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Research Article

I_2/HIO_3 IN PEG-H_2O: AN ELOQUENT SYSTEM FOR DIRECT IODINATION OF ACTIVATED ARENES

Santosh S. Chobe[1], Shankaraiah G. Konda*[2]

[1]*Organic Research Laboratory, L. V. H. College, Nashik, Maharashtra, India*

[2]*Department of Chemistry, K.J. Somaiya College, Kopargaon, Maharashtra, India*

**Corresponding author: kondasg@rediffmail.com*

ABSTRACT

Polyethylene glycol (PEG) is found to be an inexpensive, environmentally friendly reaction medium for the iodination of activated aromatic compounds by using I_2/ HIO_3 to afford the corresponding in excellent yield of the product. The remarkable features of this protocol are high conversion, shorter reaction time, easy work up, benign reaction condition, high selectivity; simple practical procedure, cleaner reaction profile and Polyethylene glycol (PEG) can be recovered and reused.

Keywords: I_2/HIO_3, Arenes, PEG(400)-H_2O, Iodination

1. INTRODUCTION

Green chemistry is becoming a central issue in both academic and industrial research in the 21st century [1], and the development of environmentally benign and clean synthetic procedures has become the goal of present day in organic synthesis. Organic reaction without the use of harmful organic solvents are now of great interest in organic synthesis [2]. More recently, attention has been drawn to the development of environmentally benign solvent such as ionic liquid [3], water [4] and Polyethylene glycol [5]. The significance of new solvent medium primarily tested on its environmental impact, the ease with which it can be recycled, low vapor pressure, non-flamibility and high polarity for solubilization. However in performing the majority of organic transformation, solvents play an important role in mixing the ingredients to make the system homogeneous and allow molecular interactions to be more efficient. The iodination of electrophilic substitution reaction and the resultant iodoarenes are valuable, versatile synthetic intermediate and have found wide application in medicine, diagnostic technique, agriculture chemicals, dyestuffs, photosensitive materials and radio-active labeled markers [6, 7].

Apart from the applications; preparation of iodo organic is also interesting are due to the least reactive nature of iodine among the halogens. Hence iodination simply by molecular iodine is not possible because of its least reactive nature. Hence, an oxidant is used along with diiodine to get more reactive electrophilic species. This is usually achieved by adding an oxidant like CrO_3 [8], NO_2 [9], $KMnO_4$ [10], iodinemercurysalts [11], NaI-chloromine [12], bis(Pyridine)iodonumtetrafluoroborate CF_3SO_3H [13], diiodinepentaxide [14]. However most of these methods are hazardous or toxic, involves costly reagents, requires high reaction temperature or demand of a long reaction time.

It has been known for over a century that iodic acid may be used an oxidant in direct iodination reactions of arenes [5a]. The application of iodic acid as oxidant in the iodination of arenes, they claimed this to be the most convenient method for the preparation of mono- or diiodo derivatives from various arenes. There has been an increasing emphasis among researchers from both academic and industry to design synthetic strategies keeping in view the principles of green chemistry adoping or eliminate the generation and use of hazardous substances. In recent year's replacement of hazardous solvents with environmentally begin solvents or development of solvents free synthesis is one of the major focus areas of green chemistry. The utility of alternative reaction solvents such as water [15, 16], ionic liquid [17], supercritical media and polyethylene glycol (PEG) [18] is rapidly growing.

Recently, liquid polymer or low melting polymers have emerged or alternative green reaction media with unique properties such as thermal stability. Commercial availability, nonvolatility, immiscibility with a number of organic solvents and recyclability PEG [19], biologically acceptable polymer used extensively in drug delivery and

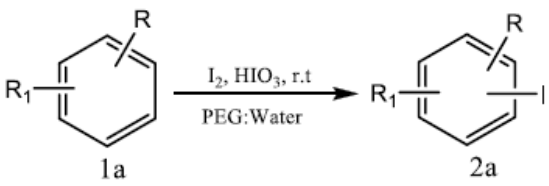
inbioconjugates as tools for diagnostics has been used as a solvent medium supports for various transformation reaction, for example Heck reaction, Catalytic hydrogenation, Baylis Hillman reaction, Beginelli reaction, and Aldol condensation [20]. However, some relative articles have focused on the use of aqueous PEG solution in organic reaction. In this article, we describe the use of simple and widely available polymer Polyethylene glycol (PEG-400)-water or benign medium. As a part of our research program to device greener chemical transformation and in continuation of our studies on developing environmental friendly methodologies [21] for organic synthesis, we reveal herein for the first time a PEG-water assisted solvent procedure for iodination activated aromatic compounds.

2. EXPERIMENTAL

Melting points were determined in an open capillary tube method and matched with reported literature [22]. Merck, pre-coated silica gel 60 F_{254} (Aluminum sheets) plates were used for analytical TLC.IR spectra were recorded (in KBr pallets) on Shimandzu spectrophotometer.^{1}H NMR spectra were recorded (in $CDCl_3$) on Varian Mercury 300 MHz spectrometer using TMS as an internal standard. The mass spectra were recorded on Shimandzu-QP 5050 GC-MS spectrometer. Elemental analysis was carried out on a Carlo Erba 1108 analyzer.

2.1. General procedure for iodination of aromatic compounds

Aromatic compounds (50 mmol), iodine (20 mmol) and iodic acid (10 mmol) dissolved by 5 ml of PEG: H_2O (60:40) solvent system. The reaction mixture was then stirred at about room temperature for 20 min. After completion (monitored by TLC), the reaction mixture was extracted with diethyl ether (2×20 ml). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was recrystallized from absolute ethanol to afford to the pure product.

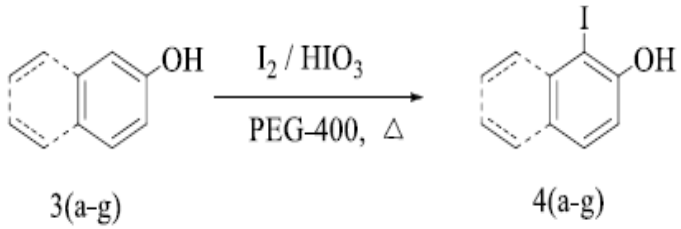


R=$COCH_3$, CHO, OH; R1= OH, Cl, F, Br, CH_3, OCH_3

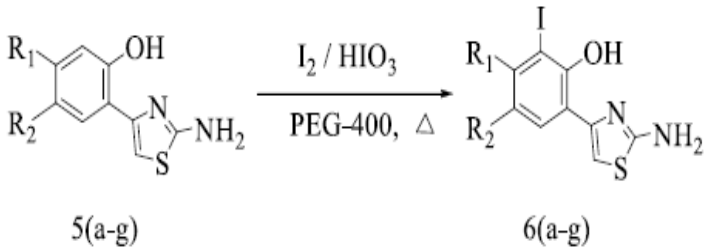
Scheme 1: Iodination of activated aromatic compounds

2.2. General procedure for synthesis of 2-(2-amino thiazol-4-yl)-substituted iodophenol (6)

A mixture of 2-(2-Amino-thiazol-4-yl)-4-chloro-phenol (1.275 gm, 0.005 mole) and iodine (0.508gm, 0.001 mole) were dissolved in poly (ethylene glycol) (PEG-400) (20 mL). The iodic acid (0.177 gm in 3 mL of H_2O, 0.001 mole) was added and stirred for 20 minutes at room temperature. The completion of the reaction was monitored by TLC, after completion of the reaction. The contents were diluted with excess of water. The unreacted iodine was decomposed by treating cooled saturated solution of sodium thiosulphate. Separated solid product was filtered and washed with ice cold water. The product obtained was recrystallized from aqueous acetic acid.



Scheme 2: Synthesis of substituted iodo phenols



Scheme 3: Iodination of heterocyclic phenols

2.3. Spectral data of iodinated aromatic compounds

4-Hydroxy-5-iodo-3-methoxybezldehyde (2a): White solid. ***IR (KBr)*** $\nu_{max}cm^{-1}$: 2835, 2740,1662, 1585; ***^{1}H NMR (300 MHz,CDCl$_3$):*** δ 3.98 (s, 3H, OCH_3), δ 7.40 (s, 1H, 2Ar-H), δ 7.60 (s, 1H, 6Ar-H), δ 8.06 (s, 1H, OH); δ 9.98 (s,1H,CHO); ***^{13}H CMR (300 MHz,CDCl$_3$):*** 56, 89, 113, 131, 132, 153, 158, 191; ***MS (m/z):*** 277 (M^+ ion); ***Anal. calcd for $C_8H_7IO_3$:*** C, 34.53; H, 2.48; I, 45.68% Found: C, 34.46; H, 2.42; I, 65.74%

2-Hydroxy-3,5-diiodobenzaldehyde (2b): Creamy white solid. ***IR (KBr)*** $\nu_{max}cm^{-1}$ **:** 2850, 2719, 1658, 1588; ***^{1}H NMR (300 MHz,CDCl$_3$):*** δ 8.02 (s, 1H, 6Ar-H), δ 8.13 (s, 1H, 4Ar-H), δ 9.98 (s, 1H, CHO), δ 11.80 (s, 1H, OH); ***^{13}H CMR (300 MHz,CDCl$_3$):*** 84,89,132,138,151,159,192; ***MS (m/z):*** 373(M^+ ion); ***Anal.calcd for $C_7H_4I_2O_2$:*** C, 22.46; H, 1.06; I, 67.92% Found: C, 22.34; H, 1.16; I, 67.92%

2,4-Dihydroxy-3,5-diiodobenzaldehyde (2g): white solid. ***IR (KBr)*** ν_{max}***cm^{-1} :*** 2813, 1646, 1580; ***^{1}H NMR (300 MHz,CDCl$_3$):*** δ 7.82 (s, 1H, 6Ar-H), δ 8.40 (s, 1H, OH), δ 10.05 (s, 1H, CHO), δ 11.86 (s, 1H, OH); ***^{13}H CMR (300 MHz,CDCl$_3$):*** 79, 82, 125, 139, 161, 162, 191; ***MS (m/z):*** 389(M^+ ion); ***Anal. calcd for C$_7$H$_4$I$_2$O$_3$:*** C, 21.54; H, 1.03; I, 65.12% Found: C, 21.49; H, 1.10; I, 65.18%

2,4-dihydroxy-3,5-diiodoacetophenone (2h): White solid. ***IR (KBr)*** ν_{max}***cm^{-1}:*** 1645, 1570; ***^{1}H NMR (300 MHz,CDCl$_3$):*** δ 2.86 (s, 3H, $COCH_3$), δ 8.72 (s, 1H, 6Ar-H), δ 8.35 (s, 1H, OH), δ 11.92 (s, 1H, OH); ***^{13}H CMR (300 MHz,CDCl$_3$):***26, 78, 82, 116, 137, 160 (2×C), 201; ***MS (m/z):*** 403 (M^+ ion); ***Anal. calcd for C$_8$H$_6$I$_2$O$_3$:*** C, 23.76; H, 1.49; X, 62.85% Found: C, 23.69; H, 1.42; X, 62.92%

4-Hydroxy-3,5-diiodoacetophenone (2k): Light yellow solid. ***IR (KBr)*** ν_{max}***cm^{-1}:*** 1658, 1580; ***^{1}H NMR (300 MHz,CDCl$_3$):*** δ 2.92 (s, 3H, $COCH_3$), δ 6.8 (s, 1H, 2Ar-H), δ 7.25 (s, 1H, 6Ar-H), δ 12.78. (s, 1H, OH); ***^{13}H CMR (300 MHz,CDCl$_3$):*** 26, 89 (2×C), 132,136(2×C), 159, 191; ***MS (m/z):*** 387 (M^+ ion); ***Anal. calcd for C$_8$H$_6$I$_2$O$_2$:*** C, 24.74; H, 1.54; X, 65.40% Found: C, 24.65; H, 1.48; X, 65.52%

5-Bromo-2-hydroxy-3-iodoacetophenone (2l): Light yellow solid. ***IR (KBr)*** ν_{max}***cm^{-1} :*** 1635, 1582; ***^{1}H NMR (300 MHz,CDCl$_3$):*** δ 2.90 (s, 3H, $COCH_3$), δ 6.92 (s, 1H, 4Ar-H), δ 7.28 (s, 1H, 6Ar-H), δ 12.85. (s, 1H, OH); ***^{13}H CMR (300 MHz,CDCl$_3$):***26, 89, 117, 125, 133, 146, 159, 201; ***MS (m/z):*** 339 (M^+ ion); ***Anal. calcd for C$_8$H$_6$BrIO$_2$:*** C, 28.16; H, 1.74; X, 59.68% Found: C, 28.08; H, 1.62; X, 60.35%

5-chloro-2-hydroxy-3-iodo-4-methylacetophenone (2r): White solid. ***IR (KBr)*** ν_{max}***cm^{-1}:*** 1638, 1576; ***^{1}H NMR (300 MHz,CDCl$_3$):*** δ 2.15 (s, 3H,CH_3), δ 2.79 (s, 3H, $COCH_3$), δ 8.69 (s, 1H, 6Ar-H), δ 11.86 (s, 1H, OH); ***^{13}H CMR (300 MHz,CDCl$_3$):***14, 26, 94, 121, 129, 152, 157, 202; ***MS (m/z):*** 309 (M^+ ion); ***Anal. calcd for C$_9$H$_8$ClIO$_2$:*** C, 34.83; H, 2.51; X, 52.34% Found: C, 34.76; H, 2.43; X, 52.45%

2.4.Spectral data iodinatation of 2-amino substituted thiazole derivatives

2-(2-aminothiazol-4-yl)-4-chloro-6-iodophenol (6a): White solid. ***IR (KBr)*** ν_{max}***cm^{-1} :*** 3451, 3342, 3110, 1596, 1245, 789; ***^{1}H NMR (300 MHz,CDCl$_3$):*** δ 7.56 (s, 2H, NH_2, D_2O exchangeable), δ 6.8-7.4 (m, 2H, Ar-H), δ 7.8 (s, 1H, 5-H of thiazole), δ 11.98 (s, 1H, OH, D_2O exchangeable); ***MS (m/z):*** 352(M^+ ion), 354(M^{+2} ion); ***Anal. calcd for C$_9$H$_6$ON$_2$SClI:*** C, 30.62; H, 1.72; X, 46.02, N, 7.90% Found: C, 30.63; H, 1.70; X, 46.09, N, 7.94%

2-(2-aminothiazol-4-yl)-6-iodophenol (6b): Light yellow solid. ***IR (KBr)*** ν_{max}***cm^{-1}:*** 3442, 3324, 3145, 1580, 1245; ***^{1}H NMR (300 MHz,CDCl$_3$):*** δ 7.63 (s, 2H, NH_2, D_2O exchangeable), δ 6.9-7.6 (m, 3H, Ar-H), δ 7.89 (s, 1H, 5-H of thiazole), δ 11.96 (s, 1H, OH, D_2O exchangeable); ***MS (m/z):*** 317(M^+ ion); ***Anal. calcd for C$_9$H$_7$ON$_2$SI:*** C, 33.96; H, 2.20; I, 39.90, N, 8.78% Found: C, 30.93; H, 2.18; I, 39.92, N, 8.81%

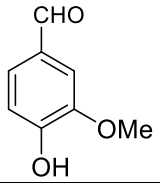
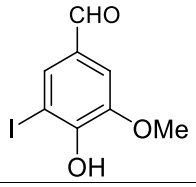
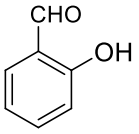
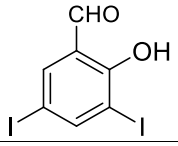
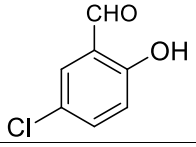
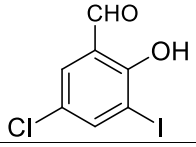
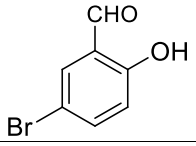
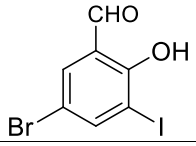
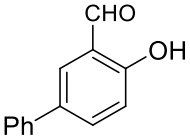
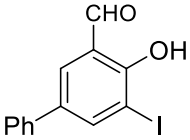
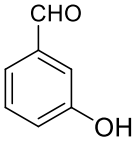
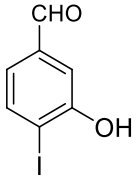
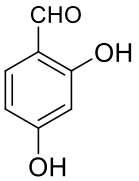
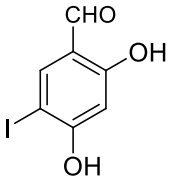
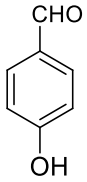
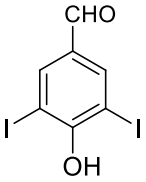
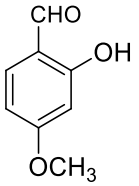
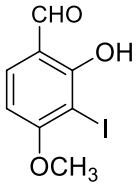
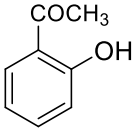
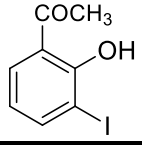
2-(2-aminothiazol-4-yl)-4-bromo-6-iodophenol (6c): White solid. ***IR (KBr)*** ν_{max}***cm^{-1} :*** 3468, 3340, 3128, 1568, 1240, 820; ***^{1}H NMR (300 MHz,CDCl$_3$):*** δ 7.58 (s, 2H, NH_2, D_2O exchangeable), δ 6.90-7.50 (m, 2H, Ar-H), δ 7.89 (s, 1H, 5-H of thiazole), δ 11.92 (s, 1H, OH, D_2O exchangeable); ***MS (m/z):*** 397(M^+ ion), 399(M^{+2} ion); ***Anal.calcd for C$_9$H$_6$ON$_2$SBrI:*** C, 27.28; H, 1.50; X, 52.09, N, 7.04% Found: C, 27.25; H, 1.52; X, 52.12, N, 6.96%

2-(2-aminothiazol-4-yl)-4-bromo-5-methyl-6-iodophenol (6f): White solid. ***IR (KBr)*** ν_{max}***cm^{-1} :*** 3462, 3336, 3122, 1572, 1240, 822; ***^{1}H NMR (300 MHz,CDCl$_3$):*** δ 2.25 (s, 3H, CH_3), δ 7.89 (s, 2H, NH_2, D_2O exchangeable), δ 7.2 (S, 1H, Ar-H), δ 7.76 (s, 1H, 5-H of thiazole), δ 11.96 (s, 1H, OH, D_2O exchangeable); ***MS (m/z):*** 366(M^+ ion), 368(M^{+2} ion); ***Anal.calcd for C$_{10}$H$_8$ON$_2$SClI:*** C, 32.72; H, 2.16; X, 44.30, N, 7.60% Found: C, 32.74.; H, 2.18; X, 44.33, N, 7.63%

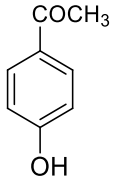
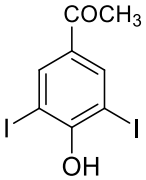
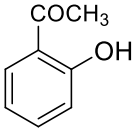
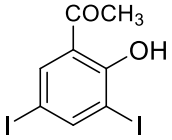
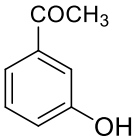
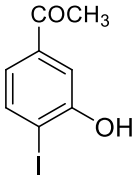
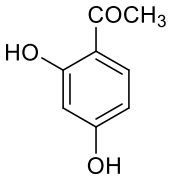
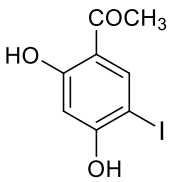
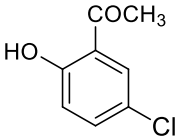
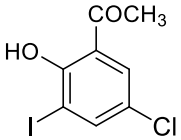
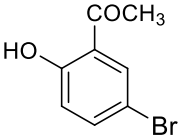
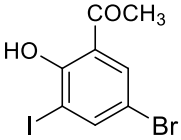
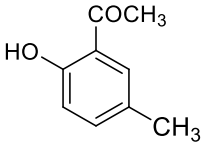
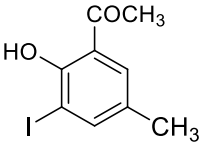
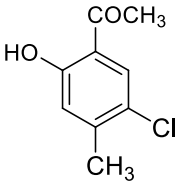
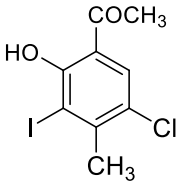
3. RESULTS AND DISCUSSION

At the beginning, we started with the iodination of aromatic compounds to illustrate the advantages of present method. Initially, we have chosen activating aromatic aldehydes (Table 1, Entry **1a**) as a model reaction (Scheme 1). Substrate **1a** with iodine and iodic acid dissolved in (5ml) of PEG-Water (60:40) solvent system. The reaction mixture was then stirred at about room temperature for 20 minutes as confirmed by TLC. The reaction poured into beaker containing sodium thiosulphate and extracted with ethyl acetate. The corresponding iodinated product was obtained in 96% yield.

Table1: Physical and analytical data of iodo aromatic aldehydes and ketones 2(a-r)

Entry	Substrate 1(a-r)	Product 2(a-r)	Yield in (%)	M.P (°C)
1			92 (75)	180 (183)
2			94 (87)	110 (110)
3			90 (85)	78 (76)
4			89(68)	82 (81)
5			85(57)	134 (136)
6			94(78)	180 (182)
7			90(70)	174 (172)
8			92(75)	190 (194)
9			90 (74)	178 (176)
10			92 (84)	142 (140)

Continued….

11			92(80)	167 (165)
12			90 (72)	172 (168)
13			95(84)	156 (155)
14			92(85)	178 (177)
15			89(82)	92 (89)
16			90(78)	105 (105)
17			92(86)	88 (90)
18			95(92)	78 (76)

Value in bracket (), Indicates reported values

Next, we investigated the effect of ratio of PEG-H_2O for the iodination of arenes, is summarized in Table 2. As we increase in the amount of water which is attributed to the loss of solubility of the substrates. Then we confirmed that 60:40 (PEG-H_2O) ratios is the best system for the present method. In order to establish the best reaction medium, we performed the reaction using substrate **1a** with various solvent such as ethanol, THF, acetonitrile, toluene, PEG-400, PEG-600 and PEG-4000. Using ethanol, THF, acetonitrile, toluene as the solvent gave low yield (60-75%) of product after 2-3 hr (Table 3, Entry1-4).

Table 2: Effect of PEG: H_2O solvent system on iodinated of aromatic compounds

PEG-400 : H_2O		Time (min)	Yield(%)[a]
90	10	20	92
80	20	20	93
70	30	22	94
60	40	20	96
50	50	35	89
40	60	40	82

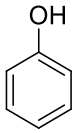
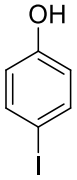
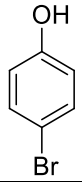
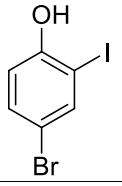
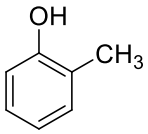
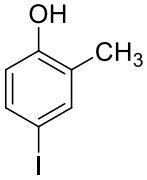
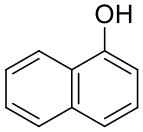
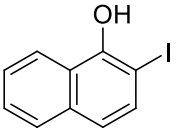
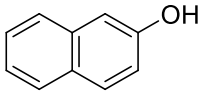
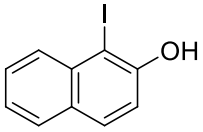
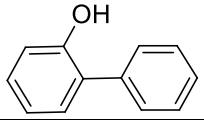
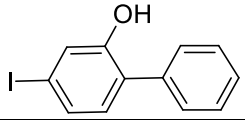
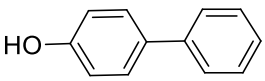
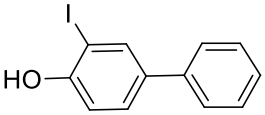
No other solvent gave better yield in iodination process as compared with polyethylene glycol. By this result, we established the polyethylene glycol-400 is best reaction solvent for this condition. To understand the role of PEG as a reaction medium, we also performed the iodination of same substrate in PEG-400, PEG-600 and PEG-4000 (Table 3, Entry 5-7). However, as the molecular weight of PEGs increases (Table 3, Entry 7), the viscosity increases. Because of this reason we raised the temperature up to 80°C to liquefy the PEG.

Table 3: Effect of solvent on the synthesis of iodinated aromatic compounds

Entry	Solvent	Time (hr)	Yield(%)[a]
1	EtOH	2.5	70
2	THF	2	64
3	Acetonitrile	2	60
4	Toluene	3	62
5	PEG-400	0.33	92
6	PEG-600	0.33	88
7	PEG-4000	0.40	86

[a] *Isolated yield.*

Table 4: Physical and analytical data of iodo phenols 4(a-g)

Entry	Substrate 3(a-g)	Product 4(a-g)	Yield (%)	M.P (°C)
1			89 (72)	42 (43)
2			92(85)	95(90)
3			90(78)	102(100)
4			92(76)	105 (103)
5			88(82)	110 (108)
6			92(76)	132 (125)
7			90(84)	128 (125)

In order to evaluate the possibility of applying this methodology on large scale, we carried out the iodination in polyethylene glycol-400 at room temperature. The yield of corresponding iodinated product was almost the same as that obtained in the small scale (92%) (Table 1, Entry 1). With this results, we used variety of substituted aromatic aldehydes [Table-1, **1(a-i)**]. In addition to this, we also successfully iodinated the variety of ketones [Table 1,**1(j-r)**]. Next, we turned towards the iodination of variety of simple phenols using

PEG-H_2O as an efficient system (Scheme 2) the corresponding yield and reaction time were summarized in Table 4.

With this prompted results, we are tried to iodination of some others phenols containing some heterocyclic moiety in similar condition (Scheme 3). The corresponding yield, reaction time are mentioned in Table 5.

To determine the reusability of the solvent, the reaction mixture was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and solvent was evaporated. The remaining mother liquor was subjected to vacuum distillation to remove water leaving PEG behind in the container. The recovered PEG was subjected to charge same substrate for several times (five times) without loss of its activity (Table 6). The role of PEG is possibly to form a complex with the cation. The iodination mechanism is based on the iodine cation formation. The formed iodine cation, may stabilize by the interaction with the oxygen atom in PEG. Therefore PEG is not only acting as an efficient solvent system, but also acts as PTC.

Table 5: Synthesis of 2-(2-amino thiazol-4-yl)-substituted iodophenol 6(a-g)

Entry	Product	R_1	R_2	Yield (%)	M.P.(˚C)
1	6a	H	Cl	90	220
2	6b	H	H	95	218
3	6c	H	Br	90	216
4	6d	H	CH_3	93	210
5	6e	CH_3	Cl	89	208
6	6f	CH_3	Br	90	206
7	6g	Cl	CH_3	92	205

Table6: Recycling of PEG-400 solvent system for the iodination of arenes

Run	1	2	3	4	5
Yield (%)[a,b]	96	96	95	94	94

[a] *All reactions were carried out with 1 mmol of substrate.* [b] *Isolated yields.*

4. CONCLUSION

In summary we have developed a new rapid and highly efficient methodology for the iodination of activated arenes by employing PEG-H_2O solvent system at room temperature. In the present protocol, neither harmful reagent are used nor toxic residue are left after completion of reaction, excellent yield of the product, easy work up, shorter times, benign reaction condition make this protocol attractive, environmentally acceptable synthetic tool for the preparation of these substrate.

5. ACKNOWLEDGEMENTS

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