Novel Atom Economic Reaction: Comprehensive Utilization of S-Alkylisothiouronium Salt in the Synthesis of Thioether and Guanidinium Salt

Pengchao Gao, Penglin Leng, Qi Sun, Xin Wang, Zemei Ge* and Runtao Li*

State key laboratory of natural and biomimetic drugs, School of Pharmaceutical Sciences,
Peking University, 38 Xueyuan Road, Beijing, 100191, China
E-mail: zmge@bjmu.edu.cn; lirt@mail.bjmu.edu.cn;
Fax: 86 10 82716956; Tel: 86 82801504
1. Experimental part

All reagents were commercially available. The waste free reactions were monitored by thin layer chromatography. $^1$H NMR spectra were recorded on 400MHz Bruker spectrometers with TMS as an internal standard.

Compounds 1a-f, 2a-c, 3a-c, 4a-r, 5a-e, 6, 7, 8, 9, 10, 11, 12 are known. 12 is a new compound. Characterization data ($^1$H NMR, $^{13}$C NMR, MP, ESI-MS) are reported below.

Typical procedure for the symbiotic reaction

To the mixed solvent (10 mL, H$_2$O/EtOH = 1:1) was added the S-alkyliothiouronium salt (4.4 mmol), the amine (4.0 mmol) and the Michael receptor (4.0 mmol), TEA (4.0 mmol). The mixture was stirred at 30 °C for 6 h, then 5 mL H$_2$O was added and the mixture was extracted with EtOAc (15 mL $\times$ 3). The remaining aqueous layer was concentrated under reduced pressure using a rotary evaporator and the resulting solid was washed with a small amount of ethanol, then recrystallized from hot water to give the corresponding guanidinium salt (5). The combined organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure, and the residue was purified by column chromatography (petroleum ether/ethyl acetate) to afford the corresponding thia-Michael addition product (4).

Methyl 3-(benzylthio)propanoate(4a)

\[
\begin{align*}
\text{CH}_3\text{C}=\text{O} & \quad \text{S} \\
\text{H} & \quad \text{C}_6\text{H}_5
\end{align*}
\]

Isolated in 83.4% yield, yellow oil, Lit$^{19}$. $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 7.25 (m, 5H), 3.66 (s, 2H), 3.61 (s, 3H), 2.61 (t, 2H, $J$ = 7.3Hz), 2.48 (t, 2H, $J$ = 7.3Hz). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 172.37, 138.05, 128.85, 128.57, 127.11, 51.80, 36.30, 34.29, 26.19

3-(Benzylthio)cyclohexanone(4b)

\[
\begin{align*}
\text{CH}_3\text{C}=\text{O} & \quad \text{S} \\
\text{H} & \quad \text{C}_6\text{H}_5
\end{align*}
\]
Isolated in 82.3% yield, yellow oil, Lit$^{19}$, $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 7.18 (m 5H), 3.67 (s, 2H), 2.85 (m 1H), 2.57 (m, 1H), 2.26 (m, 3H), 1.99 (m, 2H), 1.61 (m, 2H). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 208.68, 137.93, 128.75, 128.62, 127.16, 47.80, 41.97, 40.95, 34.93, 31.28, 24.12

3-(Benzylthio)propanenitrile(4c)

Isolated in 80.1% yield, yellow oil, Lit$^{19}$, $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 7.24 (m, 5H), 3.69 (s, 2H), 2.54 (t, 2H, $J = 7.2$Hz), 2.38 (t, 2H, $J = 7.2$Hz). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 137.43, 128.93, 128.79, 127.48, 118.50, 36.30, 26.64, 18.61

Methyl 3-(methylthio)propanoate(4d)

Isolated in 61.8% yield, pale yellow oil, Lit$^{19}$, $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 3.63 (s, 3H), 2.70 (t, 2H, $J = 7.4$Hz), 2.56 (t, 2H, $J = 7.4$Hz), 2.05 (s, 3H). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 171.38, 50.75, 33.22, 28.06, 14.46

3-(Methylthio)cyclohexanone(4e)

Isolated in 72.6% yield, yellow oil, Lit$^{19}$, $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 2.90-2.93 (m, 1H), $\delta$ 2.61-2.66 (m, 1H), $\delta$ 2.26-2.34 (m, 3H), $\delta$ 2.05-2.10 (m, 5H), $\delta$ 1.63-1.68 (m, 2H). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 208.73, 47.50, 44.12, 40.86, 30.90, 24.05, 13.48

3-(Methylthio)propanenitrile(4f)

Isolated in 58.9% yield, colorless oil, Lit$^{19}$, $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 2.71 (t, 2H, $J = 7.5$Hz), 2.60 (t, 2H, $J = 7.5$Hz), 2.13 (s, 3H). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 117.39, 28.65, 17.43, 14.58

Methyl 3-(ethylthio)propanoate(4g)
Isolated in 68.5% yield, pale yellow oil, Lit\textsuperscript{20}, \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}): \(\delta\) 3.63 (s, 3H), 2.71-2.75 (m, 2H), 2.48-2.55 (m, 4H), 1.17-1.21 (m, 3H). \textsuperscript{13}C NMR (100MHz, CDCl\textsubscript{3}): \(\delta\) 172.45, 51.75, 34.65, 26.49, 25.94, 14.64

3-(Ethylthio)cyclohexanone(4h)

\[
\begin{array}{c}
\text{O} \\
\text{S} \\
\text{S} \\
\end{array}
\]

Isolated in 81.5% yield, brown oil, Lit\textsuperscript{21}, \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}): \(\delta\) 3.03 (m, 1H), 2.61-2.65 (m, 1H), 2.50 (q, 2H, \(J = 7.4\)Hz), 2.28-2.30 (m, 3H), 2.06-2.09 (m, 2H), 1.19 (t, 3H, \(J = 7.4\)Hz). \textsuperscript{13}C NMR (100MHz, CDCl\textsubscript{3}): \(\delta\) 207.93, 47.14, 41.34, 39.96, 30.55, 23.40, 23.23, 13.78

3-(Ethylthio)propanenitrile(4i)

\[
\begin{array}{c}
\text{NC} \\
\text{S} \\
\text{S} \\
\end{array}
\]

Isolated in 77.1% yield, colorless oil, Lit\textsuperscript{22}, \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}): \(\delta\) 2.74 (t, 2H, \(J = 7.1\)Hz), 2.57 (m, 4H), 1.22 (t, 3H, \(J = 7.4\)Hz). \textsuperscript{13}C NMR (100MHz, CDCl\textsubscript{3}): \(\delta\) 118.52, 59.57, 26.00, 18.86, 14.56

Methyl 3-(cyclopentylthio)propanoate(4j)

\[
\begin{array}{c}
\text{S} \\
\text{S} \\
\text{O} \\
\text{O} \\
\end{array}
\]

Isolated in 68.1% yield, pale yellow oil, Lit\textsuperscript{19}, \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}): \(\delta\) 3.72 (s, 3H), 2.81 (t, 2H, \(J = 7.4\)Hz), 2.63 (t, 2H, \(J = 7.4\)Hz), 2.55 (m, 1H), 1.63 (m, 2H), 1.36 (m, 6H).\textsuperscript{13}C NMR (100MHz, CDCl\textsubscript{3}): \(\delta\) 171.40, 59.57, 50.70, 33.71, 28.24, 25.94, 21.30

3-(Cyclopentylthio)cyclohexanone(4k)

\[
\begin{array}{c}
\text{O} \\
\text{S} \\
\text{S} \\
\end{array}
\]

Isolated in 75.7% yield, yellow oil, Lit\textsuperscript{19}, \textsuperscript{1}H NMR(400MHz,CDCl\textsubscript{3}): \(\delta\) 2.98 (m, 1H), 2.60-2.65 (m, 1H), 2.45 (m, 2H), 2.27-2.33 (m, 3H), 2.04-2.08 (m, 2H), 1.62-1.67 (m, 2H), 1.49-1.57 (m, 2H), 1.24-1.29 (m, 3H), 0.82 (t, 2H, \(J = 7.0\)Hz). \textsuperscript{13}C NMR (100MHz, CDCl\textsubscript{3}): \(\delta\) 208.76, 48.16, 42.68, 40.90, 31.57, 31.04, 30.43, 24.18, 22.22

3-(Cyclopentylthio)propanenitrile(4l)
Isolated in 68.1% yield, pale yellow oil, Lit19, $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 2.71 (t, 2H, $J$ = 7.2Hz), 2.57 (t, 2H, $J$ = 7.2Hz), 2.52 (m, 1H), 1.53 (m, 2H), 1.28(m, 6H). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 118.45, 30.90, 29.11, 27.59, 22.24, 18.91

Methyl 3-(allylthio)propanoate(4m)

Isolated in 71.2% yield, pale yellow oil, Lit23, $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 5.61-5.80 (m, 1H), 5.05 (d, 2H, $J$ = 18.7Hz), 3.62 (s, 3H), 3.08 (d, 2H, $J$ = 6.9Hz), 2.66 (t, 2H, $J$ = 7.2Hz), 2.52 (t, 2H, $J$ = 7.2Hz). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 172.27, 134.13, 117.18, 51.69, 34.76, 34.37, 25.53

3-(Allylthio)cyclohexanone(4n)

Isolated in 82.8% yield, pale yellow oil, Lit23, $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 5.91-5.64 (m, 1H), 5.11 (d, 2H, $J$ = 13.9Hz), 3.19 (d, 2H, $J$ = 7.1Hz), 3.09-2.95 (m, 1H), 2.68 (dd, 1H, $J$ = 14.3, 4.5Hz), 2.45-2.25 (m, 3H), 2.18-2.01 (m, 2H), 1.78-1.60 (m, 2H). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 208.86, 134.23, 117.24, 47.92, 41.40, 40.97, 33.58, 31.36, 24.21

3-(Allylthio)propanenitrile(4o)

Isolated in 66.5% yield, pale red oil, Lit24, $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 5.72 (m, 1H), 5.09 (d, 2H, $J$ = 12.8Hz), 3.15 (d, 2H, $J$ = 7.2Hz), 2.66 (t, 2H, $J$ = 7.0Hz), 2.56 (t, 2H, $J$ = 7.0Hz). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 133.63, 118.41, 118.01, 34.75, 25.86, 18.66

Methyl 3-(butylthio)propanoate(4p)

Isolated in 78.8% yield, pale yellow oil, Lit25, $^1$H NMR(400MHz,CDCl$_3$): $\delta$ 3.67 (s, 3H), 2.75 (t, 2H, $J$ = 7.4Hz), 2.58 (t, 2H, $J$ = 7.3Hz), 2.50 (t, 2H, $J$ = 7.3Hz), 1.54 (m, 2H), 1.37 (m, 2H), 0.89 (s, 3H, $J$ = 7.4Hz). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 172.37, 51.66, 54.69, 31.79, 31.59, 36.92, 21.90, 13.59

3-(Butylthio)cyclohexanone(4q)
Isolated in 72.4% yield, yellow oil, Lit$^{25}$, $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 2.62-2.65 (m, 1H), 2.48 (m, 3H), 2.28-2.31 (m, 3H), 2.07-2.09 (m, 2H), 1.64-1.67 (m, 2H), 1.48 (m, 2H), 1.32 (m, 2H), 0.84 (t, 3H, $J = 7.1$Hz). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 207.91, 47.25, 41.76, 39.95, 30.78, 30.66, 29.21, 23.26, 21.03, 12.64

3-(Butylthio)propanenitrile (4r)

Isolated in 63.5% yield, yellow oil, Lit$^{26}$, $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 2.71 (t, 2H, $J = 6.9$Hz), 2.51-2.58 (dt, 4H, $J = 14.6$Hz, 7.2Hz), 1.51 (m, 2H), 1.36 (m, 2H), 0.86 (t, 3H, $J = 7.2$Hz). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 117.38, 30.96, 30.49, 26.61, 20.86, 17.91, 12.60

1-Benzylguanidine hydrochloride (5a)

Mp 175-178 °C, Lit$^{16,18}$, Mp 173-174°C, $^1$H NMR (400MHz, D$_2$O): $\delta$ 7.43 (m, 5H), 4.43 (s, 2H). ES ([M+H]$^+$) calculated: 150.24(100)

1-Benzylguanidine Half Sulfate (5b)

Mp 204-205 °C, Lit$^{15}$, Mp 208-209 °C, $^1$H NMR (400MHz, D$_2$O): $\delta$ 7.38 (m, 5H), 4.42 (s, 2H). ES ([M+H]$^+$) calculated: 150.24(100)

1-Benzylguanidine Hydrobromate (5c)

Mp 110-113°C, $^1$H NMR (400MHz, D$_2$O): $\delta$ 7.42 (m, 5H), 4.43 (s, 2H). ES ([M+H]$^+$) calculated: 150.24(100)

2-Guanidinoacetic Hydrobromate (5d)
Carbonized at 284 °C, Lit.\textsuperscript{18} Carbonized at 280-284°C, \textsuperscript{1}H NMR (400MHz, D\textsubscript{2}O) : δ 3.69 (s, 2H). ES([M+H]\textsuperscript{+}) calculated: 118.07(100)

Ismelin Half Sulfate (5e)

Mp 270-271 °C, Lit.\textsuperscript{17}, Mp 276-281°C. \textsuperscript{1}H NMR (400MHz, D\textsubscript{2}O) : δ 3.36 (t, 2H, \textit{J} = 6.4Hz), 3.31 (m, 6H), 1.80 (s, 4H), 1.60 (s, 4H). \textsuperscript{13}C NMR (100MHz, D\textsubscript{2}O): δ 156.98, 55.10, 54.66, 36.28, 25.91, 22.99. ES([M+H]\textsuperscript{+}) calculated: 185.26 (100)

Ethyl 3-(4-tert-butoxycarbonylaminomethylphenyl) acrylate (10)

Isolated in 20.5% overall yield as a brown oil, Lit.\textsuperscript{31}, \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}) δ 7.59 (d, 1H, \textit{J} = 16.0Hz), 7.40 (d, 2H, \textit{J} = 8.2Hz), 7.22 (d, 2H, \textit{J} = 8.2Hz), 6.34 (d, 2H, \textit{J} = 16.0Hz), 4.71 (s, 2H), 4.19 (q, 2H, \textit{J} = 7.1Hz), 1.38 (s, 9H), 1.26 (t, 3H, \textit{J} = 7.1Hz). \textsuperscript{13}C NMR (100MHz, CDCl\textsubscript{3}); δ 166.99, 151.49, 143.21, 139.91, 132.33, 127.07, 126.66, 117.01, 81.68, 59.43, 48.22, 26.99, 13.31

Ethyl 3-benzylthio-3-(4-guanidinomethylphenyl) propanoate Hydrochloride (12)
Isolated by column chromatography (Ethyl Acetate/MeOH = 5:1) in 42.1% yield. Yellow solid, Mp 176.1-179.6°C. $^1$H NMR (400MHz, CD$_3$OD) $\delta$ 7.34 (m, 9H), 4.33 (s, 1H), 4.16 (q, 2H, $J = 7.1$Hz), 3.91 (m, 2H), 2.74 (m, 2H), 1.22 (t, 3H, $J = 7.1$Hz). $^{13}$C NMR (100MHz, DMSO-$d_6$): $\delta$ 170.43, 163.47, 137.78, 129.84, 129.55, 129.26, 128.87, 128.23, 127.77, 127.41, 60.54, 44.64, 42.25, 42.07, 35.31, 14.67, HR ESI MS m/z calcd for C$_{20}$H$_{25}$N$_3$O$_2$S, ([M+H]$^+$) 372.17451.

2. Spectra of compounds

$^1$H NMR(400MHz, CDCl$_3$) of Compound 4a
$^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 4a

$^1$H NMR (400 MHz, CDCl$_3$) of Compound 4b
$^{13}$C NMR (100MHz, CDCl$_3$) of Compound 4b

$^1$H NMR (400MHz, CDCl$_3$) of Compound 4c
$^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 4c

$^1$H NMR (400 MHz, CDCl$_3$) of Compound 4d
$^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 4d

$^1$H NMR (400 MHz, CDCl$_3$) of Compound 4e
$^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 4e

$^1$H NMR (400 MHz, CDCl$_3$) of Compound 4f
$^{13}$C NMR(100MHz, CDCl$_3$) of Compound 4f

$^1$H NMR(400MHz, CDCl$_3$) of Compound 4g
$^{13}$C NMR (100MHz, CDCl$_3$) of Compound 4g

$^1$H NMR (400MHz, CDCl$_3$) of Compound 4h
$^{13}$C NMR (100MHz, CDCl$_3$) of Compound 4h

$^1$H NMR (400MHz, CDCl$_3$) of Compound 4i
\(^{13}\)C NMR(100MHz, CDCl\(_3\)) of Compound 4i

\(^1\)H NMR(400MHz, CDCl\(_3\)) of Compound 4j
$^{13}$C NMR(100MHz, CDCl₃) of Compound 4j

$^1$H NMR(400MHz, CDCl₃) of Compound 4k
$^{13}$C NMR(100MHz, CDCl$_3$) of Compound 4k

$^1$H NMR(400MHz, CDCl$_3$) of Compound 4l
$^{13}$C NMR (100MHz, CDCl$_3$) of Compound 4l

$^1$H NMR (400MHz, CDCl$_3$) of Compound 4m
$^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 4m

$^1$H NMR (400 MHz, CDCl$_3$) of Compound 4n
$^{13}$C NMR (100MHz, CDCl$_3$) of Compound 4n

$^1$H NMR (400MHz, CDCl$_3$) of Compound 4o
$^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 4o

$^1$H NMR (400 MHz, CDCl$_3$) of Compound 4p
C NMR (100 MHz, CDCl$_3$) of Compound 4p

$^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 4p

$^{1}$H NMR (400 MHz, CDCl$_3$) of Compound 4q
$^{13}$C NMR (100MHz, CDCl$_3$) of Compound 4q

$^1$H NMR (400MHz, CDCl$_3$) of Compound 4r
$^1$H NMR(400MHz, D$_2$O) of Compound 5a

$^1$C NMR(100MHz, CDCl$_3$) of Compound 4r
$^1$H NMR(400MHz, D$_2$O) of Compound 5b

$^1$H NMR(400MHz, D$_2$O) of Compound 5c
$^1$H NMR(400MHz, D$_2$O) of Compound Glucocyamine

$^1$H NMR(400MHz, D$_2$O) of Compound Ismelin
**13C NMR (100 MHz, D$_2$O)** of Compound **Ismelin**.

**1H NMR (400 MHz, CDCl$_3$)** of Compound **10**
$^{13}$C NMR(100MHz, CDCl$_3$) of Compound 10

$^{1}$H NMR(400MHz, CD$_3$OD) of Compound 12
$^{13}$C NMR (100MHz, DMSO-$d_6$) of Compound 12

Peking University Mass Spectrometry Sample Analysis Report

ESI of compound 12