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Thiophene-2,5-dicarboxylic Acid Bis-aryl(alkyl) Amides

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ABSTRACT: *A base-catalyzed condensation of diacetamido sulfides [$(RNHCOCH_2)_2S$)] with glyoxal affording thiophene-2,5-dicarboxylic acid bis-aryl-(alkyl)amides has been accomplished under mild conditions. Excellent results were readily obtained when R was a substituted 3-nitrophenyl, 4-nitrophenyl, 4-chlorophenyl group, but the yield was poor when R was cyclohexyl. Unknown compounds were characterized by elemental analyses, IR, ^1H, and ^{13}C NMR techniques.* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:503–506, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20153

INTRODUCTION

During the past two decades, much progress has been made in the synthetic chemistry of thiophenes [1]. 3-Thiapentane-1,5-diones have been recently used as the starting materials in some syntheses [2–5].

Diketo sulfides of the type $RCOCH_2SCH_2COR$ have two methylene groups activated by both a carbonyl and a sulfide group, and are considered to be suitable for condensation with 1,2-dicarbonyl compounds providing a thiophene nucleus. When R is O-alkyl, i.e. thiodiacetic acid ester, the reaction is the well-known Hinsberg thiophene synthesis and has been used extensively to prepare 3,4-disubstituted thiophene derivatives [6]. However, the extension of the Hinsberg reaction to diketo sulfides (R = alkly or aryl) is so far unreported in spite of a mention of this possibility by Hinsberg in his first paper [7]. On the other hand, several successful condensations of diketo sulfides with vicinal dialdehydes affording thiepin derivatives or the corresponding sulfur-eliminated aromatized products after sulfur extrusion are known [8,9]. It was expected, therefore, that the condensation of diketo sulfides with glyoxal, the simplest dialdehyde, affording the more stable thiophene ring, might be more facile.

While in the Hinsberg reaction, strong bases in high concentrations can and must be used [10] in the reaction of diketo sulfides possessing very reactive methylene and carbonyl groups in the same molecule, the use of strong basic conditions has brought about extensive self-condensation. The Cannizzaro reaction of glyoxal may also occur as evidenced by the immediate precipitation of sodium glycolate upon addition of sodium alkoxide to a solution of glyoxal in alcohol. In preference to these side reactions, the desired condensations were found to be performed efficiently by carrying out the reaction under mild conditions: thus, when a dilute solution of sodium methoxide was slowly added to a stirred solution of a diacetamido sulfide and glyoxal in methanol and, if necessary, a co-solvent such as dioxane at room temperature, thiophene-2,5-dicarboxylic acid bis-aryl(alkyl)amides **3a–e** began to precipitate generally in just a few minutes. In order to obtain pure products in high yields, the base must be added very slowly, especially at the beginning of the reaction when most of the starting materials are still present.

In light of studies on the synthetic chemistry of thiophenes during the last 15 years, we have partly contributed to this progress by developing a new

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thiophene synthesis. Finally, we have also partly contributed to this progress by obtaining a thiophene derivative, which involves formamide groups.

RESULTS AND DISCUSSION

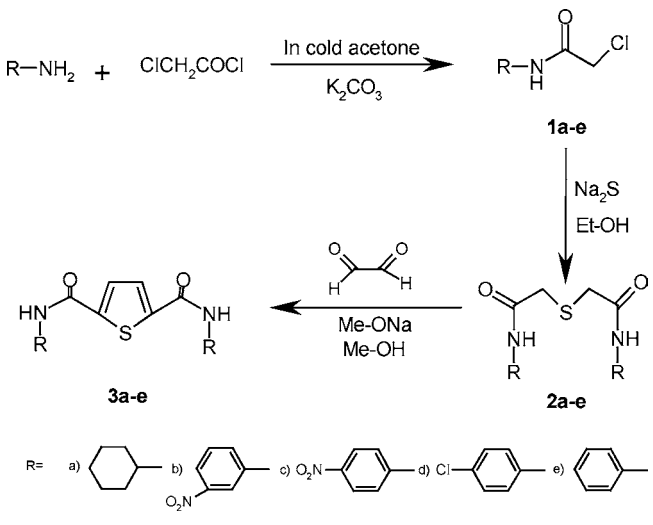
The synthesis of compounds **1–3** is outlined in Scheme 1. When chloroacetyl chloride was added to amines in the presence of potassium carbonate, **1a–e** were obtained. Reaction of **1a–e** with Na_2S in ethanol gives the cyclohexyl- or aryl-substituted diacetamido sulfides **2a–e**, respectively. Thiophene-2,5-dicarboxylic acid bis-aryl(alkyl)amides **3a–e** were then obtained from the reaction of **2a–e** with glyoxal in methanol in mild condition.

The yield of **3a** was very poor. The reason for this could be the lack of conjugation between *n*-electrons on nitrogen atom with cyclohexyl in **2a**. On the other hand, yields of **3b–e** were somewhat more satisfactory, because of an effective conjugation they have with the aromatic ring in **2b–e**. In addition, higher yields were found in the presence of substituents with higher electron attractive power.

In the IR spectrum of **3a–e**, the most characteristic absorptions are at 1640–1683 cm^{-1} ν (C=O), 3263–3290 cm^{-1} ν(—NH). The data for all compounds are given in the Experimental section.

EXPERIMENTAL

Melting points were determined on a Thomas Hover melting point apparatus and are uncorrected, but checked by differential scanning calorimetry (DSC). The IR spectra were registered with a Mattson 1000 FT-IR spectrophotometer. The NMR spectra were recorded on Varian Gemini 200 MHz and Jeol FX-90Q spectrometers and are reported in ppm (δ) relative to tetramethylsilane as the internal standard (^{1}H) or deuterochloroform (^{13}C NMR 75.5, 49.5, and 22.4 MHz). Elemental analyses were done on a LECO-CHNS-938. Starting chemicals were obtained from Merck or Aldrich.



SCHEME 1

General Procedure for the Synthesis of **1**

To an ice-cooled solution of R-NH_2 (0.05 mol) in acetone was added chloroacetylchloride (0.05 mol in acetone) dropwise, and the solution was kept for 2 h at room temperature. The resulting mixture was poured in ice-cold water, and the shiny crystalline product was collected. Then it was filtered.

2-Chloro-N-cyclohexylacetamide **1a**. White solid; yield 77%, mp 156–157°C. IR (KBr) υ: 3288 (NH), 1670, 1570, 1410 (N—C=O, amide I, II, and III bands) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.31 (br, 1H, —NH), 4.00 (s, 2H, —CH_2—Cl), 1.25–1.75 (m, 11H, cyclohexyl —CH_2—). Anal. Calcd for $C_8H_{14}ClNO$ (175): C, 54.70; H, 8.03; N, 7.97. Found: C, 54.55; H, 8.01; N, 8.01.

2-Chloro-N-(3-nitro-phenyl)acetamide **1b**. Yellow solid; yield 78%, mp 159–160°C. IR (KBr) υ: 1680 (C=O), 3278 (NH) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.57–8.62 (m, 5H, Ar-H, and —NH), 4.22 (s, 2H, —CH_2—Cl). Anal. Calcd for $C_8H_7ClN_2O_3$ (214): C, 44.77; H, 3.29; N, 13.05. Found: C, 44.71; H, 3.24; N, 13.09.

2-Chloro-N-(4-nitro-phenyl)acetamide **1c**. Yellow solid; yield 82%, mp 161–162°C. IR (KBr) υ: 1683 (C=O), 3277 (NH) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.59–8.66 (m, 5H, Ar-H, and —NH), 4.24 (s, 2H, —CH_2—Cl), Anal. Calcd for $C_8H_7ClN_2O_3$ (214): C, 44.77; H, 3.29; N, 13.05. Found: C, 44.68; H, 3.11; N, 13.00.

2-Chloro-N-(4-chloro-phenyl)acetamide **1d**. White solid; yield 65%, mp 182–183°C. IR (KBr) υ: 1670 (C=O), 3263 (NH) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.27 (br, 1H, —NH), 7.23–7.82 (m, 4H, Ar-H,), 4.21 (s, 2H, —CH_2—Cl), Anal. Calcd for $C_8H_7Cl_2NO$ (204): C, 47.09; H, 3.46; N, 6.86. Found: C, 44.98; H, 3.40; N, 6.81.

2-Chloro-N-phenylacetamide **1e**. Yellow solid; yield 65%, mp 149–150°C. IR (KBr) υ: 1669 (C=O), 3283 (NH) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.36–7.91 (m, 6H, Ar-H, and —NH), 4.23 (s, 2H, —CH_2—Cl), Anal. Calcd for C_8H_8ClNO (169): C, 56.65; H, 4.75; N, 8.26. Found: C, 56.61; H, 4.73; N, 8.19.

General Procedure for the Synthesis of **2**

To a stirred, refluxing solution of the haloacetamido compounds **1a–e** (0.2 mole) in 200 mL of ethanol, solution of sodium sulfide nonahydrate (0.1 mole) in 65 mL of water was added dropwise over a period of 25 min; the solution was added more slowly toward the end to prevent orange coloration. After refluxing for an additional 25 min, the solution was allowed to cool slowly to directly obtain pure crystals of **2a–e**.

N-Cyclohexyl-2-[(cyclohexylcarbamoyl)methylsulfanyl]acetamide **2a**. Shiny white solid; yield 69%, mp 207–208°C. IR (KBr) υ: 3280 (NH), 1655, 1570, 1410 (N—C═O, amide I, II, and III bands) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.85 (br, 2H, NH), 3.20 (s, 4H, —CH_2—S), 1.25–1.83 (m, 22H, cyclohexyl —CH_2—, and —CH—). Anal. Calcd for $C_{16}H_{28}N_2O_2S$ (312): C, 61.50; H, 9.03; N, 8.96; S, 10.26. Found: C, 61.44; H, 9.13; N, 8.78; S, 10.45.

N-(3-Nitrophenyl)-2-[(3-nitrophenylcarbamolyl)-methylsulfanyl]acetamide **2b**. Light yellow solid; yield 60%, mp 223–224°C. IR (KBr) υ: 3276 (NH) 1682, 1568, 1407 (N—C═O, amide I, II, and III bands) cm^{-1}. ^1H NMR ($CDCl_3$) δ 10.30 (br, 2H, NH), 7.43–8.56 (m, 8H, Ar-H), 3.57 (s, 4H, —CH_2—S), Anal. Calcd for $C_{16}H_{14}N_4O_6S$ (390): C, 49.23; H, 3.61; N, 14.35; S, 8.21. Found: C, 49.09; H, 3.52; N, 14.20; S, 8.33.

N-(4-Nitrophenyl)-2-[(4-nitrophenylcarbamolyl)-methylsulfanyl]acetamide **2c**. Light yellow solid; yield 68%, mp 220–221°C. IR (KBr) υ: 3280 (NH) 1679, 1568, 1398 (N—C═O, amide I, II, and III bands) cm^{-1}. ^1H NMR ($CDCl_3$) δ 10.27 (br, 2H, NH), 7.45–8.54 (m, 8H, Ar-H), 3.57 (s, 4H, —CH_2—S), Anal. Calcd for $C_{16}H_{14}N_4O_6S$ (390): C, 49.23; H, 3.61; N, 14.35; S, 8.21. Found: C, 49.29; H, 3.59; N, 14.21; S, 8.31.

N-(4-chlorophenyl)-2-[(4-chlorophenylcarbamoyl)methylsulfanyl]acetamide **2d**. Shiny white solid; yield 74%, mp 271–272°C. IR (KBr) υ: 3268 (NH) 1661, 1549, 1401 (N—C═O, amide I, II, and III bands) cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.98 (br, 2H, NH), 7.40–7.70 (m, 8H, Ar-H), 3.54 (s, 4H, —CH_2—S), Anal. Calcd for $C_{16}H_{14}Cl_2N_2O_2S$ (369): C, 52.04; H, 3.82; N, 7.59; S, 8.68. Found: C, 52.01; H, 3.79; N, 7.51; S, 8.59.

N-Phenyl-2-[(phenylcarbamolyl)methylsulfanyl]-acetamide **2e**. Light yellow solid; yield 70%, mp 213–214°C. IR (KBr) υ: 3286 (NH) 1665, 1561, 1398 (N—C═O, amide I, II, and III bands) cm^{-1}. ^1H NMR ($CDCl_3$) δ 11.05 (br, 2H, NH), 7.13–7.36 (m, 10H, Ar-H), 3.28 (s, 4H, —CH_2—S), Anal. Calcd for $C_{16}H_{16}N_2O_2S$ (300): C, 63.98; H, 5.37; N, 9.33; S, 10.67. Found: C, 63.91; H, 5.28; N, 8.29; S, 10.63.

General Procedure for the Synthesis of **3**

A solution of glyoxal was prepared by refluxing a mixture of 168 mg (0.8 mmole, 2.4 mmole as a monomer) of glyoxal trimer dihydrate and 15 mL of methanol for 1 h under magnetical stirring. The diacetoamido sulfide **2a–e**, (2.0 mmol) was dissolved in the solution by application of heat and, if necessary, addition of the appropriate amount of a co-solvent such as dioxane (benzene and dichloromethane may also be used) to keep the diacetamido sulfide in solution. To the still warm solution (ca. 40–50°), a solution of sodium methoxide (50 mg of sodium dissolved in 5 mL of methanol) was added dropwise via a hypodermic syringe over a period of 5–10 min. In course of the addition, crystals began to precipitate and thick slurry was formed rapidly. After stirring for 30 min, the crystals were collected by filtration and washed with methanol. The filtrate was diluted with water, and the precipitate was collected and recrystallized.

Thiophene-2,5-dicarboxylic Acid Bis(cyclohexylamide) **3a**. White solid; yield 45%, mp 237–238°C. IR (KBr) υ: 3285 (NH) 1648, 1487, 1378 (N—C═O, amide I, II, and III bands) cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.13–7.93 (m, 4H, thiophene —CH, and —NH), 1.24–1.83 (m, 22H, cyclohexyl —CH_2). ^{13}C NMR peaks ($CDCl_3$, TMS, δ ppm): 169.08, 156.11, 50.80, 36.91, 26.01, 25.51 Anal. Calcd for $C_{18}H_{26}N_2O_2S$ (334): C, 64.64; H, 7.84; N, 8.38; S, 9.59. Found: C, 64.60; H, 7.64; N, 8.11; S, 9.52.

Thiophene-2,5-dicarboxylic Acid Bis[(3-nitrophenyl)amide] **3b**. Yellow solid; yield 60%, mp 253–254°C. IR (KBr) υ: 3271 (NH) 1655, 1570, 1398 (N—C═O, amide I, II, and III bands) cm^{-1}. ^1H NMR ($CDCl_3$) δ 10.42 (br, 2H, NH), 7.39–8.21 (m, 10H, Ar-H, and thiophene —CH). ^{13}C NMR peaks ($CDCl_3$, TMS, δ ppm): 169.05, 159.26, 156.18, 154.00, 138.01, 129.91, 127.01. Anal. Calcd for $C_{18}H_{12}N_4O_6S$ (412): C, 52.43; H, 2.93; N, 13.59; S, 7.78. Found: C, 52.40; H, 2.90; N, 13.55; S, 7.72.

Thiophene-2,5-dicarboxylic Acid Bis[(4-nitrophenyl)amide] **3c**. Yellow solid; yield 65%, mp 249–250°C. IR (KBr) υ: 3280 (NH) 1649, 1570, 1402 (N—C═O, amide I, II, and III bands) cm^{-1}. ^1H NMR ($CDCl_3$) δ 10.41 (br, 2H, NH), 7.41–8.20 (m, 10H, Ar-H, and thiophene —CH). ^{13}C NMR peaks ($CDCl_3$,

TMS, δ ppm): 169.05, 159.27, 156.17, 154.01, 139.00, 129.90, 127.02. Anal Calcd for $C_{18}H_{12}N_4O_6S$ (412): C, 52.43; H, 2.93; N, 13.59; S, 7.78. Found: C, 52.41; H, 2.90; N, 13.57; S, 7.70.

Thiophene-2,5-dicarboxylic Acid Bis[(4-chlorophenyl)amide] **3d**. White solid; yield 65%, mp 201–302°C. IR (KBr) υ: 3265 (NH) 1655, 1570, 1411 (N—C=O, amide I, II, and III bands) cm^{-1}. ^1H NMR ($CDCl_3$) δ 10.49 (br, 2H, NH), 7.41–8.22 (m, 10H, Ar-H, and thiophene —CH). ^{13}C NMR peaks ($CDCl_3$, TMS, δ ppm): 169.05, 158.92, 156.11, 153.82, 129.99, 128.81, 125.91. Anal Calcd for $C_{18}H_{12}Cl_2N_2O_2S$ (391): C, 55.25; H, 3.09; N, 7.16; S, 8.19. Found: C, 55.20; H, 3.07; N, 7.12; S, 8.11.

Thiophene-2,5-dicarboxylic Acid Bis(phenylamide) **3e**. Yellow solid; yield 60%, mp 243–244°C. IR (KBr) υ: 3280 (NH) 1640, 1559, 1417 (N—C=O, amide I, II, and III bands) cm^{-1}. ^1H NMR ($CDCl_3$) δ 10.93 (br, 2H, NH), 7.36–7.93 (m, 12H, Ar-H, and thiophene —CH). ^{13}C NMR peaks ($CDCl_3$, TMS, δ ppm): 169.05, 159.28, 156.10, 153.99, 130.05, 129.91, 126.95. Anal Calcd for $C_{18}H_{14}N_2O_2S$ (322): C, 67.06; H, 4.38; N, 8.69; S, 9.95. Found: C, 66.98; H, 4.31; N, 8.63; S, 9.95.

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