# A Convenient Method for the Conversion of a Carboxy Group into a 4,6-Dimethoxy-1,3,5-triazine Group: Application to *N*-Benzylpyroglutamic Acids

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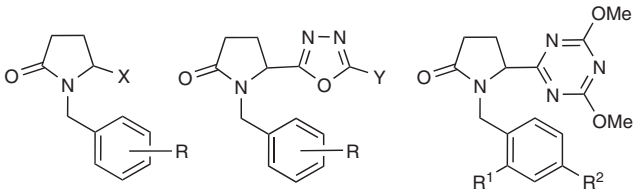
**Abstract:** Reaction of an activated form of carboxylic acids with a stoichiometric amount of zinc dimethyl imidodicarbonimidate (in $CH_2Cl_2$–pyridine with molecular sieves), led to 4,6-dimethoxy-1,3,5-triazines in high yields. This method has been applied to *N*-benzylpyroglutamic acids, in the preparation of potential antifungal products.

**Key words:** pyroglutamic derivatives, lactams, imidodicarbonimidate zinc salt, heterocycles, triazines

We have reported earlier that several *N*-benzylpyrrolidinones such as **1**[1] and **2**[2] exhibit antifungal activity. Some 2,4,6-triheteroalkyl-1,3,5-triazines show similar biological properties.[3] These results prompted us to investigate the biostatic activity of products **3**, which possess an *N*-benzylpyrrolidinone group linked to a 4,6-dimethoxy-1,3,5-triazine group at the 5-position (Figure 1).




**1** R = H, X = CN
**4** X = $CO_2H$

**2**

**3** $R^1$, $R^2$ = H, Me, Cl

**Figure 1** *N*-Benzylpyrrolidinones **1**–**4**

In order to obtain triazine derivatives **3a**–**e**, we considered a one-step synthesis from *N*-benzylpyroglutamic acids (2-pyrrolidone-5-carboxylic acids) **4**.[4] Previously, a procedure had described[5] the reaction of activated carboxy groups (acid chlorides, anhydrides, acylimidazolides) with zinc dimethyl imidodicarbonimidate (**5**), giving 6-substituted 2,4-dimethoxy-1,3,5-triazines. In this method, the conversion rate of the activated carboxy group was low, and good yields were only obtained when a very large excess of the carboxylic acid derivative was used.

Under similar experimental conditions, stoichiometric amounts of acid chloride **6a** were reacted with zinc salt **5** to give the corresponding triazine **3a** in a moderate 53% yield (Table 1, entry 1). We also observed the formation of *N*-benzylpyroglutamic acid (**4**, R = H) as an important side-product of the reaction.

Formation of *N*-benzylpyroglutamic acid (**4**, R = H) was presumably due to the hydrolysis of *N*-benzylpyroglutamic chloride **6a** by water formed during the reaction. In order to avoid this hydrolysis, we thought to trap the water by using 4 Å molecular sieves. We also studied the effect of pyridine as co-solvent. The various conditions examined are listed in Table 1.

Higher yields were obtained when acid chloride **6a** was condensed with salt **5** in the presence of 4 Å molecular sieves and pyridine as co-solvent (Table 1, entry 4). Thus, these conditions were used as a standard procedure to synthesize various triazinyl pyrrolidinones **3a**–**e** in high yields (Table 2).

As shown in Table 3, this method also succeeded with some functionalized acid chlorides and anhydrides.

In summary, we have developed an easy conversion of carboxylic acids to 4,6-dimethoxy-1,3,5-triazines. The method is very simple and, compared to the syntheses previously reported, the rate of conversion of the carboxy group is very high.

Melting points were determined using an Electrothermal apparatus and are uncorrected. $^1H$ and $^{13}C$ NMR spectra were obtained on a Varian Gemini 2000 at 200 MHz and 50 MHz, respectively. IR spectra were obtained in ATR mode on an FTIR Bruker Tensor 27 spectrometer. Microanalyses were performed by the 'Service Central de Microanalyses' of CNRS in Vernaison, France. Zinc dimethyl imidodicarbonimidate (**5**),[5a] *N*-benzylpyroglutamic acid chlorides **6a**–**e**[4] and dibromoacetyl chloride (**7d**)[6] were prepared according to literature methods.

### *N*-Benzylpyroglutamic Acid Chlorides 6a–e[4]; General Procedure

Under $N_2$, a stirred mixture of acid **4**[4] (4 mmol) and $SOCl_2$ (952 mg, 8 mmol) in $CH_2Cl_2$ (4 mL) was refluxed for 4 h. The residue obtained upon evaporation was heated at 40 °C under high vacuum (< 0.1 mmHg) for 4 h in order to remove all traces of $SOCl_2$.

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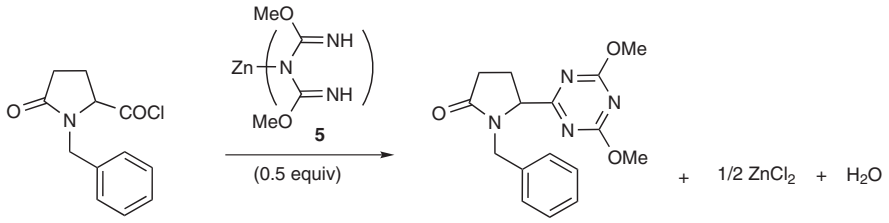
**Table 1** Condensation of Acid Chlorides **6a** with Zinc Salt **5**

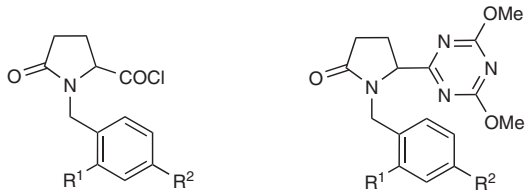



**6a** **3a**

| Entry | Conditions[a] | Yield (%)[b] |
|---|---|---|
| 1 | $CH_2Cl_2$ | 53 |
| 2 | $CH_2Cl_2$, 4 Å molecular sieves | 63 |
| 3 | $CH_2Cl_2$–pyridine | 72 |
| 4 | $CH_2Cl_2$–pyridine, 4 Å molecular sieves | 91 |

[a] All reactions were performed at r.t. for 30 min.
[b] Determined by $^1$H NMR spectroscopy.

**Table 2** Condensation of Acid Chlorides **6a–e** with Salt **5**

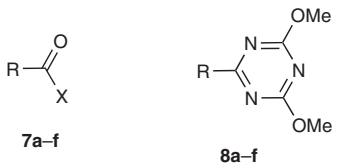



**6a–e** **3a–e**

| Reactant | $R^1$ | $R^2$ | Time (h) | Product | Yield (%)[a] |
|---|---|---|---|---|---|
| **6a** | H | H | 0.5 | **3a** | 91 (87) |
| **6b** | Me | H | 1.5 | **3b** | 83 (78) |
| **6c** | H | Me | 2 | **3c** | 85 (82) |
| **6d** | Cl | H | 0.5 | **3d** | 99 (95) |
| **6e** | H | Cl | 2 | **3e** | 80 (75) |

[a] Determined by $^1$H NMR spectroscopy. Isolated yields are given in parentheses.

**Table 3** Condensation of Acid Chlorides **7a–d** and Anhydrides **7e,f** with Salt **5**




**7a–f** **8a–f**

| Reactant | R | X | Time (h) | Product | Yield (%)[a] |
|---|---|---|---|---|---|
| **7a** | $CO_2Me$ | Cl | 1.5 | **8a** | 93 (87) |
| **7b** | $CO_2Et$ | Cl | 1 | **8b** | 92 (90) |
| **7c** | $CHCl_2$ | Cl | 0.5 | **8c** | 94 (74) |
| **7d** | $CHBr_2$ | Cl | 0.5 | **8d** | 90 (74) |
| **7e** | $CH(OMe)_2$ | $O(CO)CF_3$ | 2 | **8e** | 86 (81) |
| **7f** | $CH(OEt)_2$ | $O(CO)CF_3$ | 2 | **8f** | 84 (75) |

[a] Determined by $^1$H NMR spectroscopy. Isolated yields are given in parentheses.

**Dimethoxyacetic Trifluoroacetic Anhydride**

To a solution of potassium trimethylsilanolate (2.87 g, 22.4 mmol) in THF (45 mL), was added methyl dimethoxyacetate (2.5 g, 18.6 mmol). The mixture was stirred at r.t. for 48 h and the solvent was removed in vacuo. The residual crude potassium dimethoxyacetate was dissolved in $CH_2Cl_2$ (100 mL) and trifluoroacetic anhydride (2.7 mL, 19.4 mmol) was added dropwise at –20 °C under $N_2$. The mixture was stirred at r.t. for 1 h, and the solvent was evaporated at reduced pressure to give crude dimethoxyacetic trifluoroacetic anhydride in 44% yield ($^1$H NMR) as an orange oil that was used without further purification in the next step.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 3.46 (s, 6 H), 4.96 (s, 1 H).

**Diethoxyacetic Trifluoroacetic Anhydride**

This compound, obtained as an orange oil in 54% yield, was prepared by the same procedure as described for dimethoxyacetic trifluoroacetic anhydride using ethyl diethoxyacetate as starting material.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, $J$ = 7.3 Hz, 6 H), 3.62–3.80 (m, 4 H), 5.05 (s, 1 H).

**4,6-Dimethoxy-1,3,5-triazines 3 and 8; General Procedure**

Under $N_2$, a solution of acid chloride **6a–e**,[4] **7a–c**, **7d**[6] or anhydride **7e,f** (4.0 mmol) in anhyd $CH_2Cl_2$ (10 mL) was added dropwise (30 min) to a stirred mixture of salt **5**[5a] (651 mg, 2.0 mmol) and powdered 4 Å molecular sieves (4 g) in distilled pyridine (15 mL). After the addition was complete, the mixture was stirred at r.t. for the pe-

riod indicated in Tables 2 or 3. The mixture was filtered upon completion of the reaction, the solid was washed with $CH_2Cl_2$ and the filtrate was concentrated (rotary evaporation). The residue was co-evaporated with toluene (3 × 5 mL) in order to remove pyridine. The remaining slurry was dissolved in $CH_2Cl_2$ (10 mL), washed with 1 N HCl (3 × 10 mL), and then with aq sat. $NaHCO_3$ solution (10 mL). The residue obtained upon evaporation was crystallized, then recrystallized from appropriate solvent or distilled.

**1-Benzyl-5-(4,6-dimethoxy-1,3,5-triazin-2-yl)pyrrolidin-2-one (3a)**
Colorless oil.

IR: 1688, 1549, 1502, 1462, 1354, 1106 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 2.01–2.17 (m, 1 H), 2.29–2.80 (m, 3 H), 4.02 (s, 6 H), 4.02 (d, *J* = 14.6 Hz, 1 H), 4.46 (dd, *J* = 8.4, 2.6 Hz, 1 H), 4.92 (d, *J* = 14.6 Hz, 1 H), 7.14–7.31 (m, 5 H).

$^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 24.5, 29.6, 45.5, 55.3, 62.1, 127.4, 128.3, 128.4, 136.1, 172.6, 175.4, 181.6.

Anal. Calcd for $C_{16}H_{18}N_4O_3$: C, 61.14; H, 5.77; N, 17.82. Found: C, 61.34; H, 5.80; N, 17.88.

**5-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-1-(2-methylbenzyl)pyrrolidin-2-one (3b)**
White solid; mp 94–95 °C (cyclohexane–$Et_2O$).

IR: 1689, 1551, 1498, 1452, 1352, 1101 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 1.98–2.13 (m, 1 H), 2.26 (s, 3 H), 2.33–2.80 (m, 3 H), 4.02 (s, 6 H), 4.09 (d, *J* = 14.7 Hz, 1 H), 4.37 (dd, *J* = 8.8, 2.6 Hz, 1 H), 4.93 (d, *J* = 14.7 Hz, 1 H), 6.97–7.19 (m, 4 H).

$^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 19.2, 24.9, 29.7, 43.8, 55.4, 62.2, 125.9, 127.9, 129.6, 130.4, 133.7, 137.0, 172.8, 175.3, 182.0.

Anal. Calcd for $C_{17}H_{20}N_4O_3$: C, 62.18; H, 6.14; N, 17.06. Found: C, 62.21; H, 6.51; N, 16.96.

**5-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (3c)**
Colorless oil.

IR: 1682, 1550, 1499, 1457, 1354, 1096 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 2.07 (m, 1 H), 2.27–2.78 (m, 3 H), 2.30 (s, 3 H), 3.96 (d, *J* = 14.8 Hz, 1 H), 4.02 (s, 6 H), 4.44 (dd, *J* = 8.3, 2.8 Hz, 1 H), 4.90 (d, *J* = 14.8 Hz, 1 H), 7.06 (s, 4 H).

$^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 21.0, 24.7, 29.7, 45.3, 55.4, 62.1, 128.5, 129.1, 133.0, 137.2, 172.7, 175.4, 181.8.

Anal. Calcd for $C_{17}H_{20}N_4O_3$: C, 62.18; H, 6.14; N, 17.06. Found: C, 62.32; H, 6.05; N, 16.95.

**1-(2-Chlorobenzyl)-5-(4,6-dimethoxy-1,3,5-triazin-2-yl)pyrrolidin-2-one (3d)**
Yellowish solid; mp 137 °C (cyclohexane–$Et_2O$).

IR: 1694, 1552, 1503, 1464, 1359, 1106 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 2.02–2.20 (m, 1 H), 2.34–2.79 (m, 3 H), 4.02 (s, 6 H), 4.28 (d, *J* = 15.5 Hz, 1 H), 4.50 (dd, *J* = 8.6, 2.7 Hz, 1 H), 5.00 (d, *J* = 15.5 Hz, 1 H), 7.14–7.34 (m, 4 H).

$^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 24.9, 29.4, 43.1, 55.4, 62.4, 126.9, 128.9, 129.4, 130.4, 133.7, 133.8, 172.7, 175.7, 181.7.

Anal. Calcd for $C_{16}H_{17}ClN_4O_3$: C, 55.10; H, 4.91; N, 16.06. Found: C, 55.10; H, 5.21; N, 16.12.

**1-(4-Chlorobenzyl)-5-(4,6-dimethoxy-1,3,5-triazin-2-yl)pyrrolidin-2-one (3e)**
Yellowish solid; mp 98–99 °C ($Et_2O$).

IR: 1684, 1553, 1494, 1449, 1362, 1104 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 2.04–2.20 (m, 1 H), 2.29–2.55 (m, 2 H), 2.61–2.80 (m, 1 H), 4.02 (d, *J* = 14.9 Hz, 1 H), 4.03 (s, 6 H), 4.43 (dd, *J* = 8.7, 2.9 Hz, 1 H), 4.86 (d, *J* = 14.9 Hz, 1 H), 7.17 (dd, *J* = 24.1, 8.3 Hz, 4 H).

$^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 24.7, 29.7, 45.0, 55.5, 62.3, 128.6, 130.0, 133.4, 134.8, 172.8, 175.6, 181.6.

Anal. Calcd for $C_{16}H_{17}ClN_4O_3$: C, 55.10; H, 4.91; N, 16.06. Found: C, 54.83; H, 4.81; N, 16.03.

**Methyl 4,6-Dimethoxy-1,3,5-triazine-2-carboxylate (8a)**
White solid; mp 149–150 °C (MeOH).

IR: 1746, 1542, 1251, 1100 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 4.01 (s, 3 H), 4.13 (s, 6 H).

$^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 53.5, 55.8, 162.6, 167.1, 173.3.

Anal. Calcd for $C_7H_9N_3O_4$: C, 42.21; H, 4.55; N, 21.10. Found: C, 42.52; H, 4.78; N, 20.90.

**Ethyl 4,6-Dimethoxy-1,3,5-triazine-2-carboxylate (8b)**
White solid; mp 50-51 °C (cyclohexane).

IR: 1747, 1549, 1356, 1212, 1039 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 1.36 (t, *J* = 7.2 Hz, 3 H), 4.06 (s, 6 H), 4.41 (q, *J* = 7.2 Hz, 2 H).

$^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 14.0, 55.7, 62.9, 162.2, 167.5, 173.3.

Anal. Calcd for $C_8H_{11}N_3O_4$: C, 45.07; H, 5.20; N, 19.71. Found: C, 45.38; H, 5.45; N, 19.82.

**2-(Dichloromethyl)-4,6-dimethoxy-1,3,5-triazine (8c)[7,8]**
Colorless oil; bp 86–88 °C/0.045 mmHg (Lit.[7] bp 86–88 °C/0.045 mmHg, Lit.[8] bp 90–93 °C/0.06 mmHg).

IR: 1545, 1507, 1466, 1353, 1197, 1104 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 4.13 (s, 6 H), 6.47 (s, 1 H).

$^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 54.8, 68.2, 172.3, 175.4.

Anal. Calcd for $C_6H_7Cl_2N_3O_2$: C, 32.17; H, 3.15; N, 18.75. Found: C, 32.13; H, 3.55; N, 19.00.

**2-(Dibromomethyl)-4,6-dimethoxy-1,3,5-triazine (8d)[7]**
Colorless oil; bp 77–79 °C/0.01 mmHg (Lit.[7] bp 112–118 °C/0.017–0.027 mmHg).

IR: 1543, 1506, 1466, 1353, 1187, 1103 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 4.11 (s, 6 H), 6.35 (s, 1 H).

$^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 38.8, 55.8, 173.0, 177.0.

Anal. Calcd for $C_6H_7Br_2N_3O_2$: C, 23.03; H, 2.25; N, 13.43. Found: C, 22.66; H, 2.02; N, 13.05.

**2-(Dimethoxymethyl)-4,6-dimethoxy-1,3,5-triazine (8e)[9]**
White solid; mp 40–41 °C (cyclohexane) (Lit.[9] mp 40–41 °C).

IR: 1550, 1504, 1462, 1354, 1193, 1059 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 3.51 (s, 6 H), 4.08 (s, 6 H), 5.19 (s, 1 H).

$^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 54.4, 55.4, 102.7, 172.9, 176.5.

Anal. Calcd for $C_8H_{13}N_3O_4$: C, 44.65; H, 6.09; N, 19.53. Found: C, 44.34; H, 6.49; N, 19.81.

**2-(Diethoxymethyl)-4,6-dimethoxy-1,3,5-triazine (8f)**
Colorless oil.

IR: 1549, 1356, 1058 $cm^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.2 Hz, 6 H), 3.62–3.90 (m, 4 H), 4.07 (s, 6 H), 5.29 (s, 1 H).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 14.8, 55.0, 62.7, 101.0, 172.6, 177.0.

Anal. Calcd for $C_8H_{13}N_3O_4$: C, 44.65; H, 6.09; N, 19.53. Found: C, 44.80; H, 6.29; N, 19.83.

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