Tetrahedron Letters, Vol. 33, No. 11, pp. 1513-1516, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

New Phosphonium Ylides by Functionalization of Triphenylphosphoranylideneacetamide

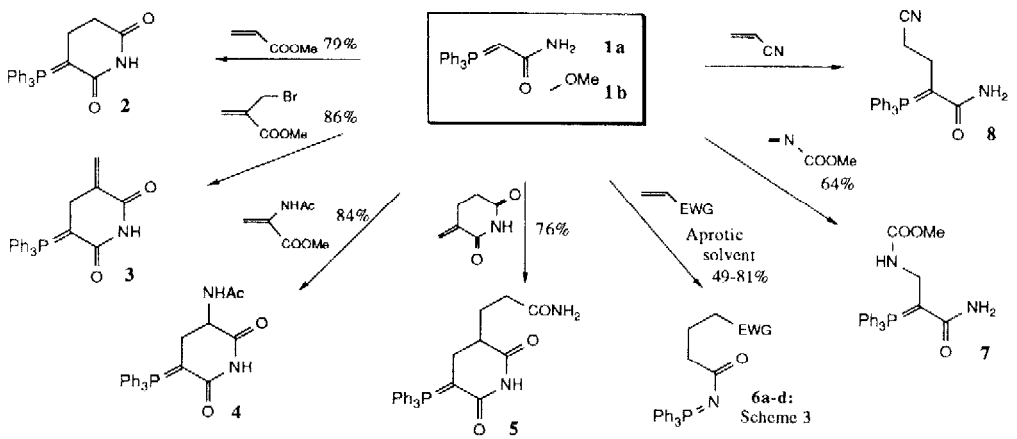
Martin J. Wanner and Gerrit-Jan Koomen*

Laboratory of Organic Chemistry, University of Amsterdam
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

Key Words: Stabilized phosphonium ylids, Wittig reaction, Michael reaction, Glutarimides,

Abstract: *Triphenylphosphoranylideneacetamide undergoes Michael reactions with several acceptors, giving rise, apart from the normal Michael adducts, to the formation of different products like glutarimide ylides and stabilized iminophosphoranes. Wittig reactions with these new ylides lead to a variety of α,β-unsaturated carbonyl compounds.*

Introduction. Phosphonium ylides of type **1** are versatile reagents in Wittig reactions with aldehydes or ketones, leading to α,β-unsaturated carbonyl compounds[1,2]. Introduction of a substituent in the α-position by direct alkylation or acylation of especially ester **1b** has found several applications[1]. There are however only a few examples of alkylation of **1b** by acrylic acid derived Michael acceptors[3], due to its low nucleophilicity. With more reactive acceptors such as nitroethene[4] or acetylenic esters[5], the corresponding ylides are formed, but consequently have only low reactivity towards aldehydes in a Wittig reaction. For the synthesis of glutarimide ylides of type **2**, the inertness of methyl triphenylphosphoranylideneacetate **1b** towards Michael-type alkylations with acryl amide directed us to triphenylphosphoranylideneacetamide[6,7] **1a** (scheme 1), a less frequently used, but more reactive carbonyl-stabilized ylide. A strong influence of the solvent on the course of the Michael reaction was observed. Except for the formation of normal Michael adducts in methanol, imino-

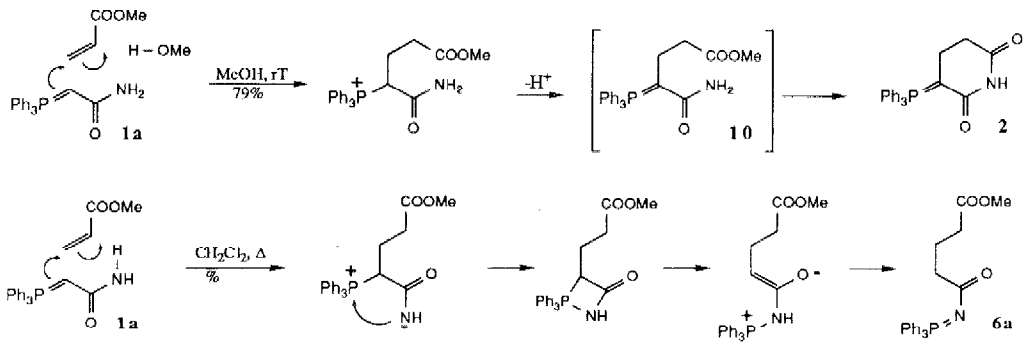


scheme 1

phosphoranes of type **6** are formed exclusively in aprotic solvents. The succesful application of the glutarimide ylides **2** and **3** in the synthesis of glutarimide C-nucleosides has been reported before[8,9]

Methyl acrylate as Michael acceptor. The first application for **1a** was found for the synthesis of glutarimide ylide **2**. Whereas ylide **1b** did not react with acryl amide or methyl acrylate as Michael acceptors, the corresponding amide **1a** gave a smooth addition reaction with methyl acrylate, leading to different products, depending on the solvent used (scheme 2).

Glutarimide ylide 2 results from normal protonation of the primairy adduct by the solvent (anhydrous methanol). Deprotonation of the amide α-hydrogen regenerates an ylide, which immediately cyclizes to glutarimide **2**. The intermediate open chain ylide **10** could never be detected in the reaction mixture. Obviously the α-anion decreases the amide resonance and increases the nucleophilicity of the amide nitrogen atom. Glutarimide ylides **2**, **3**, **4**, **5** and **7** are stable compounds and crystallize from the reaction mixture directly.



scheme 2

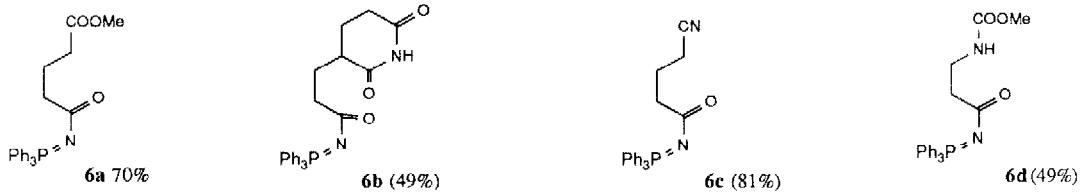
Methyl N-glutaryl-iminophosphorane **6a**[10] is formed in aprotic medium, probably via intramolecular protonation of the initially formed Michael adduct by one of the amide hydrogen atoms (scheme 2). Instead of glutarimide formation by attack on the ester, the nitrogen turns towards the phosphorus and via an azaphosphetane the triphenylphosphine substituent moves from carbon to nitrogen. The charge separation in the resulting betaine is released by a protonshift, giving **6a**. These stabilized iminophosphoranes are in general very unreactive towards hydrolysis or in reactions with aldehydes[11].

Methyl α-(bromomethyl)acrylate produces the corresponding α-methylene glutarimide ylide **3** (scheme 1). Since this reaction is in fact a S_N2' reaction, no C → N rearrangement products are expected. Extra triethyl amine is added to neutralize the HBr formed. **3** was used in Wittig reactions with e.g. ribose during the synthesis of glutarimide nucleosides[9].

Methyl α-acetamidoacrylate in a Michael reaction with **1a** follows the same pathway to **4** as the Michael addition with methyl acrylate. No attempts were made to obtain the corresponding iminophosphorane.

2-Methylene glutarimide. The solvent dependant Michael reaction is nicely demonstrated when 2-methylene glutarimide[12] is used as an acceptor. Whereas in acetonitrile the main product was the C → N rearranged iminophosphorane **6b** (scheme 3), in methanol at room temperature ylide **5** (scheme 1) was isolated from the reaction mixture in 76% yield by simple filtration. In this example the amide nitrogen attacks the glutarimide ring, yielding a new 2,4-disubstituted glutarimide **5**.

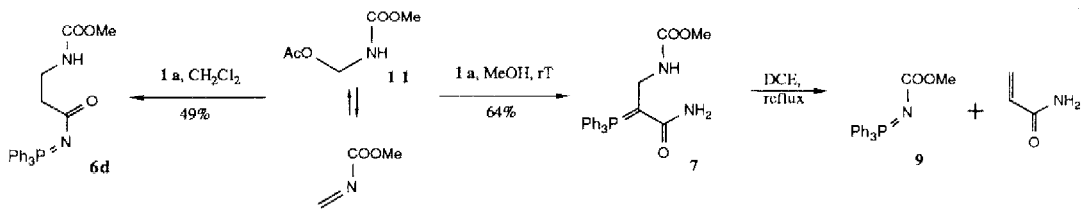
Acrylonitrile. The Michael reaction of **1a** with acrylonitrile[13] in dichloromethane at room temperature shows an efficient aprotic C → N migration of the triphenylphosphine substituent to yield iminophosphorane **6c** (81%).



scheme 3

When the Michael addition was performed in methanol, the rather unstable ylide **8** was formed in modest yield, which was treated in situ with some aldehydes. Reaction of **8** with a second molecule of acrylonitrile may explain the low yields (see table).

Methyl N-(acetoxymethyl)carbamate: "Aza-acrylate". Aminomethylation of **1a** to **7** with **11**[14] (64%) may proceed via a normal S_n2 proces (scheme 4). More likely however, is a reversible, base catalyzed elimination of acetic acid, leading to the corresponding imine ("aza-acrylate"). The addition of extra Et_3N accellerates this reaction. A second indication for a Michael type mechanism is the formation of C → N triphenylphosphine migrated product **6d** as the main product in aprotic solvents. Wittig reaction with ylide **7** proceeds well with relatively reactive aldehydes. When elevated reaction temperatures are used however, a proton shift takes place, which via an azaphosphetane leads to acrylamide and iminophosphorane **9**. This complete 2-step conversion from **1a** to acrylamide and **9** may also be regarded as a Wittig reaction, with methyl N-(acetoxymethyl)carbamate **11** as a formaldehyde equivalent[15].

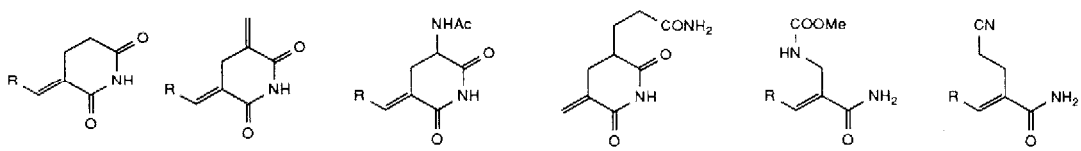


scheme 4

Limitations. No Michael reaction of **1a** was observed with methyl crotonate. Methyl methacrylate gave after prolonged reaction times only 5% glutarimide ylide. At elevated temperatures, the starting ylide **1a** decomposed.

Wittig reactions between ylides **2**, **3**, **4** and **5**[16] and several aldehydes were carried out in refluxing 1,2-dichloroethane (83°). Some of the resulting methylene glutarimides are shown in the table[17].

Wittig products



12 **13** **14** **15** **17** **18**

Ylide **7** still contains a primairy amide and is more reactive then the others. The use of dichloromethane (DCM) or chloroform instead of 1,2-dichloroethane (DCE) at reflux temperature also prevents the decomposition of **7** as is shown in scheme 4. The Wittig reactions of ylide **8** were performed in situ at room temperature, in methanol.

Starting ylide	Wittig product	R	Yield (%)	Solvent, reaction time	NMR: δ C=CH in $CDCl_3$ or DMSO (a).	
2	**12**	H	88	1,2-DCE 0.5 h	6.36	5.67
		Ph	91	,, 16 h	7.89	
3	**13**	H	79	,, 1 h	6.32	5.68
		Ph	82	,, 5 h	7.73	6.09, 5.71
4	**14**	H	78	,, 1 h	6.15[a]	5.74
		$pNO_2C_6H_4$-	64	,, 1 h	7.80[a]	
5	**15**	H	71	,, 2 h	6.11[a]	5.69
		Ph	72	48 h	7.84	
7	**17**	H	70	DCM 2 h	5.92	5.60
		Ph	64	,, 3 h	7.77	
8	**18**	Ph	32	MeOH 16 h	7.38	
		$pNO_2C_6H_4$-	35	,, 2 h	7.26[a]	

Notes and references

1. H.J. Bestmann and R. Zimmerman in: *Houben-Weyl*, 4th ed., Vol. E1, M. Regitz, (ed), Georg Thieme Verlag, Stuttgart, 1982, p 616 - 782.
2. B.E. Maryanoff and A.B. Reitz, *Chem. Rev.* **1989**, *89*, 863-927.
3. See ref. 1, p 653 - 740, and: H.J. Bestmann and F. Seng, *Angew.Chemie* **1962**, *74*, 154.
4. J. Asunskis and H. Shechter, *J.Org.Chem.* **1968**, *33*, 1164;
   D.T. Connor and M. von Strandtmann, *J.Org.Chem.* **1973**, *38*, 1074.
5. J. Barluenga, F. Lopez and F. Palacios, *Tetrahedron Lett.*, **1988**, *29*, 381;
   J.H. Labuschagne and D.F. Schneider, *Tetrahedron Lett.* **1982**, *23*, 4135; ibid, **1983**, *30*, 743.
6. S. Trippett and D.M. Walker, *J.Chem.Soc.* **1959**, 3874.
7. All ylids that are shown are tentatively drawn in the cisoid form.
8. M.J. Wanner and G.-J. Koomen, *Nucleosides and Nucleotides* **1988**, *7*, 511.
9. M.J. Wanner and G.-J. Koomen, *Tetrahedron Lett.* **1990**, *31*, 907.
10. Characteric for N-acyliminophosphoranes are two IR-absorbtions at 1565 and 1580 cm^{-1}.
    Spectral data of **6a** (oil): IR: 1435, 1480, 1565 and 1580 cm^{-1}; NMR ($CDCl_3$): 1.7-2.2 (m, 2H); 2.3-2.65 (m, 4H); 3.62 (s, CH_3O); 7.3-7.9 (15H-Ar); Mass: (FD) 405 (M^+) and 304 ($Ph_3P^+N{=}C{=}O$).
11. H. Heydt and M. Regitz in *Houben-Weyl*, 4th ed., Vol. E2, M. Regitz, (ed), Georg Thieme Verlag, Stuttgart, p 120; Additional structural proof for **6a** was obtained by heating the compound at 150° (neat), resulting in complete conversion into triphenylphosphine oxide and the corresponding glutaric ester/nitrile.
12. Obtained from **2** and paraformaldehyde, see table.
13. Ref.1, p 709; J.D. McClure, *Tetrahedron Lett.* **1967**, 2407: The reaction of **1b** with acrylonitrile at 90° proceeds via the reversible formation of a phosphocyclobutane, resulting in the formation of methyl acrylate and triphenylphosphoranylideneacetonitrile.
14. J. Oleksyszyn and L. Subotkwska, *Synthesis* **1980**, 906.
15. For a Wittig reaction with imines see H.J. Bestmann and F. Seng, *Tetrahedron* **1965**, *21*, 1373.
16. M.J. Wanner and G.-J. Koomen, *Synthesis* **1988**, 325.
17. Only small amounts of the Z-isomers were formed (0 - 10%), and were generally not isolated.
    A characteristic difference between E and Z isomers is found in NMR: the vinylic proton in the E-isomer is oriented in a cis-position towards the carbonyl shows a downfield shift of > 0.3 ppm.
18. Spectral data for all new compounds were in accord with their structures. Phosphonium ylides were further characterized by elemental analysis; high-resolution mass spectra were obtained for the other compounds.

(Received in UK 6 January 1992)