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A practical synthesis of deuterium-labeled cefuroxime

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CONTENTS

Experimental

General

Methoxyl-d_3-amine hydrochloride was purchased from Toronto Research Chemicals (TRC). All other commercially available solvents were used without further purification. ^{1}H NMR spectra was recorded with a Bruker ARX-400 spectrometer (400 MHz for ^{1}H NMR) using TMS as internal standard (chemical shifts in δ values, J in Hz). Mass spectrometry was carried out with an Agilent-6120 Quadruple LC/MS *via* a direct inlet probe in ESI mode. Chemical purity was determined with an Agilent 1200 HPLC with a Zorbax Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (Agilent Technologies). Column chromatography was performed on silica gel (200-300 mesh) (Qingdao Haiyang Chemical Ltd.). Analytical TLC was performed on plates precoated with silica gel (GF254, 0.25 mm) (Qingdao Haiyang Chemical Ltd.) and iodine vapor was used to develop color on the plates.

d$_3$-*(2Z)-2-(2-Furyl)-2-(methoxyimino)acetic acid* **3**.

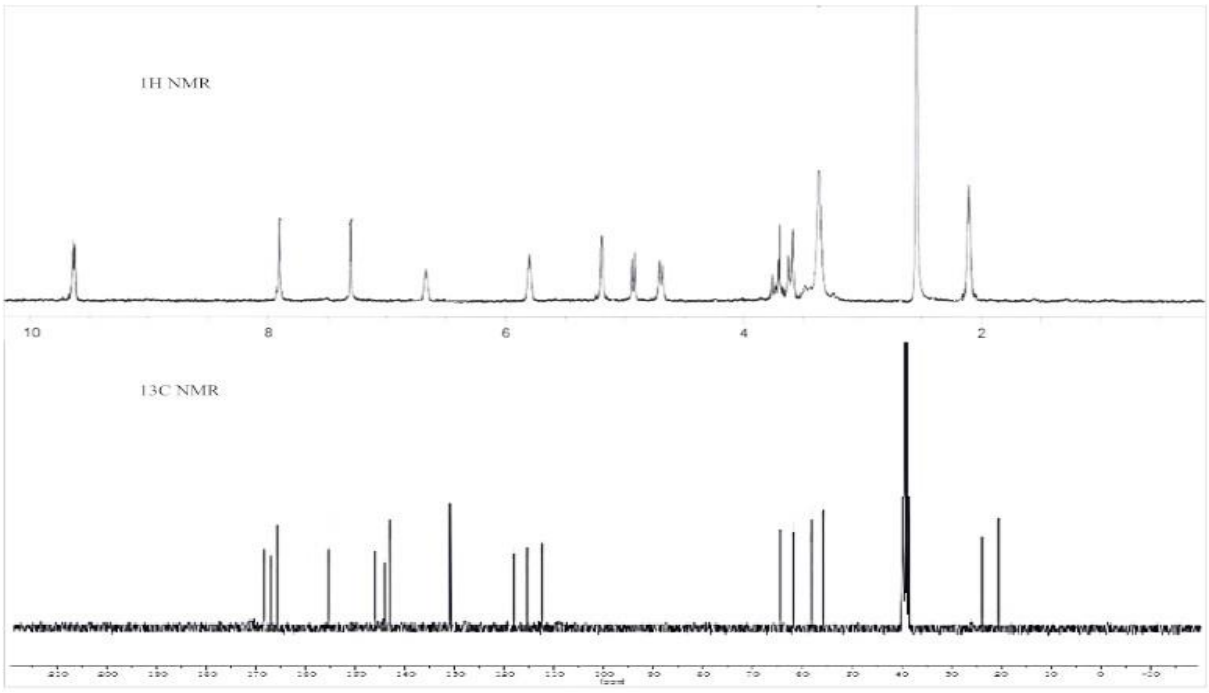
A solution of 2-(2-furyl)-2-oxoacetic acid **2** (2.80 g, 20.0 mmol), methoxyl-d_3-amine hydrochloride (1.73 g, 20.0 mmol), anhydrous K_2CO_3 (6.00 g, 44.0 mmol) in 50 ml of ethanol was stirred at reflux for 6 h. The reaction mixture was concentrated and the residue was diluted with 20 ml H_2O. Hydrochloric acid (2M) was added to adjust pH 6. The resulting solution was extracted with EtOAc (3 × 20 ml). The combined organic phase was washed with brine (20 ml), dried over anhydrous $MgSO_4$, concentrated under reduced pressure to afford a *E*/*Z* mixture of acid **3** as a yellow solid (2.96 g, 86%). Recrystallization from benzene gave the pure isomer (*Z*)-acid **3** as a white solid (2.26 g, 66%). MS-EI (m/z): 173.1 ($M+H^+$).

d$_3$-*(2Z)-2-(2-Furyl)-2-(methoxyimino)acetyl chloride* **4**.

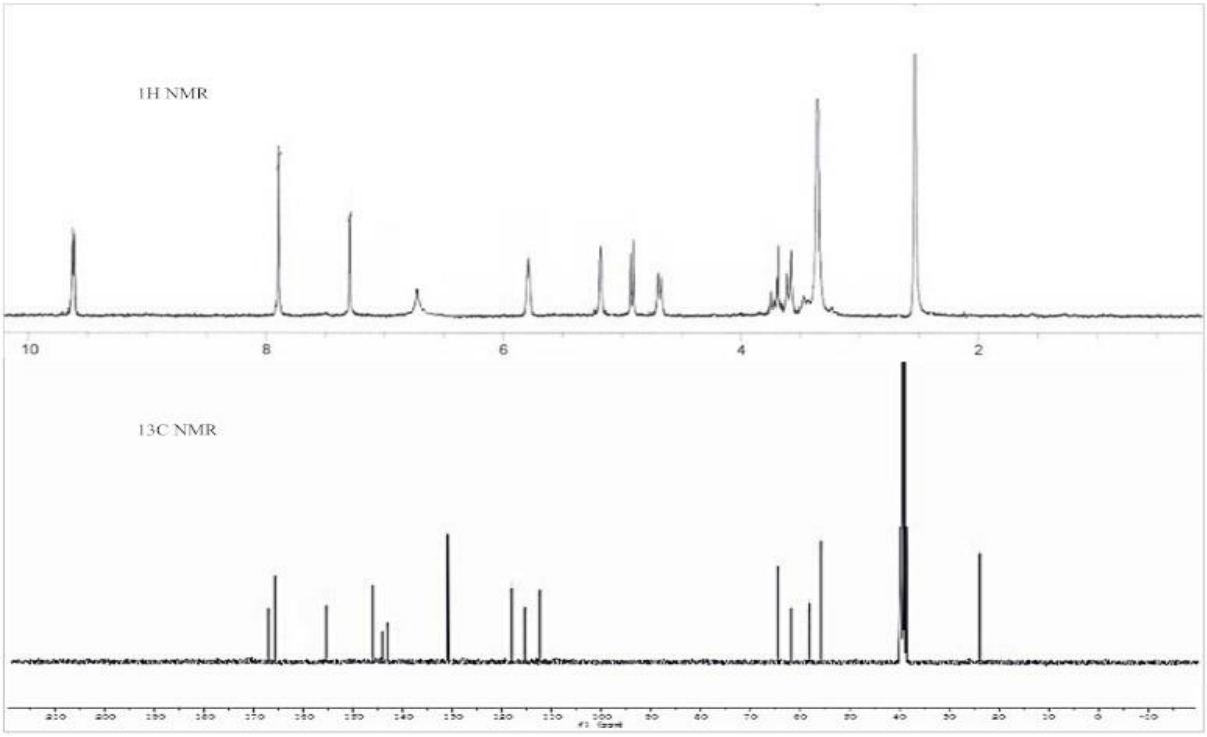
To a solution of (*Z*)-acid **3** (2.26 g, 13.1 mmol) in CH_2Cl_2 (30 ml) was added dropwise oxalyl chloride (2.48 g, 19.6 mmol). Two drops of DMF were added, and gas started to evolve immediately. The reaction mixture was stirred at room temperature for 5 h. The resulting mixture was evaporated to give crude product **4** as a light yellow oil (2.40 g, 96%), which was used directly in the next step without further purification.

d$_3$-*(6*R,*7*R*)-3-Acetoxymethyl-7-[(2*Z*)-2-(2-furyl)-2-(methoxyimino)acetylamino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid* **5**.

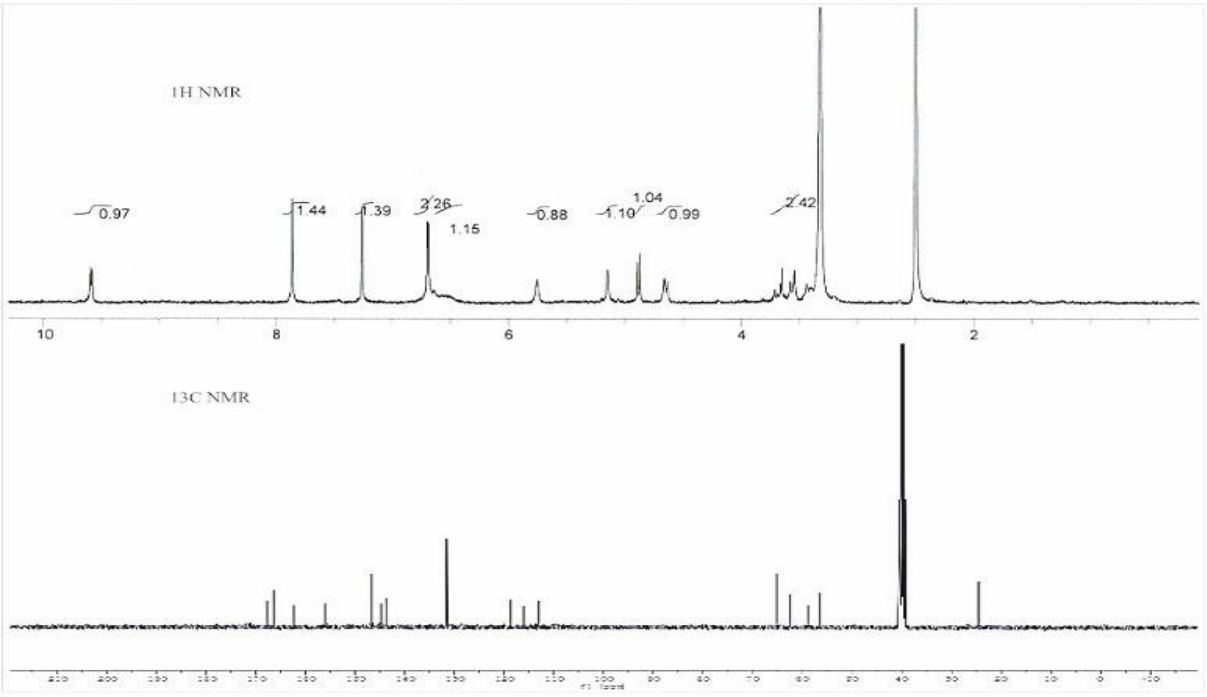
A solution of 7-ACA (3.05 g, 11.2 mmol), *N*,*N*-diisopropyl-*N*-ethylamine (1.48 g, 11.5 mmol) in CH_2Cl_2 (50 ml) was stirred at -10 ^oC for 20 min. To this solution, compound **4** (2.40 g, 12.6 mmol) in CH_2Cl_2 (10 ml) was added dropwise under stirring over 30 min. The reaction mixture was stirred at room temperature for 5 h. The resulting mixture was diluted with CH_2Cl_2 (50 ml) and washed successively with 1% hydrochloric acid solution (3 × 30 ml), saturated $NaHCO_3$ solution (30 ml), and brine (2 × 30 ml). The organic layer was dried with anhydrous $MgSO_4$ and then concentrated under reduced pressure to give a brown residue, which was purified by chromatography on a silica gel column (CH_2Cl_2 : MeOH, 30 : 1 → 5 : 1) to afford 3.20 g (67%) of product **5** as a yellow solid. MS-EI (m/z): 427.1 ($M+H^+$), ^1H NMR (DMSO-d_6): δ = 13.72 (br. s, 1H, -COOH), 9.68 (d, 1H, -OCH=, *J* 7.8 Hz), 7.91 (d, 1H, -OCH=, *J* 1.5 Hz), 7.28 (m, 1H, =CH-), 6.68 (br. s, 1H, -NH-), 5.84 (dd, 1H, -COC<u>H</u>(-NH-)-, *J* 4.4, 7.8 Hz), 5.25 (d, 1H, -(-NH-)C<u>H</u>S-, *J* 3.4 Hz), 4.91-4.97 (m, 2H, -CH_2O-), 3.45-3.60 (m, 2H, -SCH_2-). 2.12 (s, 3H, CH_3CO-). ^{13}C NMR (DMSO-d_6): δ = 168.5, 167.3, 166.8, 155.0, 147.1, 145.2, 144.1, 131.9, 119.1, 115.7, 113.6, 66.1, 62.9, 59.5, 56.1, 24.9, 20.7.



Graphical presentation of ^1H NMR and ^{13}C NMR spectra of compound **5**.



Graphical presentation of ^{1}H NMR and ^{13}C NMR spectra of compound **6**.



Graphical presentation of ^{1}H NMR and ^{13}C NMR spectra of cefuroxime-d_3 **1**.