Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient Synthesis of Phosphono- and Phosphinoxidomethylated N-Heterocycles under Solvent-Free Microwave Conditions

Ibolya Prauda [a], István Greiner [b], Krisztina Ludányi [c d] & György Keglevich [a]
[a] Department of Organic Chemical Technology, Budapest University of Technology and Economics, Budapest, Hungary
[b] Gedeon Richter Ltd., Budapest, Hungary
[c] Hungarian Academy of Sciences, Chemical Research Center, Budapest, Hungary
[d] Semmelweis University Faculty of Pharmacy, Department of Pharmaceutics, Budapest, Hungary
Published online: 25 Jul 2007.

To cite this article: Ibolya Prauda, István Greiner, Krisztina Ludányi & György Keglevich (2007) Efficient Synthesis of Phosphono- and Phosphinoxidomethylated N-Heterocycles under Solvent-Free Microwave Conditions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:2, 317-322, DOI: 10.1080/00397910601033856

To link to this article: http://dx.doi.org/10.1080/00397910601033856

Synthetic Communications®, 37: 317–322, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910601033856

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Ibolya Prauda
Department of Organic Chemical Technology, Budapest University of Technology and Economics, Budapest, Hungary

István Greiner
Gedeon Richter Ltd., Budapest, Hungary

Krisztina Ludányi
Hungarian Academy of Sciences, Chemical Research Center, and Semmelweis University Faculty of Pharmacy, Department of Pharmaceutics, Budapest, Hungary

György Keglevich
Department of Organic Chemical Technology, Budapest University of Technology and Economics, Budapest, Hungary

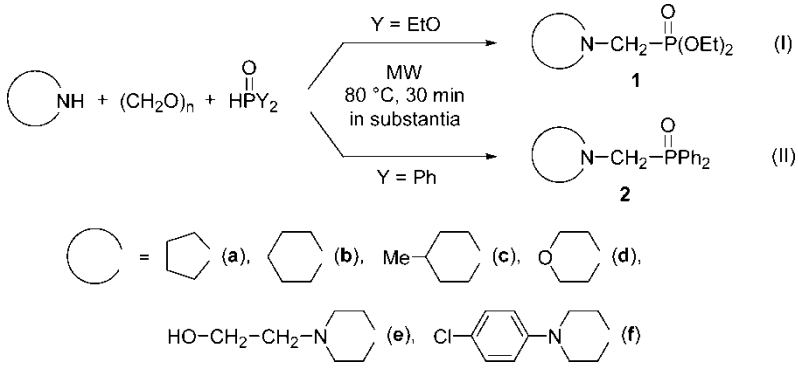
Abstract: Simple N-heterocycles were converted to N-phosphono- and phosphinoxidomethyl derivatives by a solvent-free microwave-assisted condensation of the heterocycle, paraformaldehyde, and diethylphosphite or diphenylphosphine oxide in a convenient and, in most cases, efficient way. In contrast to an earlier report, imidazole proved to be unreactive in this type of phospha-Mannich reaction.

Keywords: α-aminomethylphosphine oxides, α-aminomethylphosphonates, green chemistry, N-heterocycles, microwave synthesis, solvent-free method

Received in the U.K. March 30, 2006
Address correspondence to György Keglevich, Department of Organic Chemical Technology, Budapest University of Technology and Economics, Budapest, Hungary. E-mail: keglevich@mail.bme.hu

One of the widespread methods for the synthesis of α-aminophosphonates, which form an important class of biologically active compounds, is based on the Kabachnik–Fields reaction,[1,2] applying a ternary system of a >P(O)H reactant, an oxo-compound that is mainly an aldehyde (most frequently formaldehyde), and a secondary or primary amine.[3] The phospha-Mannich-type reaction was claimed to have been successfully applied to the phosphonomethylation of imidazole derivatives under conventional heating at 80–100°C for 6–8 h to afford the products in 73–92% yields.[4] A similar reaction of piperidine and morpholine carried out in benzene at reflux for 1.5 h using p-toluenesulfonic acid as the catalyst led to the corresponding phosphonomethyl derivatives in 70–88% yields.[3] We aimed at the microwave synthesis of phosphono- and phosphinoxidomethylated N-heterocycles under solvent-free conditions and wished to survey the immediate precedents critically. To the best of our knowledge, to date no similar study is available in the literature.

A variety of N-heterocycles, such as pyrrolidine, piperidine derivatives, morpholine, and piperazine derivatives, were converted to the corresponding diethylphosphonomethyl derivatives (**1a–g**) in a reaction with paraformaldehyde and diethylphosphite without any solvent, under microwaves (Scheme 1, I). The optimum set of reaction conditions involved heating at 80°C for 30 min in the presence of a catalytic amount of hydrochloric acid. The method was extended to the synthesis of a few diphenylphosphinoxidomethyl derivatives (**2a**, **2c**, **2d**, and **2f**) using pyrrolidine, 4-methylpiperidine, morpholine or a 4-arylpiperazine, and diphenylphosphine oxide (Scheme 1, II). From among products **1** and **2**, **1c**, **1e**, **1f**, **2c**, and **2f** are new and were fully characterized by means of ^{31}P, ^{13}C, and ^{1}H NMR, as well as mass spectroscopy. The -$CH_2P(O)<$ derivatives (**1a–d, f** and **2a, c, d, f**) were obtained in 70–93% yields (Table 1), in purities of ca. 98–99% after flash-column chromatography. It is worthy of mention that the yields were higher using $Ph_2P(O)H$ as the P-component. Comparison of the yields and δ_P shifts of



Scheme 1.

Table 1. Synthesis of phosphonomethyl- and phosphinoxidomethyl N-heterocycles (**1a–g** and **2a, c, d, f**) by the Kabachnik–Fields reaction under microwave conditions

	Experimental				Literature			
Product	Yield (%) MW/ 80°C/30 min	δ_P ($CDCl_3$)	mp (°C)	Conditions	Yield (%)	δ_P	mp (°C)	Ref.
1a	73	25.1		≥85°C, 15 min	—[a]	24.0		[5,2]
1b	70	25.0		Δ, 1.5 h, C_6H_6[b]	∼79	23.0		[3]
1c	71	24.9						
1d	70	23.9		Δ, 1.5 h, C_6H_6[b]	∼79	19.0		[3]
1e	54	24.4						
1f	71	24.1						
2a	91	26.7	158–161[c]	*d*		*e*	154–156[f]	[6]
2c	93	26.6	130–131[g]					
2d	89	27.4	166–168[g]	*h*		*e*	164[f], 158–159[i]	[6,7]
2f	73	27.4	237–238[j]					

[a]No yield was provided.
[b]PTSA catalyzed.
[c]Recrystallized from ethyl acetate/isopropanol.
[d]Prepared by substitution at P.
[e]No δ_P shift was provided.
[f]Recrystallized from cyclohexane.
[g]Recrystallized from ethyl acetate.
[h]Prepared by the Arbusov approach.
[i]Recrystallized from CH_2Cl_2/hexane.
[j]Recrystallized from isopropanol.

the products obtained also under conventional methods suggests that the solvent-free microwave synthesis may be a green alternative to traditional heating in aromatics, giving comparable or even better yields.

Russian authors claimed that they synthesized imidazolyl -$CH_2P(O)(OEt)_2$ by the solvent-free condensation reaction of imidazol, paraformaldehyde, and diethylphosphite carried out at 80–100°C for 6–8 h.[4] We found that, in this case, the real product was $HOCH_2P(O)(OEt)_2$, due to the unreactivity of imidazole in phospha-Mannich reaction. Neither reproduction of the procedure nor a solvent-free microwave irradiation of the three components at 90°C led to the desired product. The formaldehyde-diethylphoshite adduct obtained in a 54% yield was identified by ^{31}P and ^{13}C NMR [δ_p ($CDCl_3$) 24.7; δ_C 15.9 ($J = 5.5$), 56.1 ($J = 163.7$), 62.1 ($J = 6.6$)], as well as IR and mass spectrometry [ν (cm^{-1}) 1028, 1234, 3310; $(M + H)^+ = 169$] and was found to be identical with an authentic sample.[8] Russian authors identified their product(s) only by IR and UV, and in the case under discussion, this may have been misleading.

In summary, the Kabachnik–Fields reaction involving N-heterocycles, paraformaldehyde, and >P(O)H species can be accomplished in an environmentally friendly manner under solvent-free microwave conditions. The procedure can obviously be extended to other type of phospha-Mannich reactions. A discrepancy found in the literature was clarified.

EXPERIMENTAL

General

The ^{31}P, ^{13}C, and ^1H NMR spectra were obtained on a Bruker DRX-500 spectrometer operating at 202.4, 125.7, and 500 MHz, respectively. Chemical shifts are downfield relative to 85% H_3PO_4 or TMS. The couplings are given in Hertz. Mass spectrometry was performed on a ZAB-2SEQ instrument.

General Procedure for the Preparation of >P(O)CH_2-N-heterocycles (1a–f; 2a, c, d, f)

A mixture of 4.0 mmol of the N-heterocycle (pyrrolidine, pyrrole, piperidine derivatives, morpholine, and piperazine derivatives), 0.12 g (4.0 mmol) of paraformaldehyde, 4.0 mmol of dialkylphosphite or diphenylphosphine oxide, and 0.1 ml (1.0 mmol) of 37% hydrochloric acid is heated at 80°C (applying ca. 5 W) in a closed vial in a CEM Discover (300 W) microwave reactor for 45 min. The crude product was taken up in chloroform and passed through a 10-cm silica-gel column using 3% methanol in chloroform to furnish products **1a–f** and **2a, c, d, f** (Table 1).

Products **1a, b, d** are known compounds, whereas the following ones listed below are new.

New Compounds

Diethyl 4-Methyl-piperidinomethylphosphonate (1c)

Yield and δ_p in Table 1; δ_C ($CDCl_3$) 16.3 ($^3J = 5.8$, $OCH_2\mathit{C}H_3$), 21.6 ($CH\mathit{C}H_3$), 30.0 (CH), 34.1 ($CH\mathit{C}H_2$), 54.2 ($^1J = 161.9$, PCH_2), 55.4 ($^3J = 9.9$, NCH_2), 61.7 ($^2J = 6.8$, $O\mathit{C}H_2CH_3$); δ_H 0.90 (d, $J = 6.0$, 3H, $CHC\mathit{H}_3$), 1.31–1.36 (m, 3H, C*H*, $C\mathit{H}_2$), 1.33 (t, $J = 7.1$, 6H, $OCH_2C\mathit{H}_3$), 1.57–1.61 (m, 2H, $CHC\mathit{H}_2$), 2.14–2.22, 3.01–3.05 (m, 4H, NCH_2), 2.78 (d, $J = 11.4$, 2H, PCH_2), 4.12–4.18 (m, 4H, $OC\mathit{H}_2CH_3$); $(M + H)^+_{found} = 250.1559$; $C_{11}H_{25}NO_3P$ requires 250.1572.

Diethyl 4-Hydroxyethyl-piperazinomethylphosphonate (1e)

Yield and δ_p in Table 1; δ_C ($CDCl_3$) 16.4 ($^3J = 5.8$, $OCH_2\mathit{C}H_3$), 52.8 ($N\mathit{C}H_2CH_2NCH_2P$), 53.8 ($^1J = 163.3$, PCH_2), 54.8 ($^3J = 10.3$, $NCH_2\mathit{C}H_2NCH_2P$), 57.7 ($N\mathit{C}H_2CH_2O$), 59.2 (CH_2OH), 62.0 ($^2J = 6.7$, $O\mathit{C}H_2CH_3$); δ_H 1.33 (t, $J = 7.1$, 6H, $OCH_2C\mathit{H}_3$), 2.52–2.69 (m, 10H, NCH_2 and OH), 2.79 (d, $J = 11.7$, 2H, PCH_2), 3.61 (t, $J = 5.4$, 2H, $C\mathit{H}_2OH$), 4.12–4.18 (m, 4H, $OC\mathit{H}_2CH_3$); $(M + H)^+_{found} = 281.1618$; $C_{11}H_{26}N_2O_4P$ requires 281.1630.

Diethyl 4-(4-Chlorophenyl)-piperazinomethylphosphonate (1f)

Yield and δ_p in Table 1; δ_C ($CDCl_3$) 16.8 ($^3J = 5.8$, $OCH_2\mathit{C}H_3$), 49.5 ($N\mathit{C}H_2CH_2NCH_2P$), 54.2 ($^1J = 163.9$, PCH_2), 54.9 ($^3J = 10.4$, $NCH_2\mathit{C}H_2NCH_2P$), 62.0 ($^2J = 6.8$, $O\mathit{C}H_2CH_3$), 117.5 ($C_{2'}$), 124.8 ($C_{4'}$), 129.2 ($C_{3'}$), 150.1 ($C_{1'}$); δ_H 1.34 (t, $J = 7.1$, 6H, $CH_2C\mathit{H}_3$), 2.81 (t, $J = 5.0$, 4H, NCH_2), 2.84 (d, $J = 12.0$, 2H, PCH_2), 3.17 (t, $J = 5.0$, 4H, NCH_2), 4.13–4.23 (m, 4H, $C\mathit{H}_2CH_3$), 6.82 (d, $J = 9.0$, 2H, Ar), 7.19 (d, $J = 8.9$, 2H, Ar); $(M + H)^+_{found} = 347.1277$; $C_{15}H_{25}ClN_2O_3P$ requires 347.1291.

4-Methyl-piperidinomethyl-diphenylphosphine oxide (2c)

Yield and δ_p in Table 1; δ_C ($CDCl_3$) 21.6 (CH_3), 29.9 (CH), 34.1 ($NCH_2\mathit{C}H_2$) 56.0 ($^3J = 6.6$, $N\mathit{C}H_2CH_2$), 58.7 ($^1J = 81.4$, PCH_2), 128.4 ($^2J = 11.2$, $C_{2'}$)*, (may be reversed)*, 131.2 ($^3J = 8.8$, $C_{3'}$)*; 131.7 ($C_{4'}$), 132.6 ($^1J = 97.7$, $C_{1'}$), may be reversed*; δ_H 1.15–1.41 (m, 3H, C*H*, $C\mathit{H}_2CH_2N$), 1.47–1.58 (m, 2H, $C\mathit{H}_2CH_2N$), 2.22–2.43, 2.88–3.00 (m, 4H, $NC\mathit{H}_2CH_2$), 3.31 (d, $J = 6.6$, 2H, PCH_2), 7.46–7.54, 7.81–7.88 (m, 10H, Ar); $(M + H)^+_{found} = 314.1659$; $C_{19}H_{25}NOP$ requires 314.1674.

4-(4-Chlorophenyl)-piperazinomethyl-diphenyl-phosphine oxide (2f)

Yield and δ_p in Table 1; δ_C ($CDCl_3$) 49.1 ($NCH_2CH_2NCH_2$), 55.2 ($^3J = 7.9$, $NCH_2CH_2NCH_2$), 58.3 ($^1J = 87.8$, PCH_2), 117.2 ($C_{2'}$), 124.5 ($C_{4'}$), 128.9 ($C_{3'}$), 149.8 ($C_{1'}$), 128.5 ($J = 11.5$, $C_{2''}$)*, 131.2 ($J = 8.9$, $C_{3''}$)*, 131.8 ($^4J = 2.7$, $C_{4''}$) 132.3 ($^1J = 97.9$, $C_{1''}$), *may be reversed; δ_H 2.78–2.96 (m, 4H, NCH_2), 3.06–3.19 (m, 4H, NCH_2), 3.28–3.43 (m, 2H, PCH_2), 6.79 (d, $J = 8.4$, 2H, Ar), 7.18 (d, $J = 8.7$, 2H, Ar), 7.43–7.62, 7.79–7.89 (m, 10H, Ar); $(M + H)^+_{found} = 411.1375$; $C_{23}H_{25}ClN_2OP$ requires 411.1393.

ACKNOWLEDGMENT

This work was supported by the joint funds from the European Union and the Hungarian State (GVOP-3.2.2-2004-07-0006/3.0). The financial support from Gedeon Richter Ltd is also acknowledged. I. P. is grateful to the Hungarian Scientific Research Funds (OTKA PD 050010) for the support.

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