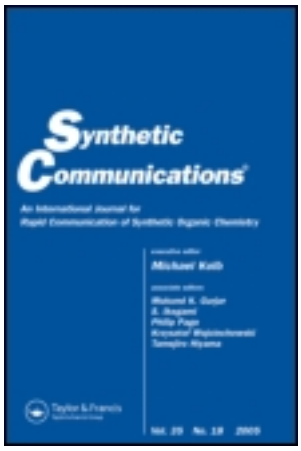


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Hypervalent Iodine in Synthesis. 90. A Mild and Efficient Method for the Iodination of Pyrazoles

Dong-Ping Cheng [b c], Zhen-Chu Chen [a b] & Qin-Guo Zheng [d]

[a] Ningbo Institute of Technology, Zhejiang University, Ningbo, P.R. China

[b] Department of Chemistry, Zhejiang University (Campus Xixi), Hangzhou, P.R. China

[c] College of Pharmaceutical Sciences, Zhejiang University of Technology, P.R. China

[d] Pharmaceutical Sciences, School of Life and Health Sciences, Aston University, Birmingham, UK

Version of record first published: 17 Aug 2006.

To cite this article: Dong-Ping Cheng , Zhen-Chu Chen & Qin-Guo Zheng (2003): Hypervalent Iodine in Synthesis. 90. A Mild and Efficient Method for the Iodination of Pyrazoles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:15, 2671-2676

To link to this article: http://dx.doi.org/10.1081/SCC-120021987

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 15, pp. 2671–2676, 2003

Hypervalent Iodine in Synthesis. 90. A Mild and Efficient Method for the Iodination of Pyrazoles

Dong-Ping Cheng,[2,3] Zhen-Chu Chen,[1,2,*] and Qin-Guo Zheng[4]

[1]Ningbo Institute of Technology, Zhejiang University, Ningbo, P.R. China
[2]Department of Chemistry, Zhejiang University (Campus Xixi), Hangzhou, P.R. China
[3]College of Pharmaceutical Sciences, Zhejiang University of Technology, P.R. China
[4]Pharmaceutical Sciences, School of Life and Health Sciences, Aston University, Birmingham, UK

ABSTRACT

The combined reagent of iodobenzene diacetate (or polymer-supported iodobenzene diacetate) with iodine was used as an effective iodinating agent of pyrazoles to the corresponding 4-iodopyrazole derivatives at room temperature with high yields.

*Correspondence: Zhen-Chu Chen, Ningbo Institute of Technology, Zhejiang University, Ningbo, 315104, P.R. China; Department of Chemistry, Zhejiang University (Campus Xixi), Hangzhou, 310028, P.R. China.

DOI: 10.1081/SCC-120021987 0039-7911 (Print); 1532-2432 (Online)

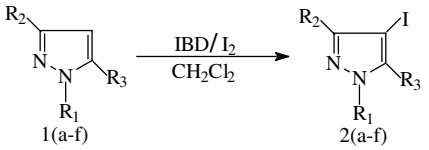
MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

As a mild oxidative reagent, the synthetic utility of iodobenzene diacetate, $PhI(OAc)_2$ (IBD) has attracted significant research interest in view of its low toxicity, ready availability, and easy handing.[1] Recently, it was shown the combined reagent of the IBD with iodine is a convenient reagent for the iodination of aromatic compounds.[2] It occurs through acetyl hypoiodite formed in situ. However, to our knowledge, there is seldom published work about using IBD/I_2 system for the iodination of heteroaromatic compounds.[3] It prompted us to examine the possibility of achieving iodination of pyrazoles to 4-iodopyrazoles using IBD/I_2 system as iodinating reagent.

4-Iodopyrazoles are valuable starting products in the synthesis of biologically active compounds.[4] They have been used in cross-coupling reactions with terminal acetylenes,[5] arylstannanes,[6] or aryl boronic acids.[7]

We found that the IBD/I_2 system is an excellent reagent for the iodination of pyrazole derivatives. Simple stirring of a mixture of IBD, iodine and a pyrazole derivative in CH_2Cl_2 at room temperature gave, after work-up and isolation, the desired 4-iodopyrazole with high yield (Sch. 1). The results are summarized in Table 1(Entries 1–6). The products were characterized by ^{1}H-NMR, IR, MS, and elemental analyses.

Compared with the hitherto used direct iodination methods, the present one has the advantages of higher yields, milder conditions, shorter time, and simpler isolation of the products. For example, using the classical iodine–iodide method, the preparation of 3,5-dimethyl-4-iodopyrazole needs refluxing for 48 h and the yield is only 55%.[8] On the other hand, it is worth mentioning that in the present method 0.5 mol of iodine per mole of substrate is enough to complete the reaction, in contrast to the iodine–iodide procedure, where one-half of part of the iodine is discarded. Recently the oxidative iodination using $CAN\text{-}I_2$ has been applied to pyrazoles,[9] but the reaction time is still long and the CAN is toxic and expensive. The more reactive iodine monochloride is also used as an iodinating agent of pyrazoles, but it is necessary to use an excessive quantity of reagent.[10]

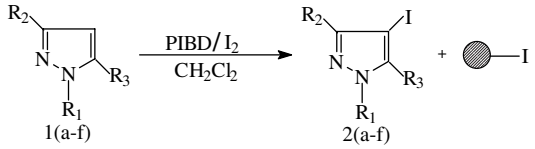


Scheme 1.

Table 1. Iodination of pyrazole derivatives.

Entry	Substrate, R_1, R_2, R_3	Product	Time (t, min)	Yield[a] (%)
1	1a, H, CH_3, CH_3	2a	15	90
2	1b, H, CH_3, C_6H_5	2b	20	88
3	1c, H, C_6H_5, C_6H_5	2c	15	91
4	1d, C_6H_5, C_6H_5, C_6H_5	2d	20	86
5	1e, 2,4-$(NO_2)_2C_6H_3$, CH_3, CH_3	2e	30	90
6	1f, *p*-ClC_6H_4, CH_3, C_6H_5	2f	30	91
7	1a, H, CH_3, CH_3	2a	25	87
8	1b, H, CH_3, C_6H_5	2b	30	87
9	1c, H, C_6H_5, C_6H_5	2c	30	89
10	1d, C_6H_5, C_6H_5, C_6H_5	2d	30	86
11	1e, 2,4-$(NO_2)_2C_6H_3$, CH_3, CH_3	2e	40	87
12	1f, *p*-ClC_6H_4, CH_3, C_6H_5	2f	35	89
13	1f, *p*-ClC_6H_4, CH_3, C_6H_5	2f	40	87[b]

[a]Isolated yields based on pyrazole derivatives.
[b]Recycle.



Scheme 2.

The advantages of polymer-supported reactive species are now widely recognized by organic chemists and the exploitation of these systems is developing both in academic and industrial laboratories.[11] Recently we studied the property and application of polymer-supported iodobenzene diacetate (PIBD) in our lab.[12] In order to explore the scope of the application of PIBD, we used the PIBD/I_2 system to the iodination of pyrazoles.[13] It was also successful (Table 1, Entries 7–12) (Sch. 2). 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.

As usual, we also examined the regeneration and recycling of the polymer reagent. The spent resin was collected by filtration and reoxi-

dized with peracetic acid.[11] The regenerated resin was used to repeat the reaction with no loss of activity (Table 1, Entry 13).

In summary, we think that the iodine/IBD and iodine/PIBD system are effective iodinating reagents for pyrazoles. The advantages of present method are ease manipulation, mild reaction conditions, and high yields.

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. Infrared 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. Pyrazole derivatives are prepared according to described procedures.[14] PIBD is prepared according to our preciously reported method.[12a]

General Procedure for the Iodination of Pyrazole Derivatives

In a 50 mL round-bottomed flask, iodine (0.5 mmol) was added to IBD (0.5 mmol) or PIBD (1 g) in dichloromethane (10 mL). The mixture was stirred for half an hour, then the pyrazole 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 obtained was purified on a silica-gel plate. If the reagent is PIBD, ether (20 mL) was added to the mixture, then filtered. After removal of the solvent, the product obtained was recrystallized with ethanol or water. The characterization and spectral data of the products are given as following:

2a. 4-iodo-3, 5-dimethylpyrazole. M.p. 134–136°C. (Lit.[15] 137°C) ^{1}H NMR: δ 4.11 (brs, 1H), 2.24–2.26 (d, 6H). *m*/*z* (%): 222 (M^+, 100), 127 (13.97), 95 (30.79), 65 (45.96), 54 (41.68), 42 (63.63), 41 (64.06).

2b. 4-iodo-3-methyl-5-phenylpyrazole. M.p. 113–115°C. ^{1}H NMR: δ 7.69–7.72 (m, 2H), 7.39–7.42 (m, 3H), 2.24 (s, 3H). *m*/*z* (%): 284 (M^+, 100), 127 (27.00), 116 (28.19), 102 (17.40), 89 (22.38), 77 (25.45), 51 (24.49). Anal. calcd. for $C_{10}H_9IN_2$: C 42.28, H 3.19, N 9.86; Found: C 42.31, H 3.05, N 9.62.

2c. 4-iodo-3, 5-diphenylpyrazole. M.p. 194–196°C. ^{1}H NMR: δ 7.72–7.75 (m, 4H), 7.42–7.48 (m, 6H), 5.95 (brs, 1H). *m*/*z* (%): 346 (M^+, 100), 189 (42.23), 116 (26.57), 89 (48.81), 77 (45.81), 63 (39.86), 51 (57.69), 50

(30.80). Anal. calcd. for $C_{15}H_{11}IN_2$: C 52.05, H 3.20, N 8.09; Found: C 52.04, H 3.05, N 8.27.

2d. 4-iodo-1, 3, 5-triphenylpyrazole. M.p. 139–140°C. ^{1}H NMR: δ 7.72–7.75 (m, 4H), 7.42–7.48 (m, 6H), 5.95 (brs, 1H). *m*/*z* (%): 422 (M^+, 100), 294 (38.03), 189 (31.99), 77 (68.79), 51 (40.21). Anal. calcd. for $C_{21}H_{15}IN_2$: C 59.73, H 3.58, N 6.63; Found: C 59.61, H 3.45, N 6.57.

2e. 4-iodo-3, 5-dimethyl-1-(2,4-dinitrophenyl)pyrazole. M.p. 162.5–163.5°C. ^{1}H NMR: δ 8.82 (s, 1H), 8.54–8.57 (d, 1H), 7.67–7.72 (d, 1H), 2.26–2.29 (d, 6H). *m*/*z* (%): 388 (M^+, 70.00), 221 (34.63), 77 (21.85), 75 (29.35), 63 (21.41), 43 (100.00). Anal. calcd. for $C_{11}H_9IN_4O_4$: C 34.04, H 2.34, N 14.44; Found: C 34.28, H 2.41, N 14.29.

2f. 4-iodo-3-methyl-5-phenyl-1-(*p*-chlorophenyl)pyrazole. M.p. 137–139°C. ^{1}H NMR: δ 7.37–7.38 (m, 3H), 7.22–7.25 (m, 5H), 7.10–7.13 (d, 2H), 2.40 (s, 3H). *m*/*z* (%): 396 (M^++2, 33.02), 394 (M^+, 100.00), 266 (23.94), 128 (22.32), 111 (34.38), 75 (41.38). Anal. calcd. for $C_{16}H_{12}ICIN_2$: C 48.69, H 3.06, N 7.10; Found: C 48.72, H 3.21, N 6.98.

REFERENCES

1. (a) Moriarty, R.M.; Prakash, O. Adv. In Het. Chem. **1998**, *69*, 1; (b) Varvoglis, A. ''The Organic Chemistry of Polyvalent Iodine,'' VCH: The New York, 1992; (c) Stang,P.J.; Zhdankin, V.V. Chem. Rev. **1996**, *96*, 1123.
2. (a) Ogata, Y.; Aoki, K. J. Am. Chem. Soc. **1968**, *90*, 6187; (b) Merkushev, E.B.; Simakhina, N.D.; Koveshuikova, G.M. Synthesis **1980**, 486.
3. Kryska, A.; Skulski, L. J. Chem. Res. **1999**, 590.
4. Sliskovic, D.R.; Roth, B.D.; Wilson, M.W.; Hoefle, M.L. Newton, R.S. J. Med. Chem. **1990**, *33*, 31.
5. Tolf, B.R.; Dahlbim, R.; Theorell, H.; Akeson, A. Acta. Chem. Scand. B **1982**, *36*, 101.
6. Elguero, J.; Jaramillo, C.; Pardo, C. Synthesis **1997**, 563.
7. Collot, V.; Dallemagne, P.; Bovy, P.R.; Rault, S. Tetrahedron Lett. **1999**, *40*, 6917.
8. Holzeer, W.; Gruber, H. J. Heterocycl. Chem. **1995**, *32*, 1351.
9. Rodriguez-Franco, M.I.; Dorronsoro, I.; Hernandez-Higueras, A.I.; Antequera, G. Tetrahedron Lett. **2001**, *42*, 863.
10. Felding, J.; Kristensen, J.; Bjerregaard, T.; Sander, L.; Vedso, P.; Begtrup, M. J. Org. Chem. **1999**, *64*, 4196.

11. (a) Bailey, D.C.; Langer, S.H. Chem. Rev. **1981**, *81*, 109; (b) Akelah, A.; Sherrington, D.C. Chem. Rev. **1981**, *81*, 557; (c) Shuttlewurth, S.J.; Allin, S.M.; Sharma, P.K. Synthesis **1997**, 1217; (d) Ley, S.V.; Baxendale, I.R.; Bream, R.N.; Jackson, P.S.; Leach, A.G.; Longbottom, D.A.; Nesi, M.; Scott, J.S.; Storer, R.I.; Tayor, S.J. J. Chem. Soc. Perkin Trans. I **2000**, 3815.
12. (a) Wang, G.P.; Chen, Z.C. Synth. Commun. **1999**, *29*, 2859; (b) Chen, D.J.; Cheng, D.P.; Chen, Z.C. Synth. Commun. **2001**, *31*, 3847; (c) Cheng, D.P.; Chen, Z.C. Synth. Commun. **2002**, *32*, 801.
13. Professor H. Togo recently reported a similar iodination of aromatic compounds using polymer-supported iodobenzene diacetate: Togo, H.; Abe, S.; Nogami, G.; Yokoyama, M. Bull. Chem. Soc. Jpn. **1999**, 72, 2351.
14. Wiley, R.H.; Hexner, P.E. Organic Synthesis Coll. Vol. 4, 351.
15. Morgan, G.T.; Ackerman, I. J. Chem. Soc. **1923**, 1304.

Received in Japan November 12, 2002