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ORIGINAL PAPER

An effective room temperature nuclear iodination of aromatic compounds using molecular iodine and ammonium acetate

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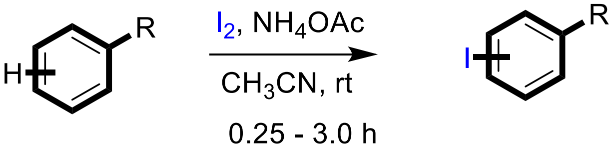
Abstract

The iodination of aromatic compounds using a simple and benign iodinating agent such as molecular iodine (I_2) under oxidant free mild conditions is a difficult and highly important task in organic synthesis since aryl iodides are the highly reactive starting materials in a variety of organic transformations. We have developed a mild and effective method for the aromatic iodination using challenging iodinating agent, I_2 under the catalytic performance of ammonium acetate (NH_4OAc). A variety of aromatic compounds are converted efficiently into their corresponding aryl iodides under developed condition with high regioselectivity.

Graphical abstract



Keywords Iodine · Ammonium acetate · Acetonitrile · Aryl iodide · Regioselectivity

Introduction

The marine organism is a significant source of organic iodides and many of these show their significance in biology [1–3]. These are used in medical imagining in the identification of diseases related to oncology and neurology [4, 5]. Moreover, the aryl halides are the most reactive starting materials in several organic reactions including cross-couplings, radical-induced reactions, and nucleophilic reactions in the presence of metals [6–9]. Aryl iodides are highly reactive than other aryl halides due to the easy cleavage of the C-I band than other C-halogen bonds [10, 11]. Besides the high reactivity of aryl iodides, the less availability and high cost of aryl iodides are because of less available iodinating agents and the requirement of oxidants, additives, and high temperature [12, 13]. In addition, *N*-iodosuccinimide [14–18], I_2 [19–30], KI [31–33], and mixed halides [34–37] are the frequently used reagents for the iodination of aromatic compounds. The substitution reactions of aryl diazonium/boronic acid compounds with

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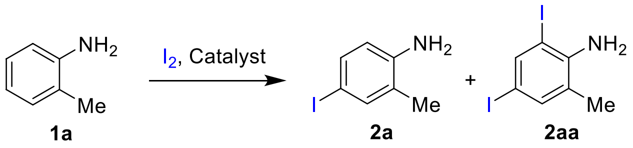
nucleophiles [38–42] are the other alternatives for the synthesis of aryl iodides but these suffer from the requirement of harsh reaction conditions and metals. The applications of I_2 as an iodinating agent represents the natural process of synthesizing organic iodides and iodine is also accepted as an environmentally benign reagent [43]. Further, I_2 is a readily available and inexpensive substance. Despite these advantages, the low reactivity of I_2 with aromatic substances is the limitation and it requires an external oxidant. In this connection $H_5PV_2Mo_{10}O_{40}$-O_2 [19], $Fe(NO_3)_3{\cdot}1.5N_2O_4$-charcoal [20], graphene oxide-CH_3NO_2 [21], NO_2 [12], [bis(trifluoroacetoxy)iodo]benzene-pyridine [22], silver sulfate [23], silica supported ferric nitrate monohydrate [24], ammonium cerium(IV) nitrate (CAN) [25], tetra-*n*-butylammoniumperoxydisulfate [26], $NaNO_2$-HCl-trifluoroethanol [27], lead(IV) acetate-AcOH-$(CH_3CO)_2O$ [28], and IBX-CH_3CN-TFA [29] in the presence of I_2 are reported as efficient catalytic systems for aryl iodination. Most of these systems suffer from drawbacks including the necessity of oxidant, high temperature, costly catalysts, or no control over monoiodination products. Hence, it is necessary in developing a simple protocol for the synthesis of aryl/heteroaryl iodides. Therefore, we directed to develop an economical protocol for the easy synthesis of aryl iodides under added oxidant free conditions and found NH_4OAc–I_2 as an advantageous catalyst–reagent system in CH_3CN (Scheme 1) in this search. Moreover, NH_4OAc is a rich source of nitrogen and is a highly convenient alternative to ammonia in a wide range of organic transformations [44–47]. NH_4OAc was also utilized as an effective catalyst in synthetic methodologies [44, 48–50]. This method can be an extra attractive addition towards the application of NH_4OAc in organic synthesis.

Table 1 Screening for reaction conditions



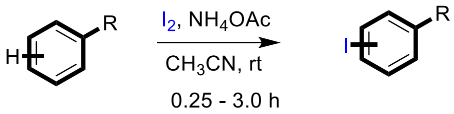
Entry	Catalyst/mmol	Solvent	Time/min	Isolated yield/%	
				2a	2aa
1	–	DMSO	30	85 [51]	–
2	NH_4OAc (0.5)	C_2H_5OH	60	34	15
3	NH_4OAc (0.5)	CH_3OH	60	20	32
4	NH_4OAc (0.5)	THF	60	39	–
5	NH_4OAc (0.5)	CH_3Cl	75	21	–
6	NH_4OAc (0.5)	CH_2Cl_2	75	41	–
7	NH_4OAc (0.5)	CH_3CN	45	67	–
8	NH_4OAc (0.5)	*n*-Hexane	120	15	6
9	NH_4OAc (0.5)	$(CH_3)_2SO$	60	62	Trace
10	NH_4OAc (0.5)	H_2O	60	55	Trace
11	**NH_4OAc (0.75)**	**CH_3CN**	**30**	**89**	–
12	NH_4OAc (1.0)	CH_3CN	30	89	–
13	NH_4OH (0.75)	CH_3CN	240	15	7
14	NH_4Cl (0.75)	CH_3CN	240	11	15
15	NH_4OCHO (0.75)	CH_3CN	180	72	Trace
16	CAN (0.38)	CH_3CN	240	59	9
17	$(NH_4)_6Mo_7O_{24}$ (0.15)	CH_3CN	240	38	18

Reaction conditions: **1a** (1.0 mmol), I_2 (1.05 mmol) and solvent (4 cm^3) at r.t

Results and discussion

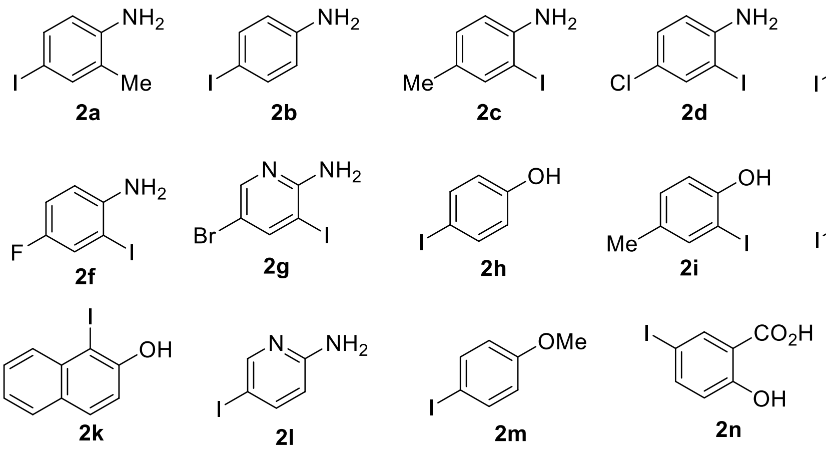
We have initiated the present iodination protocol using the reaction of *o*-toluidine (**1a**) (1.0 mmol) with I_2 (1.05 mmol) employing 0.5 mmol of NH_4OAc as a catalyst in 4 cm^3 ethanol and observed the formation of 34% of mono iodinated product, 4-iodo-2-methylaniline (**2a**) and 15% of diiodo product, 2,4-diiodo-6-methylaniline (**2aa**) in 1 h (Table 1, entry 3). To our delight, the reaction was preceded without the aid of an external oxidant. The reaction was then screened using solvents methanol, tetrahydrofuran (THF), CH_3Cl, CH_2Cl_2, CH_3CN, *n*-hexane, $(CH_3)_2SO$, and water (Table 1, entries 4–11) and identified that the CH_3CN is appropriate for the mono iodination of **1a** (Table 1, entry 7). The increase of the quantity of catalyst, NH_4OAc to 0.75 mmol and 1.0 mmol, the reaction resulted from **2a** with 89% yields in CH_3CN (Table 1, entries 11, 12) was indicated the requirement of 0.75 mmol of NH_4OAc for this selective iodination of **1a**. Other ammonium salts such as NH_4OH, NH_4Cl, NH_4OCHO, CAN, and $(NH_4)_6Mo_7O_{24}$ are also screened for the selective iodination of **1a** (Table 1, entries 13–17), and observed that the NH_4OAc was suitable among these (Table 1, entry 7).

Scheme 1



With the developed conditions, we have screened a variety of substrates for the selective monoiodination and the results were shown in Table 2. Aniline was observed as a good substrate under NH_4OAc catalyzed iodination and provided 99% of monoiodination product in 0.25 h (Table 2, entry 2). The occurrence of diiodo products was reported with several reported procedures. The substituted anilines with the functional groups such as methyl, chloro and fluoro provided 83–89% of monoiodination products, **2a** [52, 53], **2b-2f** [54–58] in 0.25—1.0 h (Table 2, entries 1, 3–6). Phenol **2h** [59] and substituted phenols **2i** [60], **2j** [61], **2k** [62, 63], and **2n** [52, 64] with the functional groups such as methyl and carboxyl produced

Table 2 Substrate scope



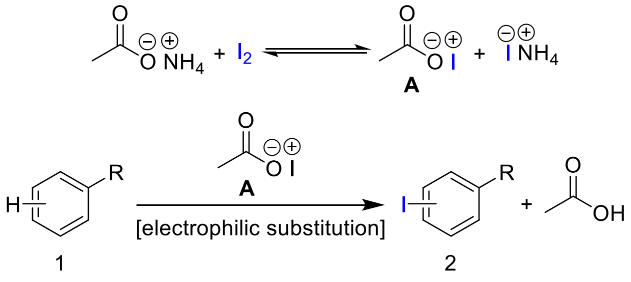
Entry	Reactant (**1**)	Product	Time/h	Isolated yield/%	Melting point/°C	
					Observed	Reported
1	*o*-Toluidine (**1a**)	**2a**	0.5	89	83–85	86–87 [71]
2	Aniline (**1b**)	**2b**	0.25	98	52–54	53–55 [18]
3	*p*-Toluidine (**1c**)	**2c**	0.5	86	Oil	Oil [18]
4	*p*-Chloroaniline (**1d**)	**2d**	1.0	85	39–41	38–40 [18]
5	*o*-Chloroaniline (**1e**)	**2e**	0.5	84	67–69	68–70 [18]
6	*p*-Fluoroaniline (**1f**)	**2f**	1.0	83	37–39	38–40 [72]
7	2-Amino-5-bromopyridine (**1g**)	**2g**	1.5	80	112–117	113–114 [73]
8	Phenol (**1h**)	**2h**	0.5	86	89–92	92–94 [18]
9	*p*-Cresol (**1i**)	**2i**	0.5	87	32–35	33–35 [74]
10	*o*-Cresol (**1j**)	**2j**	0.5	83	67–69	68.5–69 [75]
11	*β*-Naphthol (**1k**)	**2k**	0.5	87	88–91	91–92 [75]
12	2-Aminopyridine (**1l**)	**2l**	1.0	82	123–125	126–130 [76]
13	Anisole (**1m**)	**2m**	2.0	79	42–44	40–43 [18]
14	Salicylic acid (**1n**)	**2n**	3.0	78	185–189	189–191 [77]

Reaction conditions: **1** (1.0 mmol), I_2 (1.05 mmol) and CH_3CN (4 cm^3) at rt

the corresponding monoiodination products with excellent yields (Table 2, entries 8–11, 13). Anisole (**1m**) are also observed as good substrate under the present iodination procedure for **2m** [65, 66] (Table 2, entry 12). The method has also been studied for its successful application to the iodination of heteroaryl substance such as 2-aminopyridine **2l** [52, 67] and 2-amino-5-bromopyridine (**2g**) [68–70] (Table 2, entries 7, 14).

The possible mechanism of NH_4OAc catalysed iodination of aryl or heteroaryl compounds has been shown in Scheme 2. The reaction of ammonium acetate with I_2 may form acetyl hypoiodite **A** and ammonium iodide. The electrophilic iodine species, **A** on reaction with aryl or heteroaryl compounds results in the aryl iodides or heteroaryl iodides and acetic acid through a usual electrophilic substitution mechanism of aromatic compounds.

Scheme 2



Conclusion

In conclusion, an easy and simple procedure has been developed for the monoiodination of aromatic compounds using I_2 in the presence of NH_4OAc as an efficient catalyst. A variety of arylamino, phenolic, and heteroaryl compounds are regioselectively iodinated using the developed protocol at ambient conditions under external oxidant and additive-free conditions. The substrates with a wide range of functional groups such as methyl, amine, hydroxyl, methoxy, bromo, chloro, fluoro, and carboxyl are tolerated under present conditions. Quick reactions, high regioselectivity, simple reaction conditions, ambient conditions, and oxidant, and additive-free conditions are the important attributes of this iodination protocol.

Experimental

All starting materials and solvents were obtained from Sigma-Aldrich (USA). All reagents were used as it is without further purification. All reactions were conducted under standard operating conditions without the use of any stringent conditions. The reaction progress was monitored on Merck TLC Silica gel 60 F254 plates, and the spots were visualized under ultraviolet (UV) light, followed by iodine or $KMnO_4$ staining solution followed by heating. Chromatographic purifications were carried out using flash-grade silica gel (SDS Chromatogel 60 ACC, 40–60 μm). NMR spectra were recorded at 23 °C on Varian 400 Ultrashield apparatus. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz NMR spectrometer using $CDCl_3$ as solvent unless otherwise stated. Mass spectra were recorded on a Waters Acquity TQDLC/MS/MS system.

General experimental procedure

To a mixture of aromatic compound **1** (1.0 mmol), I_2 (1.05 mmol), and NH_4OAc (0.75 mmol) was added 4 cm^3 CH_3CN and stirred the resultant mixture at room temperature for an appropriate time. After the completion of the reaction, as indicated by TLC, the reaction mixture was added 5 cm^3 of water. Extracted the mixture using EtOAc (3×5 cm^3) and the combined portions of EtOAc were subjected for evaporation to obtain crude aryl iodide. The crude aryl iodides were purified by using silica packed columns using varying ratios of EtOAc and hexanes as eluent. Pure aryl iodide was subjected to the confirmation of their structures using ^{1}H NMR, ^{13}C NMR, and mass spectral data. The spectral data of representative iodo (hetero)arenes is provided in supporting material and the spectral and physical properties have been found to coincide with the reported data.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00706-023-03084-1.

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Data availability The experimental data that support the findings of this study are available from the corresponding author, S.R.G, upon reasonable request.

References

1. Gribble GW (2015) Mar Drugs 13:4044
2. McCauley EP, Lam H, Lorig-Roach N, Luu J, Lloyd C, Tenney K, Pietraszkiewicz H, Diaz C, Valeriote FA, Auerbuch V, Crews PJ (2017) Nat Prod 80:3255
3. Gribble GW (2012) Progress in the chemistry of organic natural products, vol 68. Springer Science & Business Media, Berlin
4. Pimlott SL, Sutherland A (2011) Chem Soc Rev 40:149
5. Luster M, Clarke S, Dietlein M, Lassmann M, Lind P, Oyen WJG, Tennvall J, Bombardieri E (2008) Eur J Nucl Med Mol Imaging 35:1941
6. Neilson AH, Neilson AH (eds) (2003) Organic bromine and iodine compounds. In: Handbook of environmental chemistry. Springer, Heidelberg, Berlin
7. Rao KU, Venkateswarlu K (2018) Synlett 29:1055
8. Rao KU, Appa RM, Lakshmidevi J, Vijitha R, Rao KSVK, Narasimhulu M, Venkateswarlu K (2017) Asian J Org Chem 6:751
9. Wirth T, Wirth T (eds) (2016) Hypervalent iodine chemistry. In: Topics in current chemistry, vol 373. Springer
10. Venkateswarlu K, Suneel K, Das B, Reddy KN, Reddy TS (2009) Synth Commun 39:215
11. Friedrich EC, Abma CB (1980) J Am Chem Soc 102:1367
12. Miyaura N, Suzuki A (1995) Chem Rev 95:2457
13. Ren YL, Shang H, Wang J, Tian X, Zhao S, Wang Q, Li F (2013) Adv Synth Catal 355:3437
14. Kandepi VVKM, Narender N (2012) Synthesis 44:15
15. Dušan B, Viktor M, Jakub S, Daniel V, Marek F, Peter H, Jozef K, Viera H, Michal S (2018) J Mol Struct 1166:243
16. Racys DT, Sharif SAI, Pimlott SL, Sutherland A (2016) J Org Chem 81:772
17. Bergström M, Suresh G, Naidu VR, Unelius CR (2017) Eur J Org Chem 2017:3234
18. Wu YQ, Lu HJ, Zhao WT, Zhao HY, Lin ZY, Zhang DF, Huang HH (2020) Synth Commun 50:813
19. Racys DT, Warrilow CE, Pimlott SL, Sutherland A (2015) Org Lett 17:4782
20. Branytska OV, Neumann R (2003) J Org Chem 68:9510
21. Firouzabadi H, Iranpoor N, Shiri M (2003) Tetrahedron Lett 44:8781
22. Zhang J, Li S, Deng GJ, Gong H (2018) ChemCatChem 10:376
23. Benhida R, Blanchard P, Fourrey JL (1998) Tetrahedron Lett 39:6849
24. Sy WW (1992) Synth Commun 22:3215
25. Tilve RD, Alexander VM, Khadilkar BM (2002) Tetrahedron Lett 43:9457
26. Das B, Krishnaiah M, Venkateswarlu K, Reddy VS (2007) Tetrahedron Lett 48:81
27. Yang SG, Kim YH (1999) Tetrahedron Lett 40:6051
28. Iskra J, Murphree SS (2017) Tetrahedron Lett 58:645
29. Krassowska-Świebocka B, Luliński P, Skulski L (1995) Synthesis 1995:926
30. Moorthy JN, Senapati K, Kumar S (2009) J Org Chem 74:6287
31. Yadav JS, Reddy BVS, Sengupta S, Gupta MK, Baishya G, Harshavardhana SJ, Dash U (2008) Monatsh Chem 139:1363

32. Gayakwad EM, Patel KP, Shankarling GS (2019) New J Chem 43:6001
33. Sdahl M, Conrad J, Braunberger C, Beifuss U (2019) RSC Adv 9:1949
34. Stavber G, Iskra J, Zupan M, Stavber S (2008) Adv Synth Catal 350:2921
35. Johnsson R, Meijer A, Ellervik U (2005) Tetrahedron 61:11657
36. Elmi S, Heggen P, Holmelid B, Malthe-Sørensen D, Sydnes LK (2016) Org Prep Proced Int 48:385
37. Rose MR, Roberts AL (2019) Environ Sci Technol 53:11764
38. Zarei A, Hajipour AR, Khazdooz L (2009) Synthesis 2009:941
39. Trusova ME, Krasnokutskaya EA, Postnikov PS, Choi Y, Chi KW, Filimonov VD (2011) Synthesis 2011:2154
40. Mukhopadhyay S, Batra S (2018) Chem Eur J 24:14622
41. Tale RH, Toradmal GK, Gopula VB (2015) RSC Adv 5:84910
42. Tramutola F, Chiummiento L, Funicello M, Lupattelli P (2015) Tetrahedron Lett 56:1122
43. Xu C, Chen H, Sugiyama Y, Zhang S, Li HP, Ho YF, Chuang CY, Schwehr KA, Kaplan DI, Yeager C, Roberts KA, Hatcher PG, Santschi PH (2013) Sci Total Environ 449:244
44. Das B, Venkateswarlu K, Damodar K, Suneel KJ (2007) Mol Catal A Chem 269:17
45. Domaradzki ME, Liu X, Ong J, Yu G, Zhang G, Simantov A, Perl E, Chen Y (2020) Tetrahedron 76:131437
46. Alam T, Rakshit A, Begum P, Dahiya A, Patel BK (2020) Org Lett 22:3728
47. Mitra B, Pariyar GC, Ghosh P (2021) RSC Adv 11:1271
48. Sawpath Kumar HW, Subbareddy BV, Anjaneyulu S, Yadav JS (1998) Synth Commun 28:3811
49. Tanemura K, Suzuki T, Nishida Y, Satsumabayashi K, Horaguchi T (2004) Chem Commun 470
50. Das B, Venkateswarlu K, Majhi A, Siddaiah V, Reddy KRJ (2007) Mol Catal A Chem 267:30
51. Pakorn B, Wanutcha L, Sarocha L, Prima S, Warangkana Y, Natthapatch S, Pornpawit S, Terawee K, Jin M, Satreerat L, Maitraye MA (2020) Tetrahedron Lett 61:152461
52. Palav A, Misal B, Chaturbhuj G (2021) J Org Chem 86:12467
53. Meyer-Eppler G, Kuchler L, Tenten C, Benkhauser C, Bruck S, Lutzen A (2014) Synthesis 46:1085
54. Udumula V, Nazari SH, Burt SR, Alfindee MN, Michaelis DJ (2016) ACS Catal 6:4423
55. Barluenga J, Campos PJ, González JM, Suárez JL, Asensio G (1991) J Org Chem 56:2234
56. Sharp PP, Banwell MG, Renner J, Lohmann K, Willis AC (2013) Org Lett 15:2616
57. Hosseini A, Khalilzadeh MA, Keipour H, Tajbakhsh M (2012) Synth Commun 42:2407
58. Adepu R, Rajitha A, Ahuja D, Sharma AK, Ramudu B, Kapavarapu R, Parsa KVL, Pal M (2014) Org Biomol Chem 12:2514
59. Maity S, Das D, Sarkar S, Samanta R (2017) Org Lett 20:5167
60. Mattio LM, Pinna C, Catinella G, Musso L, Pedersen KJ, Krogfelt KA, Dallavalle S, Pinto A (2021) Molecules 26:7594
61. Partibhan D, Karunakaran RJ (2018) Asian J Chem 30:2625
62. Tang RJ, Milcent T, Crousse B (2017) J Org Chem 83:930
63. Liang YF, Song S, Ai L, Li X, Jiao N (2015) Green Chem 18:6462
64. Leboeuf D, Ciesielski J, Frontier AJ (2013) Synlett 25:399
65. Molloy JJ, O'Rourke KM, Frias CP, Sloan NL, West MJ, Pimlott SL, Sutherland A, Watson AJB (2019) Org Lett 21:2488
66. Prabhala P, Savanur HM, Kalkhambkar RG, Laali KK (2019) Eur J Org Chem 2019:2061
67. Alekseyev RS, Amirova SS, Terenin VI (2017) J Heterocycl Chem 54:2656
68. Leboho TC, Giri S, Popova I, Cock I, Michael JP, DeKoning CB (2015) Bioorg Med Chem 23:4943
69. Barl NM, Sansiaume-Dagousset E, Karaghiosoff K, Knochel P (2013) Angew Chem Int Ed 52:10093
70. Murai M, Maekawa H, Hamao S, Kubozono Y, Roy D, Takai K (2015) Org Lett 17:708
71. Zielinska A, Skulski L (2005) Molecules 10:1307
72. Ahmed A, Dhara S, Singha R, Nuree Y, Sarkar P, Ray JK (2014) RSC Adv 4:53137
73. Walker SR, Czyz ML, Morris JC (2014) Org Lett 16:703
74. Cambie RC, Rutledge PS, Smith-Palmer T, Woodgate PD (1976) J Chem Soc Perkin Trans 1:1161
75. Edgar KJ, Falling SN (1990) J Org Chem 55:5287
76. Kumar KK, Elango M, Subramanian V, Das TM (2009) New J Chem 33:1570
77. Jurd L (1950) Aust J Sci Res 3:587