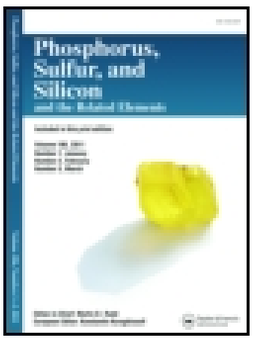

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Functionalized *N*-acylsulfenamides from primary amides

# A convenient method for the preparation of functionalized *N*-acylsulfenamides from primary amides.

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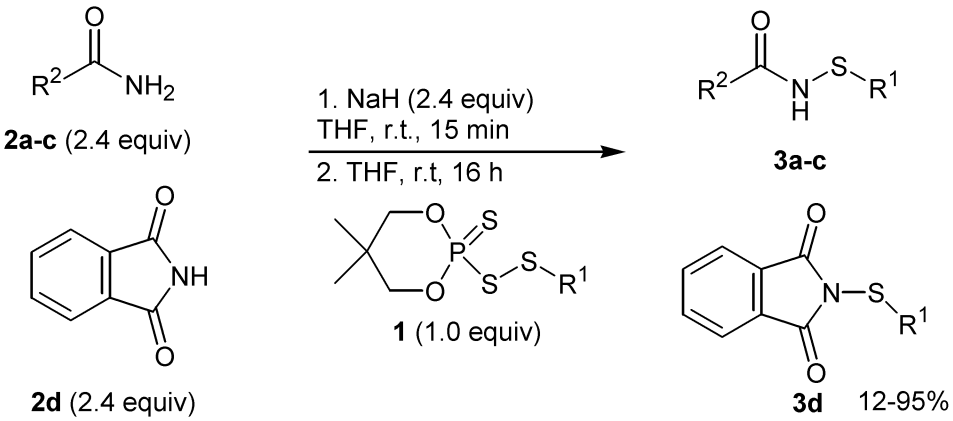
**Key words**

sulfenamide, thiols, amide, phthalimide, phosphorodithioic acid

**Abstract**

We have developed a convenient method for the synthesis of functionalized *N*-acylsulfenamides under mild conditions and in moderate to good yields. The designed method is based on the reaction of (5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)-disulfanyl derivatives with nitrogen nucleophiles generated from primary amides or imides and sodium hydride. The developed method allows for the preparation of *N*-acylsulfenamides bearing additional hydroxyl, carboxyl, or amino functionalities.



## Introduction

Sulfenamides are a class of compounds containing a trivalent nitrogen bonded to a divalent sulfur. A number of practical applications have been found for these stable and reactive sulfenylating reagents in industry, including their use as pesticides,[1,2] rubber vulcanization accelerators[1,3] and prodrugs in medicinal chemistry.[1,4] The interesting chiroptical properties of sulfenamides, based on the S-N bond, have also been studied.[5] Sulfenamides are also useful as synthetic reagents. For instance, *S*-phenyl sulfenamides have been used as a source of aminyl,[6] amidyl,[7] and thioaminyl[8] radicals. Sulfenamides have been also involved in the insertion reactions.[9] Sulfenamides have been produced as intermediates in the synthesis of disulfanes,[10] chiral amines[11] and amino acids.[12] *S,N*-diaryl sulfenamides have been utilized as a source of electrophilic arylthio units,[13] and methanesulfenamide has been used in the preparation of inversely fused bicyclic β-lactams.[14]

Although sulfenamides are quite useful functionally, their formation is generally limited to rather harsh methods that may not be compatible with other functional groups within the molecule. The synthesis of sulfenamides has been reviewed[15] recently. The most common methods for the synthesis of sulfenamides are based on the reaction of an amine or metal amide with sulfenic acid derivatives, RSX, where X may be a halogen, phthalimide, alkoxy group, or sulfur-bearing functionality.[1] Other methods involve the reaction of thiols and amines in the presence of oxidizing reagents[16] or the reaction of disulfides and amines in the presence of silver or mercuric salts.[17] Recently, sulfenamides have been obtained through the reaction of amines with glycosyl thioacetates in the presence of diethyl bromomalonate,[18] 3-phenylsulfenyl-2-(*N*-cyanoimino)thiazolidine,[19] *S*-[2-(3-oxo-1,2-benzisothiazolinyl)]-2-mercaptobenzoates[20] and *N*-

(1-alkenylthio)phthalimides,[21] respectively. Sulfenamides can also be prepared by the copper-catalyzed coupling of amines with diaryl disulfides[22] or arylthiols.[23] The literature refers to sulfenamides as $R^1$-S-$NR_2$ in which $R^1$ and R can be H, alkyl or aryl groups, whereas when one of the nitrogen R groups is an acyl group refers to them as being *N*-acylsulfenamides or N-(thioalkyl or aryl)amides. The most common methods for obtaining *N*-acylsulfenamides include the reaction of amides with *N*-sulfenylbenzimidazoles,[24] sulfenyl chlorides[25,26] and thermolysis of *N*-acetyliminodialkylsulfuranes.[27] Several methods to construct cyclic *N*-acylsulfenamides have been reported. These methods are based on the condensation of 2-(chlorocarbamoyl)-phenylsulfenyl chlorides with amines,[28] CuI-mediated reaction of 2-halo-arylamides and sulfur powder,[29] and intramolecular dehydrogenative cyclization.[30]

The major disadvantages of most of the above procedures include the thermal and moisture sensitivities of the sulfenylating reagents and their high reactivity toward nucleophilic substrates such as hydroxy and active methylene groups, as well as toward multiple bonds. These considerations prevent the synthesis of *N*-acylsulfenamides with these reactive functionalities. As a way to overcome these limitations, we designed a new method for the preparation of *N*-acylsulfenamides from 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane-2-disulfanyl derivatives **1**. The electrophilic properties of the disulfanyl derivatives **1** of phosphorodithioic acid have been previously used to produce functionalized unsymmetrical molecules such as dialkyl disulfanes,[31] alkyl-aryl disulfanes,[32] 'bioresistant' disulfanes,[33] unsymmetrical disulfanes of L-cysteine and L-cystine,[34] and diaryl disulfanes.[35] The disulfanyl derivatives **1** have also been conveniently used for the preparation of α-sulfenylated carbonyl compounds,[36] functionalized phosphorothioates[37] and symmetrical[38] and unsymmetrical[39] trisulfanes.

**Results and Discussion**

The limitations of the known methods for preparing functionalized *N*-acylsulfenamides have encouraged us to develop a new synthetic strategy. Our idea is based on the reaction of electrophilic disulfanyl derivatives of phosphorodithioic acid **1** with a nucleophilic nitrogen-centered anion generated from an amide or imide and sodium hydride (Scheme 1 and Table 1).

As the data in Table 1 demonstrate, the sulfenylation reaction of primary amides **2a-c** and phthalimide **2d** with disulfanyl derivatives **1a** and **1b** proceeds efficiently in very high yield (75-95%). This indicates that the presence of the unprotected hydroxy group did not greatly impact the sulfenylation process. However, reactions of compound **1c** ($R^1$ = Ph) with benzamide **2a** and trimethylacetamide **2c** provided *N*-acylsulfenamides **3i** and **3j** in 31% and 43% yield, respectively. In these cases, the formation of *N*-acylsulfenamides **3i** and **3j** was hampered by the formation of diphenyl disulfide (isolated in 58% and 50% yield, respectively). The presence of a carboxylic acid ester group was not tolerated under the developed conditions. The reaction of disulfanyl compound **1d** with nicotinamide **2b** and trimethylacetamide **2c** produced corresponding *N*-acylsulfenamides **3k** and **3l** in poor yield (12-20%). However, the starting material **1d** was consumed, most likely via side reactions, such as ester condensation and/or α-sulfenation,[36] which are responsible for the low yields of *N*-acylsulfenamides **3k** and **3l**. The formation of *N*-acylsulfenamides with an additional amino group was most challenging, as both hydrogens from the primary amino group had to be replaced by protective groups to avoid undesired sulfenylation. We selected compound **1e**, in which the amino functionality was

protected by two Boc groups. The reaction of disulfanyl derivative **1e** with nicotinamide **2b** and trimethylacetamide **2c** produced corresponding *N*-acylsulfenamides **3m** and **3n** in moderate yields (43-64%). However, NMR data analysis for compounds **3m** and **3n** revealed the removal of one Boc group from the protected amino group. The 2.4-fold excess of amide **2** that is required for high conversion of the reaction also appears to be responsible for the removal of one Boc group.

To demonstrate the scope and limitations of this new *N*-acylsulfenamide formation reaction, we reacted secondary amides **2e–g** with sulfenylating reagent **1a**. The 2.4 equivalents of the nitrogen nucleophile anion were generated by means of sodium hydride in tetrahydrofuran from amides **2e-g**, respectively. Then, treatment with disulfane derivative **1a** at room temperature for 16 hours afforded unexpected products **4** and **5** (Scheme 2). The results are summarized in Table 2.

The reaction of secondary amides **2e-g** with disulfanyl derivative **1a** produced didodecyldisulfane **4** and the disulfane of phosphorodithioic acid **5** in very high yields (Table 2, entry 1-3). Moreover, acetanilide **2e**, *N*-benzoylaniline **2f** and *N*-methylbenzamide **2g** were recovered in 99, 97 and 96% yield, respectively. We also performed the reaction of compound **1a** with 20 mol% of **2g** (Table 2, entry 4). We were able to isolate disulfane **4** (62%) and **5** (52%), as well as starting materials **2g** (95%) and **1a** (34%). This indicates that the amide anion is able to catalyze the formation of symmetrical disulfanes **4** and **5** from **1a**. Detailed mechanistic studies are in progress. Nevertheless, the secondary amides cannot be converted into corresponding *N*-acylsulfenamides **3** by means of disulfanyl derivatives **1** under the developed conditions.

## Conclusions

A convenient method has been developed for the preparation of functionalized *N*-acylsulfenamides **3** bearing hydroxy, ethyl ester, or tert-butoxycarbonylamino groups. Reactions of **1** with a variety of primary amides **2** in the presence of sodium hydride in tetrahydrofuran at room temperature were generally complete within 16 h and gave functionalized *N*-acylsulfenamides **3** in moderate or very good yields after purification. The simplicity and the presence of additional functional groups make this method one of the most attractive approaches for the preparation of functionalized *N*-acylsulfenamides.

## Experimental

Benzamide, nicotinamide, trimethylacetamide, phthalimide, and NaH (60% in mineral oil) are commercially available from Aldrich. 1-[(5,5-Dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)disulfanyl]dodecane (**1a**),[37a] 11-[(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)disulfanyl]undecan-1-ol (**1b**),[37a] [(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)disulfanyl]benzene (**1c**),[35] ethyl 11-[(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)disulfanyl]undecanoate (**1d**),[24a] 11-[(5,5-Dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)disulfanyl]-*N*,*N*-di-(tert-butoxycarbonyl)undecylamine (**1e**)[40] were synthesized by described procedures. THF was dried and distilled by standard procedures. Melting points are uncorrected. NMR spectra were recorded on a Varian Gemini 500 MHz or 200 MHz spectrometer. The residual solvent peak was used as internal reference ($CDCl_3$: $\delta$= 7.26 for $^1H$, $\delta$= 77.0 for $^{13}C$); $^{31}P$ NMR used an external standard as reference (85% $H_3PO_4$: $\delta$= 0). ESI-MS spectra were recorded

on a Mariner PerSeptve Biosystem. Column chromatography was performed with silica gel 60 (230–400 mesh, Merck). Preparative TLC chromatography was performed with silica gel Polygram SIL G/UV254 (Macherey-Nagel). Petroleum ether = PE.

**Synthesis of *N*-acylsulfenamides (3)**

**General Procedure**

A solution of carbonyl compound **2a**–**d** (2.4 mmol) in anhyd THF (5 mL) was added dropwise to a suspension of NaH (0.1 g, 2.5 mmol) in anhyd THF (15 mL) at r.t. under an $N_2$ atmosphere. When the evolution of $H_2$ had ceased, a soln of **1** (1.0 mmol) in anhyd THF (5 mL) was added. The mixture was stirred at r.t. for 16 h and evaporated under vacuum. The residue was dissolved in EtOAc (50 mL), washed with sat. aq $NH_4Cl$, dried ($MgSO_4$), filtered, and concentrated. The products were purified by column chromatography (Table 1). All experiments were performed in 1.0 mmol scale of **1**. Additional characterization details are provided in the Supplemental Materials.

***N*-(1-dodecylthio)benzamide (3a)**

White solid, mp 43–46 °C; $R_f$ = 0.3 (hexanes–$CH_2Cl_2$, 1:1); yield 264 mg (82%).

$^1$H NMR (200 MHz; $CDCl_3$): δ = 0.89 (t, *J* = 6.4 Hz, 3H, $CH_3$), 1.25–1.50 (m, 18H, $CH_2$); 1.55–1.75 (m, 2H, $CH_2$-C-S), 2.86 (t, *J* = 7.3 Hz, 2H, $CH_2S$), 6.90 (brs, 1H, NH), 7.40–7.60 (m, 3H, Ar), 7.72–7.85 (m, 2H, Ar).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.6, 27.8, 28.5, 28.6, 29.0, 29.1, 29.3, 29.4, 29.5, 31.8, 39.2, 127.4, 128.5, 131.9, 133.7, 169.5.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{32}NOS$: 322.2205; found: 322.2221.

**_N_-(1-dodecylthio)nicotinamide (3b)**

White solid, mp 53–55 °C; $R_f$ = 0.28 (hexanes–$CH_2Cl_2$, 1:1); yield 287 mg (89%).

$^1$H NMR (500 MHz; $CDCl_3$): δ = 0.86 (t, *J* = 6.8 Hz, 3H, $CH_3$), 1.20–1.38 (m, 16H, $CH_2$), 1.39–1.45 (m, 2H, $CH_2$), 1.62 (quint, *J* = 7.6 Hz, 2H, $CH_2$-C-S), 2.86 (t, *J* = 7.6 Hz, 2H, $CH_2S$), 7.42–7.50 (m, 1H, Ar), 7.50 (brs, 1H, NH), 8.21 (d, *J* = 7.8 Hz, 1H, Ar), 8.76 (brs, 1H, Ar), 9.10 (brs, 1H, Ar).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.6, 27.8, 28.5, 29.1, 29.2, 29.4, 29.5, 31.8, 38.7, 123.5, 129.7, 135.6, 148.3, 152.4, 168.2.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{31}N_2OS$: 323.2157; found: 323.2163.

**_N_-(1-dodecylthio)trimethylacetamide (3c)**

White solid, mp 40–42 °C; $R_f$ = 0.3 (PE–$CH_2Cl_2$, 1:1); yield 242 mg (80%).

$^1$H NMR (200 MHz; $CDCl_3$): δ = 0.87 (t, *J* = 6.4 Hz, 3H, $CH_3$), 1.18–1.40 (m, $CH_2$, 18H), 1.24 (s, 9H, tBu), 1.45-1.70 (m, 2H, $CH_2$), 2.72 (t, *J* = 7.4 Hz, 2H, $CH_2S$), 6.38 (brs, 1H, NH).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.6, 27.6, 27.7, 28.6, 29.2, 29.3, 29.4, 29.5, 29.6, 31.9, 38.4, 39.7, 180.1.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{17}H_{36}NOS$: 302.2518; found: 302.2527.

**_N_-(1-dodecylthio)phthalimide (3d)**

White solid, mp 61–63 °C; hexanes–$CH_2Cl_2$, 1:1, then $CHCl_3$; $R_f$ = 0.25 ($CHCl_3$); yield 327 mg (94%).

$^1$H NMR (200 MHz; $CDCl_3$): δ = 0.86 (t, *J* = 6.5 Hz, 3H, $CH_3$), 1.10–1.50 (m, 18H, $CH_2$); 1.50–1.70 (m, 2H, $CH_2$-C-S), 2.87 (t, *J* = 7.3 Hz, 2H, $CH_2S$), 7.73–7.84 (m, 2H, Ar), 7.87–7.98 (m, 2H, Ar).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.6, 28.1, 28.4, 29.0, 29.2, 29.3, 29.4, 29.5, 31.8, 38.6, 123.8, 132.0, 134.5, 168.5.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{30}NO_2S$: 348.1997; found: 348.2004.

***N*-(11-hydroxy-1-undecylthio)benzamide (3e)**

White solid, mp 46–48 °C; $R_f$ = 0.27 (EtOAc–$CH_2Cl_2$, 1:6); yield 243 mg (75%).

$^1$H NMR (200 MHz; $CDCl_3$): δ = 1.20–1.50 (m, 15H, OH, $CH_2$), 1.50– 1.75 (m, 4H, $CH_2$), 2.84 (t, *J* = 7.3 Hz, 2H, $SCH_2$), 3.63 (t, *J* = 6.5 Hz, 2H, $CH_2O$), 6.97 (brs, 1H, NH), 7.40–7.60 (m, 3H, Ph), 7.75–7.86 (m, 2H, Ph).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 25.6, 27.7, 28.5, 29.1, 29.3, 29.3, 29.4, 32.6, 38.7, 62.9, 127.4, 128.5, 131.9, 133.7, 169.7.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{18}H_{29}NNaO_2S$: 346.1817; found: 346.1811.

***N*-(11-hydroxy-1-undecylthio)nicotinamide (3f)**

White solid, mp 59–61 °C; $R_f$ = 0.3 (EtOAc–$CH_2Cl_2$, 1:2); yield 308 mg (95%).

$^1$H NMR (200 MHz; $CDCl_3$): δ = 1.20–1.50 (m, 14H, $CH_2$), 1.50–1.75 (m, 4H, $CH_2$), 2.87 (t, *J* = 7.3 Hz, 2H, $CH_2S$), 3.37 (brs, 1H, OH), 3.65 (t, *J* = 6.5 Hz, 2H, $CH_2O$), 7.46–7.60 (m, 1H, Ar), 7.77 (brs, 1H, NH), 8.26-8.40 (m, 1H, Ar), 8.72-8.85 (m, 1H, Ar) 9.17 (brs, 1H, Ar).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 25.6, 27.7, 28.4, 29.0, 29.2, 29.3, 32.6, 38.6, 62.7, 123.6, 129.8, 136.1, 148.1, 152.1, 168.1.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{17}H_{29}N_2O_2S$: 325.1950; found: 325.1961.

***N*-(11-hydroxy-1-undecylthio)trimethylacatamide (3g)**

Waxy solid, mp 39–41 °C; $R_f$ = 0.3 (EtOAc–$CH_2Cl_2$, 1:6); 246 mg (81%).

$^1$H NMR (200 MHz; $CDCl_3$): δ = 1.22 (s, 9H, tBu), 1.20–1.48 (m, 15H, OH, $CH_2$), 1.48-1.66 (m, 4H, $CH_2$), 2.72 (t, *J* = 7.2 Hz, 2H, $SCH_2$), 3.64 (t, *J* = 6.5 Hz, 2H, $CH_2O$); 6.39 (brs, 1H, NH).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 25.6, 27.4, 27.5, 28.4, 29.0, 29.2, 29.4, 32.6, 38.2, 39.6, 62.7, 180.3.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{16}H_{33}NNaO_2S$: 326.2130; found: 326.2143.

***N*-(11-hydroxy-1-undecylthio)phthalimide (3h)**

White solid, mp 47–49 °C; $R_f$ = 0.28 (EtOAc–$CH_2Cl_2$, 1:3); yield 329 mg (94%).

$^1$H NMR (200 MHz; $CDCl_3$): δ = 1.20–1.50 (m, 14H, $CH_2$), 1.50–1.75 (m, 4H, $CH_2$), 2.87 (t, *J* = 7.3 Hz, 2H, $CH_2S$), 3.37 (brs, 1H, OH), 3.65 (t, *J* = 6.5 Hz, 2H, $CH_2O$), 7.73–7.84 (m, 2H, Ar), 7.87–7.98 (m, 2H, Ar).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 25.6, 27.7, 28.4, 29.0, 29.1, 29.2, 29.3, 32.6, 38.6, 62.7, 123.8, 132.0, 134.5, 168.5.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{19}H_{27}NNaO_3S$: 372.1609; found: 372.1598.

***N*-(phenylthio)benzamide (3i)**

Yellowish solid, mp 113–115 °C; $R_f$ = 0.30 ($CH_2Cl_2$); yield 71 mg (31%).

$^1$H NMR (200 MHz; $CDCl_3$): δ = 7.15 – 7.65 (m, 9H, NH, Ar), 7.86 (d, *J* = 8.2 Hz, 2H, Ar).

$^{13}$C NMR (200 MHz, $CDCl_3$): δ = 125,55; 126.8, 127.6, 128.7, 132.4, 134.1, 139.0, 170.1.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{13}H_{12}NOS$: 230.0640; found: 230.0644.

***N*-(phenylothio)trimethylacetamide (3j)**

Yellowish solid, mp 98–100 °C; $R_f$ = 0.35 ($CH_2Cl_2$); yield 90 mg (43%).

$^1$H NMR (200 MHz; $CDCl_3$): δ = 1.30 (s, 9H, tBu), 6.86 (brs, 1H, NH), 7.10-7.40 (m, 5H, Ph).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 27.7, 39.9, 124.9, 126.6, 128.9, 139.0, 179.8.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{16}NOS$: 210.0953; found: 210.0949.

***N*-(10-Ethoxycarbonyl-1-decylthio)nicotinamide (3k)**

Yellowish oil; $R_f$ = 0.3 (EtOAc–$CH_2Cl_2$, 2:1); yield 44 mg (12%).

$^1$H NMR (200 MHz; $CDCl_3$): δ = 1.05 – 1.50 (m, 15H, $CH_2$, $CH_3$), 1.50-1.80 (m, 4H, $CH_2$), 2.30 (t, *J* = 7.0 Hz, 2H, $CH_2CO$), 2.84 (t, *J* = 7.4 Hz, 2H, $CH_2S$), 4.12 (q, *J* = 7.2 Hz, 2H, $OCH_2$), 7.30-7.50 (m, 1H, Ar), 7.51 (brs, 1H, NH), 8.10-8.20 (m, 1H, Ar), 8.70-8.80 (m, 1H, Ar), 9.00-9.10 (m, 1H, Ar).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 14.0, 23.4, 25.2, 27.3, 27.8, 29.1, 29.2, 29.3, 30.5, 32.3, 38.7, 60.1, 123.8, 128.9, 135.9, 148.4, 152.5, 169.8, 172.1.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{31}N_2O_3S$: 367.2055; found: 367.2064.

***N*-(10-Ethoxycarbonyl-1-decylthio)trimethylacetamide (3l)**

Yellowish oil; $R_f$ = 0.3 (EtOAc–$CH_2Cl_2$, 1:25); yield 69 mg (20%).

$^1$H NMR (200 MHz; $CDCl_3$): δ = 1.05 – 1.40 (m, 15H, $CH_2$, $CH_3$), 1.50 (s, 9H, tBu), 1.55 – 1.80 (m, 4H, $CH_2$), 2.30 (t, *J* = 7.0 Hz, 2H, $CH_2CO$), 2.83 (t, *J* = 7.4 Hz, 2H, $CH_2S$), 4.11 (q, *J* = 7.2 Hz, 2H, $OCH_2$), 7.00 (brs, 1H, NH).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 14.0, 23.4, 27.3, 27.8, 29.1, 29.2, 29.3, 29.5, 30.5, 32.3, 38.6, 39.7, 60.2, 172.1, 180.1.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{18}H_{35}NNaO_3S$: 368.2235; found: 368.2228.

***N*-(11-(*N*-tert-butoxycarbonylamino)-1-undecylthio)nicotinamide (3m)**

Yellowish oil; EtOAc–$CH_2Cl_2$, 1:5 then EtOAc–$CH_2Cl_2$, 1:1;$R_f$ = 0.27 (EtOAc–$CH_2Cl_2$, 1:1); yield 182 mg (43%).

$^{1}$H NMR (200 MHz; $CDCl_3$): δ = 1.10 – 1.40 (m, 14H, $CH_2$); 1.44 (s, 9H, Boc), 1.50-1.80 (m, 4H, $CH_2$), 2.88 (t, *J* = 7.2 Hz, 2H, $SCH_2$), 3.09 (q, *J* = 6.3 Hz, 2H, $CH_2N$), 4.50 (brs, 1H, NHBoc); 7.30-7.55 (m, 2H, S-NH, Ar), 8.23 (d, *J* = 7.9 Hz, 1H, Ar), 8.78 (brs, 1H, Ar), 9.11 (brs, 1H, Ar).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 23.4, 27.3, 27.8, 28.4, 28.6, 29.2, 29.3, 29.5, 30.5, 32.3, 38.7, 41.3, 70.6, 123.7, 128.8, 135.8, 148.3, 152.4, 156.3, 169.4.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{38}N_3O_3S$: 424.2634; found: 424.2642.

***N*-(11-(*N*-tert-butoxycarbonylamino)-1-undecylthio)trimethylacetamide (3n)**

Yellowish oil; $R_f$ = 0.25 (PE–$CH_2Cl_2$, 1:2); yield 258 mg (64%).

$^{1}$H NMR (200 MHz; $CDCl_3$): δ = 1.10 – 1.40 (m, 14H, $CH_2$); 1.44 (s, 9H, tBu), 1.50 (s, 9H, Boc), 1.50-1.80 (m, 4H, $CH_2$), 2.88 (t, *J* = 7.2 Hz, 2H, S-$CH_2$), 3.00-3.20 (m, 2H, $CH_2N$), 4.50 (brs, 1H, NHBoc); 7.0 (brs, 1H, S-NH).

$^{13}$C NMR (50 MHz, $CDCl_3$): δ = 23.4, 27.3, 27.8, 28.4, 28.6, 29.1, 29.2, 29.3, 29.5, 30.5, 32.3, 38.6, 39.7, 41.2, 70.6, 156.3, 180.1.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{21}H_{42}N_2NaO_3S$: 425.2814; found: 425.2825.

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References

1. (a) Craine, L.; Raban, M. *Chem. Rev*. **1989**, *89*, 689. (b) Koval', I. V. *Russ. Chem. Rev*. **1996**, *65*, 421. (c) Davis, F. A. *J. Org. Chem*. **2006**, *71*, 8993.

2. (a) Antifungal Compounds, Volume 1: Discovery, Development and Uses; Siegel, M. R., Sisler, H. D., Eds.; Markel Dekker: New York, 1977. (b) Ochal, Z.; Bialkowski, W.; Banach, L. *Pesticides*, **2009**, 5.

3. Hofmann, W. *Rubber Technology Handbook*; Hanser Publishers: Munich, 1989; pp 233-255.

4. (a) Guarino, V. R.; Karunaratne, V.; Stella, V. J. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 4910. (b) Hemenway, J. N.; Nti-Addae, K.; Guarino, V. R.; Stella, V. J. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 6629. (c) Huttunen, K. M.; Mannila, A.; Laine, K.; Kemppainen, E.; Leppanen, J.; Vepsalainen, J.; Jarvinen, T.; Rautio, J. *J. Med. Chem*. **2009**, *52*, 4142.

5. (a) Kost, D.; Raban, M. In *The Chemistry of Sulfenic Acids and their Derivatives*; Patai, S., Ed.; J. Wiley & Sons: New York, 1990; Chapter 2. (b) Blanca, M. B.-D.; Maimon, E.; Kost, D. *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 2216. (c) Blanca, M. B.-D.; Yamamoto, C.; Okamoto, Y.; Biali, S. E.; Kost, D. *J. Org. Chem*. **2000**, *65*, 8613.

6. (a) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron Lett*. **1991**, *32*, 6441. (b) Beckwith, A. L. J.; Maxwell, B. J.; Tsanaktsidis, J. *Aust. J. Chem*. **1991**, *44*, 1809. (c) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron Lett*. **1992**, *33*, 4993.

7. (a) Esker, J. L.; Newcomb, M. *Tetrahedron Lett*. **1993**, *34*, 6877. (b) Chen, Q.; Shen, M.; Tang, Y.; Li, C. *Org. Lett*. **2005**, *7*, 1625.

8. (a) Miura, Y.; Yamano, E.; Tanaka, A.; Yamauchi, J. *J. Org. Chem*. **1994**, *59*, 3294. (b) Miura, Y.; Yamano, E. *J. Org. Chem*. **1995**, *60*, 1070. (c) Miura, Y.; Oka, H.; Yamano, E.; Teki, Y.; Takui, T.; Itoh, K. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 1187.

9. (a) Kuniyasu, H.; Hiraike, H.; Morita, M.; Tanaka, A.; Sugoh, K.; Kurosawa, H. *J. Org. Chem*. **1999**, *64*, 7305. (b) Kondo, T.; Baba, A.; Nishi, Y.; Mitsudo, T. *Tetrahedron Lett*. **2004**, *45*, 1469. (c) Rescourio, G.; Alper, H. *J. Org. Chem*. **2008**, *73*, 1612. (d) Spitz, C.; Lohier, J.-F.; Santos, J. S. O.; Reboul, V.; Metzner, P. *J. Org. Chem*. **2009**, *74*, 3936. (e) Shiro, D.; Fujiwara, S.; Tsuda, S.; Iwasaki, T.; Kuniyasu, H.; Kambe, N. *Tetrahedron Lett*. **2015**, *56*, 1531.

10. (a) Shcherbakova, I.; Pozharskii, A. F. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R., Ramsden, Ch., Eds.; Pergamon: Oxford, 2004; Vol. 2, pp 177–187. (b) Sato, R.; Kimura, T. In *Science of Synthesis*; Kambe, N., Drabowicz, J., Molander, G. A., Eds.; Thieme: Stuttgart-New York, 2007; Vol. 39, pp 573–588. (c) Witt, D. *Synthesis* **2008**, 2491. (d) Musiejuk, M.; Witt, D. *Org. Prep. Proc. Int*. **2015**, *47*, 95.

11. (a) Yang, T.-K.; Chen, R.-Y.; Lee, D.-S.; Peng, W.-S.; Jiang, Y.-Z.; Mi, A.-Q.; Jong, T.-T. *J. Org. Chem*. **1994**, *59*, 914. (b) Yan, L.; Guishu, Y.; Yaozhong, J.; Tengkui, Y. *Synth. Commun*. **1995**, *25*, 1551.

12. Lovey, R. G.; Cooper, A. B. *Synlett* **1994**, 167.

13. (a) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *Tetrahedron* **1993**, *49*, 5365. (b) Benati, L.; Capella, L.; Montevecchi, P. C.; Spagnolo, P. *Tetrahedron* **1994**, *50*, 12395.

14. Ren, X.-F.; Konaklieva, M. I.; Turos, E. *J. Org. Chem*. **1995**, *60*, 4980.

15. (a) Davis, F. A. *Int. J. Sulfur Chem*. **1973**, *8*, 71. (b) Perrio, S.; Reboul, V.; Metzner, P. In *Science of Synthesis*, Houben-Weyl, Methods of Molecular Transformations, Thieme, Stuttgart, **2007**, Vol 31a, pp 1041-1096.

16. Barton, D. H. R.; Hesse, R. H.; O'Sullivan, A. C. *J. Org. Chem*. **1991**, *56*, 6702.

17. Davis, F. A.; Friedman, A. J.; Kluger, E. W.; Skibo, E. B.; Fretz, E. R.; Milicia, A. P.; LeMasters, W. C.; Bentley, M. D.; Lacadie, J. A.; Douglass, I. B. *J. Org. Chem*. **1977**, *42*, 967.

18. Owen, D. J.; von Itzstein, M. *Carbohydr. Res*. **2000**, *328*, 287.

19. Tanaka, T.; Azuma, T.; Fang, X.; Uchida, S.; Iwata, C.; Ishida, T.; In, Y.; Maezaki, N. *Synlett* **2000**, 33.

20. Shimizu, M.; Sugano, Y.; Konakahara, T.; Gama, Y.; Shibuya, I. *Tetrahedron* **2002**, *58*, 3779.

21. Refvik, M. D.; Schwan, A. L. *J. Org. Chem*. **1996**, *61*, 4232.

22. Taniguchi, N. *Synlett* **2007**, 1917.

23. Taniguchi, N. *Eur. J. Org. Chem*. **2010**, 2670.

24. Shimizu, M.; Fukazawa, H.; Inoue, J.; Abe, Y.; Konakahara, T. *Heterocycles* **2007**, *71*, 61.

25. Koval, I. V.; Tarasenko, A. I.; Kremlev, M. M.; Molchanova, N. R. *Zh. Org. Khim*. **1981**, *17*, 533.

26. Harpp, D. N.; Mullins, D. F.; Steliou, K.; Triassi, I. *J. Org. Chem*. **1979**, *44*, 4196.

27. Kise, H.;Whitfield, G.; Swern, D. *J. Org. Chem*. **1972**, *37*, 1125.

28. Pietka-Ottlik, M.; Potaczek, P.; Piasecki, E.; Mlochowski, J. *Molecules* **2010**, *15*, 8214.

29. (a) Bhakuni, B. S.; Balkrishna, S. J.; Kumar, A.; Kumar, S. *Tetrahedron Lett*. **2012**, *53*, 1354. (b) Wang, F.; Chen, C.; Deng, G.; Xi, C. *J. Org. Chem*. **2012**, *77*, 4148. (c) Paul, R.; Punniyamurthy, T. *RSC Adv*. **2012**, *2*, 7057.

30. (a) Sivaramakrishnan, S.; Keerthi, K.; Gates, K. S. *J. Am. Chem. Soc*. **2005**, *127*, 10830. (b) Correa, A.; Tellitu, I.; Dominguez, E.; SanMartin, R. *Org. Lett*. **2006**, *8*, 4811. (c) Shiau, T. P.; Erlanson, D. A.; Gordon, E. M. *Org. Lett*. **2006**, *8*, 5697. (d) Chen, F.-J.; Liao, G.; Li, X.; Wu, J.; Shi, B.-F. *Org. Lett*. **2014**, *16*, 5644. (e) Wang, Z.; Kuninobu, Y.; Kanai, M. *J. Org. Chem*. **2013**, *78*, 7337.

31. Lach, S.; Demkowicz, S.; Witt, D. *Tetrahedron Lett*., **2013**, *54*, 7021.

32. Antoniow, S.; Witt, D. *Synthesis* **2007**, 363.

33. Kowalczyk, J.; Barski, P.; Witt, D.; Grzybowski, B. A. *Langmuir* **2007**, *23*, 2318.

34. (a) Szymelfejnik, M.; Demkowicz, S.; Rachon, J.; Witt, D. *Synthesis* **2007**, 3528. (b) Szymelfejnik, M.; Demkowicz, S.; Witt, D.; Rachon, J. *Phosphorus, Sulfur Silicon Relat. Elem.* **2008**, *183*, 415.

35. Demkowicz, S.; Rachon, J.; Witt, D. *Synthesis* **2008**, 2033.

36. Okragla, E.; Demkowicz,S.; Rachon, J.; Witt, D. *Synthesis* **2009**, 1720.

37. Lach, S.; Witt, D. *Synthesis* **2011**, 3975.

38. (a) Kertmen, A.; Lach, S.; Rachon, J.; Witt, D. *Synthesis* **2009**, 1459. (b) Lach, S.; Witt, D. *Heteroatom Chem*., **2014**, *25*, 10.

39. (a) Lach, S.; Sliwka-Kaszynska, M.; Witt, D. *Synlett* **2010**, 2857. (b) Lach, S.; Witt, D. *Synlett* **2013**, *24*, 1927.

40. Musiejuk, M.; Klucznik, T.; Rachon, J.; Witt, D. *RSC Adv*., **2015**, *5*, 31347.

**Table 1** Synthesis of *N*-acylsulfenamides **3** [a]

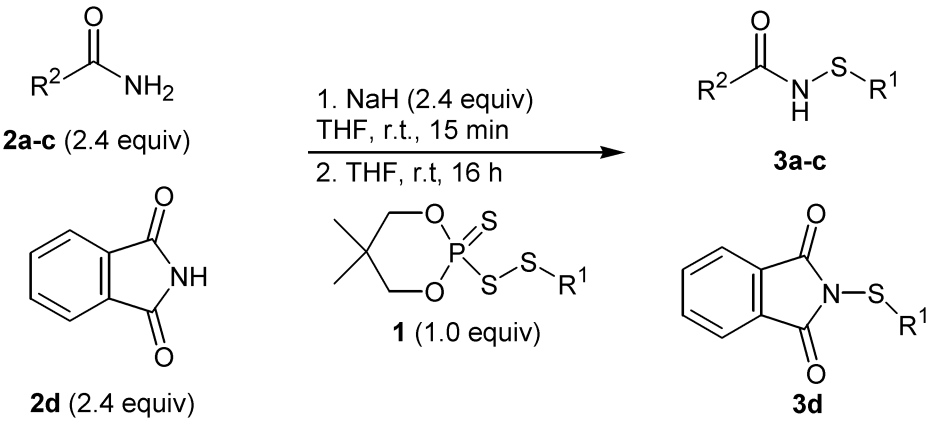
| | $R^1 = (CH_2)_{11}Me$ **1a** | $R^1 = (CH_2)_{11}OH$ **1b** | $R^1 = Ph$ **1c** | $R^1 = (CH_2)_{10}CO_2Et$ **1d** | $R^1 = (CH_2)_{11}N(R^3)Boc$ $R^3 = Boc$ **1e** |
|---|---|---|---|---|---|
| $R^2 = Ph$ **2a** | **3a** (82) | **3e** (75) | **3i** (31)[b] | - | - |
| $R^2$ = 3-pyridyl **2b** | **3b** (89) | **3f** (95) | - | **3k** (12) | $R^3 = H$ **3m**, (43) |
| $R^2$ = t-Bu **2c** | **3c** (80) | **3g** (81) | **3j** (43)[c] | **3l** (20) | $R^3 = H$ **3n**, (64) |
| Phthalimide **2d** | **3d** (94) | **3h** (94) | - | - | - |

[a] The yield (%) of the isolated product is reported in parentheses. [b] The formation of $(PhS)_2$ was observed (58%). [c] The formation of $(PhS)_2$ was observed (50%).

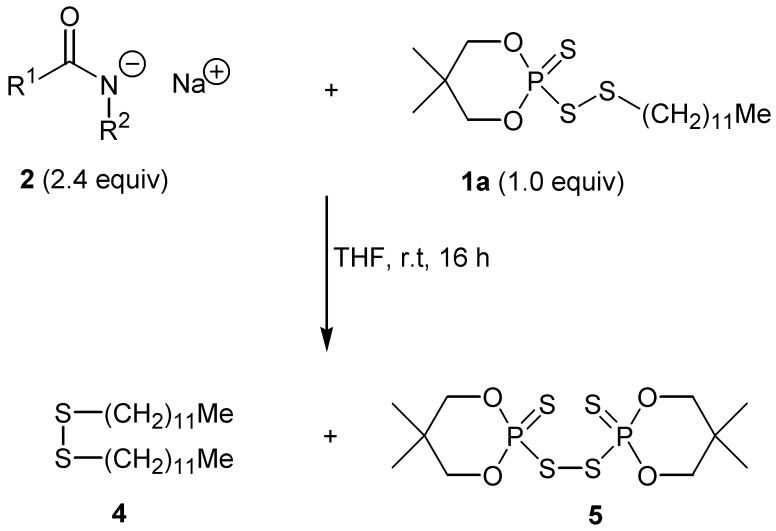
**Table 2** Reaction of secondary amides with disulfane **1a**

| Entry | $R^1$ | $R^2$ | **2** | **4** yield (%)[a] | **5** yield (%)[a] |
|---|---|---|---|---|---|
| 1 | Me | Ph | **2e** | 90 | 78 |
| 2 | Ph | Ph | **2f** | 95 | 82 |
| 3 | Ph | Me | **2g** | 97 | 81 |
| 4[b] | Ph | Me | **2g** | 62 | 52 |

[a] The yield of the isolated product. [b] The 20 mol% of **2g** was used.




Scheme 1




Scheme 2