High-Pressure Induced Domino-Horner-Wadsworth-Emmons (HWE) – Michael Reactions

Senay Has-Becker,[a] Kerstin Bodmann,[a] Reinhard Kreuder,[a] Gabriella Santoni,[b] Tobias Rein,[c] Oliver Reiser*,[a]

[a] Institut für Organische Chemie, Universität Regensburg, Universitätsstr. 31, 93053 Regensburg, Germany

[b] Dipartimento Di Chimica Organica, Universita Degli Studi di Padova, Italy.

[c] AstraZeneca R&D, Discovery Chemistry, 15185 Sodertalje, Sweden.

Fax +49-9419434121; E-mail: Oliver.Reiser@chemie.uni-regensburg.de

Received 22 May 2001

Abstract: A new protocol for the alkenylation of carbonyl compounds with phosphonates (Horner-Wadsworth-Emmons reaction) is described. Aldehydes react with phosphonates already at room temperature in the presence of triethylamine without further activation by Lewis-acids if high-pressure (8 kbar) is applied to the system. Based on this protocol a domino process was developed combining the HWE reaction with a Michael reaction, thus allowing the one-pot synthesis of β-amino esters, β-thio esters or β-thio nitriles.

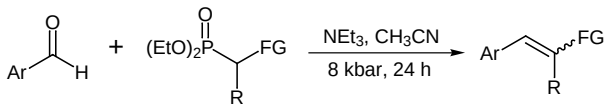
Key words: Horner-Wadsworth-Emmons reaction, Michael addition, domino reaction, β-amino esters, β-thio esters, β-thio nitriles, high-Pressure

The development of new domino reactions to achieve transformations of multiple components in a defined and controlled way is an important challenge to arrive at economical chemical processes.[1] With the advent of combinatorial chemistry,[2] domino reactions that create new reactive functionalities by subsequent addition of components appear to be especially valuable to readily arrive at libraries of molecules with high diversity.

High pressure (1-12 kbar) in liquid phases[3] has been recognized to greatly activate substrates for addition reactions,[4] most notably in Diels-Alder reactions.[5] Moreover, high-pressure reactions are commonly carried out by introducing the reactants, being sealed in small teflon vessels, into a high-pressure cell. A standard high-pressure cell has typically a reaction volume of 20-50 cm^3 that can easily hold around 10-20 individual teflon vessels at a time, and larger cells for industrial applications are also available. Therefore, reactions carried out under high-pressure appear to be well suited for parallel synthesis and might therefore find their place in the rapidly growing arsenal of new techniques in combinatorial chemistry. A few pioneering approaches towards the application of high-pressure in combinatorial chemistry have been recently disclosed.[6]

We report here a three-component process by combining a Horner-Wadsworth-Emmons reaction (HWE) with a Michael reaction to obtain β-amino esters, β-thio esters or β-thio nitriles starting from aldehydes, phosphonates and amines or thiols. Pressure plays a pivotal role to be able to carry out the title reactions under conditions that are compatible with the four classes of substrates employed.

The Horner-Wadsworth-Emmons reaction (HWE)[7] is one of the most versatile methods for the synthesis of alkenes. The common protocol for this reaction calls for the deprotonation of the phosphonate by a base such as metal hydrides, silazides, or alkoxides, and the subsequent addition of the carbonyl compound.[8] Alternatively, a mixture of stoichiometric amounts of a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), *N*,*N*-diisopropylethylamine (DIPEA) or triethylamine and lithium or magnesium salts serving as Lewis acids under rigorous anhydrous conditions has been successfully applied.[9] For the condensation of phosphorylglycine esters the use of a Lewis acid was demonstrated to be superfluous and often disadvantageous, and that DBU or tetramethylguanidine suffice as bases.[10] We have now discovered that HWE reactions of aromatic aldehydes **1** with phosphonates **2** proceed smoothly at room temperature in the absence of any Lewis acid using triethylamine as the base if high-pressure (8 kbar) is applied to the system (Scheme 1, Table 1). It has been shown previously that the parent Wittig reaction can be accelerated by pressure,[11] however, – in contrast to our work – no advantage of such high-pressure conditions with respect to a more economical use of reagents had been demonstrated.



1a: Ar = Ph
1b: Ar = 4-NO_2-Ph
1c: Ar = 4-OMe-Ph

2a: FG = CO_2Et, R = H
2b: FG = CO_2Et, R = Br
2c: FG = CN, R = H

3a-3h

Scheme 1

The electronically differentiated aldehydes **1a-c** could be alkenylated in good yields with the phosphonates **2a-c** in the presence of triethylamine at 8 kbar, in distinct contrast to reactions carried out at ambient pressure (Table 1). Moreover, excellent *E*-selectivity was observed with **2a** in all cases, while the phosphonates **2b**-**2c** gave rise to *E*/*Z*-mixtures depending on the aldehyde **1**. Interestingly, the reaction of **1a, b** with **2c** yielded the alkenes **3f** and **3g** (entries 11-14) with better selectivities under pressure condi-

Table 1 Synthesis of alkenes under high-pressure[15]

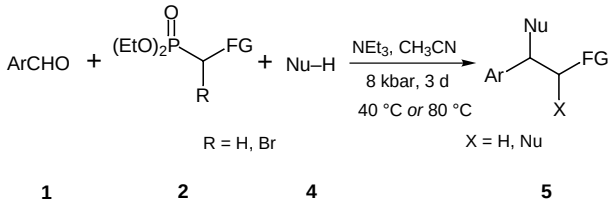
Entry	Aldehyde 1	Phosphonate 2	P	Alkene	(*E*)/(*Z*) -Ratio[a]	Yield [%][b]
1	**1a**	**2a**	1 bar	**3a**	-	0
2	**1a**	**2a**	8 kbar	**3a**	> 99:1	85
3	**1b**	**2a**	1 bar	**3b**	-	0
4	**1b**	**2a**	8 kbar	**3b**	> 99:1	80
5	**1c**	**2a**	1 bar	**3c**	-	0
6	**1c**	**2a**	8 kbar	**3c**	> 99:1	85
7	**1a**	**2b**	1 bar	**3d**	36:64	8
8	**1a**	**2b**	8 kbar	**3d**	34:66	75
9	**1b**	**2b**	1 bar	**3e**	45:55	5
10	**1b**	**2b**	8 kbar	**3e**	49:51	50
11	**1a**	**2c**	1 bar	**3f**	77:23	17
12	**1a**	**2c**	8 kbar	**3f**	85:15	76
13	**1b**	**2c**	1 bar	**3g**	76:24	47
14	**1b**	**2c**	8 kbar	**3g**	> 99:1	90
15	**1c**	**2c**	1 bar	**3h**	84:16	16
16	**1c**	**2c**	8 kbar	**3h**	60:40	85

[a]The ratio was determined by ^{1}H NMR integrals of the olefinic protons.
[b]Isolated Yield.

tions, marking one of the few examples in which pressure does not decrease selectivity under otherwise unchanged conditions.[12]

The mild conditions used in this new alkenylation protocol opened up the possibility to design a domino process by combining the HWE-reaction with a Michael addition. We expected that pressure will not only have a beneficial effect on the HWE reaction but also on the Michael reaction.[13] Thus, subjecting a mixture of an aldehyde **1**, a phosphonate **2** and a nucleophile **4** in the presence of triethylamine to 8 kbar, we envisioned a one pot synthesis of compounds with the general structure **5** (Scheme 2).

We wanted to test this hypothesis by employing amines and thiols as nucleophiles, thus arriving at β-amino and β-thio esters and nitriles, which are important intermediates of biologically potent compounds.[14] A potential complication could be the direct reaction of aldehydes **1** with **4**, but we reasoned that the overall basic conditions of this protocol should prevent the formation of aminals or thioacetals as a competing reaction pathway.



Scheme 2

Indeed, β-amino esters **5a**-**5g** could be obtained in this way in moderate to good yields (Table 2, entries 1-9). It became readily apparent that the second step, i.e. the 1,4-addition of the amine, was the limiting step of the sequence. Only secondary amines would give addition products, while with primary amines only the HWE-products are formed. Moreover, sterically hindered secondary amines (entry 10) and aromatic amines (entry 11) failed to give the desired amino esters at all. Using the phosphonate **2b**, the 1,2-diaminoester **5d** was obtained, in which the bromine substituent underwent another substitution by the nucleophile (entry 5). No aminolysis of the ethyl ester groups was observed at any point, however, when the amino alcohol **4b** was employed as the nucleophile, lactonization takes place after 1,4-addition to give rise to **5e** (entry 6).

When thiols are used as nucleophiles instead of amines, β-thio esters and β-thio nitriles are obtained (Table 2, entries 12-18). In contrast to the amine nucleophiles, there seem to be no limitations in the type of thiols being employed, i.e. aryl, benzyl and alkyl thiols all gave the expected addition products **5j**-**5p** in generally high yields.

In conclusion, a new three-component process leading to β-amino esters, β-thio esters or β-thio nitriles was developed. Further developments of new domino reactions to explore the potential of high-pressure for multi-component reactions and their application to parallel synthesis are under investigation in our laboratories.

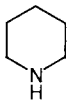
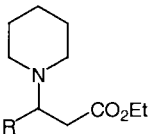
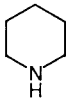
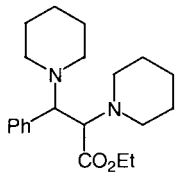
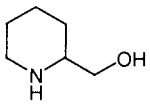
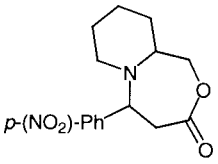
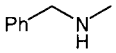
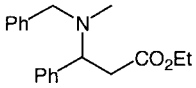
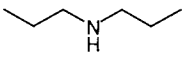
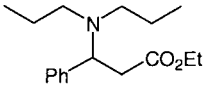
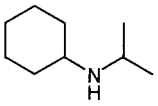
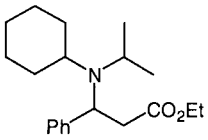
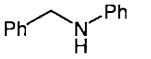
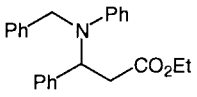
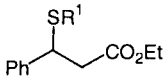
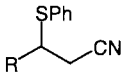
Acknowledgement

This work was supported by the DAAD (International Quality Network Program (IQN)) and the Fonds der Chemischen Industrie.

References and Notes

(1) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131.
(2) *Special issue on Combinatorial Chemistry*, J. W. Szostak (Ed), *Chem. Rev.* **1997**, *97*, 347-510.
(3) *For recent reviews on organic high-pressure chemistry see* (a) Klärner, F.-G.; Wurche, F. *J. Prakt. Chem.* **2000**, *342*, 609. (b) Matsumoto, K.; Kaneko, M.; Katsura, H.; Hayashi, N.; Uchida, T.; Acheson, R. M. *Heterocycles* **1998**, *47*, 1135. (c) Reiser, O. *Topics in Catalysis* **1998**, *5*, 105. (d) Jenner, G. *Tetrahedron* **1997**, *53*, 2669. (e) Ciobanu, M.; Matsumoto, K. *Liebigs Ann. Chem.* **1997**, 623. (f) Jurczak, J.; Gryko, D. T.

Table 2 Domino-HWE-Michael-Reactions[16,17]

Entry	Aldehyde	Phosponate	NuH		T [°C]	Product			Yield[a] [%]
1	**1a**	**2a**		**4a**	40		(R= Ph)	**5a**	56
2	**1a**	**2a**			80		(R= Ph)	**5a**	60
3	**1b**	**2a**			40		(R = *p*-(NO_2)-Ph)	**5b**	66
4	**1c**	**2a**			40		(R = *p*-(OMe)-Ph)	**5c**	45
5	**1a**	**2b**		**4a**	80			**5d**	41[b]
6	**1b**	**2a**		**4b**	80			**5e**	52[c]
7	**1a**	**2a**		**4c**	40			**5f**	40
8	**1a**	**2a**			80				70[d]
9	**1a**	**2a**		**4d**	80			**5g**	31[e]
10	**1a**	**2a**		**4e**	40			**5h**	0
11	**1a**	**2a**		**4f**	80			**5i**	0
12	**1a**	**2a**	EtSH	**4g**	80		(R^1 = Et)	**5j**	95
13	**1a**	**2a**	PhSH	**4h**	80		(R^1 = Ph)	**5k**	85
14	**1a**	**2a**	BnSH	**4i**	80		(R^1 = Bn)	**5l**	93
15	**1a**	**2a**	*p*-(Me)-PhSH	**4j**	80		(R^1 = *p*-(Me)-Ph)	**5m**	87
16	**1a**	**2c**			80		(R = Ph)	**5n**	78
17	**1c**	**2c**	PhSH	**4h**	80		(R = *p*-(OMe)-Ph)	**5o**	30
18	**1d**	**2c**			80		(R = *p*-(Cl)-Ph)	**5p**	59

[a] Isolated Yield. [b] A ratio of syn:anti isomers of 1:1 was found. [c] In addition 46% 4-NO_2-cinnamic ester (**3b**) were isolated. [d] In addition 29% cinnamic ester (**3a**) were isolated. [e] In addition 69% cinnamic ester (**3a**) were isolated.

Organic synthesis at high pressure; Eldik, R. V. and Hubbard, C. D., Ed.; John Wiley & Sons Inc: 605 3RD Ave/New York/ NY 10016, 1997, pp 163-188. (g) Isaacs, N. S. *Organic synthesis at high pressures.*; Holzapfel, W. B. and Isaacs, N. S., Ed.; Oxford Univ Press: 198 Madison Avenue/New York/ NY 10016, 1997, pp 307-329.

(4) Eldik, R. v.; Asano, T.; Noble, W. J. l. *Chem. Rev.* **1989**, *89*, 549.

(5) *Leading examples:* (a) Klärner, F.-G.; Breitkopf, V. *Eur. J. Org. Chem.* **1999**, 2757. (b) Tietze, L. F.; Henrich, M.; Niklaus, A.; Buback, M. *Chem. Eur. J.* **1999**, *5*, 297. (c) Al-Badri, H.; Maddaluno, J.; Masson, S.; Collignon, N. *J. Chem. Soc. Perkin Trans. 1* **1999**, 2255. (d) Diedrich, M. K.; Klärner, F. G. *J. Am. Chem. Soc.* **1998**, *120*, 6212. (e) Tietze, L. F.; Abeln, J.; Hübsch, T.; Ott, C.; Buback, M. *Liebigs Ann.* **1995**, 9. (f) Tietze, L. F.; Hübsch, T.; Ott, C.; Kuchta, G.; Buback, M. *Liebigs Ann.* **1995**, 1.

(6) (a) Kuster, G. J.; Scheeren, H. W. *Tetrahedron Lett.* **2000**, *41*, 515. (b) Kuster, G. J.; Scheeren, H. W. *Tetrahedron Lett.* **1998**, *39*, 3613.

(7) *For reviews of the Horner-Wadsworth-Emmons reaction see* (a) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (c) Rein, T.; Reiser, O. *Acta. Chem. Scand.* **1996**, *50*, 369.

(8) *NaH*: (a) Oppolzer, W.; Grayson, J. I. *Helv. Chim. Acta* **1980**, *63*, 1706. (b) Lerouge, P.; Paulmier, C. *Bull. Soc. Chim. Fr.* **1985**, 1225. (c) Sano, S.; Yokoyama, K.; Fukushima, M.; Yagi, T.; Nagao, Y. *Chem. Commun.* **1997**, 559.
KH: (a) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *J. Org. Chem.* **1990**, *55*, 1901. (b) Liu, A.; Dillon, K.; Campbell, R. M.; Cox, D. C.; Huryn, D. M. *Tetrahedron Lett.* **1996**, *37*, 3785.
KHMDS/NaHMDS: (a) Pedersen, T. M.; Jensen, J. F.; Humble, R. E.; Rein, T.; Tanner, D.; Bodmann, K.; Reiser, O. *Org. Lett.* **2000**, *2*, 535. (b) Lovely, C. J.; Gilbert, N. E.; Liberto, M. M.; Sharp, D. W.; Lin, Y. C.; Brueggemeier, R. W. *J. Med. Chem.* **1996**, *39*, 1917.
LDA: (a) Cardellicchio, C.; Iacuone, A.; Naso, F. *Tetrahedron Lett.* **1995**, *36*, 6563. (b) Armesto, D.; Horspool, W. M.; Gallego, M. G.; Agarrabeitia, A. R. *J. Chem. Soc. Perkin Trans. 1* **1992**, 163. (c) Mcdonald, G.; Lewis, N. J.; Taylor, R. J. K. *J. Chem. Soc. Chem. Commun.* **1996**, 2647.
BuLi: (a) Mori, K.; Amaike, M. *J. Chem. Soc. Perkin Trans. 1* **1994**, 2727. (b) Yamano, Y.; Sumiya, S.; Ito, M. *J. Chem. Soc. Perkin Trans. 1* **1995**, 167. (c) Coutrot, P.; Grison, C.; Lecouvey, M. *Bull. Soc. Chim. Fr.* **1997**, 27.
KO^{t}Bu/Triton B: Ando, K. *J. Org. Chem.* **1997**, *62*, 1934.
NaOEt/NaOMe: (a) Effenberger, F.; Kesmarszky, T. *Chem. Ber.* **1992**, *125*, 2103. (b) Torrado, A.; Iglesias, B.; Lopez, S.; Lera, A. R. d. *Tetrahedron* **1995**, *51*, 2435.
NaOH / LiOH: (a) Bonadies, F.; Cardilli, A.; Lattanzi, A.; Orelli, L. R.; Scretti, A. *Tetrahedron Lett.* **1994**, *35*, 3383. (b) Bonini, C.; Federici, C.; Rossi, L.; Righi, G. *J. Org. Chem.* **1995**, *60*, 4803.
K_2CO_3: (a) Mouloungui, Z.; Delmas, M.; Gaset, A. *Synth. Commun.* **1984**, 701. (b) Mouloungui, Z.; Elmestour, R.; Delmas, M.; Gaset, A. *Tetrahedron* **1992**, *48*, 1219.
$KHCO_3$: Villieras, J.; Raumbaud, M.; Kirschleger, B. *Phosphorus Sulfur* **1983**, *14*, 385. (c) Angeletti, E.; Tundo, P.; Venturello, P. *J. Chem. Soc. Perkin Trans. 1* **1987**, 713.

(9) (a) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sasaki, T. *Tetrahedron Lett.* **1984**, *25*, 2183. (b) Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2625. (c) Moison, H.; Texier-Boullet, F.; Foucaud, A. *Tetrahedron* **1987**, *43*, 537. (d) Aar, M. P. M. v.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1995**, *51*, 9699.

(10) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487.

(11) (a) Hebert, E.; Welvart, Z.; Ghelfenstein, M.; Szwarc, H. *Tetrahedron Lett.* **1983**, *24*, 1381. (b) Isaacs, N. S.; Obed, O. H. *Tetrahedron Lett.* **1986**, *27*, 995. (c) Nonnenmacher, A.; Mayer, R.; Plieninger, H. *Liebigs Ann. Chem.* **1983**, 2135. (d) Dauben, W. G.; Takasugi, J. J. *Tetrahedron Lett.* **1987**, *28*, 4377. (e) Isaacs, N. S.; El-Din, G. N. *Tetrahedron Lett.* **1987**, *28*, 2191. (f) Jarosz, S.; Salanski, P.; Mach, M. *Tetrahedron* **1998**, *54*, 2583.

(12) *Other examples:* (a) Tietze, L. F.; Ott, C.; Gerke, K.; Buback, M. *Angew. Chem.* **1993**, *105*, 1536. (b) Tietze, L. F.; Hübsch, T.; Voss, E.; Buback, M.; Trost, W. *J. Am. Chem. Soc.* **1988**, *110*, 4065. (c) Jenner, G. *Tetrahedron Lett.* **1994**, *35*, 1189. (d) Midland, M. M.; McLoughlin, J. I. *J. Org. Chem.* **1989**, *54*, 159. (f) Trost, B. M.; Parquette, J. R.; Marquart, A. L. *J. Am. Chem. Soc.* **1995**, *117*, 3284-3285. (g) Reiser, O. *The Review of High Pressure Science and Technology* **1998**, *8*, 111.

(13) (a) Dumas, F.; Mezrhab, B.; Angelo, J. d.; Riche, C.; Chiaroni, A. *J. Org. Chem.* **1996**, *61*, 2293. (b) Jenner, G. *Tetrahedron Lett.* **1995**, *36*, 233. (c) Mezrhab, B.; Dumas, F.; Angelo, J. d.; Riche, C. *J. Org. Chem.* **1994**, *59*, 500. (d) Matsumoto, K.; Hashimoto, S.; Uchida, T.; Okamoto, T.; Otani, S. *Chem. Ber.* **1989**, *122*, 1357. (e) Sera, A.; Takagi, K.; Katayama, H.; Yamada, H.; Matsumoto, K. *J. Org. Chem.* **1988**, *53*, 1157. (f) Angelo, J. d.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112. (g) Dauben, W. G.; Bunce, R. A. *J. Org. Chem.* **1983**, *48*, 4642. (h) Dauben, W. G.; Gerdes, J. M. *Tetrahedron Lett.* **1983**, *24*, 3841. (i) Matsumoto, K.; Uchida, T. *Chem. Lett.* **1981**, 1673. (j) Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1.

(14) *Recent examples:* (a) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 12974. (b) Miyata, O.; Yamaguchi, S.; Ninomiya, I.; Naito, T.; Okamura, K. *Chem. Pharm. Bull.* **1996**, *44*, 636. (c) Kita, Y.; Schibata, N.; Miki, T.; Takemura, Y.; Tamura, O. *Chem. Pharm. Bull.* **1992**, *40*, 12. (d) Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T.; Date, T.; Okamura, K.; Inagaki, S. *J. Org. Chem.* **1991**, *56*, 6556. (e) Allberola, A.; Alvarez, M. A.; Andrés, C.; González, A.; Pedrosa, R. *Synthesis* **1990**, 1057-1058.

(15) General procedure: A mixture of an aldehyde **1** (1 mmol), a phosphonate **2** (1 mmol) and triethylamine (1 mmol) in 1 mL CH_3CN was sealed in a Teflon bag and subjected to 8 kbar for 24 h at room temperature. The reaction mixture was diluted with diethyl ether, extracted with brine, and concentrated in vacuo. Chromatography on silica gel afforded the desired alkene **3**.

(16) General procedure: A mixture of an aldehyde **1** (1 mmol), a phosphonate **2** (1 mmol), triethylamine (1 mmol) and a nucleophile **4** (2 mmol) in 1 mL CH_3CN was sealed in a teflon bag and subjected to 8 kbar for 3 d at the indicated temperature. The reaction mixture was concentrated, the residue was purified by column chromatography over silica gel and gave the desired product **5**.

(17) All new compounds were fully characterized by spectroscopic methods and gave satisfactory combustion analyses.

Article Identifier:
1437-2096,E;2001,0,09,1395,1398,ftx,en;G09301ST.pdf