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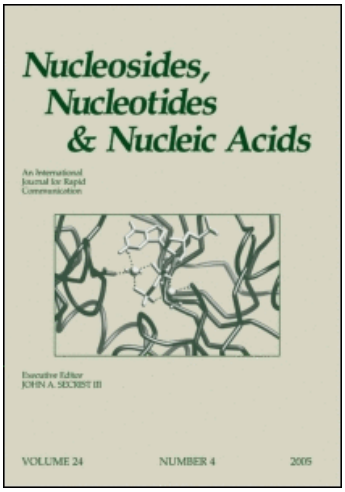

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Improvement of the Synthesis of Sugar Phosphonates Using Microwave Irradiations

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IMPROVEMENT OF THE SYNTHESIS OF SUGAR PHOSPHONATES USING MICROWAVE IRRADIATIONS

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□ *Sugar and nucleoside phosphonates have been prepared using a microwave-assisted reaction. Results concerning optimization of the reaction for various substrates as well as comparison of thermal and microwave experimental conditions of the Michaelis-Arbuzov reaction is reported.*

Keywords Arbuzov reaction; microwave-assisted reaction; nucleoside; sugar phosphonates

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INTRODUCTION

Sugar phosphonate derivatives are valuable intermediates for the synthesis of potential therapeutic compounds such as nucleotide analogues.[1,2] Although several synthetic methods are described for the preparation of such compounds, one of the most versatile is the Michaelis-Arbuzov reaction. Unfortunately, it presents some drawbacks when using classical conditions such as length of reaction time, high temperature and removal of the trivalent phosphorus ester used in large excess. These drastic conditions may be responsible for side reactions, low yields and limits the application of such reactions to sensitive substrates. Thus, we decided to explore the use of microwave (MW) irradiation for the synthesis of sugar phosphonic esters as key intermediates. Indeed, despite the considerable and still growing interest on MW irradiation applications in organic synthesis[3,4] only few reports have been made in the field of organophosphorus chemistry.[5–8]

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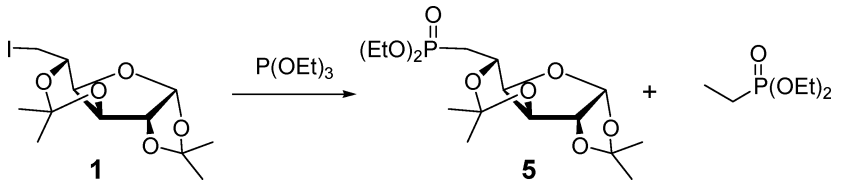
RESULTS

Optimization of the Michaelis-Arbuzov reaction conditions under MW irradiation was investigated using compound **1** as model substrate (Scheme 1). Reaction progress was monitored using TLC and ^{31}P NMR, and various experimental conditions were studied such as temperature (range of 160 to 220°C), reaction time, power of the irradiation (range of 150 to 300W), quantity of triethylphosphite engaged. This last factor is of particular importance because the removal of this reagent excess usually required fastidious and long high-vacuum evaporation. ^{31}P NMR experiments enable us to follow the disappearance of the triethylphosphite and the formation of the desired phosphonate **5** as well as the expected side-product, (diethyl) ethylphosphonate (Scheme 1). The best conditions were treating **1** for 90 minutes at 220°C, irradiation power of 300W, with 5 equivalents of $P(OEt)_3$. This experiment was reproducible and the scale of the reaction was extended to grams.



SCHEME 1 Reaction carried out for the optimization study.

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Thus, similar protocol was applied to various sugar or nucleosidic substrates, results are summarized in Table 1 and compared to thermal conditions. Concerning the sugar derivatives (**1–3**), the use of MW irradiation led to a small decrease of the yield of the corresponding phosphonates after chromatographic separation. However, the amount of trialkylphosphite engaged was significantly reduced as illustrated for substrate **2**, from 25 to 5 equivalents, and the reaction time was shortened to 1 hour, or less, instead of few days. Furthermore, we have shown that MW conditions were compatible with various sugar protections such as isopropylidene (**1**), benzoyl (**2**), and benzyl (**3**) groups. Applied to a nucleosidic derivative such as **4** both thermal and MW conditions led to disappointing results, the corresponding phosphonate was indeed isolated in less than 25% yield. Formation of a dark-coloured reaction mixture and side-products were observed, suggesting a degradation of the substrate.

In conclusion, microwave heating is an effective technique to promote the Michaelis-Arbuzov reaction with short reaction times and reduces the amount of chemical wastes, but the high temperatures required to perform the reaction under both thermal and MW conditions are still limiting its application to sensitive substrates.

TABLE 1 Comparison of thermal and microwave experimental conditions and isolated yields.

Substrate	Thermal experiments				MW experiments			
	$P(OEt)_3$ (eq.)	Temp. (°C)	Time (days)	Yield (%)	$P(OEt)_3$ (eq.)	Temp. (°C)	Time (min.)	Yield (%)
	15	110	3	60	5	220	90	50
	25	110	2	70	5	180	30	63
	10	100	2	77	5	200	90	70
	10	110	3	25	5	200	60	14

REFERENCES

1. Leblond, L.; Attardo, G.; Hamelin, B.; Bouffard, D.Y.; Nguyen-Ba, N.; Gourdeau, H. BCH-1868 [(-)-2-R-dihydroxyphosphinoyl-5-(S)-(guanin-9′-yl-methyl) tetrahydrofuran]: A cyclic nucleoside phosphonate with antitumoral activity. *Molecular Cancer Therapeutics* **2002**, 1, 737–746.
2. Nair, V.; Sharma, P.K.; Synthesis of the 5′-phosphonate of 4(S)-(6-amino-9H-purin-9-yl) tetrahydro-2(S)-furanmethanol [s,s-IsoddA]. *Arkivoc* **2003**, XV, 10–14.
3. Hayes, B.L.; Recent advances in microwave-assisted synthesis. *Aldrichimica Acta* **2004**, 37, 66–77.
4. Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. Microwave assisted organic synthesis—A review. *Tetrahedron* **2001**, 57, 9225–9283.
5. Wu, J.; Wu, H.; Wei, S.; Dai, W.M. Highly regioselective Wittig reactions of cyclic ketones with stabilized phosphorus ylide under controlled microwave heating. *Tetrahedron Lett.* **2004**, 45, 4401–4404.
6. Kiddle, J.J.; Gurley, A.F. Microwave irradiation in organaphosphorus chemistry 1: the Michaelis-Arbuzov reaction. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, 160, 195–205.
7. Kiddle, J.J. Microwave irradiation in organophosphorus chemistry. Part 2: Synthesis of phosphonium salts. *Tetrahedron Lett.* **2000**, 41, 1339–1341.
8. Sabitha, G.; Reddy, M.M.; Srinavas, D.; Yadov, J.S. Microwave irradiation: Wittig olefination of lactones and amides. *Tetrahedron Lett.* **1999**, 40, 165–166.

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