SHORT PAPER

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Hypervalent iodine in synthesis 91: a mild and efficient method for the halogenation of 6-methyluracil derivatives†

Dong Ping Cheng[a], Zhen Chu Chen[a,*] and Qin Guo Zheng[b]

[a]*Department of Chemistry, Zhejiang University, Xixi Campus, Hangzhou, 310028, P.R. China*

[b]*Pharmaceutical Sciences, School of Life & Health Sciences, Aston University, Birmingham B4 7ET, UK*

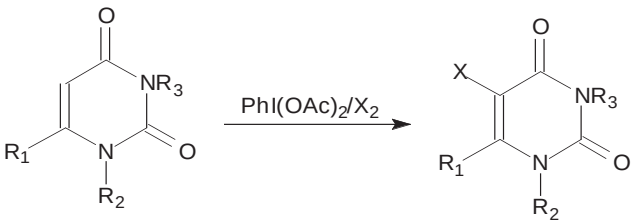
The combined reagent of iodobenzene diacetate (or polymer-supported iodobenzene diacetate) with iodine or bromine was used as an effective halogenative agent of 6-methyluracil derivatives to the corresponding 5-halo-6-methyluracil derivatives at room temperature with high yields.

Keywords: hypervalent iodine, halogenation, 6-methyluracil derivatives

A number of 5-halogenouracil derivatives have been investigated in the treatment of neoplastic and viral diseases.[1] 5-iodo-2′-deoxyuridine has been in clinical use as a herpes antiviral drug for several decades.[1] Recently 5-halogenouracil derivatives have been used as sedatives.[2] Some of these 5-halogenouracil derivatives had been shown to be good starting materals.[3] The methods reported for the preparation of 5-halogenouracil derivatives. Include direct halogenations,[4] iodine monochloride,[1] N-halogenosuccunimide.[5] However, some suffer from disadvantages such as poor yield of the product, unstable reagent, and complex manipulation. The development of convenient and efficient methods for the preparation of 5-halogenouracil derivatives is of practical importance.

The versatile synthetic utility of hypervalent iodine reagents is of current interest.[6] Recently, it was shown the combined reagent of the iodine/PhI $(OAc)_2$ is a convenient reagent for the iodination of aromatic compounds.[7] Reaction occurs through acetyl hypoiodites formed *in situ*. There is little published work on the use of the iodine/PhI $(OAc)_2$ system for the heteroaromatic compounds.[8] We examined the halogenation of 6-methyluracil derivatives using halogen/PhI $(OAc)_2$ system as the halogenating reagent.

We found that the PhI $(OAc)_2/I_2$ system is an excellent reagent for the iodination of 6-methyluracil derivatives. Simply stirring a mixture of PhI $(OAc)_2$, iodine and the 6-methyluracil derivative in an appropriate solvent at room temperature gave, after work-up and isolation, the desired 5-iodo-6-methyluracil derivative in high yield (Scheme 1)



1a–1d **2a–2d**

X=Br, I

Scheme 1

Table 1 halogenation of 6-methyluracil

Entry	Substrate, R_1, R_2, R_3	Product	Time/min	Yield/%[c]
1	**1a**, CH_3, H, H	**2a**[a]	45	93
2	**1b**, CH_3, C_6H_5, C_6H_5	**2b**[a]	45	92
3	**1c**, CH_3, $CH_2C_6H_4$, $CH_2C_6H_4$	**2c**[a]	45	91
4	**1d**, CH_3, H, C_6H_5	**2d**[a]	80	86
5	**1a**, CH_3, H, H	**2a**[b]	15	94
6	**1b**, CH_3, C_6H_5, C_6H_5	**2b**[b]	15	93
7	**1c**, CH_3, $CH_2C_6H_4$, $CH_2C_6H_4$	**2c**[b]	15	89
8	**1d**, CH_3, H, C_6H_5	**2d**[b]	50	89
9	**1c**, CH_3, $CH_2C_6H_4$, $CH_2C_6H_4$	**2c**[a]	50	87
10	**1c**, CH_3, $CH_2C_6H_4$, $CH_2C_6H_4$	**2c**[b]	20	90
11	**1c**, CH_3, $CH_2C_6H_4$, $CH_2C_6H_4$	**2c**[a]	60	87[d]
12	**1c**, CH_3, $CH_2C_6H_4$, $CH_2C_6H_4$	**2c**[b]	25	89[d]

[a]X = I; [b]X = Br; [c]Isolated yields based on 6-methyluracil derivatives; [d]The regenerated PIBD was used.

(Table 1, entries 1, 3, 5, 7). We also used the PhI $(OAc)_2/Br_2$ system to react with the above 6-methyluracil derivatives. The desired 5-bromo-6-methyluracil derivatives were obtained (entries 2, 4, 6, 8). The brominations were completed within a few minutes.

The advantages of polymer-supported reactive species are now widely recognised by organic chemists and the exploitation of these systems is developing both in academic and industrial laboratories.[9] Recently we studied the properties of polymer-supported iodobenzene diacetate (PIBD).[10] To expand the application of the PIBD, we used the iodine or bromine/PIBD system in the halogenation reactions of 6-methyluracil derivative. It was also successful (entries 9–10). The side product of the reaction is polymer-supported iodobenzene (PIB). After the completion of the reaction, ether was added to the reaction mixture to precipitate the PIB, and the product can be obtained easily by the simple filtration. Thus the manipulation is simplified.

We also examined the regeneration and recycling of the polymer reagent. The spent resin was collected by filtration and reoxidised with peracetic acid.[10a] The regenerated resin was used to repeat the reaction with no loss of activity (See Table entries 11–12).

In summary, we think that the iodine or bromine/IBD and iodine or bromine/PIBD system is an effective halogenation reagent for 6-methyluracil derivatives. This reaction makes full use of halogen atoms. The advantages of this reaction are ease manipulation, mild reaction conditions and high yields. The range of useful applications of IBD or PIBD in organic synthesis has been extended.

* To receive any correspondence. E-mail:zhenchuc@mail.hz.zj.cn

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Experimental

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 400 MHz instrument as $CDCl_3$ solutions using TMS as internal standard. IR spectra were determined on a Bruker Vector-22 spectrometer. Elemental analyses were performed on a EA-1110 instrument. MS was recorded on HP-5989B Mass Spectrometer. Uracil derivatives are prepared according to described procedures.[11] PIBD is prepared according to our preciously reported method.[10a]

General procedure for the halogenation of 6-methyluracil derivatives: In a 50 ml round-bottomed flask, iodine or bromine (0.5 mmol) was added to IBD (0.5 mmol) or PIBD (1 g) in dichloromethane or acetic acid (10 ml). The mixture was stirred for half an hour, then the 6-methyluracil derivative (1 mmol) was added to the solution. The time of the reaction was indicated in Table 1. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue which was obtained was purified on a silica-gel plate. If the products are entry (1, 4, 5, 8), the eluant was ethyl acetate: cyclohexane (2:1). If the products are entry (2, 3, 6, 7), the eluant was ethyl acetate: cyclohexane (1:2). If the reagent was PIBD, ether (20 ml) was added to the mixture, then filtered. After removal the solvent, the product which was obtained was recrystallised with ethanol or water. The characterisation and spectral data of the products are given as following:

2a:[a] m.p. 276ºC. dec. (lit[4] 280–283°C, dec.). ^{1}H NMR: (DMSO-d_6): δ11.27 (brs, 2H), 2.28 (s, 3H); *m/z* (%): 252 (M^+, 100), 209 (30.73), 168 (33.18), 127 (9.40).

2a:[b] m.p. 232–233ºC. dec. (lit[12] 230°C, dec.). ^{1}H NMR: (DMSO-d_6): δ 11.37 (brs, 1H), 11.25 (brs, 1H), 2.19 (s, 3H); *m/z* (%): 204 (M^+, 95.96), 206 (M^++2, 100), 209 (30.73), 161 (81.17), 163 (78.88), 120 (55.10), 122 (48.96).

2b:[a] m.p. 194–196°C. ^{1}H NMR: ($CDCl_3$): δ 7.38–7.51 (m, 6H), 7.24–7.28 (m, 4H), 2.32 (s, 3H); *m/z* (%): 404 (M^+, 54.98), 285 (36.07), 158 (39.86), 118 (100); Anal. Calcd. for $C_{17}H_{13}IN_2O_2$: C 50.52, H 3.24, N 6.93; Found: C 50.73, H 3.69, N 6.77.

2b:[b] m.p. 177–179°C. ^{1}H NMR: ($CDCl_3$): δ 7.39–7.53 (m, 6H), 7.25–7.30 (m, 4H), 2.21 (s, 3H); *m/z* (%): 356 (M^+, 19.47), 358 (M^++2, 19.65), 237 (23.69), 239 (23.52), 158 (20.72), 118 (91.96), 77 (100); Anal. Calcd. for $C_{17}H_{13}BrN_2O_2$: C 57.16, H 3.67, N 7.84; Found: C 56.90, H 3.56, N 7.62.

2c:[a] m.p. 125–127°C. ^{1}H NMR ($CDCl_3$): δ 7.51–7.53 (t, 2H), 7.25–7.36 (m, 6H), 7.12–7.14 (d, 2H), 5.23 (s,4H), 2.54 (s, 3H); *m/z* (%): 432 (M^+, 28.19), 298 (6.85), 180 (7.90), 91 (100), 65 (19.46); Anal. Calcd. for $C_{19}H_{17}IN_2O_2$: C 52.79, H 3.96, N 6.48; Found: C 52.63, H 3.93, N 6.64.

2c:[b] m.p. 93.5–94.5°C. ^{1}H NMR ($CDCl_3$): δ 7.51–7.53 (t, 2H), 7.25–7.36 (m, 6H), 7.12–7.14 (d, 2H), 5.21 (s, 4H), 2.43 (s, 3H);. *m/z* (%): 384 (M^+, 11.31), 386 (M^++2, 11.98), 293 (4.25), 180 (5.19), 132 (6.40), 91 (100), 65 (19.53); Anal. Calcd. for $C_{19}H_{17}BrN_2O_2$: C 59.23, H 4.44, N 7.27; Found: C 59.10, H 4.41, N 7.48.

2d:[a] m.p. 248–249°C. ^{1}H NMR (DMSO-d_6): δ 11.71 (brs, 1H), 7.38–7.46 (m, 3H), 7.19–7.26 (d, 2H), 2.36 (s, 3H);. *m/z* (%): 325 (M^+, 54.73), 209 (26.77), 168 (23.07), 119 (17.05), 91 (22.18), 77 (53.71), 42 (100); Anal. Calcd. for $C_{11}H_9IN_2O_2$: C 40.27, H 2.76, N 8.54; Found: C 40.43, H 2.91, N 8.37.

2d:[b] m.p. 258–259°C. ^{1}H NMR (DMSO-d_6): δ 11.73 (brs, 1H), 7.39–7.85 (m, 3H), 7.11–7.35 (m, 2H), 2.29 (s, 3H);. *m/z* (%): 280 (M^+, 39.06), 282 (M^++2, 38.99), 161 (24.36), 119 (45.49), 91 (29.91), 77 (53.71), 42 (100); Anal. Calcd. for $C_{11}H_9BrN_2O_2$: C 47.00, H 3.23, N 9.97; Found: C 47.15, H 3.39, N 9.71.

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