Synthesis and Decomposition of Parabanic Acid Derivatives

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As a part of a research program related to the synthesis of pharmacologically and agrochemically interesting parabanic acid derivatives, we synthesized imidazolidine-2,4,5-trione (6), 2-thioximidazolidine-1-ylimidazolidine (7), benzod[1]imidazol-2-yl imidazolidine-2,4,5-thiones (8a-c), 2-thioxobenzod[1]imidazol-2-yl imidazolidine-4,5-dione (9a-c) and 1-benzimidazol-3-imidazolidine-2,4,5-triones (10a-c), 1-phenylurea (11), 1-ethyl-3-[(3-ethyliourido)methyl]urea (12) and 1-ethyl-3-[(3-methylthioiureido)methyl]urea (13) were obtained in basic solution through ultrasound.

Key Words: Parabanic acid, Benzimidazole, 1,2-Benzothiazol-3-one-1,1-dioxide, Agrochemical fungicide, Urea derivatives.

INTRODUCTION

Parabanic acid (imidazolidine-2,4,5-trione, oxalylurea) resulting from the oxidation of biological fundamental compounds such as uric acid, guanine, uracil and alloxanic acid has attracted the attention of agricultural and medicinal chemists for many decades [1-3]. Parabanic acid derivatives are useful pharmaceuticals for the treatment of diabetic complications such as diabetic neuropathy, diabetic cataracts and diabetic dermopathy [4-6]. Further, parabanic acid derivatives are known for their herbicidal, plant growth regulating and fungicidal properties [7]. Polymers containing imidazolidine-2,4,5-trione (parabanic) rings are known as highly thermally stable polymers with improved chemical resistance in organic solvents [8-13]. Recently, many marine imidazol alkaloids have been isolated from sponges and their antitumor and antibacterial activities have also been identified [14,15]. In our previous works to obtain new agrochemicals, we reported the synthesis of new saccharin derivatives containing the 2,4,5-imidazolidinetrione group [16]. As a part of research program related to the synthetic study of pharmacologically and agrochemically important imidazolidines [16], we chose to identify imidazolidine-2,4,5-trione and imidazolidine-2,4,5-trione-2-thioxo-imidazolidine-4,5-dione, benzimidazole, orsaccharin rings as active components for the desired property, the synthesis of (imidazolidine-2,4,5-tri) imidazolidine-2,4,5-triones (1), 2,4,5-imidazolidinetrionyl-1,2-benzothiazol-3-one-1,1-di-oxide 2, 4,5-dioxo-2-thioxo imidazolidin-1-ylmethyl-imidazolidine-2,4,5-triones (2) and 1-benzimidazol-3-yl-3-imidazolidine-2,4,5-trione (3) are already reported.

EXPERIMENTAL

Melting points were determined on a Büchi 510 capillary melting point apparatus and uncorrected. Infrared spectra were recorded on a Perkin-Elmer 683 spectro-photometer. NMR spectra were recorded on a Varian XL-300 or Bruker AC 200 FT-NMR spectrometer in CDCl₃ containing Me₄Si as an internal reference. Mass spectra were obtained by using JEOL JMS DX 303 or HP 5892 Mass Spectrometer.

General procedure for the synthesis of 6,7: To a solution of 1-chloromethyl-imidazolidine-2,4,5-triones (4) (or 1-chloromethyl-2-thioxo-imidazolidine-4,5-diones (5), 1.13 × 10⁻² mol) in dry THF (15 mL) under nitrogen at room temperature was added solution of 2,4,5-imidazolidinetriones (or 2-thioxo-mimidazolidine-4,5-diones, 1.13 × 10⁻² mol) and triethylamine (0.4 mL) in dry THF (15 mL). The reaction mixture was stirred at room temperature for 0.5 h. After 0.5 h, the reaction mixture was refluxed at 60-65 °C for 7 h. The reaction mixture was cooled again to room temperature and THF (75 mL) was added. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluted with only CH₂Cl₂ to provide products 6,7.

1-[(3-Phenylimidazolidine-2,4,5-tri)on]ylmethyl]-3-methyl-imidazolidine-2,4,5-trione (6): m.p. 247-249 °C;
1H NMR (200 MHz, DMSO) 3.08 (s, 3H), 5.43 (s, 2H), 7.52 (m, 5H); 13C NMR (50 MHz, DMSO) 157.2, 156.1, 155.9, 155.7, 152.8, 151.7, 130.2, 129.3, 128.9, 126.5, 40.6, 24.5; GC/MS m/z 330 ([M]+); Anal. calc. for C_{30}H_{36}N_{10}O_{2}: C, 50.92; H, 3.05; N, 16.96. Found: C, 50.95; H, 3.04; N, 16.94.

1-[4,5-Dioxo-3-phenyl-2-thioxoimidazolidin-1-ylmethyl]-3-ethyl-imidazolidine-2,4,5-trione (7); m.p. 217-218 °C; 1H NMR (200 MHz, DMSO) 1.11 (t, J = 7.1 Hz, 6H), 3.51 (d, J = 6.9 Hz, 2H), 5.63 (s, 2H), 3.90 (d, J = 7.0 Hz, 2H); 13C NMR (50 MHz, DMSO) 180.1, 156.7, 156.0, 154.9, 154.7, 152.4, 43.6, 36.6, 33.8, 12.9, 12.5; GC/MS m/z 360 ([M]+); Anal. calc. for C_{30}H_{36}N_{10}O_{2}: C, 50.00; H, 3.36; N, 15.55. Found: C, 50.03; H, 3.35; N, 15.59.

The typical experimental procedure for 1-phenyl-3-(1,1,3-trioxo-1,3-dihydro-16-benzo[d]isothiazol-2-ylmethyl)-imidazolidine-2,4,5-trione (6) is as follows: To a solution of 1-chloromethyl-3-phenylimidazolidine-2,4,5-trione (4c) (2.38 g, 10 mmol) in dry THF (15 mL) under nitrogen at room temperature was added solution of saccharin (2.01 g, 11 mmol) and triethylamine (1.2 mL) in dry THF (15 mL). The reaction mixture was stirred at room temperature for 0.5 h. After 0.5 h, the reaction mixture was refluxed at 55-60 °C for 5 h. The reaction mixture was cooled again to room temperature and THF (50 mL) was added. The combined organic layers were dried over anhydrous Na_{2}SO_{4}, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluted with only CHCl_{3} to provide the 1-phenyl-3-(1,1,3-trioxo-1,3-dihydro-16-benzo[d]isothiazol-2-ylmethyl)-imidazolidine-2,4,5-trione (6) as a white crystalline solid (1.93 g, 50 %); m.p. 191-192 °C; 1H NMR (200 MHz, CDCl_{3}) 5.84 (s, 2H, CH_{2}), 7.3-8.1 (m, 9H, phenyl); Mass m/z (rel. intensity, %) 385 ([M]+), 40, 196 (100), 91, 77.

The typical experimental procedure for 1-ethyl-2-thioxo-3-(1,1,3-trioxo-1,3-dihydro-16-benzo[d]isothiazol-2-ylmethyl)-imidazolidine-4,5-dione (7) is as follows: To a solution of 1-ethyl-2-thioxo-imidazolidine-4,5-dione (5b) (1 g, 4.8 mmol) in the dry THF (10 mL) under nitrogen was added solution of saccharin (1.5 g, 8.2 mmol) and triethylamine (1.1 mL) in the dry THF (10 mL). The reaction mixture was stirred at room temperature for 0.5 h. After 0.5 h, the mixture was refluxed 55-60 °C for 5 h. The reaction mixture was cooled again to room temperature and THF (50 mL) was added. The combined organic layers were dried over anhydrous Na_{2}SO_{4}, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluted with only CHCl_{3} to provide the 1-ethyl-2-thioxo-3-(1,1,3-trioxo-1,3-dihydro-16-benzo[d]isothiazol-2-ylmethyl)-imidazolidine-4,5-dione (7) as a yellow crystalline solid (1.68 g, 49 %); m.p. 157-158 °C; 1H NMR (200 MHz, acetone-d_{6}) 1.17 (t, 3H, -CH_{3}), 3.99-4.06 (q, 2H, -CH_{2}-), 6.04 (s, 2H, N-CH_{2}-N), 8.05-8.20 (m, 4H, phenyl); IR (KBr, cm^{-1}): 1780, 1740, 1720, 1390, 1330, 1280, 1240, 1175; Mass m/z (rel. intensity, %) 352 ([M]+).

1-Chloromethyl-3-ethyl-imidazolidine-2,4,5-trione (8b): Yield 54 %; m.p. 191-192 °C; IR (KBr, cm^{-1}): 2981, 2885, 1746, 1425, 1340, 1293, 1251, 1180, 1115; Mass m/z (rel. intensity, %) 337 ([M]+), 2, 273 (8), 223 (4), 196 (100), 174 (15), 169 (14), 132 (20); 1H NMR (200 MHz, Acetone-d_{6}) 1.18-1.28 (t, 3H, CH_{3}), 3.64-3.75 (q, 2H, CH_{2}), 5.70 (s, 2H, N-CH_{2}-N), 8.02-8.22 (m, 4H, phenyl).

1-Chloromethyl-3-ethyl-2-thioxo-imidazolidine-4,5-dione (5a): Yield 45 %; m.p. 97-98 °C; IR (KBr, cm^{-1}): 1874, 1772, 1405, 1378, 1354; Mass m/z (rel. intensity, %) 192 ([M]+), 1; 1H NMR (200 MHz, Acetone-d_{6}) 3.38 (s, 3H, CH_{3}), 5.76 (s, 2H, CH_{2}).

1-Chloromethyl-3-ethyl-2-thioxo-imidazolidine-4,5-dione (5b): Yield 45 %; m.p. 108-109 °C; IR (KBr, cm^{-1}): 1780, 1740, 1402, 1370, 1230, 1135; Mass m/z (rel. intensity, %) 206 ([M]+); 1H NMR (200 MHz, Acetone-d_{6}) 1.21-1.28 (t, 3H, CH_{3}), 3.95-4.06 (q, 2H, CH_{2}), 5.75 (s, 2H, CH_{2}).

1-Chloromethyl-3-phenyl-2-thioxo-imidazolidine-4,5-dione (5c): Yield 40 %; m.p. 149-150 °C; IR (KBr, cm^{-1}): 1780, 1650, 1520, 1500, 1400, 1230; Mass m/z (rel. intensity, %) 254 ([M]+); 1H NMR (200 MHz, Acetone-d_{6}) 5.87 (s, 2H, CH_{2}), 7.43-7.60 (m, 5H, phenyl).

1-Chloromethyl-3-ethyl-2-thioxo-imidazolidine-4,5-dione (9a): Yield 40 %; m.p. 173-174 °C; IR (KBr, cm^{-1}): 1780, 1400, 1340, 1290, 1250, 1170, 1100; Mass m/z (rel. intensity, %) 339 ([M]+); 1H NMR (200 MHz, Acetone-d_{6}) 3.39 (s, 3H, CH_{3}), 6.04 (s, 2H, N-CH_{2}-N), 8.10-8.17 (m, 4H, phenyl).

1-Chloromethyl-3-ethyl-2-thioxo-imidazolidine-4,5-dione (9b): Yield 49 %; m.p. 157-158 °C; IR (KBr, cm^{-1}): 1780, 1740, 1720, 1390, 1330, 1280, 1240, 1175; Mass m/z (rel. intensity, %) 353 ([M]+); 1H NMR (200 MHz, Acetone-d_{6})
yielded a mixture of the expected N-hydroxy methyl dericatives and imidazolidine-2,4,5-triones. However, the instability of N-hydroxy methyl derivatives made it isolation very difficult. The use of column chromatography as a method of purification was not successful, whatever the eluent or support (silica gel, alumina) was used, because the \( R_f \) value was the same for the two compounds. For this reaction, the next chlorination step, using a large excess of thionyl chloride, was realized starting directly from a mixture of \( N \)-hydroxy methyl derivatives and imidazolidine-2,4,5-triones. The chlorinated precursors \( 4,5 \) were easily isolated by column chromatography and the product had a much higher \( R_f \) value the starting material.

When the chlorinated products \( 4 \) and \( 5 \) were allowed to react with \( N \)-methylimidazolidine-2,4,5-trione and \( N \)-phenylimidazolidine-2,4,5-trione, respectively, 1-[3-(phenylimidazolidine-2,4,5-trionyl)methyl]-3-methyl-imidazolidine-2,4,5-trione and 1-[(4,5-dioxo-3-phenyl-2-thioxoimidazolidin-1-yl)methyl]-3-ethylimidazolidine-2,4,5-trione \( 7 \) were obtained in good yields, as shown in Table-1. When chlorinated products \( 4 \) and \( 5 \) were allowed to react with 1,2-benzothiazole-3-one 1,1-dioxide by same methods, saccharin derivatives 8 containing imidazolidine-2,4,5-trionyl, 2-thioxo-imidazolidine-4,5-dionyl groups were obtained in good yields as shown in the Table-1. We also tried to obtain various parabanic acid derivatives from the reactions of the chlorinated reactants \( 4,5 \) with benzimidazole, 1-Benzimidazole-1-yl-methyl-3-imidazolidine-2,4,5-trione \( 10a \) (yield, 75 %), 1-benzimido-

| TABLE-1 | YIELDS OF PRODUCTS 6-10 |
|---|---|---|---|
| Entry | Product | Yield (%) | m.p. (ºC) |
| 1 | | 76 | 247-249 |
| 2 | | 69 | 217-218 |
| 3 | | 52 | 192-193 |
| 4 | | 54 | 182-183 |
| 5 | | 50 | 191-192 |
| 6 | | 40 | 173-175 |
| 7 | | 49 | 157-159 |
| 8 | | 30 | 191-192 |
| 9 | | 75 | 188-189 |
| 10 | | 50 | 179-180 |
| 11 | | 45 | 187-188 |

*Isolated yields

The basic catalyzed condensation between imidazolidin-2,4,5-triones and paraformaldehyde in aqueous solution

### RESULTS AND DISCUSSION

The basic catalyzed condensation between imidazolidin-2,4,5-triones and paraformaldehyde in aqueous solution

1-Phenyl-2-thioxo-3-[1,3,3-trioxo-1,3-dihydro-16benzo[d]isothiazol-2-ylmethyl]-imidazolidine-4,5-dione

1-Benzimidazole-1-yl-3-methylimidazolidine-2,4,5-trione

1-Benzimidazole-1-yl-ethyl-3-mimidazolidine-2,4,5-trione

Phenylurea

1-Ethyl-3-[3-ethylthiourea(methyl)]urea

1-Phenylurea (11): Isolated yield 41%; \( R_f 0.35 \) (TLC eluent; \( n \)-Hexane : EtOAc = 1 : 25, v/v); yield 50% ; m.p. 179-180 ºC; IR (KBr, \( \nu_{max} \), cm\(^{-1} \)) 3443, 1738, 1718, 1424, 796; Mass \( m/z \) (rel. intensity, %) 272 (93), 245 (2), 173 (5), 145 (4), 7 (100), 118 (11), 104 (8), 90 (10), 77 (12), 64 (6), 56 (26); \(^1\)H NMR (200 MHz, CDCl\(_3\)) 6.95 (s, 2H, \( N-\)), 7.19 (m, 1H), 7.43 (m, 2H), 7.61 (dd, 2H), 8.9 (s, 1H); \(^13\)C NMR (50 MHz, CDCl\(_3\)) 121.6, 128.0, 128.9, 139.4; Anal. calcd. for C\(_{16}\)H\(_{12}\)NO: C, 65.75; H, 5.92; N, 3.47; Found: C, 61.73; H, 5.91; N, 3.44.

1-Benzoimidazole-1-yl-phenyl-3-imidazolidine-2,4,5-trione (10b): \( R_f 0.7 \) (TLC eluent; \( n \)-Hexane : EtOAc = 1 : 25, v/v); yield 50%; m.p. 179-180 ºC; IR (KBr, \( \nu_{max} \), cm\(^{-1} \)) 3846, 2984, 1736, 1425, 1242, 796; Mass \( m/z \) (rel. intensity, %) 272 (93), 245 (2), 173 (5), 145 (4), 131 (100), 118 (11), 104 (8), 90 (10), 77 (12), 64 (6), 56 (26); \(^1\)H NMR (200 MHz, CDCl\(_3\)) 6.95 (s, 2H, \( N-\)), 7.19 (m, 1H), 7.43 (m, 2H), 7.61 (dd, 2H), 8.9 (s, 1H); \(^13\)C NMR (50 MHz, CDCl\(_3\)) 121.6, 128.0, 128.9, 139.4; Anal. calcd. for C\(_{16}\)H\(_{12}\)NO: C, 65.75; H, 5.92; N, 3.47; Found: C, 61.73; H, 5.91; N, 3.44.

1-Phenylurea (11): Isolated yield 41%; \( R_f 0.35 \) (TLC eluent; EtOAc : \( n \)-Hexane : EtOAc = 1 : 25, v/v); Mass \( m/z \) (rel. intensity, %) 135; \(^1\)H NMR (200 MHz, CDCl\(_3\)) 6.20 (s, 1H), 7.19 (m, 1H), 7.43 (m, 2H), 7.61 (dd, 2H), 8.9 (s, 1H); \(^13\)C NMR (50 MHz, CDCl\(_3\)) 121.6, 128.0, 128.9, 139.4; Anal. calcd. for C\(_{16}\)H\(_{12}\)NO: C, 65.75; H, 5.92; N, 3.47; Found: C, 61.73; H, 5.91; N, 3.44.
dazole-1-yl-ethyl-3-imidazolidine-2,4,5-trione (10b) (yield, 50%) and 1-benzimidazole-1-yl-phenyl-3-imidazolidine-2,4,5-trione (10c) (yield, 45%) were obtained in good yields, as shown in Table-1.

Biological tests for testing the phytocidal, herbicidal and insecticidal properties of the new synthesized compounds (6-10) are currently in progress. As a part of a research program related to the synthesis study of bioactive organo chemicals, we also report the synthesis of Di-urea derivatives in the reaction of 1-phenylimidazolidine-2,4,5-trione, 1-ethyl-3-[(3-ethyl-4,5-dioxo-2-thioxoimidazolidin-1-yl)methyl]-imidazolidine-2,4,5-trione and 1-ethyl-3-[(3-methyl-4,5-dioxo-2-thioxoimidazolidin-1-yl)methyl]-imidazolidine-2,4,5-trione with hydrolysis in basic solution through ultrasound.

1-Phenylurea (11), 1-ethyl-3-[(3-ethylthioureido)methyl]urea (12) and 1-ethyl-3-[(3-methylthioureido)methyl]urea (13) were obtained in good yields as shown in Table-2.

**TABLE-2**

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*Isolated yield

**REFERENCES**


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