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HYPERVALENT IODINE IN SYNTHESIS. 76. AN EFFICIENT OXIDATION OF 1,4-DIHYDROPYRIDINES TO PYRIDINES USING IODOBENZENE DIACETATE

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ABSTRACT

Iodobenzene diacetate was used as an effective oxidizing agent for the oxidation of 1,4-dihydropyridines to the corresponding pyridine derivatives at room temperature with high yields.

The oxidation of Hantzsch 1,4-dihydropyridines (Hantzsch 1,4-DHP) and analogs to the corresponding pyridines is of interest because of its relevance to the biological NADH redox processes[1–3] as well as to the metabolic studies pertaining to 1,4-DHP based cardiovascular drugs such as Nifedipine and Niguldipine.[3–5] Furthermore, the oxidation of readily accessible Hantzsch 1,4-DHP constitutes by for the easiest method to obtain pyridine derivatives. A number of methods and reagents have been reported recently in the literature for this purpose.[6–21] However, some of these methods suffer from disadvantages such as long reaction times,

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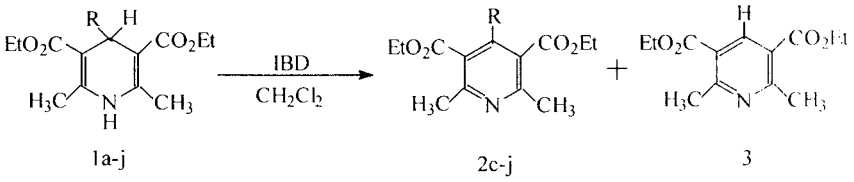
the lower yields of the products, the requirement of severe conditions and the use of strong or toxic oxidants. Therefore, development and introduction of convenient, milder and efficient method for the oxidation of 1,4-dihydropyridines to the corresponding pyridines is of practical importance and is still in demand.[6–7]

The versatile synthetic utility of hypervalent iodine reagents is of current interest. It has been demonstrated that the iodobenzene diacetate (IBD) is a general, universal oxidizing reagent.[22–24] In the course of our studies on the applications of hypervalent iodine reagent in synthesis. We planned to study the oxidation of 1,4-DHP to the corresponding pyridines employing IBD. Herein, we would like to report a milder, facile and efficient method for the oxidation of different types of 4-substituted 1,4-DHP to their corresponding pyridines with IBD (Scheme 1).



1a-j 2c-j 3

Scheme 1.

In fact, simple stirring the mixture of 1,4-DHP and IBD in methylene chloride at room temperature gave after work up and isolation, the desired pyridine derivative in good yield. The reaction is clean and efficient. The results are summarized in Table 1. The products were characterized by ^{1}H NMR, IR and m.p., which were consistent with literature data.

According to the experiment, we observed that oxidation of 1,4-dihydropyridine with alkyl group at the 4-position only gave the dealkylated pyridine derivative (**3**) (Table 1, Entry 2). This is agreement with the observation made by other.[6–7] But 4-aryl-1,4-dihydropyridines were oxidized with retention of substituent at 4-position, to afford the corresponding pyridine derivatives (Entries 3–10). We also observed that in comparison with methylene chloride, the reaction times were longer and the yields of the products were rather lower when the solvent was acetonitrile or THF.

The latest member of the family of hypervalent iodine oxidants, the hydroxy(tosyloxy)iodobenzene (HTIB) is also widely used, generally more reactive than IBD.[24] We found that HTIB is a superior reagent for the

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Table 1. Oxidation of 1,4-DHP by IBD or HTIB or PIBD

Entry	Substrate (*R*)	Product	Time (*t*, min)	Yield (%)[a]
1	1a, H	3	20	90
2	1b, *n*-C_4H_7	3	35	85
3	1c, C_6H_5	2c	60	87
4	1d, *m*-$NO_2C_6H_4$	2d	70	88
5	1e, *p*-$NO_2C_6H_4$	2e	60	89
6	1f, *p*-$CH_3OC_6H_4$	2f	30	92
7	1g, *p*-ClC_6H_4	2g	60	91
8	1h, *m*-BrC_6H_4	2h	50	86
9	1i, *p*-$CH_3C_6H_4$	2i	50	87
10	1j, 2,4-$Cl_2C_6H_3$	2j	70	89
11	1d, *m*-$NO_2C_6H_4$	2d	5	90
12	1f, *p*-$CH_3OC_6H_4$	2f	5	93
13	1c, C_6H_5	2c	120	85
14	1d, *m*-$NO_2C_6H_4$	2d	180	86
15	1e, *p*-$NO_2C_6H_4$	2e	180	84
16	1g, *p*-ClC_6H_4	2g	120	90
17	1g, *p*-ClC_6H_4	2g	120	86[b]

[a]Isolated yields based on 1,4-DHP.
[b]Use the regenerated PIBD.

oxidation of 1,4-DHP to corresponding pyridines. The reaction is very quick (Entries 11 and 12).

The advantages of polymer-supported reactive species are now widely recognized by organic chemistry and the exploitation of these systems is developing both in academic and industrial laboratories. Recently, we have already investigated the preparation and reactivity of Polystyrene-supported iodobenzene diacetate (PIBD) and found its property is similar to the property of the IBD.[25] So we have also tried to use the PIBD to oxidize the 1,4-dihydropyridines. The yield is also satisfying (Entries 13–17). Utilization of the solid-supported inorganic reagents to oxidize the 1,4-dihydropyridines has been reported,[26–30] but up to our knowledge the polymer-supported organic reagent was first applied to this reaction.

In summary, we have found IBD or HTIB or PIBD to be a valuable addition to the existing methods available for the oxidation of Hantzsch 1,4-DHP with added advantages of ease of manipulation, mild reaction conditions and high yields. Furthermore, the range of useful applications of iodobenzene diacetate in organic synthesis has been extended.

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EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Brucker 400 MHz instrument as $CDCl_3$ solutions using TMS as internal standard. IR spectra were determined on a Vector-22 spectrometer. Elemental analyses were performed on a EA-1110 instrument. 1,4-Dihydropyridines were prepared according to described procedures.[31]

General Procedure for the Oxidation of 1,4-Dihydropyridines

In a 50 ml round-bottomed flask, dichloromethane (10 ml) was added to the mixture of 1,4-dihydropyridine (1 mmol) and IBD or HTIB or PIBD (1.1 mmol). The mixture was stirred for the time indicated in Table 1. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was washed with water (3×10 ml) and dried over Mg_2SO_4. The solvent was distilled off and the residue obtained was purified on a silica-gel plate using cyclohexane–acetate (3 : 1) as developer. The pure product was obtained. If the oxidative reagent is PIBD, the mixture was washed with water (3×10 ml) and ether (20 ml) was added to the mixture, then filtered. After removal the solvent, the product obtained was recrystallized with ethanol. The characterization and spectral data of the products are given as following:

3: m.p. 70–71°C (lit[32] 72°C). ^{1}H NMR ($CDCl_3$): δ 1.39–1.44 (t, 6H, $J = 7.12$ Hz), 4.37–4.43 (q, 4H, $J = 7.12$ Hz), 2.87 (s, 6H), 8.70 (s, 1H); IR: 2977, 1719, 1591, 1556, 1297, 1222, 1123, 771 cm^{-1}.

2c: m.p. 62–63°C (lit[32] 64°C). ^{1}H NMR ($CDCl_3$): δ 0.88–0.92 (t, 6H, $J = 7.12$ Hz), 3.98–4.03 (q, 4H, $J = 7.12$ Hz), 2.65 (s, 6H), 7.24–7.38 (m, 5H); IR: 2986, 1723, 1591, 1498, 1302, 1250, 1170, 791, 760 cm^{-1}.

2d: m.p. 61.5–62.5°C (lit[32] 63°C). ^{1}H NMR ($CDCl_3$): δ 0.98–1.02 (t, 6H, $J = 7.08$ Hz), 4.04–4.09 (q, 4H, $J = 7.08$ Hz), 2.70 (s, 6H), 7.60–8.29 (m, 4H); IR: 2980, 1712, 1590, 1520, 1280, 1183, 785 cm^{-1}.

2e: m.p. 115–116°C (lit[32] 117°C). ^{1}H NMR ($CDCl_3$): δ 0.96–1.00 (t, 6H, $J = 7.04$ Hz), 4.01–4.07 (q, 4H, $J = 7.04$ Hz), 2.69 (s, 6H), 7.45–8.28 (m, 4H); IR: 2977, 1723, 1557, 1518, 1349, 1106, 865, 841, 748 cm^{-1}.

2f: m.p. 49.5–50.5°C (lit[32] 51–53°C). ^{1}H NMR ($CDCl_3$): δ 0.97–1.01 (t, 6H, $J = 7.12$ Hz), 4.03–4.09 (q, 4H, $J = 7.12$ Hz), 2.66 (s, 6H), 3.82 (s, 3H), 6.89–7.20 (m, 4H); IR: 2973, 1729, 1614, 1557, 1291, 1107, 857, 835, 779 cm^{-1}.

2g: m.p. 66–68°C (lit[32] 68°C). ^{1}H NMR ($CDCl_3$): δ 0.97–1.00 (t, 6H, $J = 7.12$ Hz), 4.03–4.08 (q, 4H, $J = 7.12$ Hz), 2.69 (s, 6H), 7.19–7.39 (m, 4H); IR: 2984, 1725, 1580, 1233, 1104, 864 cm^{-1}.

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2h: m.p. 70–72°C. ^{1}H NMR ($CDCl_3$): δ 0.97–1.01 (t, 6H, $J = 7.08$ Hz), 4.04–4.10 (q, 4H, $J = 7.08$ Hz), 2.66 (s, 6H), 7.20–7.44 (m, 4H); IR: 2976, 1729, 1561, 1291, 1230, 1108, 1044, 861, 780, 697 cm^{-1}: Anal. Calcd for $C_{19}H_{20}BrNO_4$: C 56.17, H 4.96, N 3.45; Found: C 56.22, H 5.05, N 3.17.

2i: m.p. 71–72°C (lit[32] 72–73°C). ^{1}H NMR ($CDCl_3$): δ 0.93–0.07 (t, 6H, $J = 7.12$ Hz), 4.01–4.06 (q, 4H, $J = 7.12$ Hz), 2.64 (s, 6H), 2.37 (s, 3H), 7.13–7.19 (m, 4H); IR: 2980, 1726, 1557, 1446, 1239, 1033, 821, 856, 775 cm^{-1}.

2j: m.p. 77.5–79.5°C. ^{1}H NMR ($CDCl_3$): δ 0.98–1.02 (t, 6H, $J = 7.12$ Hz), 4.02–4.09 (q, 4H, $J = 7.12$ Hz), 2.67 (s, 6H), 7.11–7.45 (m, 3H); IR: 2986, 1736, 1560, 1480, 1283, 1231, 1108, 856, 775 cm^{-1}: Anal. Calcd for $C_{19}H_{19}Cl_2NO_4$: C 57.58, H 4.83, N 3.53; Found: C 57.29, H 4.84, N 3.32.

REFERENCES

1. Stout, D.M.; Meyers, A.I. Chem. Rev. **1982**, *82*, 223.
2. Kill, R.J.; Widdowson, D.A. In *Bioorganic Chemistry*, Van Tamelon, E.E., Ed.; Academic Press: NY, 1978; Vol. 4, p. 239.
3. Sabir, H.; Mashraqui; Madhari A. Karnik. Tetrahedron Lett. **1998**, *39*, 4895.
4. Wei, X.Y.; Rutledge, D.J. J. Mol. Pharmacol. **1989**, *35*, 541.
5. Gordeev, M.F.; Patel, D.V.; Gordon, E.M. J. Org. Chem. **1996**, *61*, 924 and references cited threin.
6. Mohammadpoor-Baltork, I.; Sadeghi, M.M.; Memarian, H.R.; Pairow, R. J. Chem. Research **2000**, 40.
7. Zolfigol, M.A.; Maryam, K.B.; Sadeghi, M.M.; Mohammadpoor-Baltork, I.; Memarian, H.R. Synth. Commun. **2000**, *30*, 3919.
8. Hantzsch, A. Ann. **1882**, *215*, 1.
9. Huntress, E.H.; Shaw, E.N. J. Org. Chem. **1948**, *13*, 674.
10. Kamal, A.; Ahmad, M.; Mohd, N.; Hamid, A.M. Bull. Chem. Soc. Jpn. **1964**, *37*, 610.
11. Itoh, T.; Nagata, K.; Okada, M.; Ohsawa, A. Tetrahedron Lett. **1995**, *36*, 2269.
12. Pfister, J.R. Synthesis **1990**, 689.
13. Eisner, U.; Sadeghi, M.M.; Hambright, W.P. Tetrahedron Lett. **1978**, *19*, 303.
14. Mashraqui, S.H.; Karnik, M.A. Synthesis **1998**, 713.
15. Vanden Eynde, J.J.; Delfosse, F.; Mayence, A.; Van Haverbeke, Y. Tetrahedron **1995**, *51*, 6511.

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16. Vanden Eynde, J.J.; D'Orazio, R.; Van Haverbeke, Y. Tetrahedron **1994**, *50*, 2479.
17. Vanden Eynde, J.J.; Mayence, A.; Maquestiau, A. Tetrahedron **1992**, *48*, 463.
18. Sabir H. Mashraqui; Madhari A. Karnik. Tetrahedron Lett. **1998**, *39*, 4895.
19. Chavan, S.P.; Dantale, S.W.; Kalkote, U.R.; Jyothirmai, V.S.; Kharul, R.K. Synth. Commun. **1998**, *28*, 2789.
20. Itoh, T.; Nagata, K.; Matsuya, Y.; Miyazaki, M.; Ohsawa, A. J. Org. Chem. **1997**, *62*, 3582.
21. Bocker, R.H.; Guengerich, F.P. J. Med. Chem. **1986**, *29*, 1596.
22. Moriarty, R.M.; Prakash, O. Adv. In Het. Chem. **1998**, *69*, 1.
23. Varvoglis, A. *The Organic Chemistry of Polyvalent Iodine*, VCH: New York, 1992.
24. Stang, P.G.; Zhdankin, V.V. Chem. Rev. **1996**, *96*, 1123.
25. Wang, G.P.; Zhen, Z.C. Synth. Commun. **1999**, *29*, 2859.
26. Khadilkar, B.; Borkar, S. Synth. Commun. **1998**, *28*, 207.
27. Delgado, F.; Alvarez, C.; Garcia, O.; Penieres, G.; Marquez, C. Synth. Commun. **1991**, *21*, 2137.
28. Balogh, M.; Hermecz, I.; Meszaros, Z.; Laszla, P. Helv. Chem. Acta **1984**, *67*, 2270.
29. Garcia, O.; Deigado, F. Tetrahedon Lett. **1993**, *34*, 623.
30. Maquestiau, A.; Mayence, A.; Vanden Eynde, J.J. Tetrahedon Lett. **1991**, *32*, 3839.
31. Norcross, B.E.; Clement, G.; Weinstein, M. J. Chem. Education **1969**, *46*, 694.
32. (a) According to the handbook Beilstein: compound **3: 22**, **I** 536.; **2c**, **2c**, **2h**: **22**, **II** 127.; **2d**: **22**, **II** 128.; **2g**: **22**, **II** 206.; **2j**: **22**, **IV** 1721; (b) compound **2i**: Love, B.; Snader, K.M. J. Org. Chem. **1965**, *30*, 1914.

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