A Chlorinating Reagent Yields Vinylchlorides with High Regioselectivity under Heterogeneous Gold Catalysis

Shengzong Liang, [a] Rene Ebule, [a] Gerald B. Hammond, [a]* Bo Xu [b] *

[a] Department of Chemistry, University of Louisville, Louisville, Kentucky 40292, USA. [b] College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China

Table of contents

1. General .......................................................................................................................................................... 2

2. General procedures ...................................................................................................................................... 2
    2.1 Procedure for generation of HCl/DMPU ................................................................................................. 2
    2.2 General procedure for Au/TiO$_2$ catalyzed hydrochlorination of alkynes using HCl/DMPU2 ............ 2
    2.3 Gram-scale synthesis of 2a .................................................................................................................... 3

3. Characterization of products ........................................................................................................................ 3

4. Copies of NMR spectra for compound 2 .................................................................................................... 8
1. General

$^1$H and $^{13}$C NMR spectra were recorded at 400 MHz and 101 MHz using CDCl$_3$ as a solvent. The chemical shifts are reported in δ (ppm) values ($^1$H and $^{13}$C NMR relative to CHCl$_3$, δ 7.26 ppm for $^1$H NMR and δ 77.0 ppm for $^{13}$C NMR and CFCl$_3$ (δ 0 ppm for $^{19}$F NMR), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hexet), m (multiplet) and br (broad). Coupling constants (J), are reported in Hertz (Hz). All reagents and solvents were employed without further purification. The products were purified using a commercial flash chromatography system. TLC was developed on silica gel 60 F254 aluminum sheets. All reagents were purchased from Sigma-Aldrich or Alfa Aesar and used as received without any further purification. AuNPs supported on TiO$_2$ (1% wt/wt loading; average size of AuNPs is around 2-3 nm) was purchased from Strem.

2. General procedures

2.1 Procedure for generation of HCl/DMPU

A pressure-equalizing dropping funnel and inlet of a drying tube packed with CaCl$_2$ were attached onto a 500 mL of two-neck round-bottom flask. The outlet of the drying tube was attached to one joint of 100 mL two-neck round-bottom flask through tubing; a 5'' pipette was attached to the end of the tubing. The other joint of the same flask was attached to the second drying tube connected to a base bath.

![Diagram](image)

After flushing the whole system by argon for 10 minutes, sodium chloride and a stirring bar were placed in the 500 mL two-neck flask, the dropping funnel was charged with concentrated sulfuric acid, and DMPU and a small stirring bar were placed in a 100 mL receiving flask. Both flasks were cooled in ice-water baths.

Concentrated sulfuric acid was then gradually dropped onto sodium chloride at a rate of one drop per second, and an extremely exothermic reaction took place. During the absorption of HCl, the colorless DMPU turned into a viscous yellowish liquid.

The obtained HCl/DMPU solution was pipetted into an argon-flushed glass vessel with PTFE-lined cap. The concentration of the generated HCl/DMPU was approximately 43% by weight. This solution is slightly fuming but stable over months on a lab bench.

2.2 General procedure for Au/TiO$_2$ catalyzed hydrochlorination of alkynes using HCl/DMPU
Au/TiO₂ (158 mg, 2 mol %) was added to a solution of alkyne 1 (0.4 mmol) and DMPU/HCl (4 equiv) in DMF (0.2 mL). The mixture was stirred in an oil bath at 100 °C for designated time. After cooling down to room temperature, the reaction mixture was diluted with Et₂O (2 mL) and the solid residue was filtered off, the filtrate was washed with water and brine solution. The organic layer was dried over Na₂SO₄ and concentrated to dryness. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate).

2.3 Gram-scale synthesis of 2a

Au/TiO₂ (3.95 g, 2 mol %) was added to a solution of alkyne 1a (10 mmol) and DMPU/HCl (4 equiv) in DMF (5 mL). The mixture was stirred in an oil bath at 100 °C for 7 hour. After cooling down to room temperature, the reaction mixture was diluted with Et₂O and the solid residue was filtered off, the filtrate was washed with water and brine solution. The organic layer was dried over Na₂SO₄ and concentrated to dryness. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate). The product was isolated in 79% yield (1.16 g).

3. Characterization of products

2-chlorooct-1-ene (2a)

\[
\text{Cl} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{Cl}
\]

\[^{1}H\text{ NMR (400 MHz, CDCl₃)} \delta = 5.13 (s, 1H), 5.11 (s, 1H), 2.32 (t, J=7.4 Hz, 2H), 1.57-1.52 (m, 2H), 1.28 (m, 6H), 0.91-0.87 (t, J=6.7 Hz, 3H). \[^{13}C\text{ NMR (100 MHz, CDCl₃)} \delta = 143.15, 111.6, 39.14, 31.51, 28.20, 27.12, 22.54, 14.03.\]

Colorless oil (44.4 mg).

(4-chloropent-4-en-1-yl)benzene (2b)

\[
\text{Cl} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{Cl}
\]

\[^{1}H\text{ NMR (400 MHz, CDCl₃)} \delta 7.30 (dd, J = 9.6, 5.3 Hz, 2H), 7.21 (t, J = 6.6 Hz, 3H), 5.19 (s, 1H), 5.15 (s, 1H), 2.65 (t, J = 8.0 Hz, 2H), 2.38 (t, J = 7.4 Hz, 2H), 1.96-1.88 (m, 2H). \[^{13}C\text{ NMR (100 MHz, CDCl₃)} \delta = 142.59, 141.69, 128.42, 125.87, 112.27, 38.53, 34.60, 28.76.\]

Colorless oil (64.8 mg).

(1-chlorovinyl)cyclohexane (2c)

\[
\text{Cl} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{Cl}
\]

\[^{1}H\text{ NMR (400 MHz, CDCl₃)} \delta 5.10 (s, 2H), 2.17 (m, 1H), 1.92 (m, 2H), 1.79 (m, 2H), 1.68 (m, 1H), 1.34-1.23 (m, 4H). \[^{13}C\text{ NMR (100 MHz, CDCl₃)} \delta = 148.42, 109.58, 46.79, 46.66, 31.39, 25.98.\]

Colorless oil (42.6 mg).

5-chlorohex-5-enenitrile (2d)

\[^{1}H\text{ NMR (400 MHz, CDCl₃)} \delta 5.10 (s, 2H), 2.17 (m, 1H), 1.92 (m, 2H), 1.79 (m, 2H), 1.68 (m, 1H), 1.34-1.23 (m, 4H). \[^{13}C\text{ NMR (100 MHz, CDCl₃)} \delta = 148.42, 109.58, 46.79, 46.66, 31.39, 25.98.\]

Colorless oil (42.6 mg).
\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \delta 5.24 \text{ (s, 2H), 2.53 (t, J = 8.0 Hz, 2H), 2.37 (t, J = 8.0 Hz, 2H), 1.97-1.90 (m, 2H).} \]

\[ \text{13C NMR (100 MHz, CDCl}_3\text{)} \delta = 139.98, 118.98, 114.31, 37.48, 22.65, 15.76. \]

Colorless oil (41.5 mg).

5-chlorohex-5-enoic acid (2e)

\[ \text{HOOC} \]

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \delta 5.19 \text{ (s, 1H), 5.15 \text{ (s, 1H), 2.42-2.37 (m, 4H), 1.91 (t, J = 8.0 Hz, 2H).} \]

\[ \text{13C NMR (100 MHz, CDCl}_3\text{)} \delta = 179.53, 141.48, 113.04, 38.08, 32.43, 21.94. \]

Colorless oil (51.1 mg).

2,8-dichlorooct-1-ene (2f)

\[ \]

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \delta 5.14 \text{ (s, 1H), 5.12 \text{ (s, 1H), 3.53 (t, J = 8.0 Hz, 2H), 2.34 (t, J = 8.0 Hz, 2H), 1.81-1.74 (m, 2H), 1.62-1.53 (m, 2H), 1.50-1.42 (m, 2H), 1.37-1.30 (m, 2H).} \]

\[ \text{13C NMR (100 MHz, CDCl}_3\text{)} \delta = 142.81, 111.94, 44.97, 38.95, 32.44, 27.71, 26.91, 26.52. \]

Colorless oil (58.6 mg).

((10-chloroundec-10-en-1-yl)oxy)methyl)benzene (2g)

\[ \]

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \delta 7.35-7.26 \text{ (m, 5H), 5.14 \text{ (s, 1H), 5.12 \text{ (s, 1H), 3.53 (t, J = 8.0 Hz, 2H), 2.34 (t, J = 8.0 Hz, 2H), 2.33 (t, J = 8.0 Hz, 2H), 1.64-1.55 (m, 4H), 1.36-1.27 \text{ (m, 10H).} \]

\[ \text{13C NMR (100 MHz, CDCl}_3\text{)} \delta = 143.14, 138.70, 128.32, 127.60, 127.44, 111.94, 72.85, 70.49, 39.14, 29.76, 29.42, 29.24, 28.51, 27.15, 26.16. \]

HRMS (ESI) calcd. for [C\text{\textsubscript{18}H\textsubscript{27}ClONa\textsuperscript{+}] (\text{M+Na}\textsuperscript{+})] 317.1648; found 317.1642. Colorless oil (110.6 mg).

11-(allyloxy)-2-chloroundec-1-ene (2h)

\[ \]

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \delta = 5.95-5.86 \text{ (m, 1H), 5.26 (d, J = 16.0 Hz, 1H), 5.17-5.10 (m, 3H), 3.96 (d, J = 4.0 Hz, 2H), 3.41 (t, J = 8.0 Hz, 2H), 2.31 (t, J = 8.0 Hz, 2H), 1.59-1.54 (m, 4H), 1.29 (m, 10H).} \]

\[ \text{13C NMR (100 MHz, CDCl}_3\text{)} \delta = 143.12, 135.09, 116.63, 111.68, 71.76, 70.46, 39.11, 29.73, 29.41, 29.21, 28.49, 27.13, 26.14. \]

Colorless oil (90.8 mg).

10-chloroundec-10-en-1-yl benzoate (2i)
$^1$H NMR (400 MHz, CDCl$_3$) δ 8.05-8.03 (m, 2H), 7.56-7.53 (m, 1H), 7.45-7.41 (m, 2H), 5.12 (s, 1H), 5.10 (s, 1H), 4.31 (t, J = 8.0 Hz, 2H), 2.31 (t, J = 8.0 Hz, 2H), 1.78-1.72 (m, 2H), 1.58-1.31 (m, 12H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 166.64, 143.09, 132.75, 130.51, 129.50, 128.28, 111.67, 65.07, 39.11, 29.35, 29.19, 28.69, 28.47, 27.12, 25.99. HRMS (ESI) calcd. for [C$_{18}$H$_{25}$ClO$_2$H$^+$] ([M+H$^+$]) 309.1621; found 309.1667. Colorless oil (112.4 mg).

2-(10-chloroundec-10-en-1-yl)isoindoline-1,3-dione (2j)

![Chemical structure 2j](image)

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.84-7.81 (m, 2H), 7.70-7.68 (m, 2H), 5.11 (s, 1H), 5.09 (s, 1H), 3.66 (t, J = 8.0 Hz, 2H), 2.30 (t, J = 8.0 Hz, 2H), 1.66 (m, 2H), 1.52 (m, 2H), 1.47-1.42 (m, 2H), 1.36-1.29 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 168.41, 143.09, 133.79, 132.16, 123.10, 111.99, 39.10, 38.02, 29.39, 29.16, 29.08, 28.54, 28.45, 27.10, 26.79. HRMS (ESI) calcd. for [C$_{19}$H$_{24}$NClO$_2$Na$^+$] ([M+Na$^+$]) 356.1393; found 356.1385. Colorless oil (125.5 mg).

(7-chlorooct-7-en-1-yl)(phenyl)sulfane (2k)

![Chemical structure 2k](image)

$^1$H NMR (400 MHz, CDCl$_3$) δ = 7.34-7.25 (m, 4H), 7.66-7.62 (m, 1H), 5.14 (s, 1H), 5.11 (s, 1H), 2.92 (t, J = 8.0 Hz, 2H), 2.32 (t, J = 8.0 Hz, 2H), 1.70-1.62 (m, 2H), 1.58-1.52 (m, 2H), 1.47-1.42 (m, 2H), 1.36-1.29 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 142.90, 136.89, 128.90, 128.82, 125.68, 111.90, 39.01, 33.51, 28.98, 28.43, 28.02, 26.97. Colorless oil (92.7 mg).

((7-chlorooct-7-en-1-yl)sulfonyl)benzene (2l)

![Chemical structure 2l](image)

$^1$H NMR (400 MHz, CDCl$_3$) δ = 7.90-7.88 (m, 4H), 7.18-7.15 (m, 1H), 7.57-7.54 (m, 1H), 5.10 (s, 1H), 5.07 (s, 1H), 3.07 (t, J = 8.0 Hz, 2H), 2.27 (t, J = 8.0 Hz, 2H), 1.74-1.66 (m, 2H), 1.52-1.46 (m, 2H), 1.40-1.24 (m, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 142.57, 139.13, 133.61, 129.25, 128.00, 112.09, 56.16, 38.82, 27.92, 27.80, 26.63, 22.50. HRMS (ESI) calcd. for [C$_{14}$H$_{19}$ClO$_2$SNa$^+$] ([M+Na$^+$]) 309.0692; found 309.0691. Colorless oil (102.1 mg).

(2R,3R,4S,5R)-3,4,5-tris(benzyloxy)-2-((benzyloxy)methyl)-6-((5-chlorohex-5-en-1-yl)oxy)tetrahydro-2H-pyran (2o ($\alpha + \beta$))

![Chemical structure 2o](image)
\[^1\text{H}\text{ NMR\ (400 MHz, CDCl}_3\)] \(\delta\) 7.34-7.25 (m, 18H), 7.16 – 7.13 (m, 2H), 5.14-4.38 (m, 19H), 2.36-2.19 (m, -2H), 1.77-1.57 (m, 4H). \[^13\text{C}\text{ NMR\ (100 MHz, CDCl}_3\)] \(\delta\) 142.57, 138.87, 138.60, 138.45, 138.22, 138.08, 137.92, 128.35, 127.95, 127.91, 127.74, 127.66, 127.58, 112.26, 112.15, 103.60, 97.06, 96.93, 84.70, 82.11, 80.09, 77.80, 75.67, 74.83, 73.47, 73.40, 70.21, 69.49, 68.98, 68.53, 67.78, 38.80, 29.69, 28.64, 28.25, 23.81. HRMS (ESI) calcd. for \([\text{C}_{40}\text{H}_{45}\text{ClO}_6\text{Na}^+]\) ([M+Na\(^+\)]) 679.2802; found 679.2786. White solid (178.8 mg).

(S)-methyl 2-(5-chlorohex-5-enamido)-3-phenylpropanoate (2p)

\[^1\text{H}\text{ NMR\ (400 MHz, CDCl}_3\)] \(\delta\) 7.28-7.25 (m, 3H), 7.09-7.07 (m, 2H), 7.57-7.54 (m, 1H), 5.86 (s, 1H), 5.14 (s, 1H), 5.08 (s, 1H), 4.92-4.87 (m, 1H), 3.73 (s, 1H), 3.16-3.05 (m, 2H), 2.33 (t, \(J = 8.0\text{ Hz, 2H})\), 2.18 (t, \(J = 8.0\text{ Hz, 2H})\), 1.90-1.85 (m, 2H). \[^13\text{C}\text{ NMR\ (100 MHz, CDCl}_3\)] \(\delta\) 172.08, 171.80, 141.77, 135.74, 129.17, 128.59, 112.92, 52.89, 52.34, 38.06, 37.84, 34.61, 22.68. HRMS (ESI) calcd. for \([\text{C}_{16}\text{H}_{20}\text{NClO}_3\text{Na}^+]\) ([M+Na\(^+\)]) 332.1029; found 332.1031. Colorless oil (71.9 mg).

(8R,9S,13S,14S)-3-((7-chlorooct-7-en-1-yl)oxy)-13-methyl-7,8,9,11,12,13,15,16-octahydro-6H-cyclopenta[a]phenanthren-17(14H)-one (2q)

\[^1\text{H}\text{ NMR\ (400 MHz, CDCl}_3\)] \(\delta\) 7.18 (d, \(J = 8.0\text{ Hz, 1H})\), 6.71-6.69 (m, 1H), 6.64 (s, 1H), 5.13 (s, 1H), 5.11 (s, 1H), 3.92 (t, \(J = 8.0\text{ Hz, 2H})\), 2.89-2.87 (m, 2H), 2.53-2.46 (m, 2H), 2.40-2.32 (m, 3H), 2.26-2.22 (m, 1H), 2.18-1.93 (m, 4H), 1.80-1.73 (m, 2H), 1.64-1.37 (m, 11H), 0.90 (s, 3H). \[^13\text{C}\text{ NMR\ (100 MHz, CDCl}_3\)] \(\delta\) 220.87, 157.08, 142.94, 137.66, 131.85, 126.26, 114.52, 114.47, 112.06, 111.86, 67.72, 50.40, 47.99, 43.97, 39.04, 38.37, 25.86, 31.58, 29.64, 29.19, 28.24, 27.06, 26.56, 25.92, 25.77, 21.58, 13.84. HRMS (ESI) calcd. for \([\text{C}_{26}\text{H}_{35}\text{ClO}_2\text{Na}^+]\) ([M+Na\(^+\)]) 437.2223; found 437.2213. White solid (159.4 mg).

(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl 5-chlorohex-5-enoate (2r)
$^1$H NMR (400 MHz, CDCl$_3$) δ 5.37-5.36 (m, 1H), 5.16 (s, 1H), 5.13 (s, 1H), 4.62-4.57 (m, 1H), 2.41-2.25 (m, 6H), 1.98-1.80 (m, 8H), 1.56-0.84 (m, 32H), 0.66 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.45, 141.79, 139.57, 122.65, 112.79, 73.98, 73.89, 56.66, 56.11, 50.00, 42.28, 39.70, 39.49, 38.25, 38.12, 36.96, 36.57, 36.16, 35.77, 33.09, 31.83, 28.21, 27.99, 27.79, 24.26, 23.81, 22.80, 22.54, 22.39, 21.01, 19.31, 18.70, 11.85. HRMS (ESI) calcd. for [C$_{33}$H$_{53}$ClO$_2$Na$^+$] ([M+Na$^+$]) 539.3632; found 539.3622. White solid (198.6 mg).

2,6-dichlorohepta-1,6-diene (2s)$^{[4]}$

![2,6-dichlorohepta-1,6-diene](image)

$^1$H NMR (400 MHz, CDCl$_3$) δ 5.18 (s, 1H), 5.14 (s, 2H), 2.36 (t, $J$ = 8.0 Hz, 4H), 1.88-1.81 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 141.99, 112.65, 37.69, 24.43. Colorless oil (58.7 mg).

(E)-2-(prop-1-en-1-yl)pyridine (2u)$^{[3]}$

![E]-2-(prop-1-en-1-yl)pyridine](image)

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.52 (d, $J$ = 4.6 Hz, 1H), 7.63 (td, $J$ = 7.7, 1.8 Hz, 1H), 7.25 (d, $J$ = 3.9 Hz, 1H), 7.18-7.12 (m, 2H), 6.87 (s, 1H), 6.83 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 153.28, 149.72, 136.71, 132.59, 124.27, 122.68, 121.78. Colorless oil (40.2 mg).
4. Copies of NMR spectra for compound 2
References

[1] P. O. Miranda, D. D. Díaz, J. I. Padrón, M. A. Ramírez, V. S. Martín, J. Org. Chem. 2005, 70, 57-62.
[2] M. S. Newman, G. Fraenkel, W. N. Kirn, J. Org. Chem. 1963, 28, 1851-1853.
[3] J. Oliver-Meseguer, A. Doménech-Carbó, M. Boronat, A. Leyva-Pérez, A. Corma, Angew. Chem. Int. Ed. 2017, 56, 6435-6439.
[4] S. Dérien, H. Klein, C. Bruneau, Angew. Chem. Int. Ed. 2015, 54, 12112-12115.
[5] J. Drouin, F. Leyendecker, J. M. Conia, Tetrahedron 1980, 36, 1203-1208.