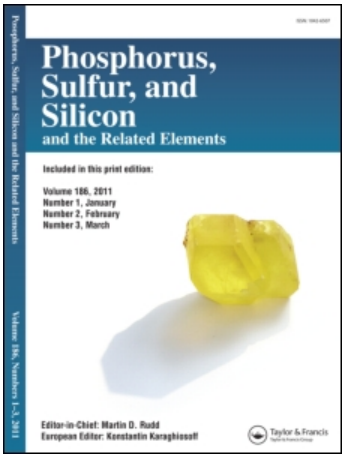

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Phase-Transfer Catalyzed Mild Synthesis of 1,5-Diacyl Thiocarbohydrazides and Their Solventless Expeditious Transformation to 1,5-Diacyl Carbohydrazides

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Phase-Transfer Catalyzed Mild Synthesis of 1,5-Diacyl Thiocarbohydrazides and Their Solventless Expeditious Transformation to 1,5-Diacyl Carbohydrazides

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1,5-diacyl thiocarbohydrazides were efficiently synthesized by the reactions of thiocarbohydrazide with a variety of aroyl chlorides at r.t. using PEG-400 as a phase-transfer catalyst. Meanwhile, 1,5-diacyl thiocarbohydrazides were be expeditiously transformed into corresponding 1,5-diacyl carbohydrazides with periodic acid by r.t. grinding a under solventless condition. This protocol has advantages of a mild condition, fast reaction rate, high yield, and simple work-up procedure.

Keywords 1,5-diacyl thiocarbohydrazide; 1,5-diacyl carbohydrazide; phase-transfer catalysis; solventless

INTRODUCTION

Thiocarbohydrazide derivatives have attracted much attention in recent years due to their applications in the synthesis of heterocyclic compounds,[1] synthesis of transition metal complexes,[2] and pharmacological studies.[3]

Meanwhile, carbohydrazide derivatives are widely used as an oxygen scavenger (metal passivator) for water treatment systems, particularly for boiler-feed systems.[4] They also are important intermediates for metal complexes.[5] Recently, Zhao et al.[6] reported the self-assembly properties of substituted carbohydrazides. Wang et al.[7] reported the

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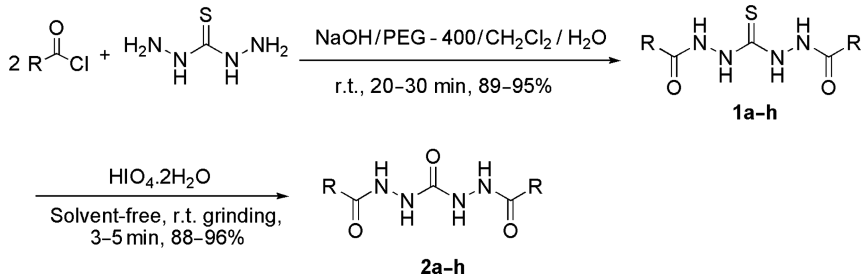

SCHEME 1

application of carbohydrazides as an inhibitor. However, the general synthetic method for carbohydrazide derivatives is to use extremely toxic phosgene as a starting material, which makes the process unsafe and environmentally unfriendly.[8]

In this article, we would like to report a mild, rapid, and high yielding method to prepare both 1,5-diacyl thiocarbohydrazides and corresponding 1,5-diacyl carbohydrazides in one route by using phase-transfer catalysis and a solventless grinding method, respectively.

RESULTS AND DISCUSSION

Reactions of thiocarbohydrazide with two equivalents of aroyl chlorides at r.t. using poly(ethylene glycol-400) (PEG-400) as a liquid–liquid phase transfer catalyst and sodium hydroxide as a base afforded 1,5-diacyl thiocarbohydrazides (**1a–h**) in a high yield (Scheme 1). In fact, all the reactions were very efficient. Although water was used as a solvent together with methylene chloride, no any hydrolysates were observed. The different substituents on aryl rings had no obvious effect on the reaction rate and yield. The reaction also was suitable to the furan heterocycle (compound **1h**). All the products were easily separated from the mixture by extraction.

Further, compounds **1a–h** were ground with periodic acid in an agate mortar with a pestle under solvent-free conditions to readily afford 1,5-diacyl carbohydrazides (**2a–h**) in an excellent yield. It was found that the periodic acid was quite an efficient reagent for the reactions. No byproducts were observed. The 1:1 molar ratio for the two reactants and about a 3–5 min reaction time were the optimized condition for giving a high yield (Table I).

From the room-temperature ^{1}H NMR spectrum of compound **1a** in DMSO-d_6, an interesting result was observed. Although there were two different kinds of NH protons in compound **1a**, four significant

TABLE I The Synthesis of Compounds 1a–h and 2a–h

Compound	R	Reaction time (min)	M.P. (°C)	Yield (%)[a]
1a	C_6H_5	30	190–192	95
1b	4-$CH_3OC_6H_4$	25	184–185	93
1c	2-$CH_3C_6H_4$	30	184–186	89
1d	3-$CH_3C_6H_4$	30	156–158	90
1e	2-ClC_6H_4	25	184–186	89
1f	4-ClC_6H_4	20	188–190	91
1g	4-BrC_6H_4	20	224–225	91
1h	Fur-2-yl	25	130–132	95
2a	C_6H_5	3	206–207	96
2b	4-$CH_3OC_6H_4$	4	203–205	94
2c	2-$CH_3C_6H_4$	4	218–219	90
2d	3-$CH_3C_6H_4$	4	180–182	91
2e	2-ClC_6H_4	3	219–220	89
2f	4-ClC_6H_4	3	241–243	88
2g	4-BrC_6H_4	5	246–248	90
2h	Fur-2-yl	4	204–205	95

[a]Yields refer to the isolated product.

NH single peaks at 10.59, 10.47, 10.22, and 9.80 ppm appeared. However, the high temperature ^{1}H NMR spectrum at 60°C for compound **1a** showed that the four peaks for NH protons were changed into two broad peaks at 9.91 and 9.06 ppm. The similar situations were also observed for compounds **1b–h**. IR spectra of compounds **1a–h** showed the characteristic absorptions at 3194–3254 cm^{-1} for N-H, 1676–1691 cm^{-1} for C=O, and 1250–1259 for C=S.

In addition, ^{1}H NMR spectra of compounds **2a–h** in DMSO-d_6 showed proton peaks at 10.10–10.23 and 8.32–8.53 ppm for NH groups. IR spectra of compounds **2a–h** showed the characteristic absorptions at 3196–3288 cm^{-1} for N-H and 1661–1688 cm^{-1} for C=O.

In summary, we have developed an efficient method to prepare both 1,5-diacyl thiocarbohydrazides and 1,5-diacyl carbohydrazides in one route. This protocol has advantages of a mild reaction condition, short reaction time, high yield, low cost of the catalyst, and simple handling procedure. It is a good alternative to the synthesis of carbohydrazide derivatives without using extremely toxic phosgene as a starting material.

EXPERIMENTAL

IR spectra were recorded using KBr pellets on a Digilab 300 FTIR spectrophotometer and ^{1}H NMR spectra on a Mercury-400BB instrument using $(CD_3)_2SO$ as a solvent and Me_4Si as an internal standard.

Elemental analyses were performed on a Vario E1 Elemental Analysis instrument. Mass spectra were recorded on a QP-1000A GC-MS using the impact mode (70 eV). Melting-points were observed in an electrothermal melting-point apparatus. Aroyl chlorides were prepared by the reactions of corresponding substituted benzoic acids with thionyl chloride. Thiocarbohydrazide was prepared according to the literature procedure.[9]

General Procedure for the Preparation of Compounds 1a–h

To a solution of sodium hydroxide (10 mmol), thiocarbohydrazide (5 mmol), and PEG-400 (0.15 mmol) in 10 mL of water, aroyl chlorides (12 mmol) in 10 mL of CH_2Cl_2 were added dropwise. Then the mixture was stirred for an appropriate time indicated in Table I. The completion of the reaction was monitored by TLC using petroleum ether, acetone, and chloroform (5:2:2) as an eluent. Then the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2X5 mL). The combined organic solution was dried by anhydrous Na_2SO_4. The solvent was evaporated off, and the residue was crystallized from EtOH-DMF-H_2O (6:3:1) to give a product. The analytic data for compounds **1a–h** follow:

1a: White crystal. ^{1}H NMR: (DMSO-d_6, 400 MHz): δ 10.59 (s, 1H, NH), 10.47 (s, 1H, NH), 10.22 (s, 1H, NH), δ 9.80 (s, 1H, NH), 7.47–7.95 (m, 10H, Ar-H). IR: (KBr, ν, cm^{-1}): 3254 (N-H), 1676(C=O), 1254(C=S). MS: m/z, 314 (M^+). Anal. calcd. for $C_{15}H_{14}N_4O_2S$: C, 57.31; H, 4.49; N, 17.82. Found: C, 57.19; H, 4.56; N, 17.73.

1b: White crystal. ^{1}H NMR: (DMSO-d_6, 400 MHz): δ 10.39 (s, 1H, NH), 10.28 (s, 1H, NH), 10.10 (s, 1H, NH), 9.67 (s, 1H, NH), 7.01–7.91 (m, 8H, Ar-H), 3.82 (s, 6H, CH_3). IR: (KBr, ν, cm^{-1}): 3212 (N-H), 1687 (C=O), 1254 (C=S). MS: m/z, 374 (M^+). Anal. calcd. for $C_{17}H_{18}N_4O_4S$:C, 54.53; H, 4.85; N, 14.96. Found: C, 54.42; H, 4.93; N, 14.88.

1c: White crystal. ^{1}H NMR: (DMSO-d_6, 400 MHz): δ 10.35 (s, 1H, NH), 10.23 (s, 1H, NH), 10.05 (s, 1H, NH), 9.61 (s, 1H, NH), 6.91–7.87 (m, 8H, Ar-H), 2.40 (s, 6H, CH_3). IR: (KBr, ν, cm^{-1}): 3199 (N-H), 1681 (C=O), 1253 (C=S). MS: m/z, 342 (M^+). Anal. calcd. for $C_{17}H_{18}N_4O_2S$:C, 59.63; H, 5.30; N, 16.36. Found: C, 59.52; H, 5.25; N, 16.47.

1d: White crystal. ^{1}H NMR: (DMSO-d_6, 400 MHz): δ 10.33 (s, 1H, NH), 10.22 (s, 1H, NH), 10.03 (s, 1H, NH), 9.58 (s, 1H, NH), 6.90–7.88 (m, 8H, Ar-H), 2.39 (s, 6H, CH_3). IR: (KBr, ν, cm^{-1}): 3194 (N-H), 1680 (C=O), 1252 (C=S). MS: m/z, 342 (M^+). Anal. calcd. for $C_{17}H_{18}N_4O_2S$:C, 59.63; H, 5.30; N, 16.36. Found: C, 59.71; H, 5.37; N, 16.41.

1e: White crystal. ^{1}H NMR: (DMSO-d_6, 400 MHz): δ 10.63 (s, 1H, NH), 10.51 (s, 1H, NH), 10.26 (s, 1H, NH), δ 9.82 (s, 1H, NH), 7.51–8.01

(m, 8H, Ar-H). IR: (KBr, ν, cm^{-1}): 3215 (N-H), 1688 (C=O), 1255 (C=S). MS: m/z, 382 (M^+). Anal. calcd. for $C_{15}H_{12}Cl_2N_4O_2S$:C, 47.01; H, 3.16; N, 14.62. Found: C, 46.91; H, 3.22; N, 14.70.

1f: White crystal. ^1H NMR: (DMSO-d_6, 400 MHz): δ 10.64 (s, 1H, NH), 10.50 (s, 1H, NH), 10.28 (s, 1H, NH), δ 9.83 (s, 1H, NH), 7.53–8.00 (m, 8H, Ar-H). IR: (KBr, ν, cm^{-1}): 3216 (N-H), 1688 (C=O), 1256 (C=S). MS: m/z, 382 (M^+). Anal. calcd. for $C_{15}H_{12}Cl_2N_4O_2S$:C, 47.01; H, 3.16; N, 14.62. Found: C, 47.12; H, 3.08; N, 14.56.

1g: White crystal. ^1H NMR: (DMSO-d_6, 400 MHz): δ 10.69 (s, 1H, NH), 10.56 (s, 1H, NH), 10.31 (s, 1H, NH), δ 9.86 (s, 1H, NH), 7.58–8.08 (m, 8H, Ar-H). IR: (KBr, ν, cm^{-1}): 3217 (N-H), 1689 (C=O), 1258 (C=S). MS: m/z, 470 (M^+). Anal. calcd. for $C_{15}H_{12}Br_2N_4O_2S$:C, 38.16; H, 2.56; N, 11.87. Found: C, 38.07; H, 2.66; N, 11.96.

1h: White crystal. ^1H NMR: (DMSO-d_6, 400 MHz): δ 10.58 (s, 1H, NH), 10.47 (s, 1H, NH), 10.23 (s, 1H, NH), 9.74 (s, 1H, NH), 7.46–7.95 (m, 6H, Fu-H). IR: (KBr, ν, cm^{-1}): 3204 (N-H), 1679 (C=O), 1250 (C=S). MS: m/z, 294 (M^+). Anal. calcd. for $C_{11}H_{10}N_4O_4S$:C, 44.89; H, 3.43; N, 19.04. Found: C, 44.94; H, 3.51; N, 19.14.

General Procedure for the Preparation of Compounds 2a–h

Compounds **1a–h** (0.5 mmol) and $HIO_4.2H_2O$ (0.5 mmol) were added to an agate mortar (6 cm in diameter). Then the mixture was ground with a pestle at r.t. for the appropriate time indicated in Table I. The completion of the reaction was monitored by TLC using petroleum ether, acetone, and chloroform (2:3:3) as an eluent. The resulting solid was washed with H_2O (3X5 mL) and recrystallized from EtOH-DMF-H_2O (6:3:1) to give the product. The analytic data for compounds **2a–h** follows:

2a: White crystal. ^1H NMR (DMSO-d_6): δ 10.17 (s, 2H, NH), 8.34 (bs, 2H, NH), 7.36–7.75 (m, 9H, Ar-H). IR (KBr, ν, cm^{-1}): 3272 (N-H), 1668 (C=O). MS: m/z, 298 (M^+). Anal. calcd. for $C_{15}H_{14}N_4O_3$: C, 60.40; H, 4.73; N, 18.78. Found: C, 60.29; H, 4.88; N, 18.84.

2b: White crystal. ^1H NMR (DMSO-d_6): δ 10.19 (s, 2H, NH), 8.36 (bs, 2H, NH), 7.38–7.77 (m, 8H, Ar-H), 3.85 (s, 6H, CH_3). IR (KBr, ν, cm^{-1}): 3212 (N-H), 1664 (C=O). MS: m/z, 358 (M^+). Anal. calcd. for $C_{17}H_{18}N_4O_5$: C, 56.96; H, 5.10; N, 15.63. Found: C, 57.03; H, 5.02; N, 15.51.

2c: White crystal. ^1H NMR (DMSO-d_6): δ 10.16 (s, 2H, NH), 8.33 (bs, 2H, NH), 7.34–7.74 (m, 8H, Ar-H), 2.35 (s, 6H, CH_3). IR (KBr, ν, cm^{-1}): 3196 (N-H), 1662 (C=O). MS: m/z, 326 (M^+). Anal. calcd. for $C_{17}H_{18}N_4O_3$: C, 62.54; H, 5.60; N, 17.16. Found: C, 62.66; H, 5.68; N, 17.21.

2d: White crystal. ^{1}H NMR (DMSO-d_6): δ 10.15 (s, 2H, NH), 8.32 (bs, 2H, NH), 7.34–7.73 (m, 8H, Ar-H), 2.34 (s, 6H, CH_3). IR (KBr, ν, cm^{-1}): 3271 (N-H), 1661 (C=O). MS: *m/z*, 326 (M^+). Anal. calcd. for $C_{17}H_{18}N_4O_3$: C, 62.54; H, 5.60; N, 17.16. Found: C, 62.47; H, 5.51; N, 17.09.

2e: White crystal. ^{1}H NMR (DMSO-d_6): δ 10.20 (s, 2H, NH), 8.37 (bs, 2H, NH), 7.35–7.80 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 3264 (N-H), 1668 (C=O). MS: *m/z*, 366 (M^+). Anal. calcd. for $C_{15}H_{12}Cl_2N_4O_3$: C, 49.07; H, 3.29; N, 15.26. Found: C, 49.14; H, 3.35; N, 15.19.

2f: White crystal. ^{1}H NMR (DMSO-d_6): δ 10.21 (s, 2H, NH), 8.38 (bs, 2H, NH), 7.37–7.83 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 3264 (N-H), 1668 (C=O). MS: *m/z*, 366 (M^+). Anal. calcd. for $C_{15}H_{12}Cl_2N_4O_3$: C, 49.07; H, 3.29; N, 15.26. Found: C, 48.99; H, 3.21; N, 15.32.

2g: White crystal. ^{1}H NMR (DMSO-d_6): δ 10.22 (s, 2H, NH), 8.39 (bs, 2H, NH), 7.36–7.81 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 3265 (N-H), 1670 (C=O). MS: *m/z*, 454 (M^+). Anal. calcd. for $C_{15}H_{12}Br_2N_4O_3$: C, 39.50; H, 2.65; N, 12.28. Found: C, 39.61; H, 2.70; N, 12.30.

2h: White crystal. ^{1}H NMR (DMSO-d_6): δ 10.10 (s, 2H, NH), 8.53 (bs, 2H, NH), 6.65–7.88 (m, 6H, Fu-H). IR (KBr, ν, cm^{-1}): 3263 (N-H), 1669 (C=O). MS: *m/z*, 278 (M^+). Anal. calcd. for $C_{11}H_{10}N_4O_5$: C, 47.49; H, 3.62; N, 20.14. Found: C, 47.56; H, 3.54; N, 20.20.

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