

Synthesis of ω -(1,1,3-trioxo-1,3-dihydrobenzo[*d*]isothiazol-2-yl)-alkanecarboxylic acids: conventional versus microwave heating

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Dedicated to Prof. J. Bosch

Abstract

The alkylation of sodium saccharin with alkyl halides to produce the intermediates ω -(1,1,3-trioxo-1,3-dihydrobenzo[*d*]isothiazol-2-yl)-alkanecarboxylic acids can be markedly improved by using microwave irradiation, both in terms of product yield and reaction time. While the process produces high yields with halo esters and halonitriles, the reaction with haloacids, which proceeds smoothly by conventional reflux, gives poorer yields with microwaves. This is due to an acid-base equilibrium produced by the rapid heating of the mixture under irradiation. Esters and nitriles can be converted into the acids by acid hydrolysis, without appreciable loss of the 1,1,3-trioxo-1,3-dihydrobenzo[*d*]isothiazole ring.

Keywords: ω -(1,1,3-Trioxo-1,3-dihydrobenzo[*d*]isothiazol-2-yl)-alkanecarboxylic acids, saccharin alkylation, microwaves

Introduction

Saccharin (1,1,3-trioxo-1,3-dihydrobenzo[*d*]isothiazole) (**1**) was discovered in 1879 and is the most widely known benzisothiazole derivative and the first non-carbohydrate sweetening agent.¹ The 1,1,3-trioxo-1,3-dihydrobenzo[*d*]isothiazol-2-yl fragment has been used in medicinal chemistry and is present in several drug molecules, e.g., Ipsapirone **2**,² and in some derivatives used as intermediates in the preparation of endothelin antagonists³ and human leucocyte elastase inhibitors.⁴ Recently, acids incorporating the ω -(1,1,3-trioxo-1,3-dihydrobenzo[*d*]isothiazol-2-yl) alkaneacyl moiety have been used to obtain a new family of non-hepatotoxic acetaminophen analogues.⁵ In addition, (1,1,3-trioxo-1,3-dihydrobenzo[*d*]isothiazol-2-yl)acetic acid **5a** has been described, with associated inhibitory activity versus aldose reductase,⁶ while its methyl ester⁷ has been used as an intermediate in the preparation, through a base-catalysed ring expansion,⁸ of

anti-inflammatory drugs such as piroxicam⁹ and isoxicam.¹⁰ Related alkanolic acids have been prepared and tested as aldose reductase inhibitors¹¹ and as anti-inflammatories.¹²

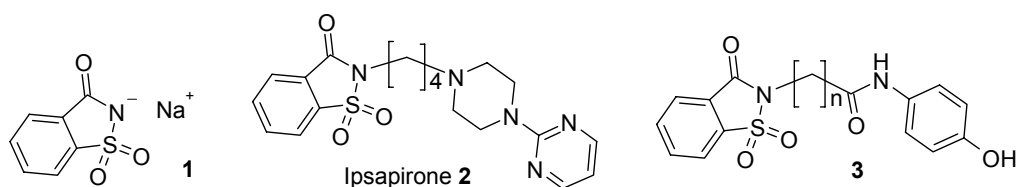


Figure 1. 1,1,3-trioxo-1,3-dihydrobenzo[d]isothiazole derivatives.

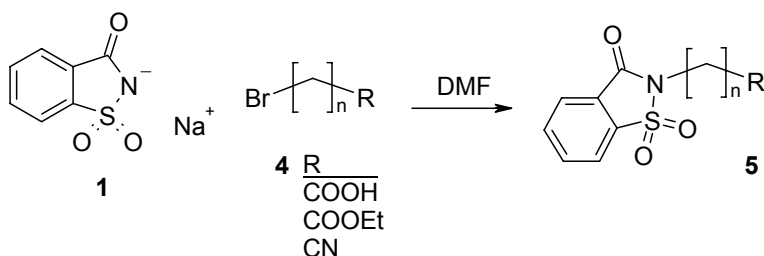
The preparation of derivatives **3**, which are analgesic acetaminophen analogues devoid of hepatotoxicity and are currently in development, requires improved synthetic methods for the corresponding acids **5a–f** or related derivatives such as the esters **5g–l** or nitriles **5m–r** (Scheme 1 and Table 1).

Examples of the N-alkylation of saccharin using microwave irradiation in dry media¹³ have been described and gave good efficiency, with the transformation completed in only a few minutes. Other N-alkylated saccharin derivatives have been obtained by microwave synthesis in DMF and were used as intermediates in the preparation of 5-HT_{1A} receptor ligands.¹⁴ In our examples, the synthesis⁵ was performed by N-alkylation, reacting sodium saccharin with several bromoderivatives **4** in DMF. The processes were performed in parallel, either by conventional reflux or, alternatively, by microwave irradiation in closed vessels.

Results and Discussion

As observed with other systems, the preparation of saccharin derivatives **5** has been more effective with regard to reaction time and yield on using microwave irradiation (Method B). In the microwave reaction with haloacids **4a–e**, however, substantial amounts of mixtures of **6** and **7** [or the corresponding salt in the case of other acids (Scheme 2), produced by an acid-base equilibrium] were detected, leading to a reduction in the overall yield of **5**. The reduction in yield is more evident in the products **5a–c**, in which low molecular weight acids are used that have higher dielectric parameters related to microwave energy absorption.^{15a}

It is not clear at which point the effect of microwaves on the mixture of sodium saccharin **1** and the halo acids **4** in DMF, a solvent that acts as the absorber medium,^{15a} can be related to a thermal effect linked to the characteristics of the acids involved.^{15b} This situation would comparatively favour the acid-base equilibrium indicated in Scheme 2 for the smaller acids, reducing the yield in the N-substitution of saccharin. Thus, conventional reflux (Method A) resulted in better yields in the cases of **5a–c**.



Scheme 1. Alkylation of sodium saccharin.

Table 1. Synthesis of ω -(1,1,3-trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)-alkanecarboxylic acids and derivatives

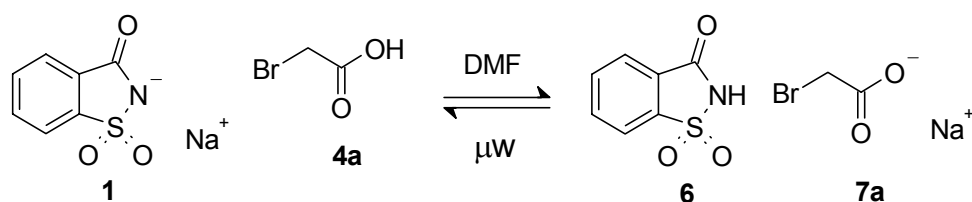
Prod.	N	R	Method A Yield (%) ^a	Method B Yield (%) ^a
5a	1	COOH	69	30
5b	2	COOH	48	41
5c	4	COOH	68	56
5d	5	COOH	85	84
5e	6	COOH	83	85
5f	7	COOH	83	96
5g	1	CO ₂ Et	83	86
5h	2	CO ₂ Et	58	64
5i^b	3	CO ₂ Et	66	87
5j	4	CO ₂ Et	71	89
5k	5	CO ₂ Et	80	93
5l	6	CO ₂ Et	54	80
5m	1	CN	66	72
5n	2	CN	34	57
5o	3	CN	82	93
5p	4	CN	37	79
5q	5	CN	83	95
5r	6	CN	78	86

Method A. Conventional reflux was performed for 3 h, at 150 °C. Method B: Microwave irradiation was performed for 5 min at 150 °C. ^aYields correspond to isolated pure compounds. ^bDescribed in ref. 5, with 66% yield after 20 h at 100 °C.

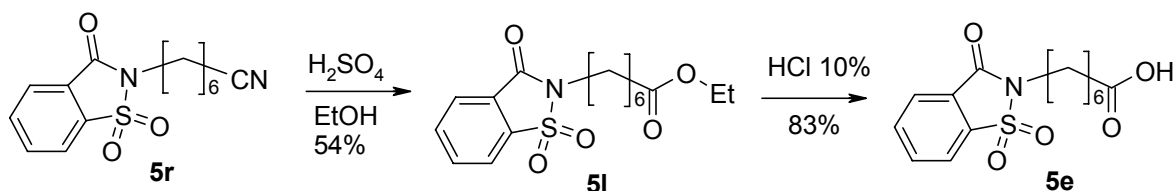
The effect described above was not observed with esters **5g–5l** and nitriles **5m–5r**, in which the microwave process was more efficient than conventional heating.

In order to assess the possible interconversion of the nitriles and esters into the acids **5e–f**, the conversion of nitrile **5r** into the ester **5l** and of **5l** into the acid **5e** was performed using acid

catalysis. The conversion was easily performed and hydrolysis of the saccharin ring was not detected (Scheme 3).



Scheme 2. Acid-base equilibrium on microwave irradiation.



Scheme 3. Conversion of nitrile **5r** into ester **5l** and acid **5e**.

In conclusion, the alkylation of sodium saccharin (**1**) with halides **4** to produce derivatives **5** can be markedly improved by using microwave irradiation, both in terms of product yield and reaction time. The reaction with haloacids, however, which is very convenient under conventional reflux, produces poorer yields with microwaves – especially with the shorter acids – due to an acid-base equilibrium process competing with N-alkylation. Esters and nitriles can be converted into the acids by acid hydrolysis, without appreciable loss of the 1,1,3-trioxo-1,3-dihydrobenzo[d]isothiazole ring.

Experimental Section

General Procedures. All melting points were measured in capillary tubes and are uncorrected. IR spectra were determined on KBr disks using a Nicolet Impact 410 spectrophotometer. 1H NMR spectra were obtained at 200 MHz (1H) and 125 MHz (^{13}C) using Varian Gemini 200 and Unity Plus spectrometers. Chemical shifts (δ) were determined using TMS as internal standard, and multiplicity (s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet) and coupling constants are indicated for each signal. HPLC-MS analyses were performed on an Agilent 1100 apparatus. A Luna C18 (150×4.6 mm) 5 μm Phenomenex chromatographic column was used, with a mobile phase formed by a triple gradient of 4% aq. formic acid (A), water (B) and acetonitrile (C). The gradient started as A (2.5%), B (93%) and C (4.5%) and in 30 min reached A (2.5%), B (4.5%) and (93%). In the mass detector, the fragmenter operated at 70 eV. Elemental analysis was performed on a LECO CHNS-932 instrument. All reactions were

performed using DMF dried by routine procedures. Conventional reflux was performed in parallel with a Radley Carousel Reaction Station. MW irradiation was performed with a CEM Discover unit, using sealed 10 ml tubes, with magnetic stirring, and temperature control was fixed at 150 °C. All yields correspond to isolated pure compounds.

Method A. Conventional heating

A mixture of 0.05 mol of anhydrous sodium saccharin and 0.05 mol of the corresponding compound **4**, in 25 mL of dry DMF, was heated under reflux for 4 h. The solvent was evaporated to dryness, ice-water (10 ml) was poured into the residue and the corresponding acid derivative **5** precipitated. The products were recrystallized from the solvent indicated.

Method B. Microwave heating

A mixture of 0.01 mol of anhydrous sodium saccharin and 0.01 mol of the corresponding compound **4** in 1 mL of dry DMF was placed in a closed cylindrical quartz tube (\varnothing 1cm). The reaction mixture was then magnetically stirred and irradiated in a microwave oven at 150 °C for 5 min. The mixture was cooled, ethyl acetate (3 mL) was added and the mixture was washed with water (5 mL). The organic layer was separated, dried over Na₂SO₄, filtered and concentrated to dryness. The products were recrystallized from the solvent indicated.

(1,1,3-Trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)acetic acid (5a). Yield: 69% (A), 30% (B).

Mp 212–215 °C (MeOH/Et₂O) (lit. 212–215 °C^{16,17}). ¹³C-NMR (125 MHz, CD₃OD): 169.4, 160.3, 139.1, 136.6, 135.9, 128.2, 126.1, 122.3, 39.6. MS (ESI⁺): *m/z*: 242 (M + 1).

(1,1,3-Trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)propionic acid (5b). Yield: 48% (A), 41% (B). Mp 164–165 °C (MeOH/Et₂O) (lit. 155–166 °C¹⁸). ¹³C-NMR (125 MHz, CD₃OD): 173.8, 160.1, 139.0, 136.4, 135.8, 128.2, 126.0, 122.0, 35.6, 33.6. MS (ESI⁺): *m/z*: 256 (M + 1).

(1,1,3-Trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)pentanoic acid (5c). Yield: 68% (A), 56% (B). Mp 116–118 °C (H₂O/AcOEt) (lit. 117–118 °C¹⁸). ¹³C-NMR (125 MHz, CD₃OD): 177.0, 160.4, 139.0, 136.3, 135.8, 128.3, 126.0, 122.0, 39.6, 34.1, 28.8, 23.1. MS (ESI⁺): *m/z*: 284 (M + 1).

(1,1,3-Trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)hexanoic acid (5d). Yield: 85% (A), 84% (B). Mp 95 °C (H₂O/AcOEt) (lit. 96–97 °C¹⁸). ¹³C-NMR (125 MHz, CD₃OD): 177.0, 160.4, 139.0, 136.3, 135.8, 128.3, 126.0, 122.0, 39.6, 34.1, 28.8, 23.1. MS (ESI⁺): *m/z*: 298 (M + 1).

(1,1,3-Trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)heptanoic acid (5e). Yield: 83% (A), 85% (B). Mp 100–101 °C (CH₂Cl₂/hexane). IR (KBr, cm⁻¹): 3434, 2941, 1731, 1707, 1595, 1463, 1334, 1264, 1184, 1061, 752, 677. ¹H-NMR (200 MHz, CDCl₃): 8.06–8.04 (m, 1H); 7.93–7.79 (m, 3H); 3.77 (t, 2H, J = 7.32 Hz); 2.35 (t, 2H, J = 7.32 Hz); 1.85 (q, 2H, J = 7.1 Hz); 1.65 (q, 2H, J = 6.95 Hz); 1.44–1.41 (m, 4H) ppm. ¹³C-NMR (125 MHz, CD₃OD): 177.5, 160.4, 139.1, 136.3, 135.7, 128.3, 125.9, 122.0, 40.0, 34.7, 29.5, 29.2, 27.4, 25.8. MS (ESI⁺): *m/z*: 312 (M + 1). Anal. Calcd. for C₁₄H₁₇NO₅S: C, 53.71; H, 5.31; N, 4.52. Found: C, 54.01; H, 5.50; N, 4.50.

(1,1,3-Trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)octanoic acid (5f). Yield: 83% (A), 96% (B). Mp 67 doublet of –68 °C (MeOH/Et₂O) IR (KBr, cm⁻¹): 2938, 2863, 1718, 1465, 1412,

1323, 1258, 1223, 1186, 1060, 980, 748. ¹H-NMR (200 MHz, CD₃OD): 8.08–7.91 (m, 4H); 3.75 (t, 2H, J = 7.34 Hz); 2.28 (t, 2H, J = 7.34 Hz); 1.81 (q, 2H, J = 6.97 Hz); 1.60 (q, 2H, J = 6.60 Hz); 1.50–1.32 (m, 4H) ppm. ¹³C-NMR (125 MHz, CD₃OD): 177.7, 160.4, 139.1, 136.3, 135.7, 128.3, 125.9, 122.0, 40.0, 35.0, 30.0, 29.7, 29.3, 27.5, 26.0. MS (ESI⁺): *m/z*: 326 (M + 1). Anal. Calcd. for C₁₅H₁₉NO₅S: C, 55.37; H, 5.89; N, 4.30; Found: C, 55.69; H, 6.11; N, 4.11.

(1,1,3-Trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)acetic acid ethyl ester (5g). Yield: 83% (A), 86% (B). Mp 103–104 °C (MeOH/Et₂O) (lit. 104–105 °C¹⁹). ¹³C-NMR (125 MHz, CDCl₃): 166.1, 159.0, 137.9, 135.3, 134.7, 127.2, 125.6, 121.4, 62.5, 39.3, 14.2. MS (ESI⁺): *m/z*: 269 (M + 1).

(1,1,3-Trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)propionic acid ethyl ester (5h).

Yield: 58% (A), 64% (B). Mp 93–96 °C (MeOH/Et₂O) (lit. 96–97 °C,¹⁹ 95 °C²²). ¹³C-NMR (125 MHz, CDCl₃): 168.9, 157.3, 136.3, 133.5, 133.1, 125.9, 123.9, 119.7, 59.8, 33.5, 31.9, 12.9. MS (ESI⁺): *m/z*: 283 (M + 1).

(1,1,3-Trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)butanoic acid ethyl ester (5i). Yield: 66% (A), 87% (B). Mp 56–57 °C (MeOH/Et₂O) (lit. Oil²⁰). ¹³C-NMR (125 MHz, CDCl₃): 172.6, 159.2, 137.8, 135.0, 134.5, 127.5, 125.4, 121.1, 60.8, 38.7, 31.4, 23.8, 14.4. MS (ESI⁺): *m/z*: 298 (M + 1). Anal. Calcd. for C₁₃H₁₅NO₅S: C, 52.52; H, 5.09; N, 4.71. Found: C, 52.37; H, 5.00; N, 4.74.

(1,1,3-Trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)pentanoic acid ethyl ester (5j). Yield: 71% (A), 89% (B). Mp 48–50 °C (MeOH/Et₂O). IR (KBr, cm⁻¹): 3442, 1727, 1466, 1376, 1327, 1301, 1267, 1186, 756, 589. ¹H-NMR (200 MHz, CDCl₃): 8.07–8.03 (m, 1H); 7.93–7.81 (m, 3H); 4.13 (q, 2H, J = 6.9 Hz); 3.79 (t, 2H, J = 6.9 Hz); 2.37 (t, 2H, J = 7.3 Hz); 1.94–1.68 (m, 4H); 1.25 (t, 3H, J = 6.9 Hz) ppm. ¹³C-NMR (125 MHz, CDCl₃): 171.7, 157.6, 136.3, 133.4, 133.0, 126.0, 123.8, 119.6, 59.1, 37.7, 32.4, 26.6, 20.9, 13.0. MS (ESI⁺): *m/z*: 311 (M + 1). Anal. Calcd. for C₁₄H₁₇NO₅S: C, 54.01; H, 5.50; N, 4.50. Found: C, 53.68; H, 5.67; N, 4.26.

(1,1,3-Trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)hexanoic acid ethyl ester (5k).

Yield: 80% (A), 93% (B). Oil. IR (KBr, cm⁻¹): 2939, 2867, 1731, 1463, 1373, 1336, 1257, 1182, 1126, 1098, 752, 587. ¹H-NMR (200 MHz, CDCl₃): 8.07–8.03 (m, 1H); 7.90–7.81 (m, 3H); 4.12 (q, 2H, J = 6.9 Hz); 3.77 (t, 2H, J = 6.9 Hz); 2.31 (t, 2H, J = 6.9 Hz); 1.87 (q, 2H, J = 7.7 Hz); 1.70 (q, 2H, J = 7.7 Hz); 1.44 (q, 2H, J = 6.9 Hz); 1.24 (t, 3H, J = 7.3 Hz) ppm. ¹³C-NMR (125 MHz, CDCl₃): 173.6, 159.1, 137.8, 134.9, 134.5, 127.5, 125.3, 121.1, 60.4, 39.3, 34.2, 28.2, 26.4, 24.5, 14.4. MS (ESI⁺): *m/z*: 326 (M + 1). Anal. Calcd. for C₁₅H₁₉NO₅S: C, 55.37; H, 5.89; N, 4.30. Found: C, 55.06; H, 6.20; N, 4.14.

(1,1,3-Trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)heptanoic acid ethyl ester (5l). Yield: 54% (A), 80% (B). Oil. IR (KBr, cm⁻¹): 2939, 2862, 1732, 1458, 1373, 1258, 1183, 1125, 912, 731, 616. ¹H-NMR (200 MHz, CDCl₃): 7.92–7.90 (m, 1H); 7.82–7.69 (m, 3H); 4.21 (q, 2H, J = 7.1 Hz); 3.64 (t, 2H, J = 7.1 Hz); 2.17 (t, 2H, J = 7.3 Hz); 1.72 (q, 2H, J = 6.59 Hz); 1.51 (q, 2H, J = 6.95 Hz); 1.38–1.22 (m, 4H); 1.11 (t, 3H, J = 7.1 Hz) ppm. ¹³C-NMR (125 MHz, CDCl₃): 173.6, 158.9, 137.6, 134.6, 134.2, 127.3, 125.0, 120.8, 60.1, 39.2, 34.1, 28.3, 28.1, 26.3, 24.3, 14.1. MS

(ESI⁺): *m/z*: 340 (M + 1). Anal. Calcd. for C₁₆H₂₁NO₅S: C, 56.62; H, 6.24; N, 4.13. Found: C, 56.91; H, 6.43; N, 3.94.

(1,1,3-Trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)acetonitrile (5m). Yield: 66% (A), 72% (B). Mp 140–142 °C (MeOH/Et₂O) (lit. 144 °C^{21,17}). ¹³C-NMR (125 MHz, CDCl₃): 159.2, 137.7, 135.9, 135.1, 126.5, 126.0, 121.7, 112.9, 25.4. MS (ESI⁺): *m/z*: 222 (M + 1).

(1,1,3-Trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)propionitrile (5n). Yield: 34% (A), 57% (B). Mp 142–145 °C (MeOH/Et₂O) (Lit. 148 °C²¹, 144 °C^{19,22}). ¹³C-NMR (125 MHz, CDCl₃): 158.7, 137.6, 135.5, 134.9, 127.0, 125.8, 121.4, 116.4, 34.5, 17.7. MS (ESI⁺): *m/z*: 236 (M + 1).

(1,1,3-Trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)butyronitrile (5o). Yield: 82% (A), 93% (B). Mp 103 °C (MeOH/Et₂O) (lit. 105 °C,²¹ 103 °C^{18,22}). ¹³C-NMR (125 MHz, CDCl₃): 159.3, 137.6, 135.3, 134.8, 127.2, 125.5, 121.3, 118.7, 37.9, 24.7, 15.2. MS (ESI⁺): *m/z*: 251 (M + 1).

(1,1,3-Trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)pentanenitrile (5p). Yield: 37% (A), 79% (B). Mp 95–97 °C (MeOH/Et₂O) (Lit. 98 °C²¹). ¹³C-NMR (125 MHz, CDCl₃): 159.2, 137.7, 135.1, 134.6, 127.3, 125.4, 121.2, 119.3, 38.3, 27.5, 22.8, 16.8. MS (ESI⁺): *m/z*: 265 (M + 1).

(1,1,3-Trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)hexanenitrile (5q). Yield: 83% (A), 95% (B). Oil. IR (KBr, cm⁻¹) (lit. 50 °C²¹). ¹³C-NMR (125 MHz, CDCl₃): 159.2, 137.7, 135.0, 134.6, 127.4, 125.3, 121.1, 119.6, 38.9, 27.8, 25.9, 25.0, 17.2. MS (ESI⁺): *m/z*: 279 (M + 1).

(1,1,3-Trioxo-1,3-dihydrobenzo[d]isothiazol-2-yl)heptanenitrile (5r). Yield: 78% (A), 86% (B). Oil. IR (KBr, cm⁻¹): 2939, 2245, 1732, 1463, 1335, 1258, 1183, 1125, 752, 677. ¹H-NMR (200 MHz, CDCl₃): 8.18–8.05 (m, 1H); 7.96–7.80 (m, 3H); 3.78 (t, 2H, J = 7.1 Hz); 2.34 (t, 2H, J = 6.95 Hz); 1.87 (q, 2H, J = 7.3 doublet of Hz); 1.68 (q, 2H, J = 6.95 Hz); 1.58–1.45 (m, 4H) ppm. ¹³C-NMR (125 MHz, CDCl₃): 159.1, 137.8, 134.9, 134.5, 127.5, 125.3, 121.1, 119.8, 39.3, 28.4, 28.2, 26.0, 25.3, 17.2. MS (ESI⁺): *m/z*: 293 (M + 1). Anal. Calcd. for C₁₄H₁₆N₂O₃S: C, 57.52; H, 5.52; N, 9.58. Found: C, 57.31; H, 5.71; N, 9.35.

Conversion of 5r into 5l. Compound **5r** (2.52 g, 8.62 mmol) was added slowly to a solution of conc. H₂SO₄ (2.01 g, 1.11 mL) in ethanol (2.76 mL) at 0 °C. After the addition was complete, the mixture was heated under reflux for 8 h and diluted with AcOEt (61 mL). The organic mixture was washed, respectively, with water (27 mL), saturated aqueous NaHCO₃ (34 mL) and brine (27 mL), dried over Na₂SO₄ and concentrated to dryness to afford compound **5l** as a pale yellow oil (1.58 g, 54%) with the same properties as described above.

Conversion of 5l into 5e. Compound **5** (1.58g, 5.07 mmol) was added to 10% HCl (147 mL) and the mixture was heated under reflux for 3 h. The mixture was cooled to 0 °C and the resulting precipitate was filtered off and recrystallized from CH₂Cl₂/hexane to yield **5e** (1.2 g, 83%) as a white solid [Mp 100–101 °C (CH₂Cl₂/hexane)], with the same properties as described above.

Acknowledgements

The authors acknowledge Louisiana State University Medical Foundation, New Orleans, LA, for financial support.

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