A Rapid and Cheap Synthesis of Cephalosporins

Mazaahir Kidwai,* Kumar Ranjan Bhushan, and Preeti Misra
Department of Chemistry, University of Delhi, Delhi 110007, India

(Received March 1, 1999; CL-990135)

A fast, cheap and pollution free microwave assisted method for the synthesis of cephalosporin and its comparison with conventional method in terms of yield and reaction time were described.

Cephalosporins are the most versatile class of antibiotics in use throughout the world. Thousands of patents have been obtained for cephem derivatives. Even so, continuous efforts are being made by scientists for synthesizing new cephem derivatives or for altering the methodologies of previously reported drugs in order to reduce production cost and increased efficiency. Recently, chemists have been adopting domestic microwave ovens as a useful laboratory instrument for carrying out reactions in a non-classical way. Microwave-irradiated reactions have been carried out in the solid phase and in sealed or open vessels.[1] In view of the importance of MORE (Microwave induced organic reaction enhancement) techniques for rapid, safe, less expensive synthesis and biological importance of cephem derivatives, it was thought worthwhile to develop a method for ecofriendly synthesis of title compounds using microwaves.[2]

A literature review shows that most of the synthetic strategies have been patented, and coupling of 7-ACA with a heterocyclic thiol[3] in the presence of sodium bicarbonate at a pH 6.0-7.0 requires 23 h[4] to 6 days.[5] Modification in the earlier method using phosphate buffer at pH 6.4 (48 h)[6] and BF_3 etherate is also reported.[7] The reaction time for coupling in aqueous medium is about 16-23 h that reduced productivity in industry. Usage of organic medium[8] like trifluoro acetic acid, boron trifluoride in acetic acid or in acetonitrile, while reducing reaction time is not desirable because of high cost and environmental polluting effluent.

Keeping this in view, we report herein a fast, cheap and pollution free microwave assisted method[9] for the synthesis of 7-amino-3-{[5-(hydro/5-methyl-1,3,4-thiadiazol-2-ylthio/ tetrazol-1-yl/quinolin-8-yloxy/4-methyl quinolin-2-yloxy) methyl]-1,3,4-thiadiazol-2-ylthiomethyl}-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acids **3a-e** and its comparison with conventional method in terms of yield and reaction time.

7-ACA was condensed with 5-[(hydro/5-methyl-1,3,4-thiadiazol-2-ylthio/tetrazol-1-yl/quinolin-8-yloxy/4-methyl-quinolin-2-yloxy)methyl]-1,3,4-thiadiazol-2-thiols **2a-e**[9e] in aqueous ammonia to afford the title compounds and the reaction was monitored by the disappearance of starting material on reverse phase HPLC, ^1H NMR spectra also showed the characteristic peaks of cepham skeleton, two doublets at 3.4 and 3.7 corresponding to 2-CH_2 protons with J = 17.0 Hz. Two another doublet at 4.74 and 4.95 with J = 5.0 Hz were assigned to hydrogen attached to C-6 and C-7 respectively revealed cis stereochemistry. Under microwave irradiation, the reaction time has been brought down from hours to minutes with improved yields as compared to the conventional heating (Table 1). Cephalosporin **3a** is a precursor for an antibiotic cefazolin sodium.[10]

Table 1.

Compd No.	R	MWI method	Conventional method
		Yield (%) / time (min)	Yield (%) / time (h)
3a	H	84 / 8.0	67 / 4.5
3b	MTD	85 / 7.5	62 / 4.0
3c	TZA	80 / 6.0	58 / 4.5
3d	8HQ	82 / 7.5	60 / 4.0
3e	CAR	81 / 8.5	73 / 5.0

7-ACA (0.01 mol), 5-substituted-1,3,4-thiadiazol-2-thiol (0.01 mol) and 25% aq. NH_3 (5 ml) were taken in Erlenmeyer flask (100 ml) and stirred to get a clear solution. The reaction mixture was subjected to microwave irradiation (MWI) at 450 watts. Reaction was monitored by HPLC after every half min. On completion of the reaction, the aq.

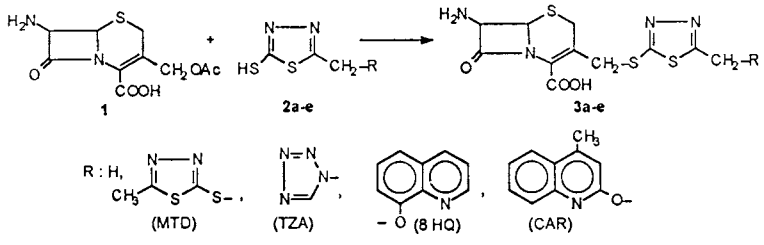

Figure 1.

layer was treated with 2 g activated charcoal for 10 min at 35 °C. After removing charcoal, the filtrate was acidified with 3N HCl to bring its pH down to 4.0. The solid separated was cooled to 5 °C, filtered, washed with acetone and dried in a vacuum oven at 30-35 °C. The product **3a** was identical to a commercial sample as varified by 400 MHz ^{1}H NMR and HPLC analysis. The products **3b-e** were characterized by analytical and spectral data.[11]

The authors are thankful to Council of Scientific and Industrial Research, New Delhi for financial assistance.

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11 Spectral and analytical data for **3b** : mp >300.0 °C. ^{1}H-NMR (DMSO-d_6+$CDCl_3$, 400 MHz) δ 2.67 (s, 3H, CH_3), 3.40 (d, 1H, 2-CH, J=17.0 Hz), 3.70 (d, 1H, 2-CH, J=17.0 Hz), 4.43 (s, 2H, SCH_2), 4.56 (s, 2H, SCH_2), 4.74 (d, 1H, 6-CH, J=5.0 Hz), 4.96 (d, 1H, 7-CH, J=5.0 Hz), 5.10 (br, 2H, NH_2). Found : C, 35.41; H, 2.95; N, 17.70%. Calcd for $C_{14}H_{14}N_6O_3S_5$: C, 35.44; H, 2.95; N, 17.72%.

3c : mp 282.0-283.0 °C (decomp). ^{1}H-NMR (DMSO-d_6+$CDCl_3$, 400 MHz) δ 3.42 (d, 1H, 2-CH, J=17.0 Hz), 3.70 (d, 1H, 2-CH, J=17.0 Hz), 4.45 (s, 2H, SCH_2), 4.50 (s, 2H, NCH_2) 4.74 (d, 1H, 6-CH, J=5.0 Hz), 4.95 (d, 1H, 7-CH, J=5.0 Hz), 5.05 (br, 2H, NH_2), 8.9 (s, 1H, H-5 of tetrazole ring). Found : C, 34.96; H, 2.91; N, 27.20%. Calcd for $C_{12}H_{12}N_8O_3S_3$: C, 34.95; H, 2.91; N, 27.18%.

3d : mp 290.0-291.0 °C (decomp). ^{1}H-NMR (DMSO-d_6+$CDCl_3$, 400 MHz) δ 3.4 (d, 1H, 2-CH, J = 17.0 Hz), 3.72 (d, 1H, 2-CH, J=17.0 Hz), 4.4 (s, 2H, SCH_2), 4.55 (s, 2H, OCH_2), 4.75 (d, 1H, 6-CH, J=5.0 Hz), 4.96 (d, 1H, 7-CH, J=5.0 Hz), 5.10 (br, 2H, NH_2), 7.14-7.54 (m, 4H, Ar-H), 8.15 (d, 1H, 4-Ar-H), 8.78 (d, 1H, 2-Ar-H). Found : C, 49.30; H, 3.50; N, 14.38%. Calcd for $C_{20}H_{17}N_5O_4S_3$: C, 49.28; H, 3.49; N, 14.37%.

3e : mp >300.0 °C. ^{1}H NMR (DMSO-d_6+$CDCl_3$, 400 MHz) δ 2.3 (s, 3H, CH_3), 3.35 (d, 1H, 2-CH, J=17.0 Hz), 3.74 (d, 1H, 2-CH, J=17.0 Hz), 4.48 (s, 2H, SCH_2), 4.56 (s, 2H, OCH_2), 4.76 (d, 1H, 6-CH, J=5.0 Hz), 4.96 (d, 1H, 7-CH, J=5.0 Hz), 5.10 (br, 2H, NH_2), 6.82 (s, 1H, 3-Ar-H), 7.26 (t, 1H, 6-Ar-H), 7.59 (t, 1H, 7-Ar-H), 7.61 (d, 2H, 5,8-Ar-H). Found : C, 50.30; H, 3.79; N, 13.95%. Calcd for $C_{21}H_{19}N_5O_4S_3$: C, 50.29; H, 3.79; N, 13.97%.