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Atypical Oxidation Reaction by Thionyl Chloride: Easy Two-Step Synthesis of N-Alkyl-1,4-dithiines

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Atypical Oxidation Reaction by Thionyl Chloride: Easy Two-Step Synthesis of *N*-Alkyl-1,4-dithiines

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Abstract: Easy two-step synthesis of a series of dithiines was performed from succinic anhydride via cyclization of the corresponding 4-(alkylamino)-4-oxobutanoic acids (succinamic acids). The reaction, carried out in polar aprotic solvents, gave 4,8-dithiine-indacene-1,3,5,7-tetraones (diimides **3**) via 3,7-bis-4,8-dithia-indacene-1,5-diones (diisoimides **2**), which could be isolated. Surprisingly, in this reaction, thionyl chloride appeared as an oxidant, and this process seemed to be useful for the syntheses of *S*-containing heterocyclic compounds such as 1,4-dithiins. A mechanistic pathway was considered.

Keywords: Dithiine, imide, isoimide, thionyl chloride

In previous works,[1–3] we have reported on the syntheses and the biological properties of a series of maleimides and succinimides. To obtain other derivates possessing higher biological activities, we have studied the cyclization of 4-(alkylamino)-4-oxobutanoic acids **1** (acyl chlorides), easily obtained from aliphatic amines and succinic anhydride. Surprisingly, the cyclization of these via the acyl chlorides, generated by thionyl chloride, did not lead to the corresponding succinimides (Fig. 1).

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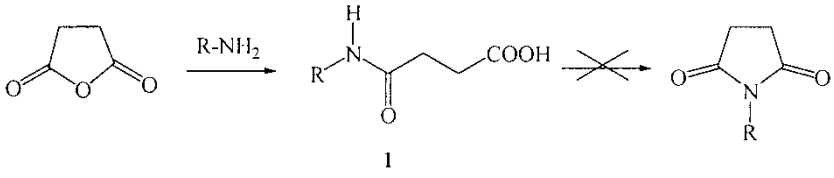

Figure 1.

The reaction, carried out in polar aprotic solvents such as dioxane, gave 4,8-dithiine-indacene-1,3,5,7-tetraones (diimides **3**) via 3,7-bis-4,8-dithia-indacene-1,5-diones (diisoimides **2**). The diisoimides **2** could be considered as the kinetically controlled compounds and may be isolated (as rose crystals) only when they had a low solubility in the reaction medium. Otherwise, a rapid isomerization occurred and led to the (green) diimides **3**, which were always insoluble (Fig. 2).

Several publications have been devoted to the ring conformation and electronic properties of 1,4-diithins, and it was also reported that 1,4-dithiins could be used as synthons (dienophiles) in cycloaddition reactions.[4]

In the literature, only a few articles referred to the syntheses of 1,4-dithiines,[5–12] and we chose an easy two-step process, depicted by Michaïlidis et al.[13]

This methodology, which was reported without experimental details, has also been used for the preparation of the ethyl, propyl, and t-butyl derivatives by Hayakawa et al.[14] and Kim et al.[15]

In these reports, no mechanistic pathway was suggested. Only one patent described a biological use of some 1,4-dithiin-2,3,5,6-tetracarboxydiimides as anthelmintics.[16]

This situation prompted us to investigate the mechanistic pathway of this reaction.

CHEMISTRY

Taking in account our experimental data, we proposed a mechanistic pathway involving the conversion of the succinamic acids **1** into isosuccinimides **4**,

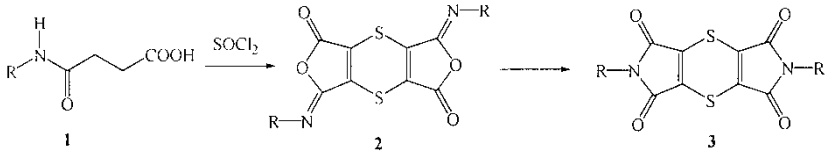

Figure 2. a) R = benzyl, b) R = cyclohexyl, c) R = isopropyl, d) R = propyl, and e) R = butyl.

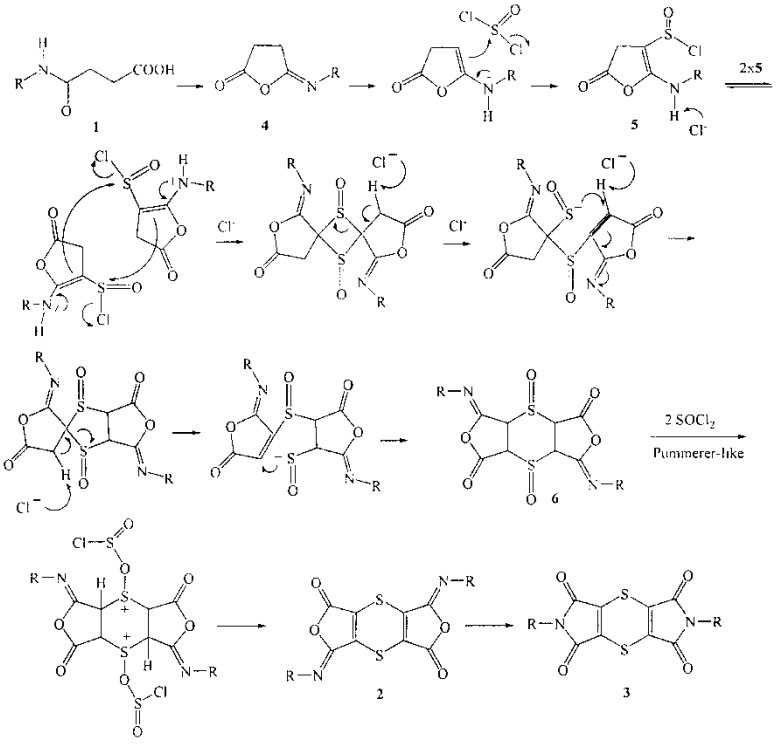

Figure 3.

which reacted with thionyl chloride to provide sulfochlorides **5**. Two linked molecules of these furnish the disulfoxides **6**. Two concomitant attacks of the Cl anion (liberated in the mixture in the precedent stage) led to the disulfoxides **7**, which, via a Pummerer-like reaction and simultaneous elimination of HCl, led to the diisomaleimide-dithiines **2** (Fig. 3). These isomerize to the more stable dithiines **3**.

A comparable reaction has been depicted by Higa and Krubsack[17] (Fig. 4).

Thionyl chloride, in this reaction, appeared as an oxidant, and this process seemed to be useful for the syntheses of *S*-containing heterocyclic compounds such as 1,4-dithiins. Furthermore, the products were easily isolated and directly recrystallized.

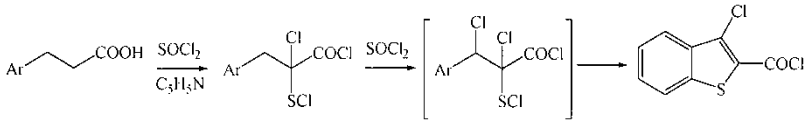

Figure 4.

EXPERIMENTAL

Melting points were taken on a Leitz 350 heated-stage microscope and are not corrected. ^{1}H NMR spectra were recorded at 400 MHz on Bruker Avance DPX 400 and Bruker WP80 DS instruments. Chemical shifts were reported in parts per million (ppm) (δ) relative to TMS. IR spectra were run on a Bruker IF 55 spectrometer.

General Procedure for the Preparation of Compounds 1

Succinic anhydride (15 mmol) was dissolved into 10 mL of dioxane, and 15 mmol of the correspondent amine in 10 mL of dioxane were slowly added. The solution was warmed at 80°C for 30 min, and the succinamic acid **1** crystallized by cooling. The white crystals were filtered off, dried, and recrystallized from dioxane.

Data

la: mp 144°C (lit.: 137.5–138.2[18]) (85%). IR (KBr): ν_{CO} 1691; 1642 cm^{-1}. ^{1}H NMR. (DMSO d-6): 4.27 (m, 2H, CH_2); 2.46 (m, 2H, CH_2); 2.38 (m, 2H, CH_2); 7.30 (m, 5H, Ar). Anal. calc. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76; O, 23.16; found: C, 63.51; H, 6.41; N, 6.68; O, 23.4.

1b: mp 171°C (lit.: 166.5–167[18]) (90%). IR (KBr): ν_{CO} 1697; 1642 cm^{-1}. ^{1}H NMR (CD_3COCD_3): 2.56 (t, $J = 7$ Hz, 2H, CH_2); 2.44 (t, $J = 7$ Hz, 2H, CH_2); 1.89 (m, 3H, $CH_2 + CH$ cyclohexane); 1.72 (m, 2H, CH_2 cyclohexane); 1.59 (m, 2H, CH_2 cyclohexane); 1.33 (m, 2H, CH_2 cyclohexane); 1.19 (m, 4H, $2 \times CH_2$cyclohexane). Anal. calc. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03; O, 24.09; found: C, 60.01; H, 8.80; N, 6.88; O, 24.31.

1c: mp 108°C (lit.: 105–107[18,19]) (90%). IR (KBr): ν_{CO} 1731; 1641 cm^{-1}. ^{1}H NMR (DMSO d-6): 3.80 (m, 1H, CH); 2.40 (t, $J = 7$ Hz, 1H, CH_2); 2.26 (t, 2H, $J = 7$ Hz, CH_2); 1.02 (d, 6H, CH_3). Anal. calc. for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80; O, 30.15; found: C, 52.69; H, 8.44; N, 8.69; O, 30.18.

1d: mp 101°C[14] (85%). IR (KBr): ν_{CO} 1714; 1642 cm^{-1}. ^{1}H NMR (DMSO d-6): 2.98 (m, 2H, CH_2); 2.41 (t, $J = 7$ Hz, 2H, CH_2); 2.29 (t, 2H, $J = 7.2$ Hz, CH_2); 1.39 (m, 2H, CH_2); 0.83 (t, 6H, $J = 7.2$ Hz, CH_3). Anal. calc. for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80; O, 30.15; found: C, 52.72; H, 8.42; N, 8.65; O, 30.21.

1e: mp 96°C[20] (85%). IR (KBr): ν_{CO} 1695; 1650 cm^{-1} ^{1}H NMR (DMSO d-6): 3.02 (m, 2H, CH_2); 2.40 (t, $J = 7.2$ Hz, 2H, CH_2); 2.28 (t, 2H,

$J = 7.2$ Hz, CH_2); 1.35 (m, 2H, CH_2); 1.26 (m, 2H, CH_2); 0.86 (t, 6H, $J = 7.2$ Hz, CH_3). Anal. calc for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09; O, 27.71; found: C, 55.22; H, 8.99; N, 7.82; O,27.97.

General Procedure for the Preparation of Compounds 2

Succinamic acid (1 g) was dissolved into 10 mL of ether, and 13 mL of thionyl chloride was slowly added. The solution was allowed to sit at rt for 6 h, and the diisoimide was filtered off, washed with 2 × 5 mL of ether, and recrystallized.

Data

2a: Rose crystal, mp: 210°C. IR: ν_{CO} 1791, 1696 cm^{-1}. ^1H NMR ($CDCl_3$): 4.78 (s, 4H, CH_2); 7.31–7.38 (m, 10H, Ar). ^{13}C NMR (DMSO d_6): CO: 163.1; CN: 162.5; Cq: 134.3, 129.2, 127.3; CH: 129.0, 128.6, 127.7; CH_2: 43.0. Anal. calc. for $C_{22}H_{14}N_2O_4S_2$: C, 60.82; H, 3.25; N, 6.45; O, 14.73; S, 14.76; found: C, 60.60; H 3.3; N, 6.42; O, 15.03; S, 14.64.

2b: Rose crystals, mp: 228°C. IR: ν_{CO} 1789, 1774, 1701 cm^{-1}. ^1H NMR ($CDCl_3$): 1.23–2.13 (m, 20H, CH_2); 3.75–3.82 (m, 2H, CH). ^{13}C NMR (DMSO d_6): CO: 160.5; CN: 130.2; Cq: 127.5, 126.5; CH: 49.7; CH_2: 32.5, 25.0, 24.9. Anal. calc. for $C_{20}H_{22}N_2O_4S_2$: C, 57.39; H, 5.30; N, 6.69; O,15.28; S, 15.32; found: C, 57.21; H, 5.53; N, 6.42; O, 15.73; S, 15.11.

General Procedure for the Preparation of Compounds 3

Succinamic acid (1g) was dissolved into 10 mL of dioxane, and 13 mL of thionyl chloride was slowly added. The solution was allowed to sit at rt for 6 h, and the diisoimide was filtered off, washed with 2 × 5 mL of ether, and recrystallized.

Data

3a: Green pellets, mp: 224°C. IR: ν_{CO} 1712. 1697 cm^{-1}. ^1H NMR ($CDCl_3$): 4.64 (s, 4H, CH_2); 7.31–7.35 (m, 10H, Ar). ^{13}C NMR (DMSO d_6): CH_2: 41.95; Cq: 135.9, 134.2; CH: 132.1, 128.8, 127.8; CO: 164.3. Anal. calc. for $C_{22}H_{14}N_2O_4S_2$: C, 60.82; H, 3.25; N, 6.45; O, 14.73; S, 14.76; found: C, 60.60; H, 3.52; N, 6.43; O, 14.91; S, 14.54.

3c: Green pellets, mp: 220°C. IR: ν_{CO} 1713, 1696 cm^{-1}. ^1H NMR (DMSO d-$_6$): 1.35 (d, 12H, CH_3, $J = 6.9$ Hz); 4.23–4.30 (m, 2H, CH) ^{13}C NMR

(DMSO d_6) CO: 164.0; Cq: 130.3; CH: 43.6; CH_3: 19.6. Anal. calc. for $C_{14}H_{14}N_2S_2$: C, 49.69; H, 4.17; N, 8.28; O, 18.99; S, 18.99; S, 18.95; found: C, 49.54; H, 4.28; N, 8.00; O, 19.03; S, 19.15.

3d: Green pellets, mp: 222°C. IR: ν_{CO} 1714, 1693 cm^{-1}. ^1H NMR (DMSO d-$_6$): 0.88 (t 6H, CH_3, $J = 7.09$ Hz). ^{13}C NMR (DMSO d_6): CO: 164.3; Cq: 130.4; CH_2: 21.0, 40.4; CH_3: 11.1. Anal. calc. for $C_{14}H_{14}N_2O_4S_2$: C, 49.69; H, 4.17; N, 8.28; O, 18.99; S, 18.95; found: C, 49.30; H, 4.27; N, 8.12; O, 19.34; S, 18.97

3e: Green pellets, mp: 288°C. IR: ν_{CO} 1713, 1693 cm^{-1} ^1H NMR (DMSO d-$_6$): 0.91 (t 6H, CH_3, $J = 7.35$ Hz); 1.26–1.35 (m, 4H, CH_2); 1.51–1.58 (m, 4H, CH_2); 3.49 (t, 4H, CH_2, $J = 7.05$ Hz). ^{13}C NMR (DMSO d_6): CO: 164.3; Cq: 130.4; CH_2: 19.3, 29.6, 40.4; CH_3: 13.4. Anal. calc. for $C_{16}H_{18}N_2O_4S_2$: C, 52.44; H, 4.95; N, 7.64; O, 17.46; S, 17.50; found: C, 52.22; H, 5.15; N, 7.51; O, 17.75; S, 17.37.

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