# A Simple Route to 4,4-Dialkoxy-2-azetidinones: Useful Intermediates for Organic Synthesis

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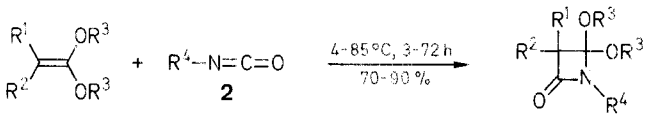
The title compounds are prepared in high yields by reaction between ketene acetals and isocyanates. They can be considered as key intermediates for the synthesis of different types of compounds.

The biologically active principle of all β-lactam antibiotics is the β-lactam ring, the reactivity and selectivity of which towards biological substrates can be decisively influenced by substituents or fused rings.[1] Therefore in the last decade, much attention has been focused on the reactivity of the β-lactam ring in view of the substitution reactions,[2] neglecting the reactions which take place via ring opening. However, the latter aspect of the reactivity of β-lactams can also be interesting and it was desirable to tackle the synthesis of derivatives which undergo easily ring opening.

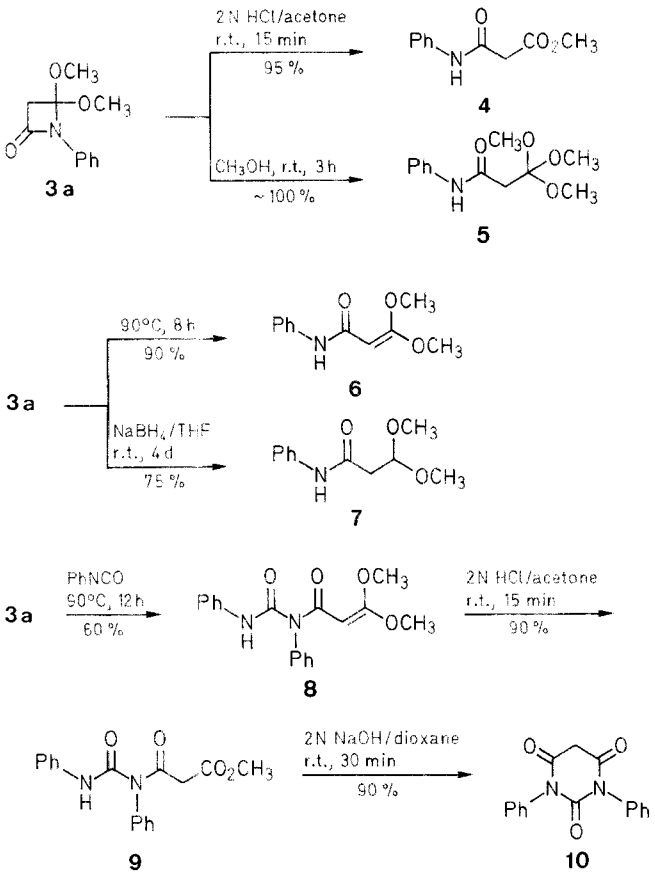
Several years ago, it was reported that phenyl isocyanate reacts with dimethyl ketene dimethylacetal at 100 °C in an 1:1 molar ratio to form 4,4-dimethoxy-3,3-dimethyl-1-phenyl-2-azetidinone.[3] However, when the reaction was carried out under the same conditions using ketene acetals having at least one hydrogen at position 2, only 3,3-dialkoxyacrylanilides were obtained.[3-5] Therefore, it seemed that from reaction of ketene acetals with isocyanates only 3,3-disubstituted azetidinones might be prepared. As it was most likely that the obtained results were due to the drastic conditions used, we have now carried out the reaction between ketene dimethylacetal **(1a)** and phenyl isocyanate **(2a)** at 4 °C in 2:1 molar ratio. In this way, we obtained 4,4-dimethoxy-1-phenyl-2-azetidinone **(3a)**, whose structure was confirmed by microanalysis and spectroscopic data (Table).




| 1 | $R^1$ | $R^2$ | $R^3$ | 2 | $R^4$ |
|---|---|---|---|---|---|
| **a** | H | H | $CH_3$ | **a** | Ph |
| **b** | H | H | Et | **b** | 4-$ClC_6H_4$ |
| **c** | H | $CH_3$ | $CH_3$ | | |
| **d** | H | Ph | $CH_3$ | | |
| **e** | H | $CH_2CO_2Et$ | $CH_3$ | | |
| **f** | $CH_3$ | $CH_3$ | $CH_3$ | | |
| **g** | $CH_3$ | $CH_2CO_2Et$ | $CH_3$ | | |

| 3 | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| **a** | H | H | $CH_3$ | Ph |
| **b** | H | H | $CH_3$ | 4-$ClC_6H_4$ |
| **c** | H | H | Et | Ph |
| **d** | H | $CH_3$ | $CH_3$ | Ph |
| **e** | H | $CH_3$ | $CH_3$ | 4-$ClC_6H_4$ |
| **f** | H | Ph | $CH_3$ | Ph |
| **g** | H | $CH_2CO_2Et$ | $CH_3$ | Ph |
| **h** | $CH_3$ | $CH_3$ | $CH_3$ | Ph |
| **i** | $CH_3$ | $CH_2CO_2Et$ | $CH_3$ | Ph |

Compounds **3** are very reactive, the amide acetal bond in a four-membered ring very readily broken. The scheme summarizes the results pertinent to **3a** obtained in some simple ring opening reactions, showing that the azetidinones **3** can be considered as key intermediates in the synthesis of many several compound types. In fact **3**, by mild acid hydrolysis and alcoholysis, give esters like **4** and orthoesters like **5**, respectively. If unsubstituted or monosubstituted at C-3, **3**, by thermal conversion, yield acrylanilides like **6**. Moreover, the reactions with sodium borohydride and phenyl isocyanate are very interesting, leading to protected formyl derivatives like **7** (starting material for several heterocyclic systems[3,4]) and the second to derivatives of barbituric acid like **10**. These can be obtained in very high yields by simple treatment with aqueous bases of the ester amides like **9**, the latter being obtained from acetals like **8** by mild acid hydrolysis. The chemical behavior of the acetals like **8** and ester amides like **9** is the reason for the previous wrong assignment of the structure of 4,4-diethoxy-2,6(1*H*,3*H*,6*H*)-pyrimidinedione to the reaction products of ketene diethyl acetal (**1b**) and isocyanates in the 1:2 molar ratio.[4,5]




As shown in the Table, the reaction between ketene acetals **1** and isocyanates **2** has a wide range of applicability and the azetidinones **3**, which have been obtained only occasionally,[3,6-9] are formed in high yields. The yields of **3** obtained using a molar ratio of **1**:**2** = 2:1 with ketene acetal as solvent are better than those obtained when the ratio is 1:1. In the case of the high boiling **1d** and **1e**, it is necessary to use the ratio **1d,e**/**2a** = 1:1, because the excess of ketene acetal cannot be removed without heating the reaction mixture. In the case of **1g**, the use of **1g**/**2a** = 1:1 ratio allows a better purification of **3i**. However, attempts to synthesize 3-acyl derivatives of **3** failed as acylketene acetals either do not react or lead to six-membered cycloadducts.

The ketene acetals **1a**,[10] **1b**[11] **1c**,[12] **1d**,[13] **1e**,[14] **1f**,[15] and **1g**[14] were prepared as previously reported.

**4,4,-Dialkoxy-2-azetidinones 3; General Procedure:**
A mixture of ketene acetal **1** (10 mmol, 5 mmol for **1d**, **1e**, and **1g**) and isocyanate **2** (5 mmol) is kept at the temperature reported in the Table under strictly anhydrous conditions until complete disappearance of **2** (IR). When the ketene acetals **1a–c, f** are used, removal of the unreacted **1** under reduced pressure at room temperature gives the crude azetidinones **3a–e, h**. In the case of the ketene acetal **1d**, dry *n*-hexane (15 mL) is added to the mixture after completion of the reaction. The resulting suspension is filtered by suction to remove solid 3,3-dimethoxy-2-phenylacrylanilide[4] formed (15%) during the course of the reaction. Removal of the solvent under reduced pressure and at room temperature gives crude **3f**. When ketene acetals **1e** and **1g** are used, the azetidinones **3g** and **3i** are directly recovered. The compounds **3** are obtained in pure form as reported in the Table.

It is to be noted that the azetidinones **3**, unsubstituted or monosubstituted at C-3 cannot be purified by chromatographic methods as they undergo hydrolysis on contact with absorbents. Moreover, they must be stored at temperature below 4°C under strictly anhydrous conditions, to avoid both hydrolysis to esters like **4** and isomerization to acetals like **6**.

**Methyl 2-(*N*-Phenylaminocarbonyl)acetate (4):**
To a solution of azetidinone **3a** (207 mg, 1 mmol) in acetone (5 mL), 2 N HCl (0.2 mL) is added. After 15 min, the solvent is removed under reduced pressure, the residue is treated with $CHCl_3$ (5 mL), and washed with water (2 × 3 mL). The organic layer is dried ($MgSO_4$), and the solvent is removed *in vacuo*. The crude **4** is purified by filtration through a short column of silica gel (10 g) using light petroleum (bp 40–70°C)/ether (1:1) as eluent; yield: 180 mg (95%); mp 43–44°C (*n*-hexane).

| | | | | |
|---|---|---|---|---|
| $C_{10}H_{11}NO_3$ | calc. | C 62.16 | H 5.74 | N 7.25 |
| (193.2) | found | 62.03 | 5.78 | 7.04 |

IR ($CHCl_3$): $\nu$ = 3320, 1740, 1670 $cm^{-1}$.

$^1$H-NMR ($CDCl_3$/TMS): $\delta$ = 3.50 (s, 3 H, $CH_2$); 3.84 (s, 3 H, $OCH_3$); 7.20–7.80 (m, 5 $H_{arom}$); 9.35 (br s, 1 H, NH).

**3,3,3-Trimethoxy-*N*-phenylpropanamide (5):**
A solution of azetidinone **3a** (207 mg, 1 mmol) in dry $CH_3OH$ (5.2 mL) is kept at room temperature. After 3 h, removal of the solvent *in vacuo* yields **5** quantitatively as oil.

| | | | | |
|---|---|---|---|---|
| $C_{12}H_{17}NO_4$ | calc. | C 60.24 | H 7.16 | N 5.85 |
| (239.3) | found | 60.35 | 7.12 | 5.78 |

IR ($CHCl_3$): $\nu$ = 3320, 1670 $cm^{-1}$.

$^1$H-NMR ($CDCl_3$/TMS): $\delta$ = 2.97 (s, 2 H, $CH_2$); 3.40 (s, 9 H, 3 $OCH_3$); 7.20–7.80 (m, 5 $H_{arom}$); 8.60 (br s, 1 H, NH).

**3,3-Dimethoxy-*N*-phenylpropenamide (6):**
Azetidinone **3a** (207 mg, 1 mmol) is heated at 90°C without solvent under strictly anhydrous conditions. After 8 h, the amide **6** is obtained in ca. 90% purity ($^1$H-NMR) as undistillable and hydrolyzable oil.

IR ($CHCl_3$): $\nu$ = 3405, 1640 $cm^{-1}$.

$^1$H-NMR ($CDCl_3$/TMS): $\delta$ = 3.70, 3.88 (2 s, 3 H each, 2 $OCH_3$); 4.31 (s, 1 H, CH); 7.00–7.60 (m, 5 $H_{arom}$); 8.5 (br s, 1 H, NH).

**3,3-Dimethoxy-*N*-phenylpropanamide (7):**
To a solution of azetidinone **3a** (207 mg, 1 mmol) in dry THF (10 mL) $NaBH_4$ (380 mg, 10 mmol) is added, and the suspension is stirred at room temperature for 4 d. Then, the solvent is removed under reduced pressure, 5% aq. $NaHCO_3$ solution (5 mL) is added to the residue under stirring, and the mixture is extracted with $CHCl_3$ (5 × 10 mL). The organic phase is washed with water (10 mL), and dried ($MgSO_4$). The solvent is evaporated, and the crude amide **7** is chromatographed on silica gel (10 g) using light petroleum (bp 40–70°C)/ether (1:1) as eluent; yield: 155 mg (75%); mp 63–64°C (*n*-hexane).

| | | | | |
|---|---|---|---|---|
| $C_{11}H_{15}NO_3$ | calc. | C 63.14 | H 7.23 | N 6.69 |
| (209.2) | found | 63.05 | 7.25 | 6.67 |

IR ($CHCl_3$): $\nu$ = 3320, 1668 $cm^{-1}$.

$^1$H-NMR ($CDCl_3$/TMS): $\delta$ = 2.71 (d, 2 H, $J$ = 5.1 Hz, $CH_2$); 3.40 (s, 6 H, 2 $OCH_3$); 4.75 (t, 1 H, $J$ = 5.1 Hz, CH); 7.20–7.80 (m, 5 $H_{arom}$); 8.70 (br s, 1 H, NH).

**Table.** 4,4-Dialkoxy-2-azetidinones **3** Prepared

| Product | Reaction Conditions: Temp (°C)/ Time (h) | Yield[a] (%) | mp (°C)[b] | Molecular Formula[c] or Lit. mp (°C) | IR ($CCl_4$)[d] $\nu$ ($cm^{-1}$) | $^1$H-NMR ($CDCl_3$/TMS)[e] $\delta$, $J$(Hz) |
|---|---|---|---|---|---|---|
| **3a** | 4/15 | 90[f] | 55–57 | $C_{11}H_{13}NO_3$ (207.2) | 1768 | 3.20 (s, 2H, $CH_2$); 3.44 (s, 6H, $2OCH_3$); 7.05–7.65 (m, $5H_{arom}$) |
| **3b** | 4/15 | 90[f] | 78–80 | $C_{11}H_{12}ClNO_3$ (241.7) | 1766 | 3.14 (s, 2H, $CH_2$); 3.45 (s, 6H, $2OCH_3$); 7.15–7.65 (m, $4H_{arom}$)[g] |
| **3c** | 4/15 | 80[h] | oil | $C_{13}H_{17}NO_3$ (235.3) | 1767 | 1.24 (t, 6H, $J$ = 7, $2CH_3$); 3.20 (s, 2H, $CH_2$); 3.65 (q 4H, $J$ = 7, $2OCH_2$); 7.05–7.65 (m, $5H_{arom}$) |
| **3d** | 18/8 | 85[h] | oil | $C_{12}H_{15}NO_3$ (221.2) | 1765 | 1.34 (d, 3H, $J$ = 7, $CH_3$); 3.43, 3.47 (2s, $2OCH_3$) and 3.44 (q, $J$ = 7, CH) (together 7H); 7.05–7.65 (m, $5H_{arom}$)[i] |
| **3e** | 18/8 | 80[f] | 66–68 | $C_{12}H_{14}ClNO_3$ (255.7) | 1766 | 1.37 (t, 3H, $J$ = 7, $CH_3$); 3.49, 3.53 (2s, $2OCH_3$) and 3.51 (q, $J$ = 7, CH) (together 7H); 7.20–7.80 (m, $4H_{arom}$) |
| **3f** | 4/72 | 70[h] | oil | $C_{17}H_{17}NO_3$ (283.3) | 1765 | 3.12, 3.63 (2s, 3H each, $2OCH_3$); 4.70 (s, 1H, CH); 7.05–7.65 (m, $10H_{arom}$) |
| **3g** | 18/24 | 80[h] | oil | $C_{15}H_{19}NO_5$ (293.3) | 1766, 1740 | 1.26 (t, 3H, $J$ = 7, $CH_3$); 2.80 (dq, 2H, AB part of ABX system, $J_{AB}$ = 18, $CH_2$); 3.41, 3.51 (2s, 3H each, $2OCH_3$); 3.85 (dd, 1H, X part of ABX system, $J_{BX}$ = 7.8, $J_{AX}$ = 4.7, CH); 4.18 (q, 2H, $J$ = 7, $OCH_2$); 7.05–7.65 (m, $5H_{arom}$)[i] |
| **3h**[j] | 85/3 | 80[k] | 45–46 | 42–43[3] | | 1.34 (s, 6H, $2CH_3$); 3.45 (s, 6H, $2OCH_3$); 7.05–7.65 (m, $5H_{arom}$) |
| **3i** | 85/3 | 80[l] | oil | $C_{16}H_{21}NO_5$ (307.3) | 1763, 1740 | 1.25 (t, 3H, $J$ = 7, $CH_3$); 1.53 (s, 3H, $CH_3$); 2.61, 2.87 (2d, 1H each, $J_{gem}$ = 16.6, $CH_2$); 3.36, 3.54 (2s, 3H each, $2OCH_3$); 4.21 (q, 2H, $J$ = 7, $OCH_2$); 7.05–7.65 (m, $5H_{arom}$)[i] |

[a] Yield of pure and isolated products, except for **3c**, **3d**, **3f**, and **3g**.
[b] Solid azetidinones **3** are crystallized from dry light petroleum (bp 40–70 °C).
[c] Satisfactory microanalyses obtained: C ±0.21, H ±0.13, N ±0.21. The oily products **3c**, **3d**, **3f**, and **3g** could not be obtained analytically pure.
[d] Recorded on a Perkin-Elmer 399 spectrophotometer.
[e] Recorded on a Varian EM-360A spectrometer.
[f] Isolated by crystallization of the crude reaction mixture.
[g] In $CCl_4$.
[h] Calculated on the basis of the $^1$H-NMR data and of the weight of the crude reaction mixture.
[i] Recorded on a Varian XL-200 spectrometer.
[j] Known product, but the $^1$H-NMR data are new.
[k] Isolated by column chromatography on neutral alumina (ratio absorbant/crude product, 50:1; eluent: light petroleum (bp 40–70 °C).
[l] Isolated by column chromatography on silica gel (ratio absorbant/crude product, 50:1; eluent: light petroleum (bp 40–70 °C)/ether, 4:1).

**3,3-Dimethoxy-*N*-phenylaminocarbonylpropenamide (8):**
A mixture of the azetidinone **3a** (300 mg, 1.45 mmol) and phenyl isocyanate (**2a**; 172 mg, 1.45 mmol) is kept at 90 °C without solvent under strictly anhydrous conditions. After 12 h, the product formed is recrystallized from dry benzene; yield: 280 mg (60%); mp 152–154 °C (benzene).

| | | | | |
|---|---|---|---|---|
| $C_{18}H_{18}N_2O_4$ | calc. | C 66.24 | H 5.56 | N 8.58 |
| (326.3) | found | 66.04 | 5.43 | 8.69 |

IR ($CHCl_3$): $\nu$ = 3180, 1690, 1645 $cm^{-1}$.

$^1$H-NMR ($CDCl_3$/TMS): $\delta$ = 3.33 (s, 3H, $OCH_3$); 3.85, 3.89 (2 s, 4H, CH + $OCH_3$); 7.00–7.60 (m, $10H_{arom}$); 11.5 (br s, 1H, NH).

**Methyl 4,6-Diaza-3,5-dioxo-4,6-diphenylhexanoate (9):**
To a solution of amide **8** (163 mg, 0.5 mmol) in acetone (3.5 mL) 2 N HCl (0.15 mL) is added. After 15 min, the solvent is evaporated, the residue is dissolved in $CHCl_3$ (5 mL), and the $CHCl_3$ phase is washed with water (2 × 3 mL). The organic layer is dried ($MgSO_4$), and the solvent is evaporated. The crude **9** is purified by filtration through a short column of silica gel (10 g) using light petroleum (bp 40–70 °C/ether (1:1) as eluent; yield: 140 mg (90%); oil.

| | | | | |
|---|---|---|---|---|
| $C_{17}H_{16}N_2O_4$ | calc. | C 65.37 | H 5.16 | N 8.97 |
| (312.3) | found | 65.21 | 5.06 | 8.90 |

IR ($CHCl_3$): $\nu$ = 3330, 1740, 1690 $cm^{-1}$.

$^1$H-NMR ($CDCl_3$/TMS): $\delta$ = 3.35 (s, 2H, $CH_2$); 3.86 (s, 3H, $OCH_3$); 7.20–7.80 (m, $10H_{arom}$); 11.3 (br s, 1H, NH).

**1,3-Diphenyl Barbituric Acid (10):**
To a solution of ester **9** (200 mg, 0.64 mmol) in dioxane (4 mL), 2 N NaOH (2 mL) is added and the resulting mixture is kept at room temperature under stirring. After 30 min 37% HCl (1 mL) is added, the mixture is extracted with $CHCl_3$ (5 × 10 mL), the organic layer is washed with water (2 × 5 mL), and dried ($MgSO_4$). The solvent is evaporated, and the crude **10** is recrystallized from EtOH; yield: 161 mg (90%); mp 252–253 °C (Lit.[16] mp 253–254 °C).

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