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Controlled C-5 Chlorination and Dichlorohydrin Formation of Uracil Ring with HCl/DMF/Oxone® System

Hyun Seung Lee, Hyun Ju Lee, Ka Young Lee,† and Jae Nyoung Kim*

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Korea
**E-mail: kimjn@chonnam.ac.kr*
†Document and Image Division, National Forensic Service, Seoul 158-707, Korea
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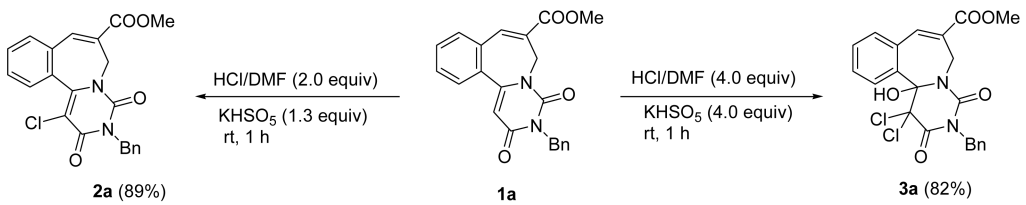
Since the serendipitous finding of Ryu and MacCoss,[1] dry HCl gas in DMF has been used as an efficient chlorinating reagent of nucleosides and nucleic acid bases in the presence of an oxidant such as *m*-CPBA.[1,2] Various modifications have been reported including the use of benzoyl chloride instead of HCl gas,[2] the use of molecular iodine for iodination,[3] and the use of Oxone® ($2KHSO_5/KHSO_4/K_2SO_4$) as an oxidant.[4] In addition, numerous substrates have been chlorinated by the above reagents system including phenols,[5a] acetanilides,[5b] ketones,[5c] α,β-enones,[5d] aldoximes,[4a] β-nitrostyrenes,[4b] and alkynes.[4c]

Recently, we reported a palladium-catalyzed synthesis of various benzazepine derivatives such as **1a** in Scheme 1.[6] During the chlorination of benzazepine derivative **1a** under the HCl/DMF/Oxone® conditions, we observed the formation of dichlorohydrin derivative **3a** in high yield (82%) instead of the desired compound **2a**.[7] The result was unexpected one as one of the authors have a long experience of the such reaction system.[2-5] We presumed that compound **3a** must be formed from **2a** by the action of hypochlorous acid (HOCl) which could be generated from HCl and Oxone® (vide infra). Accordingly, we controlled the reaction progress carefully by adding Oxone® in a portionwise manner. As expected, compound **2a** was obtained in good yield (89%) when a slight excess amount of Oxone® (0.65 equiv which corresponds to 1.30 equiv of $KHSO_5$) was used at room temperature.[7]

Encouraged by the above result, we examined the reaction of 1,3-dimethyluracil (**1b**) and related compounds, and the results are summarized in Table 1. The reaction of **1b** in the presence of a limited amount of Oxone® (0.65 equiv, 1.30 equiv of $KHSO_5$) afforded **2b** in good yield (80%) by the addition of Oxone® in a portionwise manner (entry 1). The formation of **3b** was observed on TLC, but the amount was negligible. Dichlorohydrin **3b** was obtained as a major product (88%) when we added excess amounts of Oxone® (2.0 equiv, 4.0 equiv of $KHSO_5$, entry 2). A similar observation for the formation of dichlorohydrin derivatives has been reported by Itahara and co-workers.[8] They carried out the reactions of uracil derivatives with NaCl/AcOH in the presence of $Na_2S_2O_8$; however, yields were low to moderate presumably due to the limited solubility of NaCl, while the yield of **3b** was excellent (88%) under our reaction conditions.

The reaction of 6-methyl derivative **1c** and 6-phenyl derivative **1d**[9] showed similar trends (entries 3-6). The corresponding 5-chloro derivatives **2c** and **2d** were obtained in good yields (82-90%) and dichlorohydrin derivatives **3c** and **3d** were obtained in good yields (83-84%). 5-Substituted uracil derivatives, **1e** and **1f**, produced the corresponding chlorohydrins **3e** and **3f** (entries 7 and 8). The relatively low yield of **3f** might be due to the presence of a large 5-bromo substituent in **1f**. The 5-bromination and dibromohydrin formation of **1b** were carried out with 48% aqueous HBr solution in DMF (entries 9 and 10). The yield of 5-bromo-1,3-dimethyluracil (**2e**) was reasonable (62%) while the yield of dibromohydrin **3g** was low (41%) due to a similar steric reason as in the case of **3f**. When we used aqueous HCl (37%) instead of dry HCl gas, the yield of **2b** decreased to 51% (rt, 2 h, 1.5 equiv of $KHSO_5$), as compared to the yield (80%) using dry HCl (entry 1).

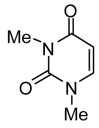
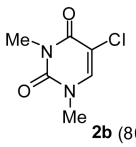
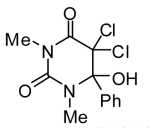
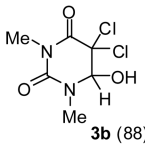
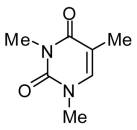
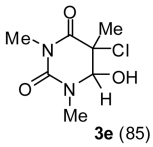
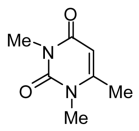
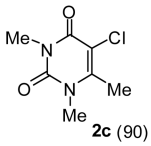
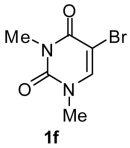
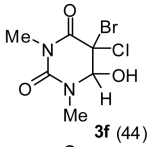
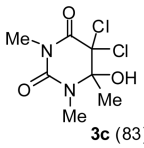
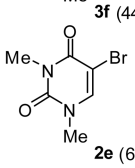
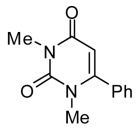
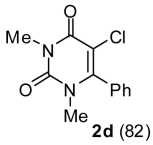
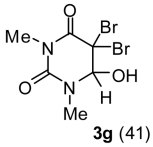
The plausible reaction mechanism for the 5-chlorination and the formation of a dichlorohydrin derivative are shown in Scheme 2, with 1,3-dimethyluracil (**1b**) as a model substrate. As shown in Scheme 2, HCl might be converted to HOCl by the action of $KHSO_5$.[4,10] An electrophilic chlori-



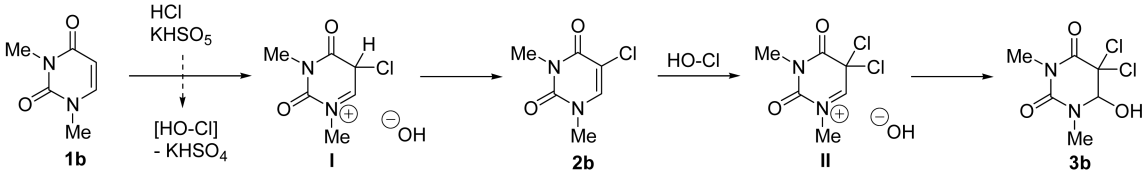
2a (89%) **1a** **3a** (82%)

Scheme 1

Table 1. Selective 5-chlorination and halohydrin formation of uracil derivatives

Entry	Substrate	Conditions[a]	Product (%)	Entry	Substrate	Conditions[a]	Product (%)
1	 **1b**	A	 **2b** (80)	6	**1d**	B	 **3d** (84)
2	**1b**	B	 **3b** (88)	7	 **1e**	B	 **3e** (85)
3	 **1c**	A	 **2c** (90)	8	 **1f**	B	 **3f** (44)
4	**1c**	B	 **3c** (83)	9	**1b**	A[b]	 **2e** (62)
5	 **1d**	A	 **2d** (82)	10	**1b**	B[b]	 **3g** (41)

[a]Conditions A: Substrate (0.5 mmol), HCl/DMF solution (2.0 equiv), Oxone (0.65 equiv), rt, 1 h; Conditions B: Substrate (0.5 mmol), HCl/DMF solution (4.0 equiv), Oxone (2.0 equiv), rt, 2 h. [b]Aqueous HBr (48%) in DMF was used instead of HCl/DMF.



Scheme 2

nation *via* the iminium salt **I** followed by deprotonation by a hydroxide ion would produce **2b**. In the presence of excess amounts of HOCl, compound **2b** was converted to **3b** *via* an iminium ion intermediate **II**.[10,11]

In summary, we disclosed an efficient method for the synthesis of 5-chlorouracil derivatives and various dichloro-, chloro-, bromo-, and dibromohydrins by controlling the amounts of Oxone® in the presence of gaseous HCl in DMF or aqueous HBr in DMF.

Experimental Section

Synthesis of 3a. To a stirred solution of **1a**[6] (187 mg, 0.5 mmol) in DMF (1.0 mL) was added a solution of 3.0 M HCl/DMF (0.67 mL, 4.0 equiv of HCl). Oxone® (614 mg, 1.0 mmol, 4.0 equiv of $KHSO_5$) was added to the reaction mixture at room temperature and stirred for 1 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/Et_2O, 1:2), compound **3a** was isolated as a white solid, 189 mg (82%). The spectroscopic data of **3a** are as follows.

Compound 3a: 82%; white solid, mp 214-216 °C; IR (KBr) 3350, 1737, 1692, 1441, 1414, 1293, 1240 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.46 (d, J = 15.0 Hz, 1H), 3.77 (s, 3H), 4.94 (d, J = 15.0 Hz, 1H), 5.02 (d, J = 15.0 Hz, 1H), 5.43 (d, J = 15.0 Hz, 1H), 7.27-7.37 (m, 5H), 7.58-7.65 (m, 3H), 7.95 (s, 1H), 8.10-8.13 (m, 1H), 8.86 (br s, OH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 40.20, 45.40, 52.23, 85.91, 91.16, 127.09, 127.30, 128.14, 128.46, 129.69, 129.94, 131.61, 132.97, 133.99, 135.51, 136.64, 143.03, 149.36, 161.99, 165.43; ESIMS *m/z* 483 (M^++Na), 485 (M^++2+Na), 487 (M^++4+Na). Anal. Calcd. For $C_{22}H_{18}Cl_2N_2O_5$: C, 57.28; H, 3.93; N, 6.07. Found: C, 57.50; H, 4.02; N, 5.89.

Typical Procedure for the Synthesis of 2b. To a stirred solution of **1b** (70 mg, 0.5 mmol) in DMF (0.5 mL) was added a solution of 3.0 M HCl/DMF (0.34 mL, 2.0 equiv of HCl). Oxone® (200 mg, 0.33 mmol, 1.3 equiv of $KHSO_5$) was added portionwise to the reaction mixture at room temperature and stirred for 1 h. After the usual aqueous extractive workup and column chromatographic purification

process (hexanes/Et_2O, 1:2), compound **2b** was isolated as a white solid, 70 mg (80%). Other compounds were prepared similarly, and the spectroscopic data of **2b-e** are as follows.

Compound 2b:[7] 80%; white solid, mp 146-148 °C (Lit.[7] 140-148 °C); IR (KBr) 1715, 1660, 1480, 1443, 1339 cm^{-1}; ESIMS *m/z* 175 (M^++H), 177 (M^++H+2).

Compound 2c:[12a] 90%; white solid, mp 148-150 °C (Lit.[12a] 151 °C); IR (KBr) 1701, 1649, 1464, 1425 cm^{-1}; ESIMS *m/z* 189 (M^++H), 191 (M^++H+2).

Compound 2d: 82%; white solid, mp 134-136 °C; IR (KBr) 1703, 1650, 1442, 1275 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.14 (s, 3H), 3.48 (s, 3H), 7.27-7.31 (m, 2H), 7.52-7.58 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.22, 35.26, 108.23, 127.70, 129.31, 130.22, 131.54, 150.49, 151.15, 159.20; ESIMS *m/z* 251 (M^++H), 253 (M^++H+2). Anal. Calcd. For $C_{12}H_{11}ClN_2O_2$: C, 57.49; H, 4.42; N, 11.17. Found: C, 57.72; H, 4.67; N, 11.01.

Compound 2e:[7] 62%; white solid, mp 184-186 °C (Lit.[7] 183-184 °C); IR (KBr) 1701, 1651, 1443, 1275, 1261 cm^{-1}; ESIMS *m/z* 219 (M^++H), 221 (M^++H+2).

Typical Procedure for the Synthesis of 3b. To a stirred solution of **1b** (70 mg, 0.5 mmol) in DMF (0.5 mL) was added a solution of 3.0 M HCl/DMF (0.67 mL, 4.0 equiv of HCl). Oxone® (614 mg, 1.0 mmol, 4.0 equiv of $KHSO_5$) was added to the reaction mixture at room temperature and stirred for 2 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/Et_2O, 1:2), compound **3b** was isolated as a white solid, 99 mg (88%). Other compounds were prepared similarly, and the spectroscopic data of **3b-g** are as follows.

Compound 3b:[10a] 88%; white solid, mp 112-113 °C; IR (KBr) 3397, 1730, 1679, 1480, 1424, 1288 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.20 (s, 3H), 3.28 (s, 3H), 4.29 (br s, OH), 5.10 (s, 1H); ESIMS *m/z* 227 (M^++H), 229 (M^++H+2), 231 (M^++H+4).

Compound 3c: 83%; white solid, mp 132-134 °C; IR (KBr) 3375, 1732, 1678, 1461, 1386, 1335 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 300 MHz) δ 1.84 (s, 3H), 3.14 (s, 3H), 3.28 (s, 3H), 6.53 (br s, OH); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75 MHz) δ 20.97, 29.42, 29.90, 85.81, 87.46, 151.59, 162.51; ESIMS *m/z* 241 (M^++H), 243 (M^++H+2), 245 (M^++H+4). Anal. Calcd. For $C_7H_{10}Cl_2N_2O_3$: C, 34.88; H, 4.18; N, 11.62. Found: C, 34.79; H, 4.34; N, 11.38.

Compound 3d: 84%; white solid, mp 76-78 °C; IR (KBr) 3386, 1734, 1674, 1453, 1379, 1327 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.96 (s, 3H), 3.38 (s, 3H), 4.28 (br s, OH), 7.36-7.47 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.95, 31.27, 86.75, 89.81, 127.78, 128.46, 130.17, 133.36, 152.00, 161.60; ESIMS *m/z* 303 (M^++H), 305 (M^++H+2), 307 (M^++H+4). Anal. Calcd. For $C_{12}H_{12}Cl_2N_2O_3$: C, 47.55; H, 3.99; N, 9.24. Found: C, 47.46; H, 4.11; N, 9.15.

Compound 3e:[8] 85%; white solid, mp 110-112 °C (Lit.[8] 110-111 °C); IR (KBr) 3377, 1721, 1672, 1483, 1425, 1294 cm^{-1}; ESIMS *m/z* 207 (M^++H), 209 (M^++H+2).

Compound 3f: 44%; white solid, mp 112-114 °C; IR (KBr) 3374, 1732, 1693, 1479, 1425, 1278 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.20 (s, 3H), 3.27 (s, 3H), 4.15 (br s, OH), 5.09 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.29, 35.30, 79.53, 86.00, 151.20, 161.88; ESIMS *m/z* 271 (M^++H), 273 (M^++H+2), 275 (M^++H+4). Anal. Calcd. For $C_6H_8BrClN_2O_3$: C, 26.54; H, 2.97; N, 10.32. Found: C, 26.43; H, 3.13; N, 10.14.

Compound 3g:[12b] 41%; white solid, mp 136-138 °C (Lit.[12b] 136-137 °C); IR (KBr) 3376, 1725, 1678, 1477, 1421, 1288 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.21 (s, 3H), 3.28 (s, 3H), 4.24 (br s, OH), 5.21 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.53, 35.41, 57.30, 86.49, 151.28, 162.25; ESIMS *m/z* 315 (M^++H), 317 (M^++H+2), 319 (M^++H+4). Anal. Calcd. For $C_6H_8Br_2N_2O_3$: C, 22.81; H, 2.55; N, 8.87. Found: C, 22.95; H, 2.71; N, 8.68.

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