The Reaction of 3,4-Dihydro-2H-Pyran with Oxalyl Chloride: Formation and Crystal Structure Analysis of an Unexpected Bicyclic Product

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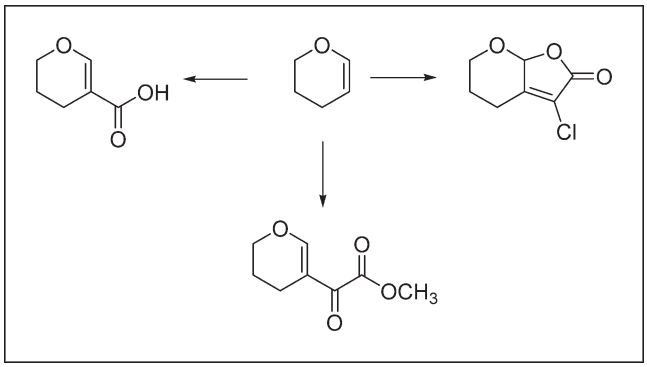

3,4-Dihydro-2-H-pyran and oxalyl chloride react, depending on the conditions, to keto esters, a pyran-3-carboxylic acid or derivatives thereof, or to an hitherto unknown bicyclic acetal containing a vinyl chloride moiety. The structure of the latter product has been unambiguously elucidated by single-crystal X-ray structure analysis. A mechanism for its formation is proposed.

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INTRODUCTION

Despite their structural simplicity, tetrahydropyran-3-carboxylic acid and its esters display interesting biological activities as attractants for cockroaches [1–3]. One approach toward these compounds proceeds via hydrogenation of dihydropyran-3-carboxylic acid derivatives **3**, which are in turn available by trichloroacetoxylation of dihydropyran (**1**) and subsequent methanolysis or basic hydrolysis of the intermediate trichloromethyl ketones **2**, as outlined in Scheme 1 [4–6]. A Cobalt-catalyzed methoxycarbonylation of vinyl bromides has also been investigated, but is less commonly used [7].

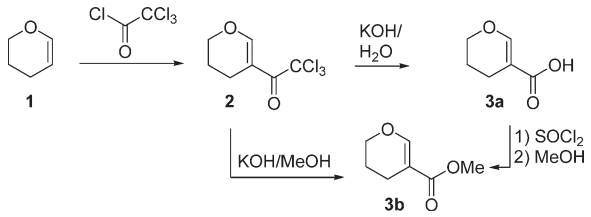
5,6-Dihydro-4*H*-pyran-3-carboxylic acid (**3a**) has also been used as an intermediate in the synthesis of pharmacologically active heterocycles, for example, pyrimidines with activity against cancer [8], anti-inflammatory peptide conjugates [9,10], or fungicides [11]. The corresponding carboxaldehyde is a useful intermediate in the synthesis of renin inhibitors [12] and anti-inflammatory agents [13].

In light of the relevance of dihydropyran-3-carboxylic acid and its derivatives, in particular for the synthesis of heterocycles, we investigated the route described in Scheme 1 in detail. While the carboxylic acid **3a** is indeed conveniently accessible via basic hydrolysis of the trichloromethyl ketone **2**, less satisfactory results were obtained for the methanolysis. However, the ester **3b** is more conveniently synthesized by converting **3a** to its chloride, which is subsequently treated with methanol. We thought that the strongly basic conditions used for the conversion of **2** to **3a** and the additional steps required to obtain the ester **3b** are disadvantageous and therefore sought for a more straightforward alternative.

RESULTS AND DISCUSSION

The reaction of alkyl vinyl ethers with oxalyl chloride was investigated by Effenberger. Thus, by adjusting the appropriate stoichiometry, symmetrical 1,2-diketones were synthesized in good yields [14]. Later, Tietze *et al.* demonstrated that the intermediate α-keto acid chlorides undergo a clean decarbonylation at temperatures above 100°C to give acyclic *E*-3-alkoxy acryloyl chlorides [15], which are useful intermediates in the synthesis of heterocycles [16]. This approach should also be applicable to dihydropyran-3-carboxylic acid (**3a**) and its derivatives, with dihydropyran (**1**). In contrast to the established two- to four-step route depicted in Scheme 1, this

Scheme 1. Established routes to tetra- and dihydropyran-3-carboxylic acids.



synthesis might potentially be conducted as a one-pot reaction. A literature search revealed that the reaction of dihydropyran (**1**) with oxalyl chloride followed by treatment with methanol gives exclusively the α-keto ester **4**, which was used as a substrate in hetero-Diels-Alder reactions [17,18]. However, this transformation was not documented in full detail in the literature, and we therefore decided to start at this point. We could indeed obtain **4** in fair yield if **1** was treated with 1.5 equivalents of oxalyl chloride at low-temperature, followed by the addition of methanol. Next, we tried to synthesize methyl ester **3b** by inducing a decarbonylation before methanolysis. To this end, the reaction mixture was heated to 120°C, after the addition of the oxalyl chloride. To our surprise, the desired ester **3b** was only obtained as a minor product. The major product showed an M^+ signal at $m/z = 174$, with the characteristic isotopic pattern for compounds with one chlorine atom. In the IR spectrum absorptions at 1793 cm^{-1} and 1771 cm^{-1} suggested the presence of a lactone moiety. On the basis of the information gathered from NMR- and mass spectra, a molecular formula of $C_7H_7O_3Cl$ was deduced. From the ^{1}H-NMR spectra, it became obvious that the six-membered oxacycle was still intact and that the protons of the CH_2-groups are no longer chemically equivalent, but are diastereotopic. This is indicative for the formation of a new stereogenic center in the course of the reaction. In the ^{13}C-NMR-spectrum two signals arising from quaternary olefinic carbon atoms at 166 ppm and 118 ppm, and a signal at 98 ppm were observed. The latter was interpreted as a cyclic acetal carbon. The proton that is attached to this carbon atom was observed at 5.59 ppm as a singlet. Notably, no methanol was incorporated in the molecule. From this information, we tentatively assigned the bicyclic structure **5** to the new compound (Scheme 2).

Scheme 2. Formation of α-keto ester **4** and the unexpected bicyclic acetal product **5** from dihydropyran.

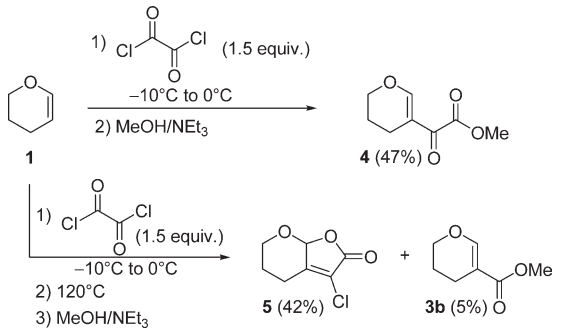


Table 1

Selected bond lengths (Å) and bond angles (°) for **5**.

Cl1A–C2A	1.704(2)	Cl1B–C2B	1.709(2)
O1A–C1A	1.362(3)	O1B–C1B	1.362(3)
O1A–C7A	1.433(3)	O1B–C7B	1.425(3)
O2A–C1A	1.201(3)	O2B–C1B	1.197(3)
O3A–C6A	1.450(4)	O3B–C6B	1.456(3)
O3A–C7A	1.396(3)	O3B–C7B	1.391(3)
C3A–C7A	1.492(3)	C3B–C7B	1.501(3)
C2A–C3A	1.320(4)	C2B–C3B	1.314(4)
Cl1A–C2A–C1A	120.62(19)	Cl1B–C2B–C1B	120.77(19)
O1A–C1A–O2A	122.2(2)	O1B–C1B–O2B	121.8(2)
O1A–C1A–C2A	107.6(2)	O1B–C1B–C2B	107.8(2)
C1A–C2A–C3A	110.1(2)	C1B–C2B–C3B	110.0(2)
C2A–C3A–C4A	134.6(2)	C2B–C3B–C4B	135.7(2)
C6A–O3A–C7A	109.1(2)	C6B–O3B–C7B	108.7(2)
O1A–C7A–C3A	105.9(2)	O1B–C7B–C3B	105.62(19)

Unambiguous proof for this structural assignment came from a single crystal X-ray structure analysis. Compound **5** has the structure of a bicyclic acetal. One chlorine atom is attached to a C-C-double bond, which is in conjugation to the carbonyl group. As the compound crystallizes in the centrosymmetric space group $P\bar{1}$, both enantiomers are found in the cell. Two molecules are present in the asymmetric unit, which are symmetry independent and therefore show slight differences in their structural parameters. Representative bond lengths and angles for both symmetry independent molecules (denoted as A and B) are listed in Table 1. A representation of both symmetry-independent molecules is given in Figure 1.

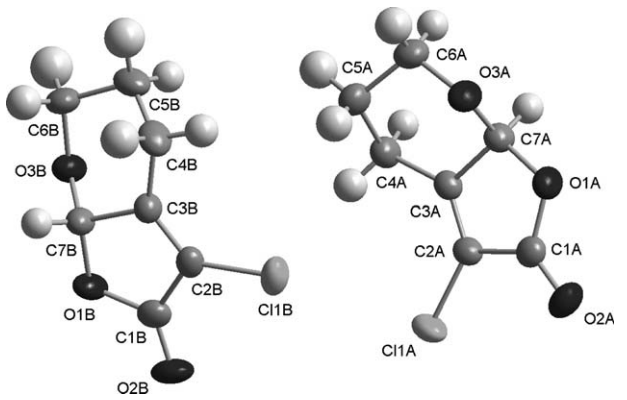


Figure 1. Molecular structure of compound **5** with thermal ellipsoids drawn at the 50% probability level.

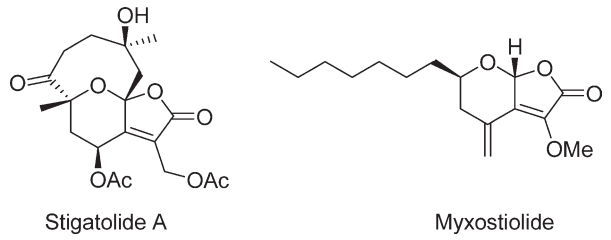
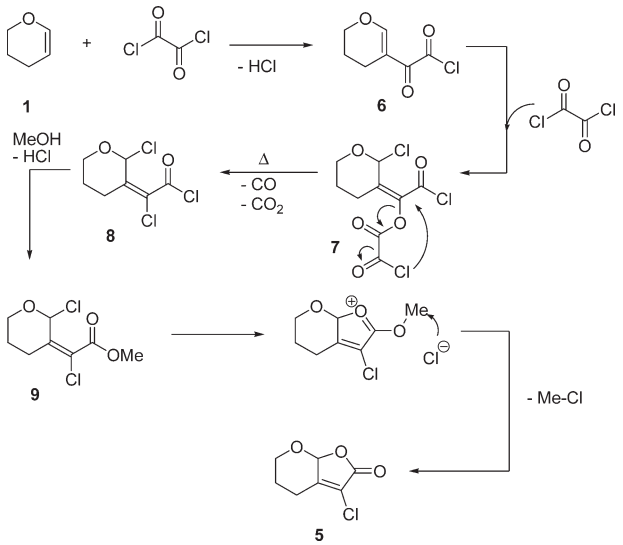


Figure 2. Structures of spicatolide A and myxostiliolide.

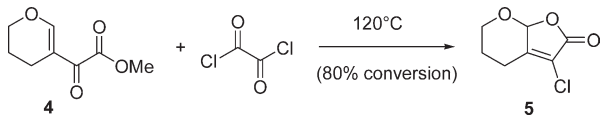
A literature search revealed, that there is ample precedence for bicyclic saturated γ-butyrolactones annellated to six-membered oxacycles. In most cases, these products result from an addition of 1,3-dicarbonyl compounds to cyclic enol ethers via a radical pathway [19–25]. In contrast, only comparatively few 3,4-unsaturated bicyclic γ-butyrolactones such as **5** have been described in the literature. Interestingly, this structural pattern is found in some biologically active natural products such as the anti-inflammatory germacranolide spicatolide A [26] or the plant-growth regulator myxostiliolide (Fig. 2) [27].

Elucidation of the mechanism for the formation of **5** is hampered by a lack of isolable intermediates. We propose the following tentative mechanism: in the first step, oxalyl chloride will most likely attack at carbon atom C3 to give the α-keto acid chloride **6**. We assume that now excess oxalyl chloride reacts with one carbonyl oxygen of **6** to give the intermediate vinyl ester **7**. Upon heating, **7** undergoes a fragmentation to CO, CO_2, and a vinyl chloride **8**, which is eventually trapped by methanol in the presence of pyridine. Most likely, the sequence is terminated by demethylation of the methyl ester **9** with a chloride ion and intramolecular nucleophilic attack of the carboxylate at the anomeric carbon, resulting in the product **5** (Scheme 3).

Scheme 3. Mechanistic proposal for the formation of the unexpected bicyclic acetal **5**.



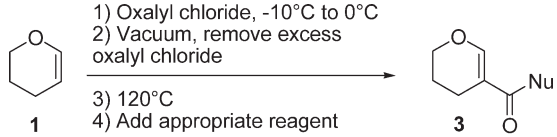
Scheme 4. Formation of bicyclic product **5** from keto ester **4**.



It should be noted that the crucial step of this sequence, the formation of the vinyl chloride moiety from a ketone, is not without precedence. A somewhat related reaction was reported for 7-keto steroids, which react with oxalyl chloride in refluxing toluene to vinylic 7-chloro steroids [28]. We do not have definite evidence that the individual steps leading to the formation of **5** indeed proceed in this order. It is, however, quite unlikely that the chlorination of the ketone moiety occurs after methanolysis of the acid chloride, because a considerable amount of the oxalyl chloride would also be destroyed. Strong support for the final demethylation step proposed by us comes from an experiment, in which pure keto ester **4** was treated with oxalyl chloride. After heating the mixture to 120°C, an 80% conversion to the expected bicyclic product **5** was observed by NMR-spectroscopy of the crude reaction mixture. The only other component that could be detected was unreacted starting material **4** (Scheme 4).

From the results discussed above, we concluded that the selective formation of the desired dihydropyran-3-carboxylic acid derivatives **3** requires careful removal of excess oxalyl chloride before the reaction mixture is heated to induce the decarbonylation. This was achieved by applying vacuum at moderately high-temperatures before the mixture is heated to 120°C to induce the decarbonylation. After completion of the decarbonylation step, different nucleophiles were added to obtain the desired derivatives **3**. Thus, with an aqueous solution of Na_2CO_3 the carboxylic acid **3a** was obtained, whereas addition of methanol and pyridine gave the ester **3b**. By using diisopropyl amine as a nucleophile,

Scheme 5. Synthesis of dihydropyran-3-carboxylic acid derivatives **3** via decarbonylation of α-keto acid chlorides.



No	Nu	Reagent	Yield
3a	-OH	Na_2CO_3 (aq)	78%
3b	-OMe	MeOH/pyridine	64%
3c	$-N(Pr^i)_2$	$HN(Pr^i)_2/NEt_3$	96%

the expected amide **3c** was obtained in nearly quantitative yield (Scheme 5).

CONCLUSION

The reaction of oxalyl chloride with dihydropyran, followed by thermal decarbonylation and trapping with an appropriate nucleophile, is a useful alternative synthesis of dihydropyran-3-carboxylic acid derivatives. An unexpected reaction pathway was observed in the course of this synthesis, leading to an interesting bicyclic vinyl chloride. The structure of this product was unambiguously elucidated by X-ray crystal structure analysis.

EXPERIMENTAL

All reactions were run under an atmosphere of dry nitrogen in dried glassware. Commercial reagents were used as received. Methanol was obtained dried and degassed in a septum bottle under argon and used as received. ^{1}H-NMR-spectra were obtained at 300 MHz in $CDCl_3$ with $CHCl_3$ ($\delta = 7.26$ ppm) as an internal standard. Coupling constants are given in Hz. ^{13}C-NMR spectra were recorded at 75 MHz in $CDCl_3$ with $CDCl_3$ ($\delta = 77.0$ ppm) as an internal standard. IR spectra were recorded as films on NaCl or KBr plates or as KBr-discs. The peak intensities are defined as strong (s), medium (m), or weak (w). Mass spectra were obtained at 70 eV.

Methyl 2-(5,6-dihydro-4H-pyran-3-yl)-2-oxoacetate (4). Oxalyl chloride (2.20 mL, 24.9 mmol) was cooled to −10°C. 3,4-Dihydro-2*H*-pyran (**1**, 1.50 mL, 16.6 mmol) was slowly added, and the mixture was warmed to ambient temperature. Stirring at ambient temperature was continued for 12 h, and the mixture was then recooled to 0°C. Triethyl amine (4.60 mL, 33.2 mmol) followed by methanol (1.40 mL, 33.2 mmol) were slowly added. Water was added to the reaction mixture, which was then extracted with dichloromethane, dried with Na_2SO_4, filtered, and evaporated. The residue was purified by chromatography on silica (eluent hexane/MTBE mixtures of increasing polarity) to give the title compound **4** (1.32 g, 47%) as a colourless oil. Analytical data match those reported in the literature [29]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.82 (s, 1H, H-2), 4.14 (t, 2H, $J = 5.2$ Hz, H-6), 3.83 (s, 3H, OMe), 2.28 (t, 2H, $J = 6.2$ Hz, H-4), 1.87 (m, 2H, H-5); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 184.3 (O=*C*—COOMe), 163.9 (*C*OOMe), 163.4 (C-2), 114.1 (C-3), 67.8 (C-6), 52.4 (OMe), 20.5, 17.4 (C-4, C-5); IR: 1731 (s), 1653 (m), 1599 (s), 1172 (s) cm^{-1}; MS (EI): *m*/*z* 170 (M^+), 111 (M^+-CO_2Me), 83.

3-Chloro-5,6-dihydro-4*H*-furo[2,3-b]pyran-2-(7a*H*)-one (5). Oxalyl chloride (2.00 mL, 23.2 mmol) was cooled to −10°C. 3,4-Dihydro-2*H*-pyran (**1**, 1.40 mL, 15.5 mmol) was slowly added, and the mixture was warmed to ambient temperature. Stirring at ambient temperature was continued for 12 h. The solution was then heated to 120°C for 0.5 h, cooled to ambient temperature, and then to 0°C. Pyridine (1.30 mL) and methanol (0.7 mL) were added and stirring was continued at ambient temperature for 2 h. All volatiles were removed in vacuo, and the residue was purified by chromatography on silica (eluent hexane/MTBE mixtures of increasing polarity). The title compound **5** (1.11 g, 42%) was obtained as a colourless solid, mp 49°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.58 (s, 1H, H-7a), 4.10 (dddm, 1H, $J = 1.9$, 4.1, 12.2 Hz, H-6), 3.76 (dt, 1H, $J = 2.4$, 12.2 Hz, H-6), 2.98 (dm, 1H, $J = 14.5$ Hz, H-4), 2.47 (ddm, 1H, $J = 6.4$, 14.5 Hz, H-4), 1.95 (m, 1H, H-5), 1.77 (ddm, 1H, $J = 4.8$, 12.4 Hz, H-5); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 165.6 (C-2), 156.5 (C-3a), 118.4 (C-3), 98.1 (C-7a), 65.3 (C-6), 25.7, 23.9 (C-4, C-5); IR: 1793, 1771, 1086, 990 cm^{-1}; MS: *m*/*z* 176/174 (M^+), 145/147; Anal. calcd. for $C_7H_7ClO_3$: C, 48.2; H, 4.0. Found: C, 47.9; H, 4.1.

Single crystal X-ray structure determination of 5. Suitable crystals were obtained by dissolving a sample of **5** in dichloromethane and slowly evaporating the solvent at 4°C in an open vessel. Single-crystal diffraction data were measured at 210 K on an imaging plate diffraction system IPDS-II (Stoe) using graphite-monochromated Mo-K_α radiation ($\lambda = 0.71073$ Å). One hundred eighty frames were collected with ω scan widths of 0.5° and 3 min exposure times. The data were corrected by a spherical absorption correction using the program X-Area [30] as well as for Lorentz, polarization and extinction effects. Crystal data: $C_7H_7ClO_3$, $M_r = 174.58$, space group $P\bar{1}$, $a = 8.4324(16)$ Å, $b = 8.6447(17)$ Å, $c = 10.8716(19)$ Å, $\alpha = 77.477(15)°$, $\beta = 78.056(15)°$, $\gamma = 76.460(15)°$, $V = 741.9(2)$ Å^3, $Z = 4$, $d_{calc} = 1.563$ g·cm^{-3}, colorless block, 0.55 × 0.31 × 0.19 mm, $\mu = 0.464$ mm^{-1}, 4819 total reflections ($2\theta_{max} = 50.00°$), 2452 independent ($R_{int} = 0.0571$), 1854 observed [$I < 2\sigma(I)$], 256 parameters. Final $R1$ [$I < 2\sigma(I)$] = 0.0393, $wR2$ (all data) = 0.0947, $S = 0.955$, largest difference peak and hole 0.272 and −0.220 e·Å^3. The structure was solved by direct methods using the SHELXS-97 [31] program and refined by full-matrix least-squares of F^2 using the program SHELXL-97 [32]. All nonhydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were located in a difference Fourier map. CCDC 755365 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

5,6-Dihydro-4H-pyran-3-carboxylic acid (3a). Oxalyl chloride (3.60 mL, 41.5 mmol) was cooled to 0°C, and 3,4-dihydro-2*H*-pyran (**1**, 2.50 mL, 27.7 mmol) was added. The solution was slowly warmed to ambient temperature and stirring was continued for 1 h. Excess oxalyl chloride was evaporated in vacuo (10 mbar) at 30°C. The mixture was then heated to 120°C for 0.5 h, cooled to ambient temperature, and poured into an ice-cold aqueous solution of Na_2CO_3. The alkaline solution was extracted with dichloromethane, and then acidified with hydrochloric acid (6 M). The aqueous layer was extracted with dichloromethane, and the organic solution was dried with $MgSO_4$, filtered, and evaporated to yield the title compound **3a** (2.76 g, 78%) as a colourless solid, mp 72–74°C. Analytical data match those reported in the literature [5]. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 10.42 (bs, 1H, COOH), 7.69 (s, 1H, H-2), 4.07 (t, 2H, $J = 5.2$ Hz, H-6), 2.23 (dt, 2H, $J = 6.5$, 1.2 Hz, H-4), 1.86 (m, 2H, H-5); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 173.4 (C=O), 157.4 (C-2), 105.1 (C-3), 66.8 (C-6), 20.9, 18.8 (C-4-5); IR: 1661 (s), 1623 (s), 1431 (s), 1175 (s) cm^{-1}; MS (EI): *m*/*z* 128 (M^+), 83 (M^+-CO_2H), 55; Anal. calcd. for $C_6H_8O_3$: C, 56.3; H, 6.3. Found: C, 56.3; H, 6.2.

Methyl 5,6-dihydro-4H-pyran-3-carboxylate (3b). Oxalyl chloride (3.60 mL, 41.5 mmol) was cooled to 0°C, and 3,4-dihydro-2H-pyran (**1**, 2.50 mL, 27.7 mmol) was added. The solution was slowly warmed to ambient temperature and stirring

was continued for 1 h. Excess oxalyl chloride was evaporated in vacuo (10 mbar) at 30°C. The mixture was then heated to 120°C for 0.5 h, and subsequently cooled to ambient temperature. A mixture of methanol (2.60 mL, 64.2 mmol) and pyridine (5.00 mL) was added, and the solution was stirred at ambient temperature for 12 h. All volatiles were evaporated, and the residue was purified by chromatography on silica (eluent hexane/MTBE mixtures of increasing polarity) to give the title compound **3b** (2.52 g, 64%) as a colourless liquid. The compound was found to be sufficiently pure by ^{1}H-NMR spectroscopy, although repeated attempts to obtain microanalytical data within the usual limits were unsuccessful. Analytical data match those reported in the literature [6]. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.52 (s, 1H, H-2), 3.99 (t, 2H, J = 5.3 Hz, H-6), 3.65 (s, 3H, OMe), 2.21 (t, 2H, J = 6.4 Hz, H-4), 1.82 (m, 2H, H-5); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 168.1 (C=O), 155.3 (C-2), 105.7 (C-3), 66.5 (C-6), 50.9 (OMe), 21.0, 19.1 (C-4-5); IR: 1700 (s), 1628 (s), 1261 (s), 1171 (s) cm^{-1}; MS: m/z 142 (M^+), 111 (M^+-OMe), 83 (M^+-CO_2Me), 55.

***N*,*N*-Diisopropyl-5,6-dihydro-4H-pyran-3-carboxamide (3c).** Oxalyl chloride (1.40 mL, 16.6 mmol) was cooled to 0°C, and 3,4-dihydro-2H-pyran (**1**, 1.00 mL, 11.0 mmol) was added. The solution was slowly warmed to ambient temperature and stirring was continued for 1 h. Excess oxalyl chloride was evaporated in vacuo (10 mbar) at 30°C. The mixture was then heated to 120°C for 0.5 h, and subsequently cooled to ambient temperature. A mixture of diisopropyl amine (3.00 mL, 21.2 mmol) and triethyl amine (3.00 mL) was added, and the solution was stirred at ambient temperature for 12 h. All volatiles were evaporated, and the residue was purified by chromatography on silica (eluent hexane/MTBE mixtures of increasing polarity) to give the title compound **3c** (2.25 g, 96%) as a highly viscous oil. The compound was found to be sufficiently pure by ^{1}H-NMR spectroscopy. Repeated attempts to purify the compound by crytallization were unsuccessful. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.46 (s, 1H, H-2), 3.88 (t, 2H, J = 5.1 Hz, H-6), 3.73 (sept, 2H, J = 6.8 Hz, C*H*-Me_2), 2.12 (t, 2H, J = 6.2 Hz, H-4), 1.79 (m, 2H, H-5), 1.16 (d, 12 H, J = 6.8 Hz, Me); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 170.3 (C=O), 143.6 (C-2), 111.3 (C-3), 65.3 (C-6), 47.8 (2*C*H-Me_2), 21.5, 21.1 (C-4-5), 20.8 (4*Me); IR: 1612 (s), 1434 (s), 1157 (s)1029 (s) cm^{-1}; MS: m/z 211 (M^+), 111 [M^+-CO(NPr^i)$_2$].

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