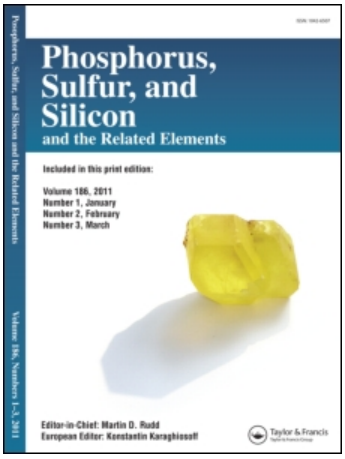

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Rapid Synthesis of *N*-Acyl Ureas from Their Thio Analogues Using Wet Silica-Supported Permanganate Under Solvent-Free Conditions

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To cite this Article Li, Zheng , Yu, Jin-Lan , Shi, Sheng-Yi and Zhu, Wei(2006) 'Rapid Synthesis of *N*-Acyl Ureas from Their Thio Analogues Using Wet Silica-Supported Permanganate Under Solvent-Free Conditions', Phosphorus, Sulfur, and Silicon and the Related Elements, 181: 5, 1031 — 1037
To link to this Article: DOI: 10.1080/10426500500272343
URL: http://dx.doi.org/10.1080/10426500500272343

Phosphorus, Sulfur, and Silicon, 181:1031–1037, 2006

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500500272343

Taylor & Francis
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Rapid Synthesis of *N*-Acyl Ureas from Their Thio Analogues Using Wet Silica-Supported Permanganate Under Solvent-Free Conditions

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A rapid method to N*-acyl ureas from corresponding* N*-acyl thioureas is described.* N*-coumaroyl-*N′*-arylthioureas, which are easily prepared by the reaction of coumarin-3-carboxylic acid chloride with potassium thiocyanate and arylamines, can be expeditiously transformed into corresponding* N*-acyl ureas via r.t. grinding with wet silica supported potassium permanganate under solvent-free conditions in an excellent yield.*

Keywords *N*-acyl urea; *N*-acyl thiourea; potassium permanganate; solvent-free

INTRODUCTION

N-acyl ureas are compounds of great interest because of their important biological activities[1] and their applications as intermediates for the synthesis of many important heterocyclic compounds.[2]

The general synthesis of *N*-acyl ureas involves the reactions of substituted ureas with acyl chlorides at elevated temperatures[3] the rather the slow reaction of amides with isocyanates[4] and the reaction of amines with unstable *N*-acyl isocyanates.[5] Recently, methods by the reaction of *S*-allyl *N*-acylmonothiocarbamates with amines[6] and the rearrangement of *O*-acyl isoureas[7] have also been reported. Very recently, we

Received April 28, 2005; accepted April 28, 2005.
The authors thank the Chun-Hui Project of the Minister of Education of China (Z2004-1-62034) for the financial support of this work.
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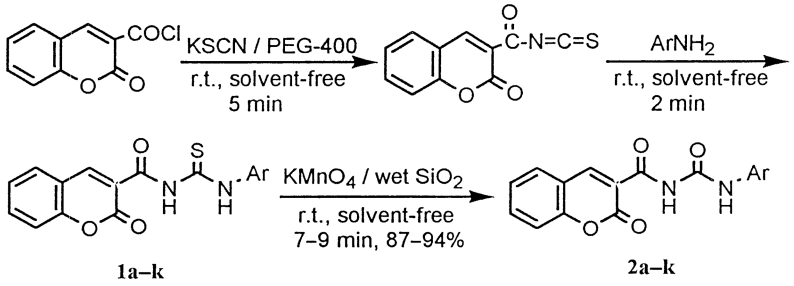
have found that *N*-acyl ureas can be generated from corresponding *N*-acyl thioureas by refluxing a suspension of the substrate in an aqueous solution of potassium iodate for several hours.[8] This new route thoroughly eliminated the employment of very toxic phosgene, which was the starting material of isocyanates, and therefore represented a good alternative to *N*-acyl ureas. As a part of our ongoing studies, herein we report a more expeditious solvent-free strategy for *N*-acyl ureas from their thio analogues by r.t. grinding with wet silica supported potassium permanganate.

In a typical investigation, we selected ureas containing a coumaroyl moiety as target products, which might be good candidates for biologically active[9] or optically active[10] compounds.

RESULTS AND DISCUSSION

The required *N*-coumaroyl-*N'*-arylthioureas (**1a–k**) were easily prepared by solvent-free grinding of coumarin-3-formyl chloride with potassium thiocyanate in the presence of a catalytic amount of poly(ethylene glycol)-400 (PEG-400) followed by further grinding with arylamines at r.t. in a high yield. Compounds **1a–k** were further ground with an equivalent of wet silica supported potassium permanganate in a mortar under a solvent-free condition at r.t. to afford *N*-coumaroyl-*N'*-arylureas (**2a–k**) in an excellent yield (Scheme 1). The overall reactions studied were complete within 14–16 minutes with slightly quicker rate for aryl rings bearing electron-donating groups and slightly slower for those bearing electron-withdrawing groups. The products could be readily obtained by extracting the resulting mixture with DMF.



SCHEME 1 **a**: Ar=C_6H_5; **b**: Ar=$O_2NC_6H_4$; **c**: Ar=3-$O_2NC_6H_4$; **d**: Ar=4-$O_2NC_6H_4$; **e**: Ar=3-BrC_6H_4; **f**: Ar=4-BrC_6H_4; **g**: Ar=2-ClC_6H_4; **h**: Ar=4-ClC_6H_4; **i**: Ar=4-CH3OC_6H_4; **j**: Ar=1-Naphthyl; **k**: Ar=2-Naphthyl.

The reagent, potassium iodate, used in the literature[8] also was tested for the solvent-free reaction; however, no products were observed

although it gave good yields in aqueous solution after a long period of refluxing.

In conclusion, *N*-acyl ureas could be easily generated from the corresponding *N*-acyl thioureas. The features of expeditiousness, the ease of handling, the high yield, and the solvent-free and phosgene-free procedure allow this protocol to be well suitable to the synthesis of ureas bearing various *N*-acyl substituents.

EXPERIMENTAL

IR spectra were recorded using KBr pellets on an Alpha Centauri FTIR spectrophotometer and ^{1}H NMR spectra on a FT-80A instrument using $(CD_3)_2SO$ as solvent and Me_4Si as internal standard. Elemental analyses were performed on a Carlo-Erba 1106 Elemental Analysis instrument. Mass spectra were recorded on a QP-1000A GC-MS using the impact mode (70 eV). Melting points were observed in a melting point apparatus and are uncorrected. Coumarin-3-formyl chloride was prepared by refluxing coumarin-3-carboxylic acid with thionyl chloride.

General Procedure for the Preparation of Compounds 1a–k

To 3 mmol of coumarin-3-formyl chloride, 4.5 mmol of potassium thiocyanate and 0.1 mmol of PEG-400 were added. The mixture was ground in a mortar with a pestle for 5 min at r.t., then 2.95 mmol of arylamine was added, and the reaction mixture was ground for additional 2 min at r.t. until TLC indicated the completion of the reaction. To the resulting mixture, 20 mL of distilled water was added, then the slurry was filtered, and the solid was washed with 3 × 5 mL of water and recrystallized from DMF-EtOH-H_2O (6:3:1) to give the products. The physical and spectral data of compounds **1a–k** follow.

1a: Yellow solid. yield: 89%. m.p: 218–220°C. ^{1}H NMR (200 MHz, DMSO-d_6) δ12.39 (s, 1H, NH), 11.77 (s, 1H, NH), 9.12 (s, 1H, =CH), 7.33–8.06 (m, 9H, Ar-H). IR (KBr, ν, cm^{-1}): 3201 (N–H), 1717, 1663 (C=O), 1153 (C=S). MS (*m/z*): 324 (M^+). Anal. calcd. for $C_{17}H_{12}N_2O_3S$: C, 62.95; H, 3.73; N, 8.64%. Found: C, 62.86; H, 3.90; N, 8.51%.

1b: Yellow solid. yield: 93%. m.p: 232–233°C. ^{1}H NMR (200 MHz, DMSO-d_6) δ12.63 (s, 1H, NH), 11.93 (s, 1H, NH), 9.15 (s, 1H, =CH), 7.52-8.11 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 3216 (N–H), 1722, 1676 (C=O), 1158 (C=S). MS (*m/z*): 369 (M^+). Anal. calcd. for $C_{17}H_{11}N_3O_5S$: C, 55.28; H, 3.00; N, 11.38%. Found: C, 55.19; H, 2.89; N, 11.52%.

1c: Yellow solid. yield: 92%. m.p: 239–241°C. ^{1}H NMR (200 MHz, DMSO-d_6) δ12.59 (s, 1H, NH), 11.92 (s, 1H, NH), 9.13 (s, 1H, =CH), 7.53–8.12 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 3217 (N–H), 1724, 1675

(C=O), 1157 (C=S). MS (*m/z*): 369 (M^+). Anal. calcd. for $C_{17}H_{11}N_3O_5S$: C, 55.28; H, 3.00; N, 11.38. Found: C, 55.17; H, 2.92; N, 11.45.

1d: Yellow solid. yield: 95%. m.p: 262°C (dec). ^{1}H NMR (200 MHz, DMSO-d_6) δ12.60 (s, 1H, NH), 11.91 (s, 1H, NH), 9.14 (s, 1H, =CH), 7.51–8.09 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 3219 (N—H), 1723, 1674 (C=O), 1161(C=S). MS (*m/z*): 369 (M^+). Anal. calcd. for $C_{17}H_{11}N_3O_5S$: C, 55.28; H, 2.98; N, 11.38%. Found: C, 55.36; H, 3.11; N, 11.20%.

1e: Yellow solid. yield: 90%. m.p: 249–251°C. ^{1}H NMR (200 MHz, DMSO-d_6) δ12.51 (s, 1H, NH), 11.82 (s, 1H, NH), 9.14 (s, 1H, =CH), 7.48–8.07 (m, 8H, Ar-H). IR (KBr,ν, cm^{-1}): 3215 (N—H), 1728, 1683 (C=O), 1145 (C= S). MS (*m/z*): 402 (M^+). Anal. calcd. for $C_{17}H_{11}N_2O_3SBr$: C, 50.63; H, 2.75; N, 6.95%. Found: C, 50.71; H, 2.63; N, 7.04%.

1f: Yellow solid. yield: 95%. m.p: 238–240°C. ^{1}H NMR (200 MHz, DMSO-d_6) δ12.55 (s, 1H, NH), 11.84 (s, 1H, NH), 9.14 (s, 1H, =CH), 7.49-8.09 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 3217 (N—H), 1730, 1686 (C=O), 1147 (C=S). MS (*m/z*): 402 (M^+). Anal. calcd. for $C_{17}H_{11}N_2O_3SBr$: C, 50.63; H, 2.75; N, 6.95%. Found: C, 50.74; H, 2.67; N, 6.86%.

1g: White solid. yield: 89%. m.p: 234–235°C. ^{1}H NMR (200 MHz, DMSO-d_6) δ12.45 (s, 1H, NH), 11.82 (s, 1H, NH), 9.13 (s, 1H, =CH), 7.44–8.06 (m, 8H, Ar-H). IR (KBr, v, cm^{-1}): 3216 (N—H), 1730, 1684 (C=O), 1145 (C=S). MS (*m/z*): 358 (M^+). Anal. calcd. for $C_{17}H_{11}N_2O_3SCl$: C, 56.91; H, 3.09; N, 7.81%. Found: C, 56.82; H, 2.99; N, 7.89%.

1h: White solid. yield: 92%. m.p: 236–237°C. ^{1}H NMR (200 MHz, DMSO-d_6) δ12.46 (s, 1H, NH), 11.83 (s, 1H, NH), 9.13 (s, 1H, =CH), 7.44–8.05 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 3218 (N—H), 1716, 1682 (C=O), 1144 (C=S). MS (*m/z*): 358 (M^+). Anal. calcd. for $C_{17}H_{11}N_2O_3SCl$: C, 56.91; H, 3.09; N, 7.81%. Found: C, 56.98; H, 3.13; N, 7.74%.

1i: White solid. yield: 95%. m.p: 252–253°C. ^{1}H NMR (200 MHz, DMSO-d_6) δ12.53 (s, 1H, NH), 11.80 (s, 1H, NH), 9.14 (s, 1H, =CH), 7.47-8.10 (m, 8H, Ar-H), 3.84 (s, 3H, OCH_3). IR (KBr, ν, cm^{-1}): 3214 (N—H), 1713, 1668 (C=O), 1157 (C=S). MS (*m/z*): 354 (M^+). Anal. calcd. for $C_{18}H_{14}N_2O_4S$: C, 61.01; H, 3.98; N, 7.90%. Found: C, 60.93; H, 3.86; N, 8.04%.

1j: Yellow solid. yield: 94%. m.p: 234–235°C. ^{1}H NMR (200 MHz, DMSO-d_6)δ12.43 (s, 1H, NH), 11.79 (s, 1H, NH), 9.13 (s, 1H, =CH), 7.51–8.09 (m, 11H, Ar-H). IR (KBr, ν, cm^{-1}): 3213 (N—H), 1718, 1665 (C=O), 1154 (C=S). MS (*m/z*): 374 (M^+). Anal. calcd. for $C_{21}H_{14}N_2O_3S$: C, 67.37; H, 3.77; N, 7.48%. Found: C, 67.28; H, 3.65; N, 7.40%.

1k: Yellow solid. yield: 88%. m.p: 243–244°C. ^{1}H NMR (200 MHz, DMSO-d_6)δ 12.44 (s, 1H, NH), 11.80 (s, 1H, NH), 9.13 (s, 1H, =CH),

7.52–8.09 (m, 11H, Ar-H). IR (KBr, ν, cm^{-1}): 3214 (N—H), 1715, 1667 (C=O), 1149 (C=S). MS (*m/z*): 374 (M^+). Anal. calcd. for $C_{21}H_{14}N_2O_3S$: C, 67.37; H, 3.77; N, 7.48%. Found: C, 67.24; H, 3.90; N, 7.53%.

General Procedure for the Preparation of Compounds 2a–k

Wet silica gel was prepared by shaking silica gel (20 g, 200–400 mesh) with distilled water (5 mL). The reagent was prepared by mixing $KMnO_4$ (1 mmol, 0.16 g) with wet silica gel (3 g) using a pestle and mortar until a fine, homogeneous, and purple powder was obtained. A mixture of *N*-acyl thioureas **1a–k** (1 mmol) and $KMnO_4$/wet SiO_2 (1 mmol) was ground with a pestle in a mortar until a color change from purple to black was observed, which required 7–9 min. Then DMF (20 mL) was added to the reaction mixture. After vigorous stirring, the solid was filtered and the filtrate was then evaporated under vacuum to remove the solvent, and the residue was crystallized from DMF-EtOH (2:1) to give the product. The physical and spectral data of compounds **2a–k** follow.

2a: White solid. yield: 93%. m.p: 208–210°C. ^1H NMR (200 MHz, DMSO-d_6) δ 10.61 (s, 1H, NH), 10.29 (s, 1H, NH), 8.89 (s, 1H, =CH), 7.32–7.93 (m, 9H, Ar-H). IR (KBr, ν, cm^{-1}): 3187 (N—H), 1690 (C=O). MS (*m/z*): 308 (M^+). Anal. calcd. for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92; N, 9.09%. Found: C, 66.14; H, 4.02; N, 8.91%.

2b: Yellowish solid. yield: 90%. m.p: 240–242°C. ^1H NMR (200 MHz, DMSO-d_6) δ10.98 (s, 1H, NH), 10.55 (s, 1H, NH), 9.06 (s, 1H, =CH), 7.51–8.09 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 3265 (N—H), 1705 (C=O). MS (*m/z*): 353 (M^+). Anal. calcd. for $C_{17}H_{11}N_3O_6$: C, 57.80; H, 3.14; N, 11.89%. Found: C, 57.76; H, 3.08; N, 11.72%.

2c: Yellowish solid. yield: 92%. m.p: 252–253°C. ^1H NMR (200 MHz, DMSO-d_6) δ 10.96 (s, 1H, NH), 10.51 (s, 1H, NH), 9.05 (s, 1H, =CH), 7.42–8.03 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 3263 (N—H), 1704 (C=O). MS (*m/z*): 353 (M^+). Anal. calcd. for $C_{17}H_{11}N_3O_6$: C, 57.80; H, 3.14; N, 11.89%. Found: C, 57.92; H, 3.24; N, 11.75%.

2d: White solid. yield: 87%. m.p: > 300°C. ^1H NMR (200 MHz, DMSO-d_6) δ 10.97 (s, 1H, NH), 10.53 (s, 1H, NH), 9.04 (s, 1H, =CH), 7.46–8.03 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 3266 (N—H), 1706 (C=O). MS (*m/z*): 353 (M^+). Anal. calcd. for $C_{17}H_{11}N_3O_6$: C, 57.80; H, 3.14; N, 11.89%. Found: C, 57.68; H, 3.11; N, 11.97%.

2e: Yellow solid. yield: 94%. m.p: 254°C (dec.). ^1H NMR (200 MHz, DMSO-d_6) δ10.80 (s, 1H, NH), 10.46 (s, 1H, NH), 8.99 (s, 1H, =CH), 7.49–8.16 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 3256 (N—H), 1697 (C=O). MS (*m/z*): 386 (M^+). Anal. calcd. for $C_{17}H_{11}N_2O_4Br$: C, 52.74; H, 2.86; N, 7.24%. Found: C, 52.81; H, 2.71; N, 7.38%.

2f: White solid. yield: 93%. m.p: 256–257°C. ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.82 (s, 1H, NH), 10.48 (s, 1H, NH), 9.00 (s, 1H, =CH), 7.46–8.07 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 3258, 3053 (N—H), 1698 (C=O). MS (*m/z*): 386 (M^+). Anal. calcd. for $C_{17}H_{11}N_2O_4Br$: C, 52.74; H, 2.86; N, 7.24%. Found: C, 52.67; H, 2.92; N, 7.12%.

2g: White solid. yield: 93%. m.p: 248–249°C. ^{1}H NMR (200 MHz, DMSO-d_6) δ10.78 (s, 1H, NH), 10.42 (s, 1H, NH), 8.92 (s, 1H, =CH), 7.39-8.02 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 3252 (N—H), 1692 (C=O). MS (*m/z*): 342 (M^+). Anal. calcd. for $C_{17}H_{11}N_2O_4Cl$: C, 59.58; H, 3.24; N, 8.17%. Found: C, 59.64; H, 3.18; N, 8.24%.

2h: Yellow solid. yield: 92%. m.p: 251–253°C. ^{1}H NMR (200 MHz, DMSO-d_6) δ10.79 (s, 1H, NH), 10.43 (s, 1H, NH), 8.93 (s, 1H, =CH), 7.37–8.08 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 3255 (N—H), 1694 (C=O). MS (*m/z*): 342 (M^+). Anal. calcd. for $C_{17}H_{11}N_2O_4Cl$: C, 59.58; H, 3.24; N, 8.17%. Found: C, 59.44; H, 3.10; N, 8.11%.

2i: White solid. yield: 91%. m.p: 252–253°C. ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.79 (s, 1H, NH), 11.46 (s, 1H, NH), 8.95 (s, 1H, =CH), 7.30–7.90 (m, 8H, Ar-H), 3.82 (s, 3H, OCH_3). IR (KBr, ν, cm^{-1}): 3246 (N—H), 1687 (C=O). MS (*m/z*): 338 (M^+). Anal. calcd. for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28%. Found: C, 63.81; H, 4.24; N, 8.19%.

2j: Orange solid. yield: 89%. m.p: >300°C. ^{1}H NMR (200 MHz, DMSO-d_6) 10.68 (s, 1H, NH), 10.32 (s, 1H, NH), 8.90 (s, 1H, =CH), 7.52–8.16 (m, 11H, Ar-H). IR (KBr, ν, cm^{-1}): 3190 (N—H), 1688 (C=O). MS (*m/z*): 358 (M^+). Anal. calcd. for $C_{21}H_{14}N_2O_4$: C, 70.39; H, 3.94; N, 7.82%. Found: C, 70.47; H, 3.78; N, 7.91%.

2k: Yellow solid. yield: 90%. m.p: >300°C. ^{1}H NMR (200 MHz, DMSO-d_6) 10.70 (s, 1H, NH), 10.31 (s, 1H, NH), 7.53–8.18 (m, 11H, Ar-H), 8.90 (s, 1H, =CH). IR (KBr, ν, cm^{-1}): 3186 (N—H), 1686 (C=O). MS (*m/z*): 358 (M^+). Anal. calcd. for $C_{21}H_{14}N_2O_4$: C, 70.39; H, 3.94; N, 7.82%. Found: C, 70.48; H, 4.05; N, 7.77%.

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