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N-Chlorosuccinimide as a versatile reagent for the sulfenylation of ketones: a facile synthesis of α-ketothioethers

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Abstract

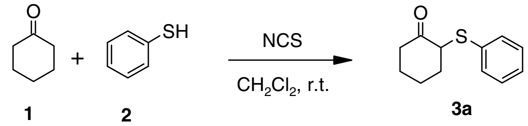
The sulfenylation of ketones having α-hydrogens has been achieved using *N*-chlorosuccinimide (NCS) under mild reaction conditions to produce α-ketothioethers in excellent yields with high selectivity. The use of NCS makes this method quite simple, convenient and practical.

Keywords: Sulfenylation; Ketones; Aromatic thiols; α-Ketothioethers

α-Sulfenylketones are important intermediates[1] for the mono- and dialkylation of ketones[2] preparation of 1,2-diketones by bis-sulfenylation[3] alkylation of the less reactive α-position after bis-sulfenylation[4] 1,2-carbonyl transposition[5] and for the preparation of α,β-unsaturated ketones.[6] The most common methods for α-sulfenylation of ketones involve the reactions of enolates[7–12] (generated from ketones using LDA in THF at −78 °C) with various sulfenylating reagents such as PhSSPh, MeSSMe, methylmethanthiosulfate ($MeSSO_2Me$) or PhSCl and *N*-(phenylthio)phthalimide or *N*-phenylthiocaprolactam. Generally, the sulfenylation reactions of preformed enolates[13,14] or enamines,[15–17] require multi-step sequences for the preparation of the substrate thiol, strongly basic conditions and anhydrous conditions. To our knowledge, no direct method for α-sulfenylation of unmodified ketones has been reported.

In this Letter, we report a simple, direct and efficient method for the preparation of α-ketothioethers from ketones and aromatic thiols.

Initially, we attempted the sulfenylation of cyclohexanone (**1**) with thiophenol (**2**) using a stoichiometric amount of *N*-chlorosuccinimide. The reaction went to completion within 50 min at room temperature and the product, 2-(phenylthio)cyclohexanone **3a** was obtained in 80% yield (Scheme 1). Similarly, cyclohexanone reacted with *p*-chloro- and *p*-bromothiophenol to give 2-(arylthio)cyclohexanones in good yields (Table 1, entries **b** and **c**). This result provided the incentive to extend this sulfenylation to other cyclic ketones such as cyclopentanone, dodecanone, β-tetralone, α-tetralone and 4-phenylcyclohexanone. Interestingly, these cyclic ketones reacted efficiently with *p*-chlorothiophenol to give the corresponding α-sulfenylketones (Table 1, entries **d**–**h**). Similarly, *p*-chloropropiophenone also underwent smooth α-sulfenylation under these conditions (Table 1, entries **i** and **j**). This method was successfully applied to a number of acyclic ketones including 2-butanone, 3-pentanone, methyl isopropyl ketone, diisopropyl ketone, methyl isobutyl ketone and 2-heptanone (Table 1, entries **k**–**v**). In all cases, the reactions



Scheme 1. Sulfenylation of cyclohexanone.

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Table 1
NCS-promoted α-sulfenylation of ketones with aromatic thiols

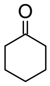
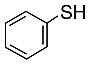
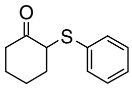
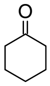
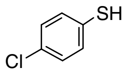
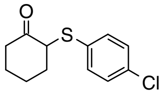
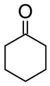
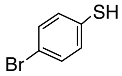
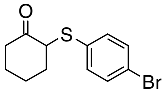
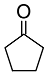
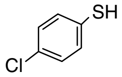
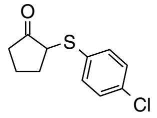
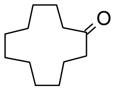
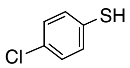
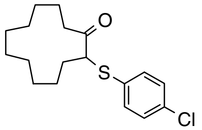
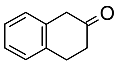
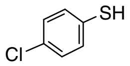
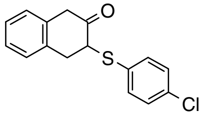
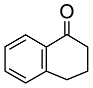
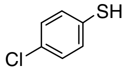
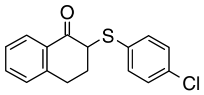
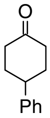
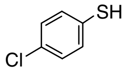
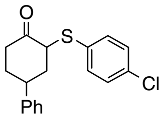
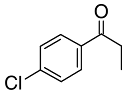
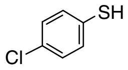
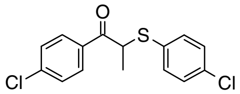
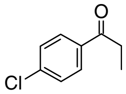
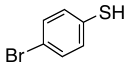
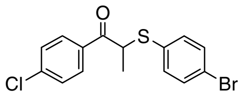
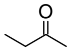
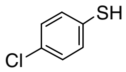
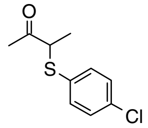
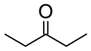
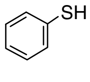
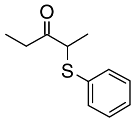
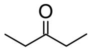
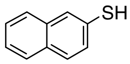
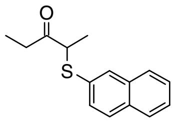
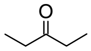
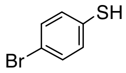
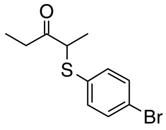
Entry	Substrate	Thiophenol	Product[a]	Reaction time (min)	Yield[b] (%)
a				48	80
b				42	82
c				38	89
d				45	78
e				40	79
f				44	80
g				42	82
h				49	75
i				52	72
j				55	75
k				20	94
l				38	89
m				25	90
n				15	89

Table 1 (*continued*)

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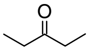
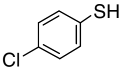
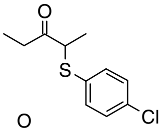
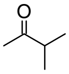
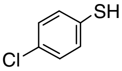
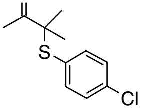
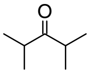
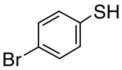
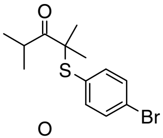
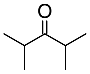
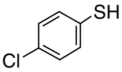
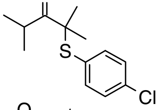
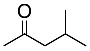
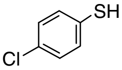
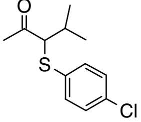
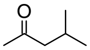
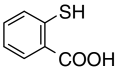
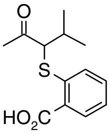
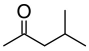
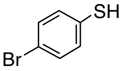
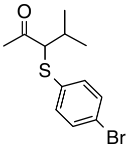
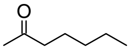
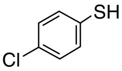
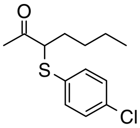
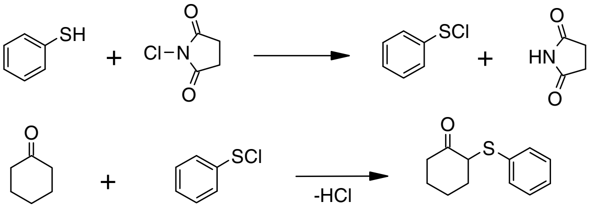
o				18	98
p				32	90
q				24	84
r				26	87
s				35	85
t				98	49
u				35	78
v				40	79

[a] All products were characterized by ^{1}H NMR, IR and mass spectrometry.

[b] Yield (wt %) refers to pure products after chromatography.

proceeded smoothly at room temperature under the influence of 1.1 mol equiv *N*-chlorosuccinimide. No additives or acidic promoters were required for the reaction to proceed. However, a trace amount of diphenyldisulfide was detected by LC–MS as a side product. The reagent is readily available at low cost and is highly efficient in promoting sulfenylations. All the products were characterized by ^{1}H NMR, IR and mass spectrometry and by comparison with known samples.[7–12] The effects of various solvents such as THF, diethyl ether, acetonitrile and dimethoxyethane were screened for this reaction. Of these solvents, dichloromethane gave the best results. Mechanistically, it is known that NCS reacts rapidly with an aromatic thiol to generate a sulfenyl chloride[18,19] which subsequently interacts with ketones to give α-sulfenylketones. A plausible reaction mechanism is depicted in Scheme 2.

The α-halogenation of ketones with *N*-halosuccinimide was previously reported only under acidic conditions. In the absence of acid, the reaction was very sluggish.[20,21] The scope of this method is demonstrated with respect to various ketones and aromatic thiols and the results are presented in Table 1.[22]



Scheme 2. A plausible reaction mechanism.

In summary, we have developed a simple, efficient, selective and metal-free approach for the direct α-sulfenylation of ketones using *N*-chlorosuccinimide as a safe and environmentally friendly promoter. In addition to its efficiency, simplicity and mild reaction conditions, this method provides excellent yields of products with high α-selectivity.

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22. *General procedure*: To a stirred solution of ketone (1 mmol) and thiol (1.2 mmol) in dichloromethane (10 mL), *N*-chlorosuccinimide (1.1 mmol) was added at 0 °C and the reaction was allowed to stir at room temperature for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was quenched with water and extracted with dichloromethane (2 × 10 mL). Removal of the solvent followed by purification on silica gel using ethyl acetate/*n*-hexane (1:9) as eluent afforded the pure α-sulfenylketone. The by-product succinimide was isolated from the aqueous layer by lyophilization. The reaction was also carried out on large scale (1 g) following this procedure. Spectral data for selected products:
(**e**) *2-(4-Chlorophenylthio)cyclododecanone*: Liquid, IR (KBr): ν_{max} 2932, 2860, 1705, 1472, 1441, 1340, 1149, 1093, 1012, 819 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.38 (m, 4H), 3.60 (dd, $J = 3.6$, 11.7 Hz, 1H), 2.53–2.46 (t, $J = 5.8$ Hz, 2H), 2.10–1.65 (m, 4H), 1.60–1.21 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.9, 137.6, 133.6, 131.9, 129.2, 55.6, 40.2, 35.8, 25.6, 25.9, 24.7, 24.5, 24.1, 23.7, 23.6, 22.1. LC–MS: *m*/*z*: 325 $(M+1)^+$. HRMS calculated for $C_{18}H_{25}OSClNa$ $(M+Na^+)$: 347.1213. Found: 347.1212.
(**i**) *1-(4-Chlorophenyl)-2-(4-chlorophenylthio)propan-1-one*: Liquid, IR (KBr): (ν_{max}): 2978, 2935, 1687, 1590, 1481, 1400, 1349, 1217, 1091, 1010, 951, 739 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.53 (m, 6H), 7.28 (m, 2H), 4.00 (q, $J = 6.6$ Hz, 1H), 2.02 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.2, 139.1, 136.1, 135.1, 133.8, 130.0, 129.3, 129.1, 128.8, 45.9, 16.6. LC–MS: *m*/*z*: 311 (M+1). HRMS calculated for $C_{15}H_{13}OSCl_2Na$ $(M+Na^+)$: 311.0068. Found: 311.0064.
(**m**) *2-(Naphthalen-2-ylthio)pentan-3-one*: Solid, mp 123–126 °C, IR (KBr): ν_{max} 3052, 2975, 2932, 1708, 1624, 1585, 1498, 1451, 1345, 1129, 1069, 813, 743 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.73–7.63 (m, 4H), 7.48–7.31 (m, 3H), 3.86 (q, $J = 6.7$, 1H), 2.63 (q, $J = 7.5$ Hz, 2H), 1.40 (d, $J = 6.7$ Hz, 3H), 1.08 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.5, 136.5, 131.7, 130.4, 129.8, 128.9, 127.9, 127.7, 126.9, 126.7, 125.9, 51.5, 32.6, 16.7, 8.4. LC–MS: *m*/*z*: 267 $(M+23)^+$. HRMS calculated for $C_{15}H_{16}OSNa$ $(M+Na^+)$: 267.0818. Found: 267.0819.
(**o**) *2-(4-Chlorophenylthio)pentan-3-one*: Liquid, IR (KBr): ν_{max} 2970, 2927, 1710, 1573, 1470, 1382, 1093, 1011, 819 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24 (m, 4H), 3.69 (q, $J = 7.5$ Hz, 1H), 2.73–2.60 (dq, $J = 6.7$, 14.3 Hz, 2H), 1.38 (d, $J = 7.5$ Hz, 3H), 1.05 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.1, 134.5, 129.6, 129.5, 129.4, 51.3, 32.5, 16.3, 8.3. LC–MS: *m*/*z*: 229 $(M+1)^+$. HRMS calculated for $C_{11}H_{13}OSClNa$ $(M+Na^+)$: 251.0279. Found: 251.0273.
(**r**) *2-(4-Chlorophenylthio)-2,4-dimethylpentan-3-one*: Liquid, IR (KBr): ν_{max} 2972, 2932, 2872, 1699, 1572, 1471, 1384, 1092, 1033, 822 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.26 (m, 4H), 3.40 (m, 1H), 1.40 (s, 6H), 1.15 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.6, 136.8, 135.4, 130.1, 129.0, 56.4, 34.1, 24.5, 21.0. LC–MS: *m*/*z*: 257 (M+1). HRMS calculated for $C_{13}H_{17}OSClNa$ $(M+Na^+)$: 279.0584. Found: 279.0586.