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Unprecedented formation of stable ketene-*N*,*O*-acetals and their rearrangement under basic conditions

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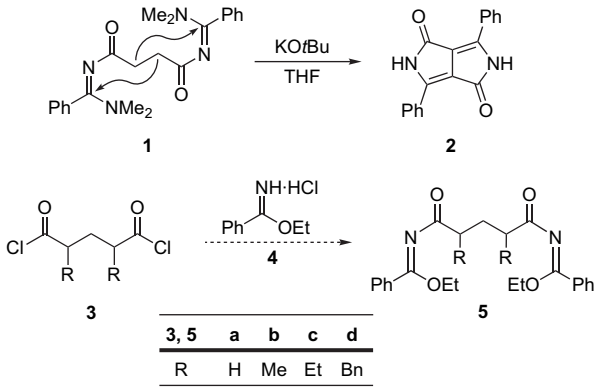
Dedicated to Professor M. Christl on the occasion of his 65th birthday

Abstract—Treatment of 2,4-disubstituted glutaryl dichlorides with benzimidic acid ethyl ester hydrochloride in the presence of triethylamine did not give the expected bis(acylbenzimidates), but delivered *O*-acyl-*N*-ethoxybenzylidene-ketene-*N*,*O*-acetals in good to excellent yields. These compounds, which are stable to moisture and chromatography on silica gel, underwent an unprecedented rearrangement to cyclic enamides under stronger basic conditions. A mechanism for this rearrangement is proposed.

1. Introduction

Acylimidates and -amidates are unsymmetric imide derivatives[1] that possess an electrophilic carbon atom in the C=N moiety and, upon deprotonation, also a nucleophilic carbon atom in α-position to the carbonyl group.[2,3] This bifunctional reactivity pattern was used by Closs and Gompper in an elegant synthesis of the diazapentalenedione **2** (Scheme 1).[4] Treatment of the succinyl bisamidate **1** with KO*t*-Bu in THF induced a 2-fold cyclization affording **2** in a single step and in quantitative yield. Since further examples of such ring closure reactions are unknown, we were interested in whether this principle can be extended to other 1,*n*-diacid derived bis(acylimidates) or bis(acylamidates),[5] which would allow a facile access to bridged bicyclic diamides.[6] Within these investigations we intended to prepare the glutaryl bisimidates **5** from the corresponding dichlorides **3** and benzimidic acid ethyl ester hydrochloride (**4**). In this paper we report about the unexpected and unprecedented formation of stable *O*-acyl-*N*-ethoxybenzylidene-ketene-*N*,*O*-acetals, which occurred in the attempted syntheses of **5b–d** from the 2,4-disubstituted glutaryl dichlorides **3b–d** and **4**, and their rearrangements upon treatment with base.



Scheme 1. Synthesis of the diazapentalenedione **2** from the succinyl bisamidate **1** according to Closs and Gompper[4] and our attempted preparation of the glutaryl derived bis(acylimidates) **5**.

2. Results and discussion

2.1. Preparation of the glutaryl dichlorides 3c and 3d

The 2,4-dialkylglutaryl dichlorides **3c** and **3d** were synthesized from the tetramethyl ester **6**[7] in a three-step sequence (Scheme 2).[8] Deprotonation of **6** with NaOMe in MeOH and 2-fold alkylation with ethyl iodide and benzyl bromide delivered the esters **7**, which were hydrolyzed and decarboxylated in refluxing half-concentrated H_2SO_4 to give the crude diacids **8**. Chromatographic purification and crystallization from Et_2O/*n*-pentane afforded analytically pure **8c**[9] and **8d** as mixtures of their *dl*- and *meso*-isomers.[10] The desired dichlorides **3c** (*dl*/*meso*=36:64) and **3d** (*dl*/*meso*=44:56) were

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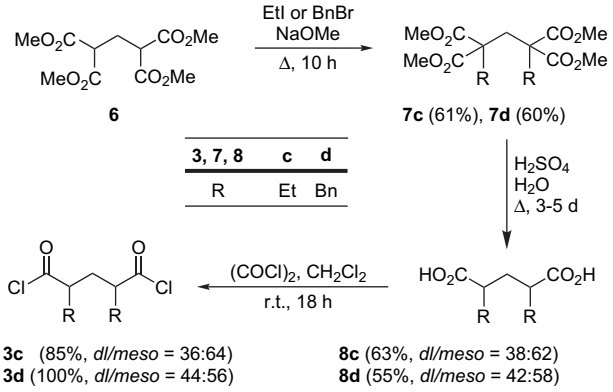
obtained by treatment with oxalyl chloride in CH_2Cl_2. The overall yield for the preparation of **3c** and **3d** from **6** was 33% each.



Scheme 2. Preparation of the glutaryl dichlorides **3c** and **3d**.

2.2. Formation of the ketene-*N*,*O*-acetals 9

The synthesis of the glutaryl derived bis(acylbenzimidates) **5** was attempted in analogy to known standard procedures.[11] Treatment of commercially available glutaryl dichloride (**3a**) with benzimidic acid ethyl ester hydrochloride (**4**) in the presence of triethylamine afforded, as expected, the glutaryl bisimidate **5a** in 44% yield (Scheme 3).[12] The analogous reactions of **4** with the 2,4-disubstituted glutaryl dichlorides **3b**,[13,14] **3c**, and **3d**, in contrast, delivered the ketene-*N*,*O*-acetals **9b–d** as the sole products in high yields (73–95%). Thus, the monoacylimidates **10** formed in the first step did not undergo a second addition of **4**, but an intramolecular cyclization. Most likely, a nucleophilic attack of the carbonyl oxygen of the acylimidate group at the ketene moiety of **11**, as generated from the acyl chloride function in the presence of base, occurred.

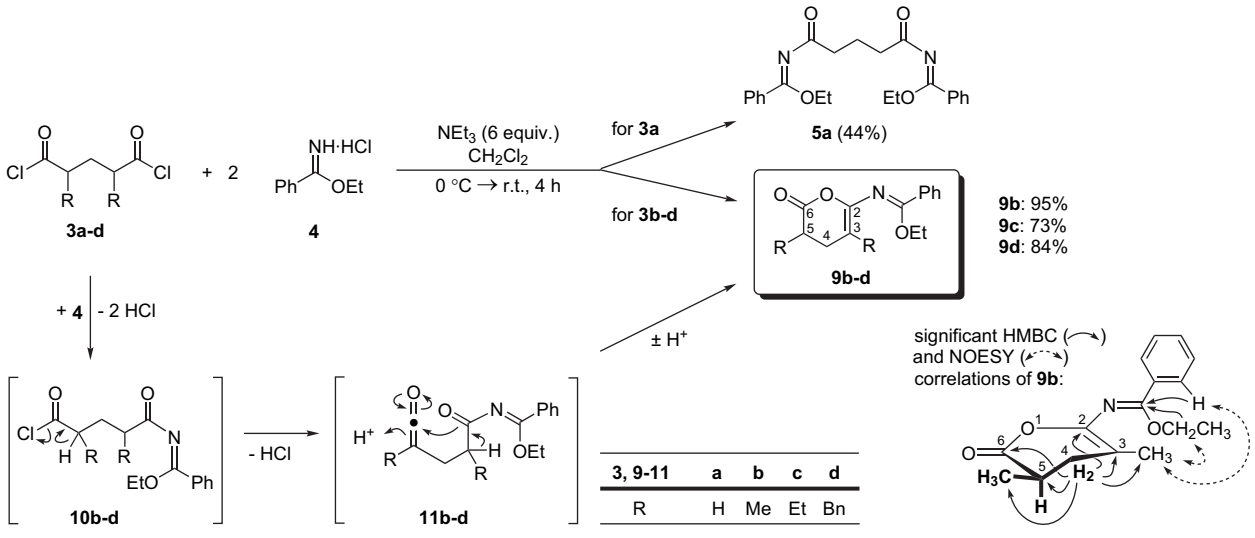
The different reactivity of the 2,4-disubstituted glutaryl dichlorides **3b–d** compared to **3a** is probably the result of the increased steric hindrance in the α-positions. All attempts to generate a bis(acylimidate) of type **5** from **3b–d**, e.g. by treatment of **3b–d** with an excess of **4**, or a ketene-*N*,*O*-acetal of type **9** from **3a**, e.g. by reaction of **3a** with a substoichiometric amount of **4**, failed.

Exemplarily for the ketene-*N*,*O*-acetals **9** prepared, the structure of **9b** was established unambiguously by two-dimensional NMR spectroscopy; some significant HMBC correlations are depicted in Scheme 3. The configuration of the C=N double bond is unknown. A mixture of cis and trans isomers, however, is very unlikely since only a single set of signals was detected in all NMR spectra. NOESY interactions of the protons of the methyl group at C-3 were found with those of the methylene unit of the ethoxy substituent as well as with the *ortho*-protons of the phenyl group. Thus, the 2-aza-1,3-diene subunit cannot be aligned in plane, probably due to steric interactions. As a consequence, the electronic resonance stabilization within the 2-aza-1,3-diene system has to be low.

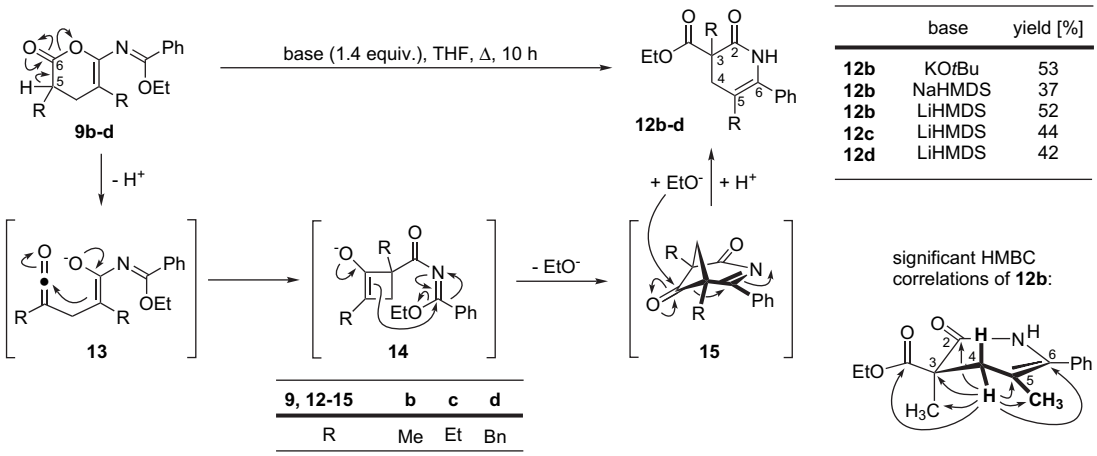
The combination of structural elements in **9**—an *O*-acyl-*N*-alkoxyalkylidene ketene-*N*,*O*-acetal function that is not stabilized, e.g. by an aromatic system[15]—is unprecedented. The stability of **9b–d** is also extraordinary: these compounds show no tendency to decompose, neither by exposure to moisture nor by column chromatography on silica gel.

2.3. Rearrangement of the ketene-*N*,*O*-acetals 9 under basic conditions

Deprotonation of the ketene-*N*,*O*-acetals **9** will lead to the corresponding ester enolates. A direct intramolecular attack of the enolates at the electrophilic acylimidate function present, however, seems to be unlikely due to the largely planarized structures of **9**. And indeed, skeletal rearrangements were observed in refluxing THF upon treatment of **9b–d** with LiHMDS and, in the case of **9b**, also with NaHMDS and KO*t*-Bu, delivering the enamides **12b–d** in 37–53% yields (Scheme 4). The formation of **12**, which requires a cleavage of the C-6–C-5 bond of **9**, can be explained by



Scheme 3. Unexpected formation of the ketene-*N*,*O*-acetals **9b–d** from **3b–d** and **4** and significant HMBC and NOESY correlations of **9b**.



Scheme 4. Base induced rearrangement of the ketene-*N*,*O*-acetals **9b–d** to the enamides **12b–d** and significant HMBC correlations of **12b**.

a mechanism that involves all functional groups present. In the first step, abstraction of the acidic proton of **9** is followed by ring opening to give the acylimidate enolate **13**, which is the deprotonated analog of **11** (see Scheme 3). The reactive ketene moiety concurrently created is trapped intramolecularly by the amide enolate to deliver the strained cyclobutanone enolate **14**, which attacks the C=N double bond of the regenerated acylimidate function. Finally, the four-membered ring of the resulting 3-azabicyclo[3.1.1]hept-3-ene-2,6-dione **15** is cleaved by ethanolate, liberated in the preceding step, in the sense of a retro-Claisen condensation to give the observed enamides **12** after protonation. The driving force for the last step is probably the release of ring strain.

3. Conclusion

Treatment of glutaryl dichloride (**3a**) with benzimidic acid ethyl ester hydrochloride (**4**) in the presence of triethylamine afforded the expected bis(acylimidate) **5a**. The analogous reactions with the 2,4-disubstituted glutaryl dichlorides **3b–d**, however, delivered the *O*-acyl-*N*-ethoxybenzylidene-ketene-*N*,*O*-acetals **9b–d**, which were found to be stable to moisture and chromatography on silica gel. Under stronger basic conditions, **9b–d** rearranged to give the enamides **12b–d**.

4. Experimental

4.1. General

All reactions were performed in flame-dried glassware under a static argon atmosphere using dried solvents. Melting points were determined with a Kofler melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AV 400 instrument operating at 400 MHz (^{1}H) and 100 MHz (^{13}C) or on a Bruker DMX 600 instrument operating at 600 MHz (^{1}H) and 150 MHz (^{13}C). Chemical shifts are reported in δ units using the deuterated solvent as an internal reference. Elemental analyses were performed in the Institute of Inorganic Chemistry, University of Würzburg. Mass spectra were measured on a Finnigan MAT 8200 instrument and on a Bruker Daltonics micrOTOF focus. IR spectra were recorded on a Jasco FT-IR-410 spectrometer.

4.2. Tetramethyl heptane-3,3,5,5-tetracarboxylate (7c)

The tetramethyl ester **6** (5.00 g, 18.1 mmol) was added at rt to a methanolic solution of NaOMe, prepared from Na (1.00 g, 43.4 mmol) in MeOH (50 mL). After 30 min, EtI (5.61 mL, 8.47 g, 54.3 mmol) was added and the reaction mixture was stirred at rt for 2 h and refluxed for 8 h. Most of the solvent was removed under reduced pressure. The oily residue was diluted with water (50 mL) and extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Chromatographic purification on silica gel (*n*-pentane/Et_2O 5:1→1:1) delivered a colorless oil, which started to crystallize upon standing. Crystallization from Et_2O/*n*-pentane gave **7c** (3.67 g, 11.0 mmol, 61%) as a colorless solid, mp 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, J=7.5 Hz, 6H), 1.89 (q, J=7.5 Hz, 4H), 2.71 (s, 2H), 3.68 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1, 27.1, 35.5, 52.2, 56.7, 171.5; IR (film) 2979, 2958, 1736, 1438, 1298, 1240, 1210, 1130, 1105 cm^{-1}; HRMS (ESI, MeCN/$CHCl_3$) calcd for $C_{15}H_{24}O_8$+Na 355.1363; found 355.1370.

4.3. Tetramethyl 1,5-diphenylpentane-2,2,4,4-tetracarboxylate (7d)

The tetramethyl ester **7d** was prepared in analogy to the synthesis of **7c** described above. Deprotonation of **6** (2.00 g, 7.24 mmol) with NaOMe in MeOH and alkylation (6 h at rt, 4 h reflux) with BnBr (2.60 mL, 3.71 g, 21.7 mmol) yielded, after work up, column chromatography (*n*-pentane/Et_2O 2:1), and crystallization from Et_2O, **7d** (1.98 g, 4.34 mmol, 60%) as a colorless solid, mp 116–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (s, 2H), 3.26 (s, 4H), 3.62 (s, 12H), 7.14–7.19 (m, 4H), 7.22–7.31 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.8, 42.5, 52.0, 57.9, 127.0, 128.0, 130.4, 136.0, 170.8; IR (film) 2995, 2949, 1743, 1723, 1440, 1337, 1278, 1205, 1108 cm^{-1}; HRMS (ESI, MeCN/$CHCl_3$ 1:1) calcd for $C_{25}H_{28}O_8$+Na 479.1676; found 479.1677.

4.4. 2,4-Diethylglutaric acid (8c)[9]

A solution of **7c** (3.00 g, 9.03 mmol) in half-concentrated H_2SO_4 (40 mL) was refluxed for 3 d. The reaction mixture was diluted with water (200 mL), carefully neutralized at 0 °C with solid NaOH, slightly re-acidified with 2 N HCl, and extracted with Et_2O (2×200 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Fast column chromatography on silica gel (*n*-pentane/Et_2O 2:1) gave a colorless oil, which was crystallized from Et_2O/*n*-pentane to yield a 38:62-mixture of the *dl*-**8c** (**A**) and *meso*-**8c** (**B**) (1.07 g, 5.69 mmol, 63%), mp 74–107 °C;[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J=7.4 Hz, 6H **A**), 0.96 (t, J=7.4 Hz, 6H **B**), 1.42–1.56 (m, 2H **A**, 2H **B**), 1.59 (dt, J=14.0, 2.8 Hz, 1H **B**), 1.65–1.85 (m, 2H **A**, 2H **B**), 2.02 (t, J=5.8 Hz, 2H **A**), 2.08 (dt, J=13.9, 11.6 Hz, 1H **B**), 2.34 (dddd, J=11.4, 8.4, 5.6, 2.8 Hz, 2H **B**), 2.46 (m, 2H **A**), 12.5 (br s, 2H **A**, 2H **B**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6 (**B**), 11.8 (**A**), 24.5 (**A**), 26.6 (**B**), 32.4 (**A**), 34.7 (**B**), 43.3 (**A**), 47.1 (**B**), 182.3 (**A**), 182.7 (**B**); IR (film) 3600–2400, 2971, 1710, 1458, 1279, 1238, 932 cm^{-1}; HRMS (ESI, MeCN/$CHCl_3$ 1:1) calcd for $C_9H_{16}O_4$+Na 211.0941; found 211.0941.

4.5. 2,4-Dibenzylglutaric acid (8d)

The glutaric acid derivative **8d** was prepared in analogy to the synthesis of **8c** described above. Refluxing a solution of **7d** (1.81 g, 3.96 mmol) in half-concentrated H_2SO_4 (20 mL) for 5 d, work up, column chromatography (*n*-pentane/Et_2O 2:1→1:3), and crystallization from Et_2O/*n*-pentane delivered a 42:58-mixture of the *dl*-**8d** (**A**) and *meso*-**8d** (**B**) (681 mg, 2.18 mmol, 55%) as a colorless solid, mp 129–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67 (br d, J=13.9 Hz, 1H **B**), 1.98 (t, J=5.6 Hz, 2H **A**), 2.09 (m, 1H **B**), 2.57 (dd, J=13.8, 8.4 Hz, 2H **A**), 2.66 (m, 4H **B**), 2.91 (m, 2H **A**), 3.02 (m, 2H **B**), 3.09 (dd, J=13.8, 6.2 Hz, 2H **A**), 7.05 (m, 4H **A**), 7.12 (m, 4H **B**), 7.17–7.29 (m, 6H **A**, 6H **B**), 12.5 (br s, 2H **A**, 2H **B**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3 (**A**), 33.1 (**B**), 36.6 (**A**), 38.9 (**B**), 43.3 (**A**), 46.9 (**B**), 126.5 (**A**), 126.6 (**B**), 128.5 (PhC **A**, PhC **B**), 128.9 (PhC **A**, PhC **B**), 138.1 (**B**), 138.4 (**A**), 181.9 (**A**), 182.0 (**B**); IR (KBr) 3600–2400, 3033, 2923, 1738, 1718, 1297, 1246, 1230, 1180, 697 cm^{-1}; HRMS (ESI, MeCN/$CHCl_3$ 1:1) calcd for $C_{19}H_{20}O_4$+Na 335.1254; found 335.1254.

4.6. 2,4-Diethylglutaryl dichloride (3c)

To a suspension of **8c** (376 mg, 2.00 mmol) in CH_2Cl_2 (11 mL) was added $(COCl)_2$ (698 μL, 1.02 g, 8.00 mmol) and a catalytic amount of DMF. After 18 h of stirring at rt, the solvent was removed under reduced pressure. Drying at 50 °C/0.5 mbar gave a 36:64-mixture of the dichlorides *dl*-**3c** (**A**) and *meso*-**3c** (**B**) (382 mg, 1.70 mmol, 85%) as a slightly yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (m, 6H **A**, 6H **B**), 1.76 (m, 4H **A**, 5H **B**), 1.93 (dd, J=7.8, 6.5 Hz, 2H **A**), 2.25 (m, 1H **B**), 2.79 (m, 2H **A**, 2H **B**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8 (**A**, **B**), 24.7 (**B**), 25.9 (**A**), 32.2 (**B**), 33.0 (**A**), 55.5 (**B**), 56.3 (**A**), 176.2 (**B**), 176.5 (**A**); IR (KBr) 2971, 2937, 2880, 1801, 1764, 1709, 1460, 1056, 1027, 789 cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 189 (12) [M$^+$−Cl], 161 (10) [M$^+$−COCl], 125 (11), 97 (100), 83 (20); HRMS (EI, 70 eV) calcd for $C_9H_{14}O_2Cl$ (=M−Cl) 189.0677; found 189.0675.

4.7. 2,4-Dibenzylglutaryl dichloride (3d)

$(COCl)_2$ (804 μL, 1.17 g, 9.21 mmol) and a catalytic amount of DMF were added to a solution of **8d** (720 mg, 2.30 mmol) in CH_2Cl_2 (13 mL). The reaction mixture was stirred for 18 h at rt and the solvent was removed under reduced pressure. Drying at 50 °C/0.5 mbar gave a 44:56-mixture of the dichlorides *dl*-**3d** (**A**) and *meso*-**3d** (**B**) (804 mg, 2.30 mmol, 100%) as a slightly yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77 (m, 1H **B**), 1.94 (m, 2H **A**), 2.32 (m, 1H **B**), 2.85 (m, 2H **A**, 2H **B**), 3.13 (m, 4H **A**, 4H **B**), 7.08 (m, 4H **B**), 7.14 (m, 4H **A**), 7.20–7.35 (m, 6H **A**, 6H **B**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.2 (**B**), 33.1 (**A**), 37.6 (**B**), 38.6 (**A**), 56.2 (**B**), 56.4 (**A**), 127.3 (2×PhC), 128.8, 128.9 (3×PhC), 136.1 (**A**), 136.2 (**B**), 175.7 (**B**), 175.8 (**A**); IR (KBr) 3063, 3030, 2927, 1801, 1765, 1497, 1455, 1041, 751, 700 cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 313 (12) [M$^+$−Cl], 284 (8), 249 (12), 221 (11), 145 (21), 117 (52), 91 (100); HRMS (EI, 70 eV) calcd for $C_{19}H_{17}O_2Cl$ (=M−HCl) 312.0912; found 312.0910.

4.8. Glutaric acid bis(1-phenyl-1-ethoxymethylidene-amide) (5a)

Triethylamine (2.95 mL, 2.13 g, 21.0 mmol) was added to a suspension of benzimidic acid ethyl ester hydrochloride (**4**, 1.30 g, 7.00 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 30 min at rt, cooled to 0 °C, and a solution of glutaryl dichloride (**3a**, 447 μL, 592 mg, 3.50 mmol) in CH_2Cl_2 (5 mL) was added slowly. After 24 h at rt, the reaction mixture was diluted with satd aq NH_4Cl (50 mL) and extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Chromatographic purification on silica gel (*n*-pentane/Et_2O 100:0→50:50) delivered **5a** (612 mg, 1.55 mmol, 44%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J=7.1 Hz, 6H), 1.86 (quin., J=7.3 Hz, 2H), 2.32 (t, J=7.3 Hz, 4H), 4.25 (q, J=7.1 Hz, 4H), 7.36 (m, 4H, PhH), 7.45 (m, 2H, PhH), 7.60 (m, 4H, PhH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.2, 38.2, 63.5, 128.3, 128.6, 131.3, 131.6, 156.2, 183.8; IR (KBr) 3062, 2980, 2940, 2905, 1769, 1660, 1279, 1098, 698 cm^{-1}; MS (CI, CH_4, 150 eV) *m*/*z* (%) 395 (31) [M+H]$^+$, 260 (8), 246 (100), 151 (29), 115 (32). Anal. Calcd for $C_{23}H_{26}N_2O_4$: C 70.03; H 6.64; N 7.10; found: C 69.66; H 6.59; N 7.00.

4.9. General procedure for the preparation of the ketene-*N*,*O*-acetals 9b–d

A suspension of **4** (2.0 equiv) in CH_2Cl_2 (10 mL/mmol **3**) was treated with triethylamine (6.0 equiv). After 30 min, a solution of the 2,4-disubstituted glutaryl dichlorides **3b–d** (1.0 equiv) in CH_2Cl_2 (5 mL/mmol **3**) was added slowly at 0 °C. After 5 h of stirring, the reaction mixture was diluted with satd aq NH_4Cl (40 mL/mmol **3**) and extracted with Et_2O (2×40 mL/mmol **3**). The combined organic layers were washed with brine (20 mL/mmol **3**), dried over $MgSO_4$, and concentrated under reduced pressure. Chromatographic

Table 1. NMR spectroscopic data of **9b**[a]

Position	^{13}C ($CDCl_3$) [ppm]	^{1}H ($CDCl_3$) [ppm]	COSY ($CDCl_3$)	HMBC ($CDCl_3$)	INADEQUATE[b] ($CDCl_3$)	^{1}H (C_6D_6) [ppm]	NOESY (C_6D_6)[c]
2	144.6				3 (93)		
3	93.5				2 (87), 4 (43), 8 (43)		
4	32.8	2.06 (m, 2H)	5,8	2,3,5,6,7,8	3 (37), 5 (37)	α: 1.46 (dd, *J*=16.1, 7.3 Hz, 1H); β: 1.57 (ddd, *J*=16.1, 12.1, 1.3 Hz, 1H)	4β,5,7,8; 4α,5,7,8
5	34.0	2.54 (ddq, *J*=11.1, 8.2, 6.9 Hz, 1H)	4,7	4,6,7	4 (37), 6 (53), 7 (37)	2.13 (dquin., *J*=12.1, 6.9 Hz, 1H)	4α,4β,7
6	172.0				5 (50)		
7 (5-Me)	15.2	1.22 (d, *J*=6.9 Hz, 3H)	5	4,5,6	5 (37)	0.97 (d, *J*=6.8 Hz, 3H)	4α,4β,5
8 (3-Me)	15.7	1.41 (s, 3H)	4	2,3,4	3 (45)[d]	1.36 (s, 3H)	4α,4β,(10),(13)
9 (6-N=C)	164.8						
10 (OCH_2CH_3)	63.1	4.39 (q, *J*=7.1 Hz, 2H)	11	9,11	11 (36)	4.26 (q, *J*=7.1 Hz, 2H)	(8),11,13
11 (OCH_2CH_3)	14.1	1.41 (t, *J*=7.1 Hz, 3H)	10	10	10 (42)	1.12 (t, *J*=7.1 Hz, 3H)	10
12 (*ipso*-Ph)	132.4				9 (68), 13 (57)		
13 (*ortho*-Ph)	127.5	7.50 (m, 2H)	14	9,13,15	12 (58), 14 (55)	7.50 (m, 2H)	(8),10,14
14 (*meta*-Ph)	128.1	7.36 (m, 2H)	13,15	12,14	13 (50), 15 (57)	7.00 (m, 2H)	13
15 (*para*-Ph)	130.5	7.42 (m, 1H)	14	13	14 (59)	7.00 (m, 1H)	

[a] Recorded at 400 MHz (^{1}H, COSY, HMBC, NOESY) and 150 MHz (^{13}C, INADEQUATE).
[b] Coupling partner; in parentheses: coupling constant *J* (Hz).
[c] In parentheses: weak interactions.
[d] Signal too weak.

purification on silica gel (*n*-pentane/Et_2O 100:0→60:40) delivered the ketene-*N*,*O*-acetals **9b–d** as slightly yellow oils.

4.9.1. *N*-(3,5-Dimethyl-6-oxo-5,6-dihydro-4*H*-pyran-2-yl)benzimidic acid ethyl ester (9b). According to the general procedure, **3b** (144 mg, 730 μmol) was converted into **9b** (190 mg, 695 μmol, 95%); IR (KBr) 2979, 2933, 1758, 1699, 1641, 1448, 1363, 1283, 1109, 701 cm^{-1}; MS (CI, CH_4, 150 eV) *m*/*z* (%) 547 (15) $[2M+H]^+$, 501 (17) $[2M-OEt]^+$, 274 (100) $[M+H]^+$, 228 (48). Anal. Calcd for $C_{16}H_{19}NO_3$: C 70.31; H 7.01; N 5.12; found: C 70.09; H 7.04; N 5.24; HRMS (ESI, MeCN) calcd for $C_{16}H_{19}NO_3$+Na 296.1257; found 296.1251; the NMR spectroscopic data are summarized in Table 1.

4.9.2. *N*-(3,5-Diethyl-6-oxo-5,6-dihydro-4*H*-pyran-2-yl)-benzimidic acid ethyl ester (9c). As described in the general procedure, the ketene-*N*,*O*-acetal **9c** (49.1 mg, 163 μmol) was obtained from **3c** (50.0 mg, 222 μmol) in 73% yield; ^{1}H NMR[16] (400 MHz, $CDCl_3$) δ 0.67 (t, *J*=7.5 Hz, 3H, 3-CH_2CH_3), 0.97 (t, *J*=7.5 Hz, 3H, 5-CH_2CH_3), 1.41 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 1.48 (dquin., *J*=14.4, 7.2 Hz, 1H, 5-C*H*HCH_3), 1.86 (m, 3H, 3-CH_2CH_3, 5-CH*H*CH_3), 1.99 (dd, *J*=16.1, 10.6 Hz, 1H, 4-H), 2.19 (dd, *J*=16.1, 6.7 Hz, 1H, 4-H), 2.35 (dq, *J*=10.4, 6.8 Hz, 1H, 5-H), 4.38 (q, *J*=7.1 Hz, 2H, OCH_2CH_3), 7.32–7.44 (m, 3H, PhH), 7.51 (m, 2H, PhH); ^{13}C NMR[16] (100 MHz, $CDCl_3$) δ 11.4 (3-CH_2CH_3, 5-CH_2CH_3), 14.2 (OCH_2CH_3), 23.0 (3-CH_2CH_3, 5-CH_2CH_3), 27.3 (C-4), 40.6 (C-5), 63.1 (OCH_2CH_3), 98.7 (C-3), 127.8 (PhC), 128.1 (PhC), 130.6 (PhC), 132.3 (PhC), 143.9 (C-2), 164.5 (C=N), 171.3 (C-6); IR (KBr) 2964, 2927, 2852, 1763, 1698, 1640, 1281, 1109, 1031, 700 cm^{-1}; HRMS (ESI, MeCN/$CHCl_3$ 1:1) calcd for $C_{18}H_{23}NO_3$+Na 324.1576; found 324.1575.

4.9.3. *N*-(3,5-Dibenzyl-6-oxo-5,6-dihydro-4*H*-pyran-2-yl)benzimidic acid ethyl ester (9d). According to the general procedure, **3d** (50.1 mg, 143 μmol) was converted into **9d** (51.0 mg, 120 μmol, 84%); ^{1}H NMR[16] (400 MHz, $CDCl_3$) δ 1.42 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 1.89 (dd, *J*=16.5, 9.5 Hz, 1H, 4-H), 1.99 (dd, *J*=16.5, 6.7 Hz, 1H, 4-H), 2.53 (dd, *J*=13.8, 9.7 Hz, 1H, 5-C*H*HPh), 2.68 (tdd, *J*=9.6, 6.7, 4.3 Hz, 1H, 5-H), 3.11 (d, *J*=14.9 Hz, 1H, 3-C*H*HPh), 3.14 (dd, *J*=13.7, 4.3 Hz, 1H, 5-CH*H*Ph), 3.26 (d, *J*=14.8 Hz, 1H, 3-CH*H*Ph), 4.42 (q, 2H, *J*=7.1 Hz, OCH_2CH_3), 6.92 (m, 4H, PhH), 7.18 (m, 6H, PhH), 7.37 (m, 2H, PhH), 7.45 (m, 1H, PhH), 7.54 (m, 2H, PhH); ^{13}C NMR[16] (100 MHz, $CDCl_3$) δ 14.2 (OCH_2CH_3), 26.9 (C-4), 35.6 (5-CH_2Ph), 36.0 (3-CH_2Ph), 40.9 (C-5), 63.4 (OCH_2CH_3), 97.2 (C-3), 126.2 (PhC), 126.4 (PhC), 127.8 (PhC), 128.3 (PhC), 128.4 (2×PhC), 128.6 (PhC), 129.0 (PhC), 130.8 (PhC), 132.5 (PhC), 138.3 (PhC), 139.4 (PhC), 145.2 (C-2), 164.5 (C=N), 170.7 (C-6); IR (KBr) 3027, 2925, 2851, 1765, 1694, 1638, 1494, 1283, 1108, 699 cm^{-1}; HRMS (ESI, MeCN/$CHCl_3$ 1:1) calcd for $C_{28}H_{27}NO_3$+Na 448.1889; found 448.1886.

4.10. General procedure for the rearrangement of 9b–d

LiHMDS (1.0 M in hexanes, 1.4 equiv) was added at rt to a solution of the ketene-*N*,*O*-acetals **9b–d** (1.0 equiv) in THF (20 mL/mmol **9**). After refluxing for 10 h, satd aq NH_4Cl (40 mL/mmol **9**) was added and the reaction mixture was extracted with Et_2O (2×40 mL/mmol **9**). The combined organic layers were washed with brine (20 mL/mmol **9**), dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed on silica gel (*n*-pentane/Et_2O 100:0→70:30) to give the enamides **12b–d** as slightly yellow solids.

4.10.1. 3,5-Dimethyl-2-oxo-6-phenyl-1,2,3,4-tetrahydropyridine-3-carboxylic acid ethyl ester (12b). According to the general procedure, **9b** (78.0 mg, 285 μmol) was rearranged to give **12b** (40.5 mg, 148 μmol, 52%) as a slightly yellow solid, mp 75 °C; IR (KBr) 3210, 3102, 2983, 2932, 1728, 1683, 1669, 1386, 1260, 1180, 1109, 701; MS (EI,

Table 2. NMR spectroscopic data of **12b**[a]

Position	^{13}C [ppm]	^{1}H [ppm]	COSY	HMBC
1 (NH)		6.81 (br s, 1H)		
2	170.2			
3	49.3			
4	39.2	α: 2.46 (dd, *J*=16.2, 1.2 Hz, 1H); β: 2.80 (d, *J*=16.2 Hz, 1H)	4β,8; 4α,8	2,3,5,6,7,8,9; 2,3,5,6,7,8,9
5	110.7			
6	130.8			
7 (3-Me)	20.0	1.50 (s, 3H)		2,3,4,9
8 (5-Me)	18.4	1.77 (s, 3H)	4α,4β	4,5,6
9 (3-CO)	172.6			
10 (O*C*H$_2$CH$_3$)	61.5	α: 4.19 (dq, *J*=10.7, 7.1 Hz, 1H); β: 4.25 (dq, *J*=10.7, 7.1 Hz, 1H)	10β,11; 10α,11	9,11; 9,11
11 (OCH$_2$*C*H$_3$)	14.2	1.26 (t, *J*=7.1 Hz, 3H)	10α,10β	10
12 (Ph)	135.1, 128.4, 128.5, 128.6	7.20–7.45 (m, 5H)	[b]	6[b]

[a] Recorded at 400 MHz (^{1}H, COSY, HMBC) and 100 MHz (^{13}C).
[b] Further correlations were not assigned due to signal overlap.

70 eV) *m*/*z* (%) 273 (4) [M]$^{+}$, 258 (12), 200 (100), 182 (6), 77 (14), 41 (7); HRMS (ESI, MeCN) calcd for $C_{16}H_{19}NO_3$+Na 296.1257; found 296.1257; the NMR spectroscopic data are summarized in Table 2.

The analogous reactions of **9b** with NaHMDS and KO*t*-Bu as the bases gave **12b** in 37% and 53% yields, respectively.

4.10.2. 3,5-Diethyl-2-oxo-6-phenyl-1,2,3,4-tetrahydropyridine-3-carboxylic acid ethyl ester (12c). As described in the general procedure, the enamide **12c** (18.8 mg, 62.4 μmol) was obtained from **9c** (42.8 mg, 142 μmol) in 44% yield, mp 104–106 °C; ^{1}H NMR[16] (400 MHz, $CDCl_3$) δ 1.02 (t, *J*=7.5 Hz, 3H, 5-CH$_2$C*H*$_3$), 1.05 (t, *J*=7.5 Hz, 3H, 3-CH$_2$C*H*$_3$), 1.27 (t, *J*=7.2 Hz, 3H, OCH$_2$C*H*$_3$), 2.00 (m, 2H, 3-C*H*$_2$CH$_3$), 2.08 (q, *J*=7.5 Hz, 2H, 5-C*H*$_2$CH$_3$), 2.51 (d, *J*=16.2 Hz, 1H, 4-H), 2.75 (d, *J*=16.2 Hz, 1H, 4-H), 4.18 (dq, *J*=10.8, 7.1 Hz, 1H, OC*H*HCH$_3$), 4.25 (dq, *J*=10.8, 7.1 Hz, 1H, OCH*H*CH$_3$), 6.72 (br s, 1H, NH), 7.25 (m, 2H, PhH), 7.35 (m, 3H, PhH); ^{13}C NMR[16] (100 MHz, $CDCl_3$) δ 9.2 (3-CH$_2$*C*H$_3$), 12.8 (5-CH$_2$*C*H$_3$), 14.3 (OCH$_2$*C*H$_3$), 25.0 (5-*C*H$_2$CH$_3$), 26.5 (3-*C*H$_2$CH$_3$), 33.2 (C-4), 53.2 (C-3), 61.4 (O*C*H$_2$CH$_3$), 116.4 (C-5), 128.3 (PhC), 128.5 (PhC), 128.7 (PhC), 130.4 (C-6), 135.1 (PhC), 169.4 (C=O), 171.9 (C=O); IR (film) 3229 (br), 2958, 2925, 2853, 1731, 1684, 1462, 1259, 1028, 749, 700 cm^{-1}; HRMS (ESI, MeCN) calcd for $C_{18}H_{23}NO_3$+Na 324.1570; found 324.1571.

4.10.3. 3,5-Dibenzyl-2-oxo-6-phenyl-1,2,3,4-tetrahydropyridine-3-carboxylic acid ethyl ester (12d). According to the general procedure, **9d** (41.1 mg, 96.6 μmol) was converted into **12d** (17.3 mg, 40.7 μmol, 42%), mp 166–168 °C; ^{1}H NMR[16] (400 MHz, $CDCl_3$) δ 1.21 (t, *J*=7.1 Hz, 3H, OCH$_2$C*H*$_3$), 2.38 (d, *J*=16.4 Hz, 1H, 4-H), 2.58 (d, *J*=16.4 Hz, 1H, 4-H), 3.18 (d, *J*=13.6 Hz, 1H, 3-C*H*HPh), 3.33 (d, *J*=15.4 Hz, 1H, 5-C*H*HPh), 3.39 (d, *J*=15.4 Hz, 1H, 5-C*H*HPh), 3.40 (d, *J*=13.6 Hz, 1H, 3-C*H*HPh), 4.06 (dq, *J*=10.7, 7.1 Hz, 1H, OC*H*HCH$_3$), 4.15 (dq, *J*=10.7, 7.1 Hz, 1H, OCH*H*CH$_3$), 6.83 (br s, 1H, NH), 7.08 (m, 2H, PhH), 7.19–7.31 (m, 11H, PhH), 7.37 (m, 2H, PhH); ^{13}C NMR[16] (100 MHz, $CDCl_3$) δ 14.1 (OCH$_2$*C*H$_3$), 33.6 (C-4), 37.9 (3-*C*H$_2$Ph), 38.9 (5-*C*H$_2$Ph), 54.5 (C-3), 61.7 (O*C*H$_2$CH$_3$), 112.9 (C-5), 126.3 (PhC), 126.9 (PhC), 128.1 (PhC), 128.3 (PhC), 128.5 (2×PhC), 128.9 (2×PhC), 130.7 (PhC), 132.3 (C-6), 134.8 (PhC), 136.2 (PhC), 139.0 (PhC), 168.6 (C=O), 171.4 (C=O); IR (film) 3210 (br), 2955, 2925, 2854, 1732, 1684, 1458, 1261, 799, 700 cm^{-1}; HRMS (ESI, MeCN) calcd for $C_{28}H_{27}NO_3$+H 426.2064; found 426.2073.

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10. The *dl*/*meso*-ratios of pure **8c** and **8d** can vary depending on the crystallization conditions. As observed for other 2,4-disubstituted glutaric acid derivatives,[8b,9a] the *meso*-isomers can be enriched by fractional crystallization.
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12. According to NMR, the glutaryl bisimidate **5a** is a stereochemically homogenous compound; the two C=N double bonds can be either both cis or both trans configured.
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14. Glutaryl dichloride **3b** is a 1:1-mixture of *dl*-**3b** and *meso*-**3b**.
15. Several compounds are known in which an *O*-acyl-*N*-alkoxy-alkylidene ketene-*N,O*-acetal function is incorporated into a hetarene (e.g., 6-alkoxypyridin-2-yl alkanoic acid esters) or a heterocycle with aromatic character (e.g., 6-oxo-6*H*-1,3-oxazin-4-yl alkanoic acid esters, 4-alkoxy-2-alkylidene-2*H*-oxazol-5-ones). To the best of our knowledge, compounds **9b–d** are the only examples of stable ketene-*N*,*O*-acetals devoid of such an electronic stabilization.
16. The ^{1}H and ^{13}C NMR signals were assigned by 2D experiments.