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-butanone (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[1] and photolytic[2] rearrangement of the corresponding 4-isoxazolin-3-ones. We have focused on the chemistry of 4-oxazolin-2-ones and previously reported that acylhydroxamic 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 acylhydroxamic 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 dication equivalent (**8**), and halopinacolone (**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 dication 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-butanone (**9a**) and 2.2 eq of lithium bis(trimethylsilyl)amide [$LiN(TMS)_2$][4] 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

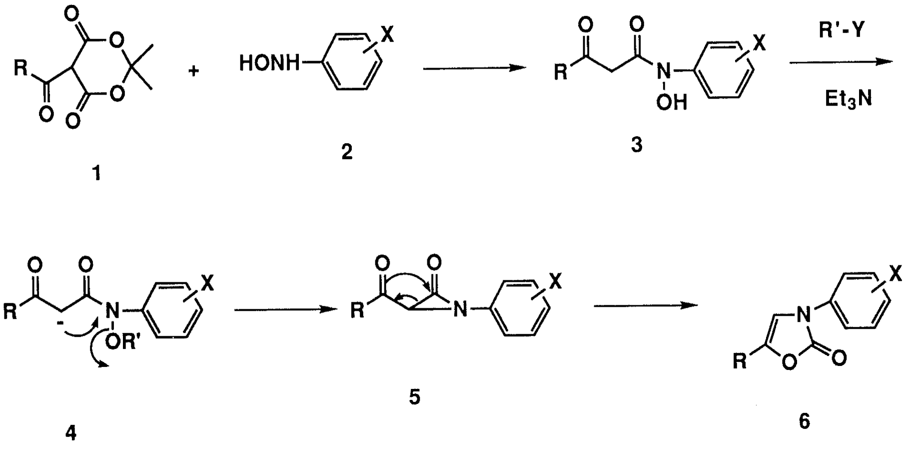

Chart 1

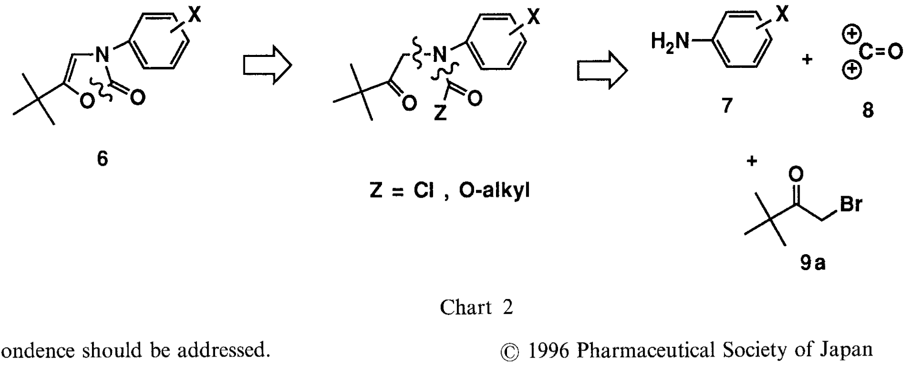

Chart 2

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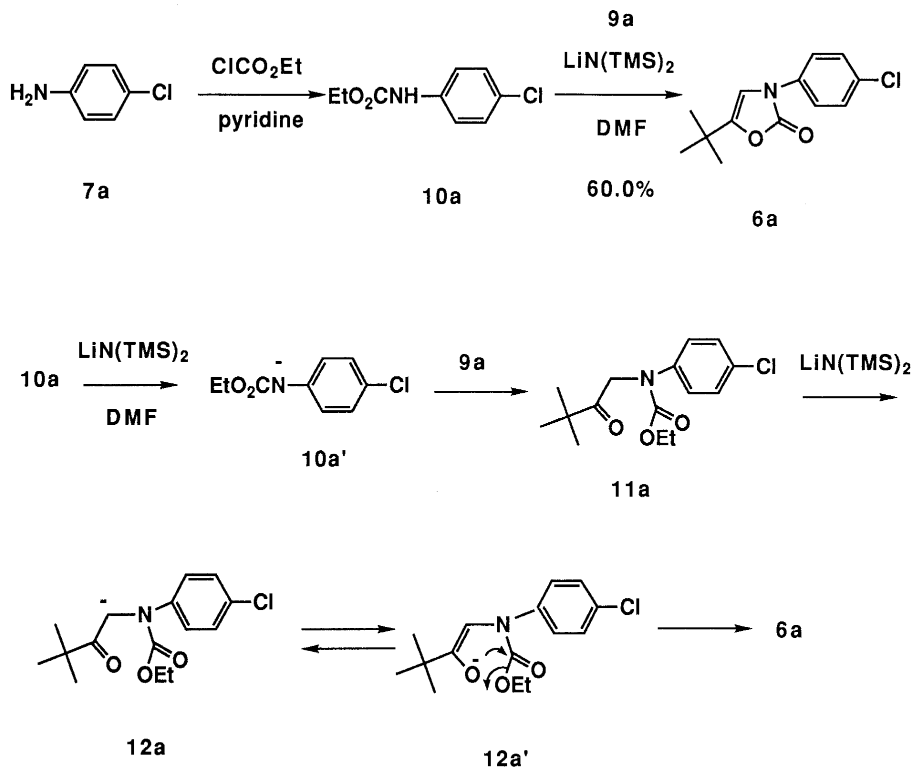


Chart 3

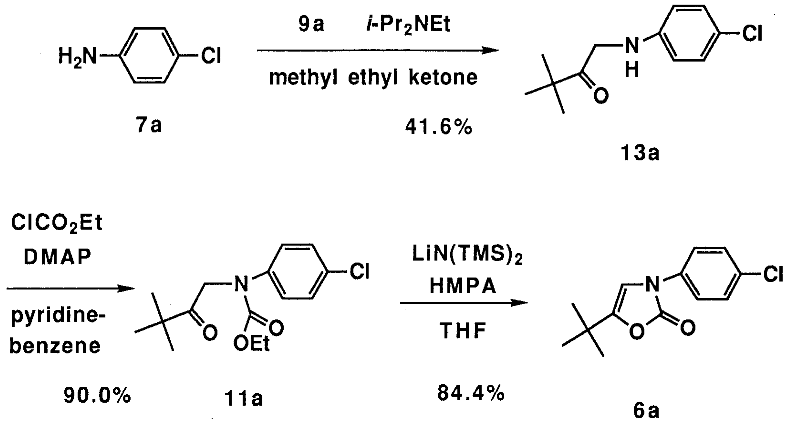


Chart 4

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 aminoketone (**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 α-cyanoketone (**16**) in 71.1% yield.[5,6] Acid hydrolysis of **16** yielded a β-ketoacid (**17**), which was decarboxylated under the reaction conditions to afford **18** in 35.8% yield.[6] Finally, bromination of **18** in the absence of solvents gave the α-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

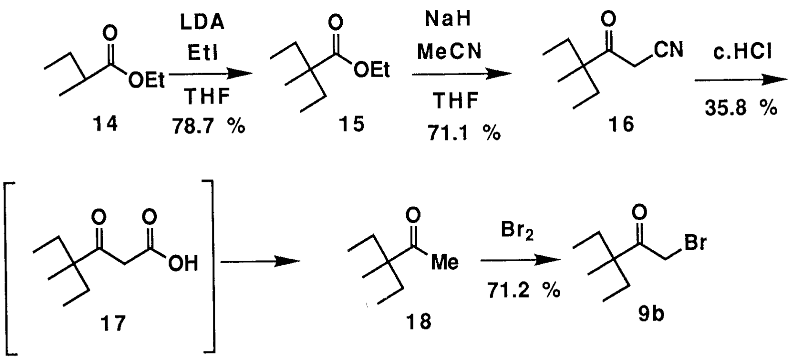
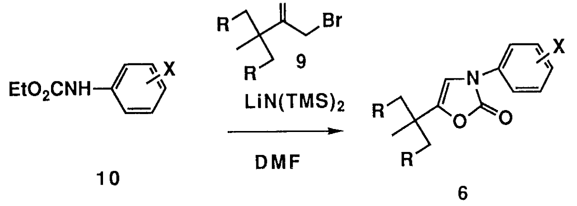


Chart 5

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



10	R	X	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
a	H	4-Cl	60.0	172—174	$C_{13}H_{14}ClNO_2$	61.94	5.65	5.55	62.03	5.61	5.56
b	H	4-F	85.6	159.5—162	$C_{13}H_{14}FNO_2$	66.37	6.25	5.70	66.40	6.25	5.70
c	H	2,4-Cl_2	97.1	Oil	$C_{13}H_{13}Cl_2NO_2$	54.57	4.58	4.89	55.06	5.19	4.52
d	H	3,4-Cl_2	54.5	135—139	$C_{13}H_{13}Cl_2NO_2$	54.57	4.58	4.89	54.98	4.87	4.96
e	H	3,5-Cl_2	55.6	107—109.5	$C_{13}H_{13}Cl_2NO_2$	54.57	4.58	4.89	54.79	4.81	4.89
f	H	2-F,4-Cl	80.0	Amorphous	$C_{13}H_{13}ClFNO_2$	57.89	4.86	5.19	58.02	5.11	5.15
g	H	3-CF_3	77.5	153—157	$C_{14}H_{14}F_3NO_2$	58.95	4.95	4.91	58.41	5.24	4.80
h	H	4-OMe	89.7	70—75	$C_{14}H_{17}NO_3$	68.00	6.93	5.66	67.55	6.92	5.76
i	Me	2-F,4-Cl	62.7	94—96	$C_{15}H_{17}ClFNO_2$	60.51	5.76	4.70	60.79	5.55	4.73

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-butanone (**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-butanones (**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. ^{1}H-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-butanone (**9a**) (4.07 g, 22.7 mmol) in *N,N*-dimethylformamide (DMF) (15 ml) at room temperature. After having been stirred at room temperature for 1 h, the reaction mixture was poured into aqueous NH_4Cl and extracted with ethyl acetate (AcOEt) (3 times). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to silica gel chromatography to give 2.64 g (60.0%) of **6a** as crystals. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.66—6.90 (4H, m), 6.41 (1H, s), 1.26 (9H, s). IR ν_{max} cm^{-1}: 3140, 1745, 1665, 1520. MS *m/z*: 235 (M$^+$), 176, 161, 149, 122 (base), 109, 95. Compounds **6b**—**i** were synthesized in the same manner.

5-*tert*-Butyl-3-(4-fluorophenyl)-4-oxazolin-2-one (6b) ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.60—7.20 (4H, m), 6.45 (1H, s), 1.28 (9H, s). IR ν_{max} cm^{-1}: 3140, 1740, 1655, 1595, 1500. MS *m/z*: 251 (M$^+$), 236 (base), 192, 177, 157, 138.

5-*tert*-Butyl-3-(2,4-dichlorophenyl)-4-oxazolin-2-one (6c) ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.55—7.30 (3H, m), 6.28 (1H, s), 1.27 (9H, s). IR ν_{max} cm^{-1}: 3120, 1755, 1740, 1650, 1585, 1560, 1490. MS *m/z*: 285 (M$^+$), 270 (base), 246, 226, 202, 174.

5-*tert*-Butyl-3-(3,4-dichlorophenyl)-4-oxazolin-2-one (6d) ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.68 (1H, m), 7.43 (2H, m), 6.42 (1H, s), 1.25 (9H, s). IR ν_{max} cm^{-1}: 1740, 1665, 1595, 1485. MS *m/z*: 285 (M$^+$), 270 (base), 226, 198, 191, 122.

5-*tert*-Butyl-3-(3,5-dichlorophenyl)-4-oxazolin-2-one (6e) ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.63 (2H, d, J=1.8 Hz), 7.33 (1H, t, J=1.8 Hz), 6.55 (1H, s), 1.27 (1H, s). IR ν_{max} cm^{-1}: 3140, 1745, 1660, 1590, 1575. MS *m/z*: 285 (M$^+$), 270 (base), 226, 211, 191, 172.

5-*tert*-Butyl-3-(4-chloro-2-fluorophenyl)-4-oxazolin-2-one (6f) ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.80—7.10 (3H, m), 6.37 (1H, d, $J=3.0$ Hz), 1.27 (9H, s); IR ν_{max} cm^{-1}: 3150, 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) ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.85—7.40 (4H, m), 6.49 (1H, s), 1.27 (9H, s). IR ν_{max} 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) ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.40 (2H, d, $J=9.0$ Hz), 6.86 (2H, d, $J=9.0$ Hz), 6.35 (1H, s), 1.25 (9H, s). IR ν_{max} 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) ^{1}H-NMR (200 MHz, $CDCl_3$) 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 (3H, s), 0.83 (6H, t, $J=7.5$ Hz). IR ν_{max} 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)** Diisopropylethylamine (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 $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (hexane : AcOEt = 10 : 1) to give 1.05 g (41.6%) of **13a**. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.08 (2H, d, $J=9.6$ Hz), 6.47 (2H, d, $J=9.6$ Hz), 4.62 (1H, br s), 4.01 (2H, s), 1.21 (9H, s). IR ν_{max} cm^{-1}: 3400, 1700. MS *m*/*z*: 225 (M$^+$), 194, 165, 140 (base), 105. HRMS Calcd for $C_{12}H_{16}ClNO$: 225.0920. Found: 225.0918.

***N*-(3,3-Dimethyl-2-pentanonyl)-*N*-ethoxycarbonyl-4-chloroaniline (11a)** Ethyl chloroformate (0.64 ml, 6.70 mmol) was added to a solution of **13a** (150 mg, 0.665 mmol) in benzene (3 ml) and pyridine (1 ml), followed by the addition of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (16 mg, 0.13 mmol). After having been stirred at 90 °C for 1 h, the reaction mixture was diluted with water and extracted with AcOEt (3 times). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel using a stepwise gradient of AcOEt (25—75%) in hexane as the eluent to give 178.2 mg (90.0%) of **11a**. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 7.20 (4H, s), 4.47 (2H, s), 4.11 (2H, q, $J=7.0$ Hz), 1.18 (9H, s), 1.15 (3H, t, $J=7.0$ Hz). IR ν_{max} cm^{-1}: 1722, 1708, 1496, 1386, 1237. MS *m*/*z*: 297 (M$^+$), 212, 168, 142 (base). HRMS Calcd for $C_{15}H_{20}ClNO_3$: 249.1131. Found: 249.1133.

Reaction of 11a with LiN(TMS)$_2$ A solution of **11a** (15 mg, 0.0504 mmol) in THF (1 ml) containing hexamethylphosphoramide (HMPA) (26 μl, 0.151 mmol) was treated with a 1.0 M solution of LiN(TMS)$_2$ 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 NH_4Cl and the whole was extracted with AcOEt (3 times). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane : AcOEt = 20 : 1) to give 10.7 mg (84.4%) of **6a**.

Ethyl 2-Ethyl-2-methylbutyrate (15) Compound **14** (15.0 ml, 100 mmol) was added to a solution of lithium diisopropylamide (prepared from diisopropylamine (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 $MgSO_4$ and evaporated. The residue was distilled (133—145 °C/760 mmHg) to give 12.45 g (78.7%) of **15**. ^{1}H-NMR (200 MHz, $CDCl_3$) 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).

4-Ethyl-4-methyl-3-oxohexanonitrile (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 acetonitrile (52.5 ml, 1.00 mol) in THF (500 ml), and the resulting mixture was heated under reflux for 63 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 (CH_2Cl_2) (3 times). The aqueous layer was acidified (to pH 1) and extracted with CH_2Cl_2 (4 times). The combined extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was distilled (95—97 °C/5 mmHg) to give 54.5 g (71.1%) of **16**. ^{1}H-NMR (200 MHz, $CDCl_3$) 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 extracted with CH_2Cl_2 (3 times). The combined extracts were washed with aqueous $NaHCO_3$, dried over $MgSO_4$, 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. ^{1}H-NMR (200 MHz, $CDCl_3$) 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 $NaHCO_3$ and extracted with CH_2Cl_2 (3 times). The combined extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was distilled (69—71 °C/4 mmHg) to give 14.73 g (71.2%) of **9b**. ^{1}H-NMR (200 MHz, $CDCl_3$) 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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