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Microwave-Assisted Carbonyl–Carbonyl Coupling Route for the Preparation of a Useful Intermediate in the Synthesis of Carbapenems

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Abstract: Microwave-assisted organic synthesis has been used for the cyclization of a monocyclic oxoamide to the corresponding bicyclic derivative via a Wittig-type coupling by means of phosphite reagents. The parameters influencing the reaction yields under microwave (dielectric heating) and classical conditions (convective heating) have been evaluated.

Keywords: Carbapenem, imipenem, MAOS (microwave-assisted organic synthesis), phosphite-mediated cyclization, Wittig intramolecular reaction

INTRODUCTION

A valuable route to the synthesis of the bicyclic scaffold of penem, independently developed by the pioneering work of two research groups,[1–3] is based on the carbonyl–carbonyl coupling via a phosphite-mediated reductive olefination–cyclization of a suitable oxoamide and has been demonstrated to be very useful for the preparation of other β-lactam carbapenem antibiotics[4,5] including bicyclic meropenem[6] and tricyclic sanfetrinem (Scheme 1).[7,8]

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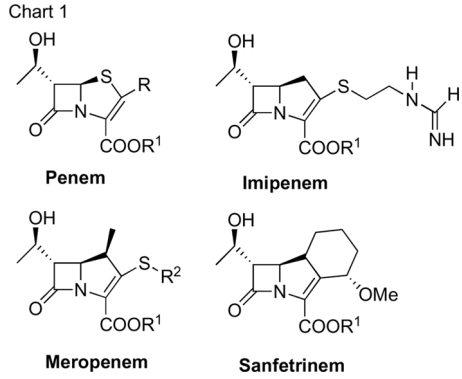
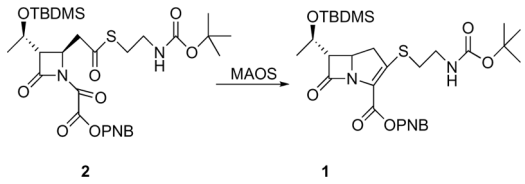


Scheme 1. Popular nontraditional β-lactam antibiotics.

From an experimental point of view, one equivalent of β-lactam-oxoamide of type **2** (Scheme 2) is treated in a high-boiling hydrocarbon solvent with several equivalents (from four to eight) of a trialkylphosphite for several hours at high temperature. Usually yields are from satisfactory to good. [Triethylphosphite (TEP) is the most popular one because of its low cost, relative low toxicity, good stability, and commercial availability, although alkyldiethoxyphosphite have been shown to be more reactive.[4,8]]

In the course of our studies on the synthesis of carbapenem antibiotics, we became interested in devising rapid cyclization of an intermediate oxalimide **2**, synthetized in our laboratory, to a bicyclic intermediate **1** (Scheme 2), taking advantage of our experience in the use of MAOS (microwave-assisted organic synthesis).[9]

The final goal of our research was to establish an easy, rapid procedure that could be adopted for a liquid-phase combinatorial synthesis of different intermediates of type **1** and a scale-up application of the resulting MAOS technology to the synthesis of Imipenem[10] and related β-lactam antibiotics (Scheme 1). As a matter of fact, MAOS has been proved to be an efficient and rapid method: dramatically reduced reaction times, increased product yields, and enhanced product purities[11,12]



Scheme 2. Cyclization mediated by microwaves.

are among the several advantages generated by this technique. On the other hand, after the discovery of thienamycin, a prototype of the well-known commercial carbapenems such as imipenem and meropenem, research on such compounds is needed to test the new compounds with molecular diversity against strains of antibiotic-resistant bacteria, including the very dangerous MRSA (methicillin-resistant *Staphylococcus aureus*).

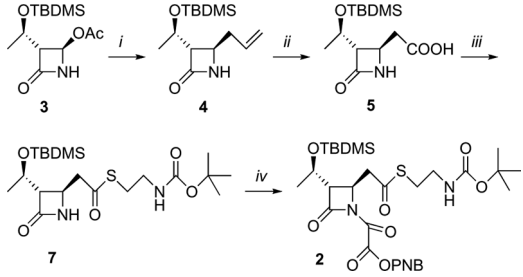
RESULTS AND DISCUSSION

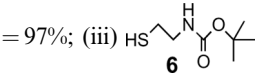
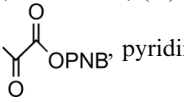
Compound **2** was prepared according to the synthetic path in the literature with slight modifications in reagents and conditions (Scheme 3).[13]

As the starting point of this study to establish reliable experimental conditions for those we were going to test by MAOS, compound **1** was prepared by classical heating (CH) using commercially available TEP as the cyclization agent. After several attempts, the best conditions in term of yields and ratios of the reagents were as follows.

Preparation of 1 from 2 by Classical Heating in a Single Step

A dry, three-necked flask, equipped with a magnetic stirrer and a reflux condenser and under a nitrogen atmosphere, was charged with the oxo-amide **2** (5.83 g, 8.9 mmol) and 264 ml of anhydrous xylene. TEP [$P(OEt)_3$] (12.3 ml, 71.7 mmol) and ρ-dihydroxybenzene (0.29 g, 2.6 mmol) were



Scheme 3. Reagents and conditions: (i) Allyl bromide, Zn (2 eq), Y% = 98; (ii) $KmnO_4$, CH_3COOH, acetone, H_2O, Y% = 97%; (iii)  DMAP (cat.), DCC, toluene Y% = 93; and (iv)  , pyridine, toluene, Y% = 81.

added, and the mixture was heated at 139 °C. The reaction mixture was stirred for 3.5 h and monitored by thin-layer chromatography (TLC) until the starting material disappeared. The reaction mixture was cooled and washed with saturated aqueous $NaHCO_3$ solution, $KHSO_4$ solution (1 M), and finally brine. The organic layer was dried, and the solvent was removed under vacuum. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2–acetone 98:2) to give **1** (1.77 g, 32.1%) as an amorphous solid (>95% purity).

Mp 54–58°C. IR (KBr) υ (cm^{-1}): 1778, 1709, 1607, 1523, 1333. ^{13}C NMR δ, 400 MHz ($CDCl_3$): −5.005, −4.311, 17.916, 22.462, 25.667, 28.319, 32.389, 40.216, 40.925, 52.170, 64.977, 65.743, 67.508, 76.684, 77.00, 77.316, 79.858, 123.623, 124.008, 127.956, 143.152, 147.558, 155.72, 160.754, 176.08. ^1H NMR δ, 400 MHz ($CDCl_3$): −0.084 (s, 6H), 0.873 (s, 9H), 1.25 (d, 3H), 1.441 (s, 9H), 2.9 (m, 1H), 3.0–3.1 (m, 2H), 3.16 (dd, 1H), 3.34 (m, 3H), 4.24 (m, 2H), 4.92 (bs, 1H), 5.20, 5.40 (AB, 2H), 7.65 (d, 2H), 8.2 (d, 2H). Anal. calcd. for $C_{29}H_{43}N_3O_8SSi$: C, 56.01; H, 6.97; N, 6.76. Found: C, 56.03; H, 6.95; N, 6.78.

Preparation of 1 from 2 by Classical Heating in a Two-Step Procedure

As for the previous procedure, the flask was charged with the oxoamide **2** (0.330 g, 0.5 mmol) and 5 ml of anhydrous toluene. TEP [$P(OEt)_3$] (0.450 ml, 3.7 mmol) was added, and the mixture was heated at 90°C under stirring for 4 h. After cooling at rt, the liquid phase was evaporated at reduced pressure by a rotavapor, the residue was dissolved in xylene (5 ml), catalytic p-dihydroxybenzene (0.04 g) was added, and the resulting mixture was heated at reflux for 1 h. The reaction mixture was cooled and washed with saturated aqueous $NaHCO_3$ solution, $KHSO_4$ solution (1 M), and finally brine. The organic layer was dried, and the solvent was removed under vacuum. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2–acetone 98:2) to give **1** (0.125 g, 40.3%) and **12** (0.022 g, 7%).

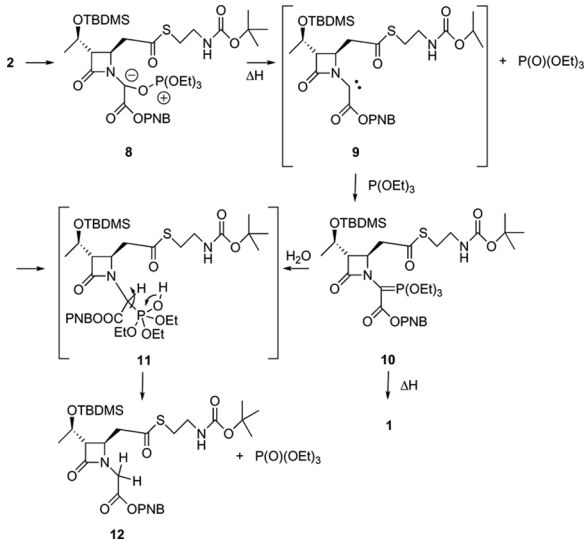
Compound **12**: oil. IR ($CHCl_3$) υ (cm^{-1}): 1750, 1708; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 5.23 (s, 2H), 4.78 (bs, 1H), 4.12 (m, 3H), 3.24 (m, 1H), 2.95 (m, 5H), 1.43 (s, 9H), 1.20 (d, J = 6 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H).

Microwave-Assisted Wittig Cyclization

To assess the ability of microwave heating to drive the cyclization as good as or possibly better than under CH conditions, we performed a series of

experiments under microwave irradiation, changing different parameters. Generally speaking, for the sake of simplicity, we decided to use a single solvent (the higher boiling xylene) and skip the removal of excess TEP (a dedicated experiment showed no significant variation in the final yield). Accordingly, a mixture of TEP (excess) and oxoamide **2** in xylene was exposed to irradiation in a sealed tube using the monomode CEM Discover and the multimode Milestone MicroSYNTH microwave ovens.

The reaction of oxamides of type **2** and excess TEP is supposed to take place[1,14] via an initial formation of the betaine **8** by a two-electron transfer from the phosphorous atom to the imides carbonyl oxygen (Scheme 4). The betaine **8**, under the thermal conditions of the reaction, generates the transition carbene **9** by elimination of triethylphosphate. In turn, carbene **9** is trapped by the excess of TEP to furnish the phosphite ylide **10**, which generates the bicyclic compound **1** via a classical intramolecular Wittig reaction. On the other end, decomposition of unreacted phosphite ylide **10** with water presumably results in the formation of the reduced product **12** (Scheme 4, path **10** ⇒ **11** ⇒ **12**). It has been reported that the formation of the ylide **10** takes place at a relatively cool temperature,[13] whereas the Wittig cyclization step needs much great temperature. With this information, we started our research studies, planning a two-step, one-pot reaction as previously described for CH on the base of different operational temperatures during the reaction cycle.



Scheme 4. Proposed mechanism for Wittig-type cyclization.

The results obtained, reported in Table 1, warrant some comments:

1. The increase of yields and the shorter reaction time from CH to DH is evident from entries 1, 2, 3, and 6 respectively. Once again, MAOS has displayed the advantages claimed.
2. There are no dramatic differences in the reaction time using monomode or multimode ovens (entries 3–5 and 6–8). However, significant differences in yields are observed. No dedicated studies on this aspect have been performed at this time.
3. Hydrocarbon solvents have been shown to be more efficient (as already known using CH) than other solvents, and xylene is better than toluene, probably because of the greater boiling point (entries 3, 6, and 9).

Table 1. Synthesis of **1** from **2** with different temperature, time, and solvent

Entry	Solvent	Temperature[a]	Heating	Yield[b] (%)
1	Toluene/xylene	90°C / 240 min then 139°C/ 60 min	CH	40.3[c]
2	Xylene	139°C / 210 min	CH	32.1
3	Xylene	115°C / 70 min then 150°C / 95 min	DH[d]	61.8
4	Xylene	115°C / 35 min then 150°C / 60 min	DH[d]	57.9
5	Xylene	115°C / 15 min then 150°C / 30 min	DH[d]	42.6
6	Xylene	115°C / 30 min then 150°C / 95 min	DH[e]	50.5
7	Xylene	115°C / 30 min then 150°C / 60 min	DH[e]	40.2
8	Toluene	80°C / 30 min then 115°C / 70 min	DH[e]	Trace
9	Toluene	115°C / 40 min then 150°C / 70 min	DH[d]	53.4
10	Toluene	150°C / 90 min	DH[d]	29.5
11	Toluene	115°C / 90 min	DH[d]	6.3
12	Cl-benzene	115°C / 65 min then 135°C / 95 min	DH[d]	45.6
13	CH_2Cl_2	50°C / 210 min	DH[d]	0
14	$CHCl_3$	65°C / 60 min	DH[d]	0
15	1,4-Dioxane	102°C / 180 min	DH[d]	0
16	DMF	153°C / 30 min	DH[d]	0

Note. A ratio of 1/8/0.20 (in mmol) of oxoamide **2**, TEP, and dihydroxybenzene was used in all the experiments reported.

[a]The reaction temperatures were reached by applying a power of 280 W for CEM monomode and 300 W for MicroSYNTH.

[b]Yields have been calculated for entries 1, 2, and 6 on pure isolated products. The yields for entries 3–5 and 6–12 were calculated by HPLC analysis by the support of a standard calibration curve. For entries 13–16, no traces of **1** were detected in HPLC analyses.

[c]The product was fully identified by standard analytical data.

[d]Monomode CEM-Discover was used as the microwave oven model.

[e]Multimode MicroSYNTH (Milestone) was used as the microwave oven model.

4. The best ratio (1/8) between oxoamide **2** and TEP has been demonstrated to be identical to that used in the CH experiment.
5. Better yields are achieved with a two-step reaction (entries 8 and 9) in accordance with Scheme 4 and related discussion.

Preparation of 1 from 2 by Dielectrical Heating (Multimode MicroSYNTH Milestone) (Table 1, Entry 6)

A mixture of **2** (0.4 mmol, 0.26 g), TEP (3.2 mmol, 0.390 ml), a catalytic amount of p-dihydroxybenzene, and xylene (0.1 mmol, 0.01 g) was irradiated in a closed system for 70 min at a temperature of 115 °C. After this period, the temperature rose to 150 °C, and irradiation was continued for an extra 95 min until high-performance liquid chromatography (HPLC) showed the disappearance of the starting material. The crude reaction mixture was cooled at rt, and the solvent was removed by rotavapor. The residue was dissolved in ethyl acetate (30 ml) and washed with an aqueous solution (5%) of 5 ml of $NaHCO_3$, 5 ml of a solution of $KHSO_4$ (1 M), and brine. The organic phase was dried, the solvent was removed, and the residue was purified by flash chromatography (methylene chloride/acetone 95/5) to give pure **1** (0.125 g, 50.5% yields).

Determination of Content/Concentration of 1 in the Crude Reaction Mixture by the *Standard Curve Method*

General

A Shimadzu LC-10AT HPLC system, HPLC columm (250×4.6 mm i.d.), and Kromasil C18 5 micrometer (Dalian Elite Analytical Instrument Co., Ltd., China) were used. All the samples were analyzed under the same conditions: mobile phase: 85% acetonitrile, 15% water; flow rate: 1 mL/min; detection wavelength: 254 nm.

Determination of Standard Curve

1. Flash-chromatography-purified **1** was crystallized and dissolved into mobile-phase solution (85% acetonitrile and 15% water). A stock standard solution of 1.00 mg/ml was prepared.
2. The series of standard solutions with different concentrations of **1** (Table 1) were obtained by diluting the stock solution into mobile-phase solution. After injection of 20-ml standard samples into the

Table 2. Standard curve calibrations

Concentration (mg/mL)	Peak area (μV^a s)
0.08	1484073
0.09	1588699
0.10	1811760
0.20	3485764
0.40	7023536
0.60	10581910
0.80	13908490

[a]μV is millivolts.

HPLC, the relative peak areas were automatically calculated by work station (Table 2).

3. The standard curve was made according to the peak areas against the relative concentrations (Fig. 1).
4. From the peak area of **1**, its amount can be calculated through the standard curve (Fig. 1).

Preparation of 1 from 2 by Dielectrical Heating (Monomode CEM) (Table 1, Entry 3 as Typical Example)

A mixture of **2** (0.1 g), TEP (0.08 ml), a catalytic amount of p-dihydroxybenzene, and xylene (2 ml) was irradiated in a closed system for 70 min at

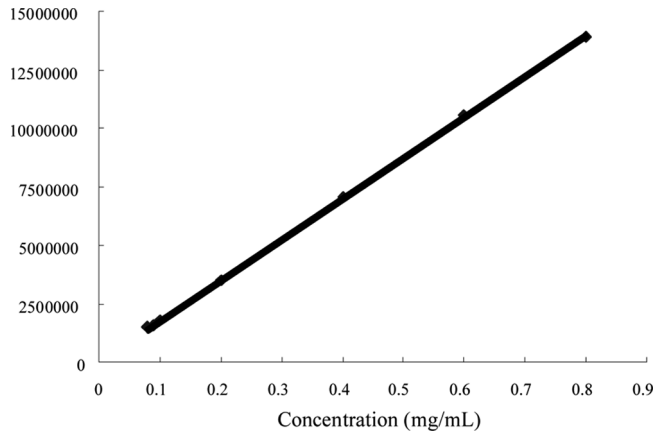


Figure 1. Standard curve calibration of **1**: $y = 2E + 07x$; correlation coefficient $R^2 = 0.9998$.

a temperature of 115 °C in a CEM Discover oven. After this period, the temperature was rose to 150 °C, and irradiation was continued for an extra 95 min until HPLC showed the disappearance of the starting material. The yields (61.8%) were calculated by HPLC on the crude reaction mixture.

CONCLUSION

In this article, we have demonstrated that the MAOS technique shows better results, in terms of yields and reaction time, than the classical CH method. The efficiency of this technique on a highly functionalized substrata confers extra value, in our opinion, to the MAOS.

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