2-Substituted Glutarimides via Preformed Wittig Reagents

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Triphenylphosphoranylideneacetamide (**1**) reacts with some Michael-acceptors to give crystalline 2-triphenylphosphoranylidene glutarimides. The Wittig reaction of **2** with several aldehydes in refluxing 1,2-dichloroethane affords the corresponding 2-alkylideneglutarimides **7** in 50–98% yield.

The glutarimide entity constitutes an essential part of many natural products with antibacterial, antiviral or cytotoxic activity. A general synthetic procedure for the preparation of glutarimide derivatives therefore is of interest to many natural product chemists.

Working on glutarimide nucleosides we needed a method to introduce a glutarimide ring in one step. Alkylation of the glutarimide 2,6-dianion is known,[1] but requires too drastic reaction conditions. In analogy with the synthesis of showdomycin via the Wittig reaction of protected ribose with triphenylosphoranylidenesuccinimide,[2] we prepared the corresponding glutarimide ylid **2**.

Michael additions of stabilized phosphonium ylides have been described in the literature.[3] Addition of triphenylphosphoranylideneacetamide **1** to methyl acrylate in methanol occurred at room temperature. The intermediate glutamic ester could not be detected, but directly cyclized to 2-triphenylphosphoranylideneglutarimide **2**, which crystallized from the reaction mixture. Extension of this reaction could be achieved with some

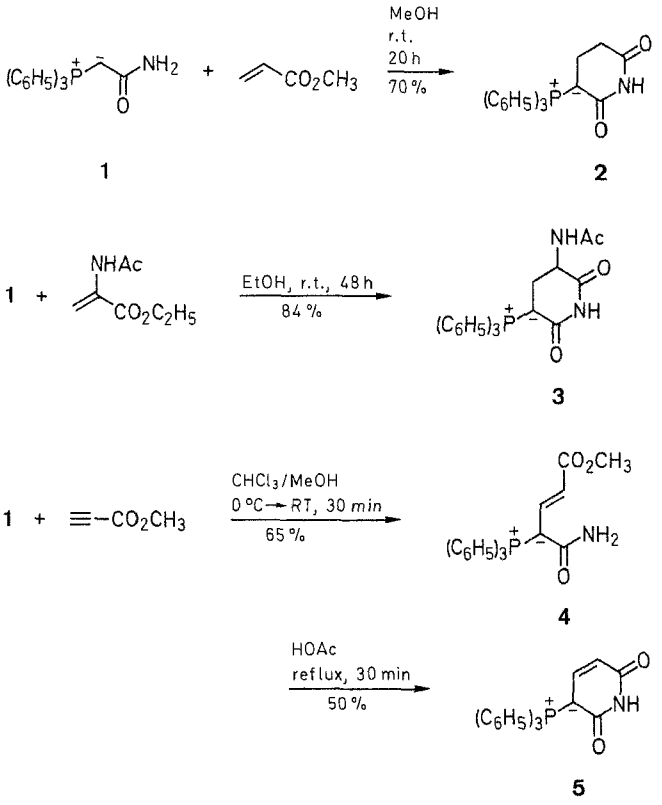


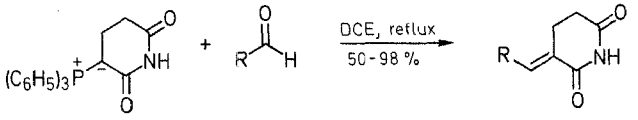
Table 1. Phosphorus Ylides **2–5** Prepared

Product	Yield[a] (%)	mp (°C)[b] (solvent)	Molecular Formula[c]	IR ($CHCl_3$)[d] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)
2	70	262–263 (CH_2Cl_2/ether)	$C_{23}H_{20}NO_2P$ (373.4)	3400, 1685, 1600	2.0–2.6 (m, 4H); 7.6 (m, 15H)
3	84	152–155 (DMF)	$C_{25}H_{23}N_2O_3P$ (430.5)	3400, 1690, 1670, 1605	1.89 (s, 3H); 2.0–2.6 (m, 3H); 5.60 (m, 1H); 6.81 (d, 1H, J = 6, NH); 7.6 (m, 15H)
4	65	177–181 (CH_2Cl_2/ether)	$C_{24}H_{22}NO_3P$ (403.4)	3520, 3405, 1670, 1605, 1545	3.56 (s, 3H); 5.34 (d, 1H, J = 15); 5.4 (br s, NH_2); 7.14 (dd, 1H, J = 15, J = 18); 7.6 (m, 15H)
5	50	291–293 (DMF)	$C_{23}H_{18}NO_2P$ (371.4)	3390, 1630, 1610, 1550	5.52 (dd, 1H, J = 9, J = 3); 6.67 (dd, 1H, J = 13, J = 9); 7.6 (m, 15H)

[a] Yield of isolated products.
[b] Uncorrected.
[c] Satisfactory microanalysis obtained: C ±0.34, H ±0.08, N ±0.11, except **3**, which contains varying amounts of DMF.
[d] Recorded on a Perkin Elmer 1310 spectrophotometer.
[e] Recorded on Bruker WM 250 and AC 200 instruments.

activated α,β-unsaturated esters. With methyl propiolate the intermediate adduct **4** was isolated. Cyclization to **5** occured during *E*/*Z*-isomerization in refluxing acetic acid. With substituted acrylic esters such as methyl crotonate and methyl methacrylate, no glutarimides were formed. At elevated temperatures the starting ylide **1** decomposed.

The ylide **2** proved to be a very versatile and extremely stable reagent, that could be applied to the synthesis of a variety of substituted glutarimides in good yields. In Table 2 the reactions with aliphatic, aromatic and carbohydrate aldehydes are summarized. Best results were obtained by carrying out the reaction in 1,2-dichloroethane, this solvent being superior to toluene or acetonitrile. With the more stable ylids **3** and **5** no Wittig reactions were observed with unactivated aldehydes. The conversion of **7e** to *C*-nucleosides will be reported elsewhere.[4]



2 **6** **7**

Triphenylphosphoranylideneacetamide (1):
Ylide **1** is prepared according to Ref. 5 from triphenylphosphine and chloroacetamide.

2-Triphenylphosphoranylideneglutarimide (2):
Methyl acrylate (4.93 mL, 55 mmol) is added to a suspension of triphenylphosphoranylideneacetamide (**1**, 15.95 g, 50 mmol) in absolute MeOH (120 mL). This suspension is stirred at room temperature and after 20 h the precipitated product is isolated by filtration, washed with MeOH (2 × 20 mL) and Et_2O (3 × 25 mL) and air-dried; yield: 13.05 g (70 %).

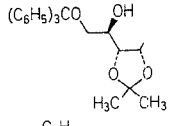
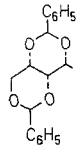
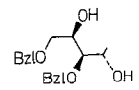
4-Acetylamino-2-triphenylphosphoranylideneglutarimide (3):
A suspension of triphenylphosphoranylideneacetamide (**1**; 0.479 g, 1.5 mmol) and ethyl 2-acetylamino acrylate (0.157 g, 1.0 mmol) in absolute EtOH (3 mL) is stirred at room temperature for 48 h. The precipitate is filtered, washed with EtOH (2 × 1 mL) and Et_2O

Table 3. IR- and NMR-spectral Data for 2-Alkylideneglutarimides **7**

7	IR[a] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[b], δ, J(Hz)
a	3370, 1725, 1710, 1635	2.70 (s, 4H); 5.67 (br s, 1H); 6.36 (br s, 1H); 8.55 (br s, 1H, NH)
b	3380, 1720, 1690, 1640	0.96 (t, J = 7, 3H); 1.52 (m, 2H); 2.24 (m, 2H); 2.65 (m, 4H, glutarimide); 7.01 (dt, 1H, J = 1, 8); 8.2 (br s, 1H, NH)
c	3360, 1715, 1685, 1620	2.62 (m, 2H); 3.0 (m, 2H); 7.39 (s, 5H); 7.89 (br s, 1H); 8.04 (br s, 1H, NH)
d	3380, 1720, 1695, 1640	(DMSO-d_6): 2.54 (m, 2H); 2.93 (m, 2H); 7.75 (s, 1H); 7.77 (d, 1H, J = 8.7); 8.29 (d, 1H, J = 8.7); 11.05 (s, 1H, NH)
e(*E*)	3380, 1725, 1705, 1650	1.38 (s, 3H); 1.45 (s, 3H); 2.40 (d, 1H, J = 4.9, OH); 2.6–2.7 (m, 4H, glutarimide); 3.34 (m, 2H); 3.65 (m, 1H); 4.25 (dd, 1H, J = 9.3, 6.1); 5.01 (dd, 1H, J = 9.3, 6.1); 6.89 (d, 1H, J = 9.3); 7.2–7.5 (m, 15H); 7.45 (s, 1H, NH)
e(*Z*)	3380, 1730, 1710, 1655	1.34 (s, 3H); 1.39 (s, 3H); 2.5 (m, 4H, glutarimide); 3.26 (m, 2H); 3.7 (m, 1H); 4.42 (m, 1H); 5.56 (dd, 1H, J = 6.9, 7.8); 6.15 (d, 1H, J = 6.9); 7.2–7.5 (m, 15H); 8.02 (br s, 1H, NH)
f(*E*)	(KBr): 3240, 1720, 1690, 1650	DMSO-d_6: 2.5 (m, 2H, glutarimide); 2.7 (m, 2H, glutarimide); 4.0–4.2 (m, 4H); 5.10 (d, 1H, J = 7.3); 5.68 (s, 1H); 5.86 (s, 1H); 6.78 (d, 1H, J = 7.3); 7.4 (m, 10H); 10.88 (s, 1H, NH)
f(*Z*)	3380, 1720, 1700, 1650	2.5–2.8 (m, 4H, glutarimide); 3.96 (d, 1H, J = 1.2); 4.28 (s, 1H); 4.29 (AB-system, 2H, J = 12.6, 1.0); 5.48 (dd, 1H, J = 7.3, 2.5); 5.57 (s, 1H); 5.72 (s, 1H); 6.44 (d, 1H, J = 7.3); 7.2–7.6 (m, 10H); 8.24 (s, 1H, NH)
g	3370, 1720, 1700, 1645	1.75 (br s, 1H, OH); 2.4–2.7 (m, 4H, glutarimide); 3.0 (br s, 1H, OH); 3.55 (m, 2H); 3.85 (m, 1H); 4.53 (s, 2H); 4.66 (s, 2H); 6.89 (d, 1H, J = 8.3); 7.3 (s, 10H); 8.30 (s, 1H, NH)

[a] Recorded on a Perkin Elmer 1310 spectrophotometer in $CHCl_3$, except **7f**(*E*).
[b] Obtained on Bruker WM 250 and AC 200 instruments in $CDCl_3$, unless stated otherwise.

Table 2. 2-Alkylideneglutarimides **7** Prepared

Product	R	Reaction Time (h)	Yield[a] (%)	*E* : *Z*	mp (°C)[b] (solvent)	Molecular Formula[c]
7a	H	0.5	88	–	116–117 (CH_2Cl_2/ether)	$C_6H_7NO_2$ (125.1)
b	$CH_3CH_2CH_2$	24	52	*E*	103–105 (ether/hexane)	$C_9H_{13}NO_2$ (167.2)
c	C_6H_5	16	91	*E*	209–210 (CH_2Cl_2/hexane)	$C_{12}H_{11}NO_2$ (201.2)
d	4-$O_2NC_6H_4$	0.25	98	*E*	231–233 (DMF/ether)	$C_{12}H_{10}N_2O_4$ (246.2)
e		120	50	3 : 1	*E*: 183–185 (CH_2Cl_2/ether) *Z*: oil	$C_{32}H_{33}NO_6$ (527.6)
f		2	91	1.6 : 1	*E*: 285–287 (DMF/ether) *Z*: oil	$C_{24}H_{23}NO_6$ (421.5)
g		32	68	*E*	oil	$C_{24}H_{27}NO_6$ (425.5)

[a] Yield of isolated product **7** based on **2**.
[b] Uncorrected.
[c] Satisfactory microanalyses obtained: C ± 0.23, H ± 0.20, N ± 0.10. Exceptions: **7f**, C −0.85, H +0.11, N +0.26; **7g**, C −0.84, H +0.25, N −0.06.

(3 × 2 mL), and air-dried. According to ^{1}H-NMR the product contains 0.5 mol of ethanol, which is removed by recrystallization from DMF; yield: 0.38 g (84%); physical data are given in Table 1.

Methyl-4-Carbamoyl-4-triphenylphosphoranylidene-2-butenoate (4):
Methyl propiolate (88.5 µL, 1.0 mmol) is added dropwise to a solution of triphenylphosphoranylideneacetamide (**1**; 0.319 g, 1.0 mmol) in a mixture of $CHCl_3$ (2 mL) and absolute MeOH (2 mL) at 0°. The solution is stirred at room temperature for 30 min, the solvents are removed in vacuo and the yellow product is crystallized from CH_2Cl_2/Et_2O; yield: 0.26 g (65%); see Table 1.

2,6-Dioxo-3-triphenylphosphoranylidene-1,2,3,6-tetrahydropyridine (5):
Ylid **4** (0.101 g, 0.25 mmol) is refluxed in acetic acid (1 mL) for 30 min. The solvent is evaporated and the residue is recrystallized from DMF; yield 0.046 g (50%); see Table 1.

2-Alkylideneglutarimides 7; General Procedure:
A suspension of 2-triphenylphosphoranylideneglutarimide (**2**; 0.373 g, 1.1 mmol) and aldehyde **6a–g** (1.0 mmol) is stirred and refluxed in 1,2-dichloroethane (4 mL) under nitrogen for the time indicated in Table 2. To suppress the formation of blue colored by-products, a small amount of hydroquinone is added. The reaction is followed with TLC (silica gel, EtOAc/hexanes). The products are isolated by direct crystallization from the reaction mixture (**7d** and **7e-Z**) or by flash chromatography (silica gel, 230–400 mesh, EtOAc/hexanes). Yields and physical data are given in Tables 2 and 3.

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