-methyl-2-pentanone (9b) using 2.2 eq of lithium bis(trimethylsilyl)amide afforded 6 in good yields. The reaction mechanisms are discussed.

Key words 4-oxazolin-2-one; α-bromoketone; cyclization

Several methods are known for the synthesis of 4-oxazolin-2-ones by thermal and photolytic rearrangement of the corresponding 4-isoxazolin-3-ones. We have focused on the chemistry of 4-oxazolin-2-ones and previously reported that acyldihydroxamic acids (3) which are easily obtained from acyl Meldrum's acid (1) and aryl hydroxylamines (2), cyclized to 5-alkyl-3-aryl-4-oxazolin-2-ones (6) via intermediates 4 and 5, as shown in Chart 1. 3)

During the course of our investigations on the generality and limitations of this reaction, it has become apparent that disubstituted phenylhydroxylamines (e.g., 2,4-dichlorophenylhydroxylamine) are unstable, and certain acyldihydroxamic acids (3) bearing a bulky acyl group (e.g., pivaloyl) are inaccessible from an acylated Meldrum's acid. These limitations led us to develop a new, efficient synthetic method for 4-oxazolin-2-ones. We wish to report here an efficient and convenient method for synthesizing 4-oxazolin-2-ones substituted by bulky groups such as tert-butyl and 1-ethyl-1-methylpropyl groups. From the standpoint of retro-synthetic analysis, substituted aniline (7), carbonyl cation equivalent (8), and halopinanocolone (9) were considered to be appropriate synthons, as shown in Chart 2. After some initial difficulties, ethyl carbamates (10), which were prepared easily from anilines (7) and ethyl chloroformate acting as a carbonyl cation equivalent, were successfully employed to form the desired 4-oxazolin-2-one derivatives (Chart 3).

Typically, treatment of ethyl N-(4-chlorophenyl)carbamate (10a) with 1-bromo-3,3-dimethyl-2-butane (9a) and 2.2 eq of lithium bis(trimethylsilyl)amide [LiN(TMS)_2] at room temperature for 15 min gave the desired 5-tert-butyl-3-(4-chlorophenyl)-4-oxazolin-2-one (6a) in 60.0% yield after silica gel column chromatography. The reaction mechanism is proposed to be as follows: the nitrogen anion (10a') initially generated from the carbamate (10a) with 1 eq of LiN(TMS)_2 is alkylated by the bromide (9a) to afford an intermediate 11a, which is deprotonated with another 1 eq of LiN(TMS)_2 to give the

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enolate 12a'. Finally, 12a' undergoes intramolecular cyclization to give the 4-oxazolin-2-one (6a).

Examination of the reaction conditions revealed several characteristic features of the process. As for the base, the use of 2 eq of LiN(TMS)$_2$ was essential, and no intermediate 11a was detected. When 1 eq of LiN(TMS)$_2$ was used, only the carbamate 10a and product 6a were observed, and the proposed intermediate 11a was not detected in the reaction mixture. In order to clarify the reaction mechanism, compound 11a was independently prepared from 9a and 7a as illustrated in Chart 4. Bromopinacolone (9a) reacted with aniline (7a) in the presence of $N,N$-diisopropylethylamine to give the amino-ketone (13a) in 41.6% yield, and 13a was subsequently treated with ethyl chloroformate to afford 11a in 90.0% yield as stable crystals. On simply treating the proposed intermediate 11a with 1.6 eq of LiN(TMS)$_2$, the desired cyclization proceeded efficiently to provide the 4-oxazolin-2-one (6a) in 84.4% yield. These observations support the proposed mechanism. The intermediate 11a had an extraordinary high reactivity under these reaction conditions.

1-Bromo-3-ethyl-3-methyl-2-pentanone (9b), a starting material for the 4-oxazolin-2-ones substituted with a 1-ethyl-1-methylpropyl group at the 5-position, was prepared as shown in Chart 5. First, ethyl 2-methylbutyrate (14) was ethylated to give 15 in 78.7% yield, and 15 was reacted with an anionic acetonitrile species to afford the $\alpha$-cyanoacetone (16) in 71.1% yield. Acid hydrolysis of 16 yielded a $\beta$-ketoacid (17), which was decarboxylated under the reaction conditions to afford 18 in 35.8% yield. Finally, bromination of 18 in the absence of solvents gave the $\alpha$-bromoketone (9b) in 71.2% yield. Further attempts to synthesize the 4-oxazolin-2-one substituted with a phenyl group at the 5-position by using phenacyl bromide instead of 9 met with failure, probably due to
the increased acidity of the α-hydrogen of phenacyl bromide.

The results of the present study are compiled in Table 1. A variety of N-arylcarbamates (10) reacted with 1-bromo-3,3-dimethyl-2-butane (9a) or 1-bromo-3-ethyl-3-methyl-2-pentanone (9b) in the presence of 2.2 eq of LiN(TMS)₂ and cyclization occurred to give the corresponding 4-oxazolin-2-ones (6) in satisfactory yields.

In conclusion, an efficient synthetic method for 4-oxazolin-2-ones (6) from N-arylcarbamates (10) and 1-bromo-3,3-dimethyl-2-butanes (9) has been devised. Application of this method to prepare 4-oxazolin-2-ones having a variety of substituents and examination of the biological activities of the synthesized compounds are in progress.

**Experimental**

All melting points (mp) are uncorrected. Infrared (IR) spectra were measured as Nujol mulls on a JASCO A-102 spectrometer. ¹H-NMR spectra were recorded at 60 MHz on a Varian 360A spectrometer and at 200 MHz on a Varian Gemini 200 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained with a JEOL JMS-D300 mass spectrometer.

**5-tert-Butyl-3-(4-chlorophenyl)-4-oxazolin-2-one (6a)** A 1.0 M solution of LiN(TMS)₂ in tetrahydrofuran (THF) (38 mL, 38 mmol) was added to a solution of ethyl N-(4-chlorophenyl)carbamate (10a) (3.5 g, 17.5 mmol) and 1-bromo-3,3-dimethyl-2-butane (9a) (4.07 g, 22.7 mmol) in N,N-dimethyformamide (DMF) (15 mL) at room temperature. After having been stirred at room temperature for 1 h, the reaction mixture was poured into aqueous 

**Table 1. Synthesis of 3-Aryl-5-tert-butyl-4-oxazolin-2-ones (6)**

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<th></th>
<th>R</th>
<th>X</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
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<th>Calcd</th>
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<td>C₁₇H₁₆N₂O₂</td>
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5-tert-Butyl-3-(4-chloro-2-fluorophenyl)-4-oxazolin-2-one (6f) 1H-NMR (60 MHz, CDCl₃) δ: 7.80–7.10 (H, m), 6.37 (1H, d, J = 3.0 Hz), 2.57 (1H, t, J = 8.3 Hz). IR: vₚₑₜₑₚₑₚₑ (cm⁻¹) 1310, 3080, 1745, 1660, 1590, 1510. MS m/z: 269 (M⁺), 254 (base), 210, 175, 156, 57.

5-tert-Butyl-3-(3-trifluoromethylphenyl)-4-oxazolin-2-one (6g) 1H-NMR (60 MHz, CDCl₃) δ: 7.85–7.40 (4H, m), 6.49 (1H, s), 1.27 (9H, s). IR: vₚₑₜₑₚₑₚₑ (cm⁻¹) 1735, 1655, 1605, 1595, 1495. MS m/z: 285 (M⁺), 270 (base), 226, 211, 172.

5-tert-Butyl-3-(4-methoxyphenyl)-4-oxazolin-2-one (6h) 1H-NMR (60 MHz, CDCl₃) δ: 7.80 (2H, d, J = 9.0 Hz), 6.86 (2H, d, J = 9.0 Hz), 6.35 (1H, s), 1.25 (9H, s). IR: vₚₑₜₑₚₑₚₑ (cm⁻¹) 3140, 1720, 1665, 1585, 1515. MS m/z: 247 (M⁺), 232 (base), 188, 173, 145, 134, 122, 107.

3-(4-Chloro-2-fluorophenyl)-5-(1-ethyl-1-methylpropyl)-4-oxazolin-2-one (6i) 1H-NMR (200 MHz, CDCl₃) δ: 7.66 (1H, t, J = 8.9 Hz), 7.27–7.22 (2H, m), 6.45 (1H, dd, J = 2.1, 0.9 Hz), 1.71–1.42 (4H, m), 1.11 (9H, s), 0.83 (6H, t, J = 7.5 Hz). IR: vₚₑₜₑₚₑₚₑ (cm⁻¹) 3135, 2970, 1746, 1515, 1418, 1227. MS m/z: 297 (M⁺), 268 (base), 224, 189, 156.

N-(3,3-Dimethyl-2-pentanonyl)-4-chloroaniline (13a) Disopropylethylamine (7.8 mL, 44.8 mmol) was added to a solution of 9a (2.0 g, 11.2 mmol) and 7a (1.425 g, 11.2 mmol) in methyl ethyl ketone (20 mL), and the resulting mixture was stirred at 80 °C for 8 h. The reaction mixture was neutralized with diluted HCl and extracted with AcOEt (3 times). The combined extracts were dried over MgSO₄ and evaporated. The residue was chromatographed on silica gel (hexane: AcOEt = 10:1) to give 1.05 g (41.6%) of 13a. 1H-NMR (60 MHz, CDCl₃) δ: 7.08 (2H, d, J = 9.6 Hz), 6.47 (2H, d, J = 9.6 Hz), 4.62 (1H, brs), 4.01 (2H, s), 1.21 (9H, s). IR: vₚₑₜₑₚₑₚₑ (cm⁻¹) 3400, 1700. MS m/z: 225 (M⁺), 194, 165, 140 (base). HRMS Calcd for C₁₃H₁₅ClN: 225.0920. Found: 225.0918.

N-(3,3-Dimethyl-2-pentanonyl)-4-nitroso-2-carboxyl-4-chloroaniline (11a) Ethyl chloroformate (0.64 mL, 6.70 mmol) was added to a solution of 11a (15 mg, 0.0904 mmol) in THF (1 mL) containing hexamethyldisilazane (HMDS) (26 μL, 0.151 mmol) was treated with a 1.0 M solution of Li(N₃)₂ (2 μL, 0.0044 mmol) in THF (81 μL, 0.081 mmol) at room temperature. The mixture was stirred at room temperature for 50 min, then the reaction was quenched with aqueous NH₄Cl and the whole was extracted with AcOEt (3 times). The combined extracts were washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane: AcOEt = 20:1) to give 10.7 mg (84.4%) of 11a.

Ethyl 2-Ethyl-2-methylbutyrate (15) Compound 14 (15.0 mL, 100 mmol) was added to a solution of lithium disopropylamide (prepared from disopropylamine (21.0 mL, 150 mmol) and n-butyl lithium (1.6 M solution 90.0 mL, 144 mmol)) in THF (50 mL) at ~78 °C, and after 30 min, ethyl iodide (14.0 mL, 175 mmol) was added to the mixture. Stirring was continued at ~78 °C for 1 h, at 0 °C for 30 min, and at room temperature for 30 min. The reaction was quenched with water and the whole was extracted with ether (2 times). The combined extracts were dried over MgSO₄ and evaporated. The residue was distilled at (133–145 °C (4 mmHg)) to give 12.45 g (78.7%) of 15. 1H-NMR (200 MHz, CDCl₃) δ: 4.12 (2H, q, J = 7.1 Hz), 1.72–1.37 (4H, m), 1.24 (3H, t, J = 7.1 Hz), 1.08 (3H, s), 0.81 (6H, t, J = 7.5 Hz).

Ethyl-4-ethyl-3-hydroxyxanthene (16) Sodium hydride (60% in mineral oil 31.4 g, 785 mmol) was added to a solution of 15 (79.17 g, 500 mmol) and acetone (52.5 mL, 1.00 mol) in THF (500 mL), and the resulting mixture was heated under reflux for 6 h. The mixture was cooled, and the reaction was quenched with methanol and water. The organic solvents were removed in vacuo and the residual aqueous suspension was washed with dichloromethane (CH₂Cl₂) (3 times). The aqueous layer was acidified (to pH 1) and extracted with CH₂Cl₂ (4 times). The combined extracts were dried over MgSO₄, and evaporated in vacuo. The residue was distilled (95–97 °C 5 mmHg) to give 54.5 g (71.1%) of 16. 1H-NMR (200 MHz, CDCl₃) δ: 3.35 (2H, s), 1.69–1.41 (4H, m), 1.09 (3H, s), 0.80 (6H, t, J = 7.5 Hz).

3-Ethyl-3-methyl-2-pentanone (18) A mixture of 17 (3.14 g, 20.5 mmol) and concentrated HCl (100 mL) was refluxed for 4 h. After cooling, the reaction mixture was washed with CH₂Cl₂ (3 times). The combined extracts were washed with aqueous NaHCO₃, dried over MgSO₄, and evaporated in vacuo to give 0.941 g (35.8%) of 18 as a crude oil, which was subjected to the next reaction without further purification. 1H-NMR (200 MHz, CDCl₃) δ: 2.06 (3H, s), 1.68–1.36 (4H, m), 1.02 (3H, s), 0.76 (6H, t, J = 7.5 Hz).

1-Bromo-3-ethyl-3-methyl-2-pentanone (9b) Bromine (5.2 mL, 101 mmol) was carefully added to 18 (14.73 g, 99.95 mmol) under water cooling, and the resulting mixture was stirred for 4.5 h. It was neutralized with aqueous NaHCO₃ and extracted with CH₂Cl₂ (3 times). The combined extracts were dried over MgSO₄, and evaporated in vacuo. The residue was distilled (69–71 °C 4 mmHg) to give 14.73 g (71.2%) of 9b. 1H-NMR (200 MHz, CDCl₃) δ: 4.12 (2H, s), 1.74–1.42 (4H, m), 1.14 (3H, s), 0.80 (6H, t, J = 7.5 Hz).

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References
4) A 1.0 M THF solution of Li(N₃)₂ was purchased from Aldrich Chemical Company.