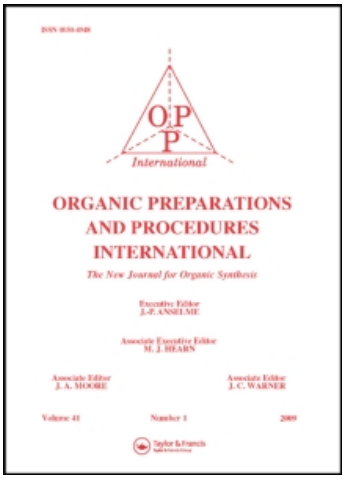

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MICROWAVE-ASSISTED SYNTHESIS OF ERYTHROMYCIN DERIVATIVES ON SODIUM ACETATE-DOPED CALCIUM CHLORIDE

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MICROWAVE-ASSISTED SYNTHESIS OF ERYTHROMYCIN DERIVATIVES ON SODIUM ACETATE-DOPED CALCIUM CHLORIDE

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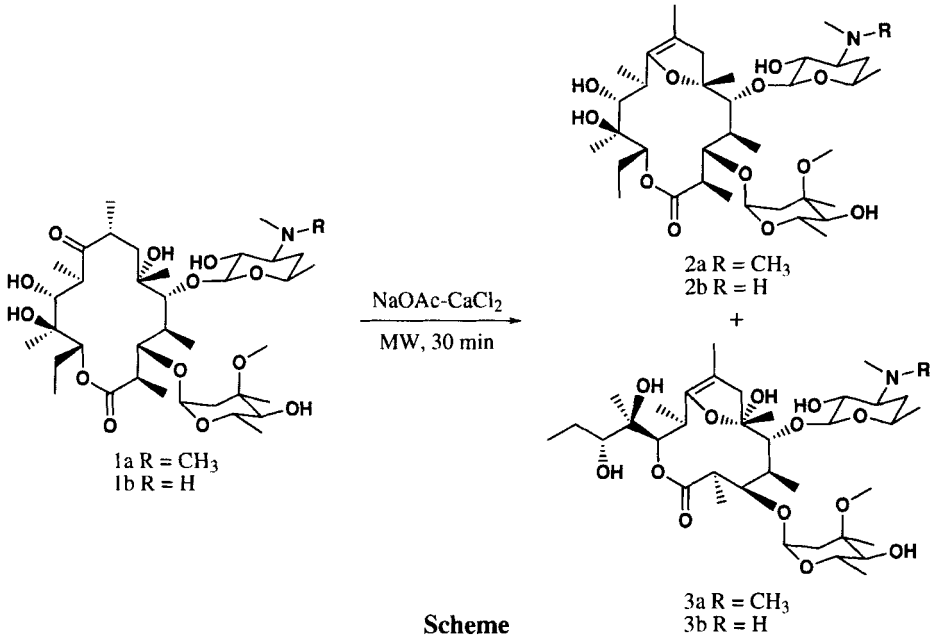
Erythromycin (**1a**) has been clinically used for more than 50 years.[1] In addition to its antimicrobial effect, the unique anti-inflammatory activity of erythromycin derivatives has been reported as a new therapeutic potential.[2] In our effort to maximize the anti-inflammatory activity of erythromycin, the derivative of erythromycin (**3a**), which exhibited potent *in vitro* anti-inflammatory activity,[3] was selected as one of our target compounds.

The conventional synthesis of **3a** involves the intramolecular transesterification of 8,9-anhydroerythromycin 6,9-hemiketal (**2a**), obtained by dehydration of **1a** dissolved in glacial acetic acid, with potassium carbonate in refluxing methanol for 90 min.[4] The overall yield of the two steps is 37%. On the other hand, compound **3a** could be prepared directly by heating **1a** at 70°C for 24 hr with a 3:1 mixture of pyridine and acetic acid to afford a mixture of **2a** and **3a** in 19% and 71% yields respectively.[5] Herein, we report a facile and straightforward synthesis of **3a** from **1a** under microwave irradiation in the absence of solvents.



Scheme

To find the optimal conditions, the reaction was carried out on various types of solid supports respectively as presented in *Table 1*. When $CaCl_2$ was used as solid support in this reaction, we found that the reaction was more efficient and **3a** could be prepared in 19% yield. In addition, the yield of **3a** increased to 24% when $CaCl_2$ was doped with NaOAc (the molar ratio of $CaCl_2$ to NaOAc was 5:1). To the best of our knowledge, the use of $CaCl_2$ as adsorbent under microwave irradiation has never been documented. We observed that the ratio of $CaCl_2$, NaOAc and water of the solid support affects the yields of **2a** and **3a**. Therefore, we examined the influence of various ratios on the yields of this reaction and found that the optimal molar ratio of $CaCl_2$, NaOAc and water is 2:1:2.4 (*Table 2*).

Table 1. Intramolecular Transesterification of **1a** under Microwave Irradiation[a]

Supports	Time (min)	Yield (%)	
		2a	**3a**
Silica gel	30	11	----
Silica gel-NaH_2PO_4	30	15	13
Silica gel-NaOAc	30	16	----
$CaCl_2$	30	27	19
$CaCl_2$-NaOAc(5 : 1)	30	30	24

a) The MW power was set at 400W and the temprature was controlled automatically at 190°C by intermittent irradiation.

Table 2. Influence of Ratio of $CaCl_2$, NaOAc, H_2O on the Yields of **2a** and **3a**[a]

$CaCl_2$:NaOAc:H_2O	Time (min)	Yield (%)	
		2a	**3a**
20 : 1: 0	30	----	----
10 : 1: 0	30	27	----
5 : 1: 0	30	30	24
2 : 1: 0	30	35	31
2 : 1: 3.5	30	34	23
2 : 1: 2.4	20	44	35
2 : 1: 2.4	30	24	52
2 : 1: 2.4	40	22	53

a) The MW power was set at 400W and the temprature was controlled automatically at 190°C by intermittent irradiation.

It was shown that the yield of compound **3a** increased steadily to 52% when the reaction time was increased to 30 min while the yield of **2a** decreased if the time of irradiation was longer than 20 min. Increasing the time to over 30 min did not affect the composition of compounds **1a**, **2a** and **3a**.

In order to verify the effect of this reaction, *N*-demethylated erythromycin A (**1b**) obtained by the treatment of **1a** with iodine and NaOAc,[6] was coated onto the surface of NaOAc-$CaCl_2$. Under the standardized reaction condition, the *N*-demethylated derivative of erythromycin A (**3b**) which has been shown to possess some anti-inflammatory activity [7] and *N*-demethylated 8,9- anhydroerythromycin A 6,9-hemiketal (**2b**) were obtained in 48% and 20% yields, respectively.

In conclusion, we found an economical and efficient method to finish the synthesis of ring-contracted derivatives of erythromycin on NaOAc-doped $CaCl_2$ *via* intramolecular dehydration and transesterification under microwave irradiation. It is to be noted that the use of water soluble $CaCl_2$ affords a facile isolation of the desired products.

EXPERIMENTAL SECTION

The reactions were carried out in a laboratorial microwave oven (XH-100) made in Beijing Xianghu Science & Technology Development Co., LTD. The reactions were conducted at a MW power setting of 400W and the temperature of the reaction mixture (190°C) was measured by an immersed platinum resistance thermometer. The temperature of the mixture was controlled at 190°C automatically by discontinuous microwave irradiation during the reactions. Melting points for the compounds were determined using a hot-stage microscope and are uncorrected. ^1H and ^{13}C-NMR spectra were obtained in $CDCl_3$ solution on Bruker ARX-300 spectrometers with TMS as the internal reference. MS spectra were acquired using JMS-DX300 spectrometer. Column chromatography was performed on silica gel (200-300 mesh) from Qingdao Ocean Chemicals. Unless otherwise noted, all the materials were obtained from commercially available sources and were used without purification.

Ring-contracted Derivative of Erythromycin (3a). Typical Procedure.- Anhydrous $CaCl_2$ (2.0g, 18.20mmol) and anhydrous NaOAc (0.75g, 9.15mmol) were dissolved in water (5 mL) and dried in a drying oven at 90°C for about 48 hr (till the weight of the mixture was about 3.14g and the molar ratio of $CaCl_2$ to NaOAc to H_2O was found to be 2:1:2.4). To a solution of erythromycin A (0.2 g, 0.27mmol) in EtOAc (10 mL), 2g of the solid support was added. EtOAc was removed under reduced pressure until the mixture was powdery. Then the mixture was irradiated three times under microwave at 400W, 190°C for 10 min. After cooling, H_2O (20 mL) was added and the solution was extracted with chloroform (3 x 10 mL), washed with saturated brine, and dried over anhydrous Na_2SO_4, filtered and the organic phase was evaporated to dryness. The resulting crude product was purified by column chromatography on silica gel eluting with chloroform-methanol-ammonium hydroxide solution (10:0.5:0.01 to 10:1:0.05) to give compound **2a** (0.047g, 24%) and compound **3a** (0.10g, 52%) as a white amorphous solid respectively.

3a: mp. 127-130°C, *lit.*[3] mp. 126-130°C; IR(KBr): 3509.8, 2973.7, 2937.1, 2877.3, 1702.8, 1457.9, 1380.8, 1319.1, 1256.1, 1166.7, 1114.7, 1076.1, 1049.1, 1016.3 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 2.83(dd, 1H, J = 10.0, 7.0), 4.27(dd, 1H, J = 10.0, 3.0), 1.76(ddq, 1H, J = 3.0, 9.5, 7.0), 3.70(d, 1H, J = 9.5), 2.78(AMX, 1H, J = 16.0, 1.5), 2.03(AMX, 1H, J = 16.0, 1.5), 2.93(dq, 1H, J = 2.7,

7.0), 5.06(d, 1H, *J* = 2.7), 2.83(dd, 1H, *J* = 10.0, 2.5), 1.68(m, 1H), 1.36(m, 1H), 0.98(d, 3H, *J* = 7.0), 1.27(s, 3H), 1.10(d, 3H, *J* = 7.0), 1.42(s, 3H), 1.55(br s, 3H), 1.22(d, 3H, J = 7.1), 1.20(s, 3H), 4.33(d, 1H, J = 7.0), 3.20(dd, 1H, J = 7.0, 10.0), 2.48(m, 1H), 1.68(m, 1H), 1.26(m, 1H) , 3.48(m, 1H), 1.19(d, 3H, J = 7.0), 2.29(s, 6H), 4.89(d, 1H, J = 7.0), 2.38(dd, 1H, J = 10.0, 7.0), 1.51(dd, 1H, J = 10.0, 7.0), 3.03(d, 1H, J = 9.5), 4.07(m, 1H), 1.33(m, 3H), 1.21(s, 3H), 3.28(s, 3H); ^{13}C-NMR ($CDCl_3$): δ 175.72, 46.56, 80.20, 38.49, 81.22, 85.77, 43.15, 101.04, 149.34, 31.41, 77.49, 76.28, 77.23, 22.27, 11.68, 14.94, 9.13, 26.49, 10.80, 11.05, 16.39, 103.61, 70.69, 65.03, 28.57, 68.64, 21.01, 40.06, 97.27, 34.95, 72.44, 77.83, 65.07, 21.21, 49.11, 18.12; HRMS (FAB) m/z: Calcd for $C_{37}H_{66}NO_{12}$ $[M+H]^+$716.4585. Found 716.4581.

The *N*-demethylated ring-contracted derivative of erythromycin (**3b**) was obtained in the similar way as **3a**.

3b: mp. 190-193°C, *lit.*[8] mp. 193-195°C; IR(KBr): 3311.2, 2969.8, 2931.3, 2861.8, 1706.7, 1459.8, 1378.9, 1263.1, 1166.7, 1128.2, 1097.3, 1074.2, 1037.5, 1018.2 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.80(dd, 1H, J = 10.0, 7.0), 4.23(dd, 1H, J = 10.0, 2.8), 1.78(ddq, 1H, J = 2.8, 9.5, 7.0), 3.78(d, 1H, J = 9.5), 2.74(AMX, 1H, J = 14.6, 1.5), 2.05(AMX, 1H, J = 14.6, 1.5), 3.05(m, 1H), 5.10(d, 1H, J = 2.6), 2.87(dd, 1H, J = 10.0, 2.5), 1.71(m, 1H), 1.36(m, 1H), 1.00(d, 3H, J = 7.0), 1.28(s, 3H), 1.11(d, 3H, J = 7.0), 1.43(s, 3H), 1.62(br s, 3H), 1.22(d, 3H, J = 7.0), 1.24(s, 3H), 4.37(d, 1H, J = 7.0), 3.25(dd, 1H, J = 7.0, 10.0), 2.51(m, 1H), 1.82(m, 1H), 1.28(m, 1H), 3.59(m, 1H), 1.20(d, 3H, J = 7.0), 2.38(s, 3H), 4.95(d, 1H, J = 7.2), 2.37(dd, 1H, J = 10.0, 7.2), 1.41(dd, 1H, J = 10.0, 7.2), 3.06 (d, 1H, J = 9.5), 4.12(m, 1H), 1.34(m, 3H), 1.24(s, 3H), 3.28(s, 3H); ^{13}C-NMR ($CDCl_3$): δ 175.8, 46.76, 80.25, 38.51, 81.67, 86.00, 43.22, 101.29, 149.56, 31.56, 77.47, 76.53, 77.20, 22.50, 11.88, 15.08, 9.89, 26.58, 11.06, 11.23, 16.53, 103.27, 74.41, 60.00, 36.84, 68.59, 20.95, 32.92, 97.38, 35.11, 72.44, 77.97, 65.27, 18.27, 21.42, 49.29; HRMS (FAB) m/z: Calcd for $C_{36}H_{63}NO_{12}Na$ $[M+Na]^+$724.4248. Found 724.4230.

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IODINE AS AN EFFICIENT CATALYST FOR THE SYNTHESIS OF BENZIMIDAZOLES AND IMIDAZOLINES FROM PRIMARY ALCOHOLS AND DIAMINES

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Benzimidazoles and imidazolines are very useful intermediates for the development of molecules of pharmaceutical or biological interest. Substituted benzimidazole derivatives have found applications in diverse therapeutic areas including antiulcers, antihypertensives, antivirals, antifungals, anticancers, and antihistaminics to name just a few.[1] In addition, imidazoline units are also used as synthetic intermediates, chiral auxiliaries, chiral catalysts and ligands for asymmetric catalysis.[2] Due to their wide range of pharmacological activity, industrial and synthetic applications, a number of methods have been reported for the synthesis of benzimidazoles and imidazolines, which include preparation from esters using aluminium organic reagents as the catalyst,[3a] the reaction between *N*-ethoxycarbonylthioamides with 1,2-diamines,[3b] and the reaction of aldehydes with 1,2-diamines followed by *N*-halosuccinimides (X = Cl, Br, I).[3c] Recently, several methods have been developed, where azalactones,[4a] 2-aryl-1,1-dibromoethanes,[4b] nitriles[4c] and amino amides[4d] have been used as starting materials for this synthesis. However, many of the synthetic protocols suffer from disadvantages, such as requring anhydrous[4a] or harsh reaction conditions,[3a] prolonged reaction times,[3c] use of metals and expensive reagents,[3a] etc.

Recently, molecular iodine[5] has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations to afford the corresponding