Pergamon

Tetrahedron Letters 42 (2001) 2089–2092

TETRAHEDRON LETTERS

Aromatic iodination in aqueous solution. A new lease of life for aqueous potassium dichloroiodate

Simon J. Garden,* José C. Torres, Simone C. de Souza Melo, Alexandre S. Lima, Angelo C. Pinto and Edson L. S. Lima*

Instituto de Química, Departamento de Química Orgânica, Universidade Federal do Rio de Janeiro, Ilha do Fundão, Rio de Janeiro, CEP 21945-970, Brazil

Received 27 November 2000; revised 11 January 2001; accepted 15 January 2001

Abstract—A re-investigation of the use of aqueous potassium dichloroiodate ($KICl_2$) as an iodinating agent for aromatic compounds has found the reagent to be more generally applicable than previously known. The reagent has been found to give excellent yields of iodinated heterocyclic compounds, such as isatin, imidazole and pyrazole. © 2001 Published by Elsevier Science Ltd.

Larsen and co-workers first reported the use of potassium dichloroiodate ($KICl_2$) as an iodinating agent, in reactions with 3,5-diaminobenzoic acid derivatives, in 1956.[1] Since their study no further reports on the use of this reagent for aromatic iodination have appeared. However, the reagent has found use in the syntheses of *vic*-iodochlorides and iodolactones.[2] More recently, the use of related reagents, such as Py·ICl,[3] IPy_2BF_4[4] and $BTMAICl_2$,[5] has been reported. One of the general problems with introducing iodine as a substituent on an aromatic ring is the lack of reactivity of molecular iodine. This problem is overcome by the use of iodonium equivalents ('I^+') or reagent combinations that generate electrophilic iodine(I) species.[6] Such protocols have found application for the synthesis of iodinated heterocyclic compounds with variable results.[7] In the case of imidazoles, iodination has been conducted with I_2/KI in aqueous NaOH solution.[8] However, conflicting literature data[8c] reports the preparation of both 4,5-diiodoimidazole[8a–d] (55–80% yield[8d]) and 2,4,5-triiodoimidazole[8e–g] (49–75% yield[8g]) by variations of this procedure. Herein we report an efficient method for the iodination of representative aromatic and heteroaromatic rings using an aqueous $KICl_2$ solution.

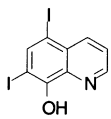
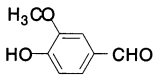
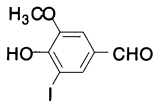
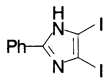
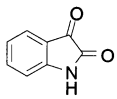
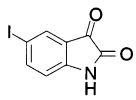
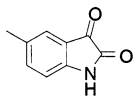
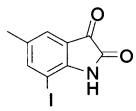
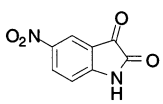
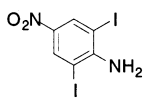
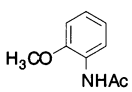
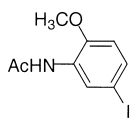
The initial experiments using aqueous $KICl_2$ investigated the reaction with 8-hydroxyquinoline. The addition of this substrate to a solution of $KICl_2$ resulted in the rapid dissolution of the substrate. This was followed almost immediately by the rapid precipitation of 5,7-diiodo-8-hydroxyquinoline[9] in near quantitative yield (Table 1, entry 1). This result prompted further investigation with a variety of substrates. The details of some of these experiments are summarized in Table 1.

During experiments involving the iodination of vanillin, it was noted that different experimental procedures could markedly affect the outcome of the reaction. These procedures included the addition of the substrate as a solution or solid to the aqueous $KICl_2$ solution or vice versa. In the case where an aqueous solution of vanillin (10 mmol, 0.2 M) was added to the $KICl_2$ solution (2.2 equivalents, 0.73 M) the reaction mixture became very darkly colored and a darkly colored precipitate was obtained. This was isolated by filtration, treated with aqueous sodium thiosulfate and recrystallized from aqueous ethanol to give 5-iodovanillin in 22% yield as slightly brown crystals. When the same experiment was repeated but by adding the $KICl_2$ solution to an aqueous solution of vanillin (10–50 mmol), the reaction mixture did not become darkly colored and a slightly gray product was precipitated. Isolation of this product and purification in an identical manner to that above gave an 80% yield of colorless 5-iodovanilin (Table 1, entry 2). Adding vanillin as a solid to an aqueous solution of $KICl_2$ did not result in the formation of a darkly colored precipitated product, but did give an overall lower yield of purified product (50–55%). Similar observations were made with the reaction of imidazole derivatives (Table 1, entries 3–5), where both the order of addition and a careful control of the

* Corresponding authors. E-mail: garden@iq.ufrj.br; edlima@iq.ufrj.br

0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)00105-8

Table 1. Substrates and their respective iodinated products as well as a comparison with literature data[a]

Table entry	Substrate	Method[b]; reaction time	Product	Yield (%); mp (°C); (recryst.) lit. (%); mp (°C)[Ref.]
1		***A***; 1 hour		94–97; 190–200sub.; (see Ref. 9); lit. (84–93)[c]; 198–200[9]
2		***A***; 1 hour		80–87; 180–181; (EtOH/H_2O); lit. (63–90)[d] 181–182[20]
3		***C***; 6 hours		91; 189–191; (MeOH); lit. (55–80)[d] 191–192[8b]
4		***A***; 6 hours		89; 200 dec.; (MeOH); ----
5		***A***; 6 hours		79; 200; (MeOH); lit. (64)[d] 194–195[8f]
6		***A***; 6 hours		95; 108–110; ($CHCl_3$); lit. (80)[e] 108–110[3a]; (51)[c, 7d]
7		***B***; 2 days		90–97; 280–281(dec.); (EtOH); lit. (77)[f] 281–2[21]
8		***B***; 5 days		90–95; 203–205; (EtOH) –
9		***B***; 3 months		83; 246–248; (see Ref. 22); lit. (91)[g] 246–248[3a]; (56–64)[f, 22]
10		***D*** (slow addition); 4 hours		73; 147–149; (EtOH/H_2O); lit. (67)[h] 147–148[13]

[a] Representative spectroscopic and analytical data are included in reference 19.

[b] Methods (for experimental quantities see the text, all reactions were performed at room temperature on a 10–100 mmol scale): ***A***, a solution of $KICl_2$ (generally 2 equiv. of a 1 or 2 molar solution) was added to a solution or suspension of the substrate in water (a quantity sufficient to solubilize the substrate or to provide a means for the facile, magnetically induced, agitation of the reaction medium for the stated time). Products were isolated by filtration of the precipitated solid and purified as indicated in the text/table.; ***B***, addition of the $KICl_2$ solution to a solution or suspension of the substrate in methanol; ***C***, method ***A*** inverted; ***D***, method ***B*** inverted.

[c] Use of ICl in aqueous HCl.

[d] Use of aqueous $NaOH/I_2$.

[e] Use of pyridine–ICl complex in concentrated aqueous NH_4OH.

[f] Use of ICl in AcOH.

[g] Use of pyridine–ICl complex in H_2SO_4 and with Ag_2SO_4.

[h] Use of $BTMAICl_2$ and $ZnCl_2$ in AcOH.

pH were necessary to achieve good yields of the iodinated products. Thus, an aqueous solution of imidazole (15 mmol, 0.3 M) was slowly added to a solution of $KICl_2$ (2.5 equiv., 2.0 M) at room temperature. A colorless solid readily formed. The mixture was stirred for an additional 6 h, after which time aqueous 2 M NaOH solution was added until complete dissolution occurred. The clear solution was then acidified to pH 10 by the slow dropwise addition of concentrated HCl, which resulted in the precipitation of a colorless solid.[10] The resulting product was removed by filtration and recrystallized from methanol to afford 4,5-diiodoimidazole in 91% yield. When this protocol was applied to 2-substituted imidazoles, poor yields of the corresponding 4,5-diiodoimidazoles were obtained. A significant improvement was observed by inverting the order of addition of the reagents. Thus, to an aqueous solution of 2-phenylimidazole (15 mmol, 0.3 M) at 50°C, was added a room temperature solution of $KICl_2$ (2.5 equiv., 2.0 M).[11] After stirring at room temperature for 6 h, 2 M NaOH was added to give a clear solution which in turn was neutralized (pH 7) with concentrated HCl, resulting in the precipitation of 4,5-diiodo-2-phenylimidazole which was subsequently isolated in 89% yield as a yellow solid. The same procedure was employed for the preparation of 4,5-diiodo-2-methylimidazole and 4-iodopyrazole (Table 1, entry 6), in 79 and 95% yield, respectively.[12]

In cases where the substrate had poor water solubility the use of methanol as a co-solvent proved to be beneficial. For example, the reactions of isatin (100 mmol) and 5-methylisatin (100 mmol) were performed by the addition of aqueous $KICl_2$ (2 equiv., 2 M) to an equal volume of a methanolic solution/suspension of the respective isatin (Table 1, entries 7 and 8). These reactions required a few days at room temperature to complete, but the long reaction time is offset by the excellent yield of mono-iodinated product. Neither 5-iodoisatin nor the 5-bromo- or 5-chloro-isatin derivatives were found to react with $KICl_2$ under the aforementioned reaction conditions.[13] In contrast, 5-nitroisatin reacted very slowly over a prolonged period to yield 2,6-diiodo-4-nitroaniline (Table 1, entry 9).

Once again in reactions where iodination of an aromatic compound occurred relatively rapidly (hours) but the substrate was water insoluble, the order of addition of the reagents was found to be important. In the case of *o*-methoxyacetanilide the best method for the iodination of this substrate was found to be the dropwise addition of the methanolic substrate solution (50 mmol, 0.67 M) to the $KICl_2$ solution (2 equiv., 0.4 M) over a period of 4 hours. During the addition the product precipitated. After complete addition the reaction mixture was maintained at room temperature overnight before diluting with water and removing the product by filtration (92% yield). Analysis of the ^1H NMR spectrum of the crude product revealed it to be an approximately 1:3 mixture of the isomers 4-iodo-2-methoxy- and 5-iodo-2-methoxy-*N*-acetanilide. The structure of the principle isomer was confirmed by comparison with data from the literature[14] (table entry 10). In contrast *p*-methoxyacetanilide was found to be unreactive.[15]

In conclusion, an aqueous solution of $KICl_2$ has been found to be a versatile agent for the iodination of aromatic[16] and heteroaromatic compounds. This reagent has been found to be the reagent of choice for, amongst others, the iodination of isatin[17] and imidazole[18] derivatives resulting in considerably superior and reproducible yields. In addition, the use of aqueous $KICl_2$ for the iodination of aromatic compounds offers a number of advantages in terms of safety and ease of use in comparison to other methods that often employ toxic and hazardous materials.

Acknowledgements

The authors would like to thank CNPq, FAPERJ and the Fundação Oswaldo Cruz, Farmanguinhos, Rio de Janeiro for financial support. S.J.G. acknowledges support from the PAPES II program. The analytical facilities of the Universidade de São Paulo are acknowledged for the elemental analyses.

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10. The addition of HCl must be slow and, if the pH is lower than 10, the 4,5-diiodoimidazole will be contaminated with a yellow solid.
11. A few drops of concentrated HCl were needed to ensure complete solubilization of 2-phenylimidazole in the water.
12. The iodination of pyrazole was carried out at room temperature. However, 2-methylimidazole was solubilized in water at 80°C, prior to the addition of the solution of $KICl_2$.
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15. Kajigaeshi and co-workers have found that this substrate undergoes iodination using $BTMAICl_2$ and $ZnCl_2$ in acetic acid although the reaction time is considerably longer than that required for the *ortho*-methoxy-*N*-acetanilide, see reference 14.
16. We have found it possible to selectively mono- or di-iodinate substituted anilines (methyl, chloro, bromo, nitro or carboxylic acid derivatives) as well as a number of phenolic compounds such as salicylate derivatives, whereas phenol readily yields 2,4,6-triiodophenol. A number of activated aromatic compounds, particularly methoxyanilines or 1,2- and 1,4-dihydroxy- or hydroxymethoxy-benzene derivatives were readily oxidized to dark intractable products. Full details of these experiments will be made available in due course.
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18. For reviews on the chemistry of imidazole, see: (a) Grimmett, M. R. *Adv. Heterocycl. Chem.* **1970**, *12*, 103–183; (b) Grimmett, M. R. *Adv. Heterocycl. Chem.* **1980**, *27*, 241–326.
19. All compounds were characterized spectroscopically and new compounds gave satisfactory elemental and or high-resolution mass analyses. Some representative data follow: **4,5-Diiodoimidazole** IR (ν cm^{-1}): 2794, 2586, 2362, 1507, 1376, 1248, 1155, 959; ^1H NMR (MeOD-d_4): δ 7.92(s); ^{13}C NMR: δ 88.5, 142.8; HRMS: calc. 319.83075; obs. 319.83025. **2-Phenyl-4,5-diiodoimidazole** IR: 3103, 2960, 2863, 1491, 1458, 969, 705, 691; ^1H NMR (CD_3OD): 8.00 (d, 2H, *J* 8.0), 7.75 (m, 3H); ^{13}C NMR: 87.3, 126.6, 130.1, 130.7, 154.3; mass (*m*/*z* [% abun.]): 396(26), 304(26), 294(100), 254(31), 162(63), 127(61). **2-Methyl-4,5-diiodoimidazole** IR: 3112, 2994, 2848, 2714, 1547, 1387, 1186, 1019, 967, 856; ^1H NMR (DMSO-d_6): 2.37 (s, 3H), 12.55 (NH); ^{13}C NMR (CD_3OD): 14.0, 84.5, 152.6; HRMS: calc. 333.84640, obs. 333.84624. **4-Iodopyrazole** IR: 3287, 3112, 1050, 939, 597; ^1H NMR (CD_3OD): 7.92 (s); ^{13}C NMR: 81.0, 139.3, 143.2; HRMS: calc. 193.93410, obs. 193.93411. **5-Iodoisatin** IR: 3242, 3092, 1746, 1732, 1606, 1460, 1438, 1264, 1200, 1125, 834, 745, 670; ^1H NMR (DMSO-d_6): 6.75 (d, *J* 8.2), 7.76 (d, *J* 0.9), 7.88 (dd, *J* 0.9, 8.2), 11.10 (bs, NH); ^{13}C NMR: 85.8, 115.1, 120.4, 132.9, 146.2, 150.4, 159.1, 183.5; mass: 273(53), 245(100), 217(19), 90(29). **5-Methyl-7-iodoisatin** IR: 3162, 3086, 2972, 2899, 1726, 1619, 1585, 1473, 1299, 1185, 1031, 1001, 943, 860, 768; ^1H NMR ($CDCl_3$): 2.32 (s, 3H), 7.39 (s), 7.72 (s), 7.86 (bs); ^{13}C NMR (DMSO-d_6): 20.0, 78.5, 120.0, 124.9, 134.6, 147.0, 151.2, 160.4, 185.1; chem. anal. calc.: C, 37.66; H, 2.11; N, 4.88; found: C, 37.75; H, 2.17; N, 4.79. **5-Iodo-2-methoxy-*N*-acetanilide** IR: 3268, 3100, 1666, 1525, 1482, 1403, 1247, 1211, 1131, 1019, 798; ^1H NMR ($CDCl_3$): 2.19 (s, 3H), 3.85 (s, 3H), 6.60 (d, 1H, *J* 8.5), 7.32 (dd, 1H, *J* 1.3, 8.5), 7.69 (bs, 1H, NH), 8.69 (d, 1H, *J* 1.3); ^{13}C NMR: 25.1, 56.1, 83.5, 112.0, 128.0, 129.2, 132.5, 147.6, 168.3; mass: 291(100), 249(81), 234(83), 206(15), 164(5), 79(31). **2,6-Diiodo-4-nitroaniline** ^1H NMR ($CDCl_3$/DMSO-d_6): 6.13 (s), 8.45 (s); ^{13}C NMR: 76.5, 133.5, 136.6, 151.4; chem. anal. calc.: C, 18.48, H, 1.03, N, 7.18; found: C, 18.68, H, 1.24, N, 6.99.
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