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Convenient, Efficient Synthesis of Amide-Thioethers in Ionic Liquids

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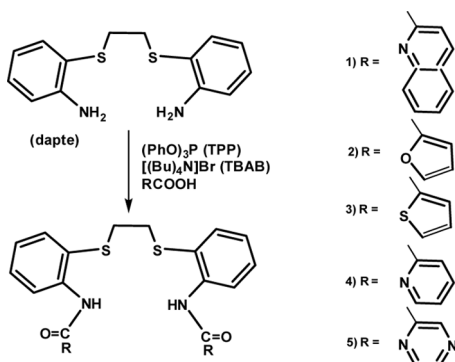
CONVENIENT, EFFICIENT SYNTHESIS OF AMIDE-THIOETHERS IN IONIC LIQUIDS

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GRAPHICAL ABSTRACT



Abstract An improved method for the synthesis of carboxamide ligands containing thioether donor sites is described. This replaces the pyridine as the reaction medium used in the classical method by tetrabutylammonium bromide. The desired products, 1,4-bis[o-(R-2-carboxamidophenyl)]-1,4-dithiobutane, R = quinoline (1), furan (2), thiophene (3), pyridine (4), and pyrazine (5), were obtained in good yields and shorter reaction times.

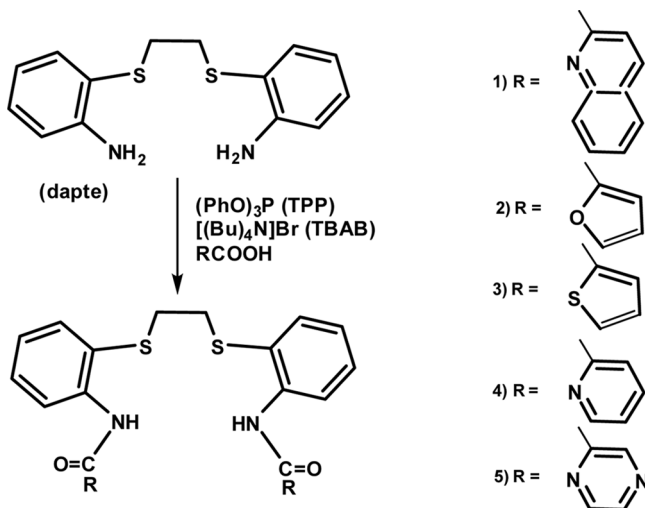
Keywords Amide-thioethers; environmentally friendly conditions; ionic liquid; synthesis

INTRODUCTION

The transition-metal coordination chemistry of flexible hybrid N,S-donor ligands in designing new molecular architectures^[1,2] and in bioinorganic chemistry^[3–5] has been the focus of growing attention.^[6–9] Many of these efforts have been devoted to the design and synthesis of new caboxamide ligands, and the standard preparation method uses pyridine as the solvent.^[10–15] Drawbacks of this method include modest yields as well as potential health hazards resulting from the pyridine solvent. Thus, preparation

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Scheme 1. Synthesis of amide-thioethers in ionic liquid, TBAB, as reaction medium.

of differently functionalized carboxamide ligands under green conditions with shorter reaction time and better yield would be highly desirable for a range of applications. In this context, we have recently developed a benign and efficient method for the synthesis of these ligands using tetrabutylammonium bromide (TBAB) as the reaction medium, eliminating the necessity to use pyridine as solvent.^[16]

Described here is an extension of this technique to new carboxamide ligands that incorporate thioether donor sites. We report the synthesis of three new ligands (**1–3**), plus two previously reported ones (**4** and **5**),^[3] from the appropriate precursors using TBAB as the reaction medium (Scheme 1).

RESULTS AND DISCUSSION

Our goal was to apply the newly developed method of synthesis that we used for carboxamides^[16] to the production of amide-thioethers in the ionic liquid, TBAB. We demonstrate here that the coupling between the diamine thioether and carboxylic acid occurs under benign conditions with moderate to excellent yields, when pyridine is replaced by TBAB as the reaction medium (Scheme 1). To optimize the reaction conditions, the reaction temperature, period of heating, and amount of TBAB were examined. Interestingly, the reaction time was reduced from 5 h in the established method^[3] to 1 h in the new method and better yields were obtained in most cases.

The spectral analysis showed infrared (IR) bands for N–H and C=O groups in their respective regions, listed in the Experimental section. The ¹H NMR spectra display resonances for the amidic N–H's, aromatic ring protons, and aliphatic protons in the 9.21–11.47, 6.55–9.45, and 2.90–3.16 regions respectively. The mass spectral data and elemental analyses are in excellent agreement with the molecular weight of the amide-thioethers prepared by this method.

EXPERIMENTAL

Materials

All solvents and chemicals were purchased from Merck and Aldrich (Grade Pro Analysis). 1,2-Di(o-aminophenylthio)ethane (DAPTE) was prepared using the reported procedure.^[2] ¹H NMR spectra were recorded on a Bruker Avance 500 (500-MHz) spectrometer. Infrared (IR) spectra were obtained with a ATI Mattson Research Series II Fourier transform (FT)–IR spectrophotometer. The mass spectra were recorded using a Waters micromass Q-TOF-2 spectrometer in positive-ion mode. Elemental analyses were performed using a CE440 elemental analyzer.

General Procedures

A dried, 25-mL, round-bottom flask was charged with triphenylphosphite (TPP) (10 mmol, 3.10 g), tetrabutylammonium bromide (TBAB) (5 mmol, 1.61 g), the appropriate carboxylic acid (10 mmol), and DAPTE (5 mmol, 1.38 g). The flask was placed in an oil bath, and the reaction mixture was heated until a homogeneous solution was formed. The solution was stirred for 1 h at 120 °C. The viscous slurry was treated with 10 ml methanol, and the resulting solid was filtered off, washed with cold ethanol, and dried in vacuo.

Selected Data

1,4-Bis[o-(quinoline-2-carboxamidophenyl)]-1,4-dithiobutane (1). White solid (yield: 91%). IR (KBr, cm⁻¹) 3297 (N-H), 1685 (C=O). ¹H NMR (500 MHz, CDCl₃): δ (ppm from TMS): 11.47 (s, 2H, amide NH), 8.67(d, 2H, ArH), 8.14 (d, 2H, ArH), 8.10 (d, 2H, ArH), 7.92 (d, 2H, ArH), 7.78 (d, 2H, ArH), 7.63 (t, 2H, ArH), 7.59 (d, 2H, ArH), 7.55 (m, 2H, ArH), 7.40 (t, 2H, ArH), 7.03 (t, 2H, ArH), 3.16 (s, 4H, SCH₂). ESI-MS: *m/z* = 609.14 [M + Na]⁺. Anal. calcd. for C₃₄H₂₆N₄O₂S₂: C, 69.60; H, 4.47; N, 9.55. Found: C, 69.10; H, 4.40; N, 9.52.

1,4-Bis[o-(furan-2-carboxamidophenyl)]-1,4-dithiobutane (2). White solid (yield: 60%). IR (KBr, cm⁻¹) 3343 (N-H), 1682 (C=O). ¹H NMR (500 MHz, CDCl₃): δ (ppm from TMS): 9.50 (s, 2H, amide NH), 8.56 (d, 2H, ArH), 7.50 (m, 4H, ArH), 7.40 (t, 2H, ArH), 7.24 (d, 2H, ArH), 7.06 (t, 2H, ArH), 6.55 (t, 2H, ArH), 2.91 (s, 4H, SCH₂). ESI-MS: *m/z* = 487.09 [M + Na]⁺. Anal. calcd. for C₂₄H₂₀N₂O₄S₂: C, 62.05; H, 4.34; N, 6.03. Found: C, 61.50; H, 4.25; N, 6.12.

1,4-Bis[o-(thiophene-2-carboxamidophenyl)]-1,4-dithiobutane (3). White solid (yield: 50%). IR (KBr, cm⁻¹) 3315 (N-H), 1650 (C=O). ¹H NMR (500 MHz, CDCl₃): δ (ppm from TMS): 9.21 (s, 2H, amide NH), 8.52 (d, 2H, ArH), 7.67 (d, 2H, ArH), 7.54 (d, 2H, ArH), 7.49 (d, 2H, ArH), 7.41 (t, 2H, ArH), 7.13 (t, 2H, ArH), 7.07 (t, 2H, ArH), 2.90 (s, 4H, SCH₂). ESI-MS: *m/z* = 519.04 [M + Na]⁺. Anal. calcd. for C₂₄H₂₀N₂O₂S₄: C, 58.04; H, 4.06; N, 5.64. Found: C, 57.60; H, 3.94; N, 5.69.

1,4-Bis[o-(pyridine-2-carboxamidophenyl)]-1,4-dithiobutane (4). White solid (yield: 90%). IR (KBr, cm⁻¹) 3287 (N-H), 1690 (C=O). ¹H NMR (500 MHz,

CDCl₃): δ (ppm from TMS): 11.18 (s, 2H, amide NH), 8.65 (d, 2H, ArH), 8.53 (d, 2H, ArH), 8.23 (d, 2H, ArH), 7.86 (t, 2H, ArH), 7.51 (d, 2H, ArH), 7.40 (m, 4H, ArH), 7.04 (t, 2H, ArH), 3.00 (s, 4H, SCH₂). ESI-MS: m/z = 509.12 [M + Na]⁺. Anal. calcd. for C₂₆H₂₂N₄O₂S₂: C, 64.17; H, 4.56; N, 11.51. Found: C, 64.22; H, 4.59; N, 11.46.

1,4-Bis[o-(pyrazine-2-carboxamidophenyl)]-1,4-dithiobutane (5). Pale yellow solid (yield: 66%). IR (KBr, cm⁻¹) 3295 (N-H), 1686 (C=O). ¹H NMR (500 MHz, CDCl₃): δ (ppm from TMS): 10.86 (s, 2H, amide NH), 9.45 (s, 2H, ArH), 8.78 (d, 2H, ArH), 8.61 (d, 2H, ArH), 8.51 (d, 2H, ArH), 7.51 (d, 2H, ArH), 7.41 (t, 2H, ArH), 7.07 (t, 2H, ArH), 2.94 (s, 4H, SCH₂). ESI-MS: m/z = 511.10 [M + Na]⁺. Anal. calcd. for C₂₄H₂₀N₆O₂S₂: C, 59.00; H, 4.13; N, 16.50. Found: C, 58.5; H, 4.07; N, 17.20.

SUMMARY

We have described a new and convenient method for the synthesis of five potentially hexadentate amide-thioether ligands containing thioether donor sites. To the best of our knowledge, this is the first time that an ionic liquid has been used as the reaction media for the synthesis of the aforementioned ligands. This relatively benign method affords good yields and shorter reaction times, and, most important, replaces the toxic pyridine by TBAB. These advantages open a new avenue in the synthesis of amide-thioether ligands using more environmentally friendly conditions. Further application of TBAB in the green and efficient synthesis of other carboxamide ligands is under way in our laboratory.

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