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Full Paper

2-Methoxyethanol: A remarkably efficient and alternative reaction medium for iodination of reactive aromatics using iodine and iodic acid

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ABSTRACT: Remarkably effective iodination of reactive aromatics carried out using iodine and iodic acid in 2-methoxyethanol as an efficient and alternative reaction medium. The comparison has been made by carrying out iodination reaction in acetic acid and ethanol. The 2-methoxyethanol is found to be excellent reaction solvent in terms of clean reaction conditions, short reaction time giving quantitative yields of product and no need of further purification.

Keywords: iodoaromatics; 2-methoxyethanol; iodine; iodic acid

Introduction

Aromatic iodo compounds are valuable and versatile synthetic intermediates in organic chemistry [1]. They react with nucleophiles such as amines or alkoxides to give the corresponding substituted products and can be lithiated to introduce electrophiles via halogen lithium exchange reaction [2]. They are also important and most reactive intermediate for various cross-coupling reactions and especially useful for formation of carbon-carbon and carbon-heteroatom bonds [3].

The moderate reactivity of iodine with aromatic substrates requires the addition of activating agents for its utilization. Generally, aromatic compounds are iodinated using iodine in presence of Lewis acid or an oxidizing agent [4].

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Synthesis of iodoaromatics using various reaction medium and iodinating reagent involves I_2/petroleum ether [5], KI/H_2SO_4 in H_2SO_4 [6], NaI/Chloramine-T in methanol [7], NaOCl/NaI in aqueous alcohol medium [8], KI/H_2O_2 in CH_3COOH [9], $KClO_3$ /KI/HCl in aqueous medium [10], and $I_2/NaBO_3.H_2O$ in ionic liquid [11]. The utility of alternative reaction solvents such as water [12], ionic liquid [13], flourous [14], supercritical media [15] and polyethylene glycol [PEG] [16] is rapidly growing. These solvents have attracted the attention of organic chemists due to their solvating ability and aptitude to act as a phase transfer catalyst, negligible vapour pressure, non-hazardous, easy work- up and economical cost. However many of these reported procedures have one or more disadvantages such as use of expensive catalysts, long reaction time, low selectivity, requirements of special apparatus and side reaction.

In continuation of earlier research program on iodination of reactive aromatics using iodine and iodic acid [17], herein we wish to report the use of 2-methoxyethanol as a reaction solvent.

Material and Methods

Melting points were determined in an open capillary tube and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer spectrometer. ^1H NMR spectra were recorded on a Gemini 300-MH_Z instrument in $CDCl_3$ as solvent and TMS as an internal standard. The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

General procedures for iodination of hydroxy aromatic aldehydes, hydroxy acetophenones, substituted anilines and phenols in ethanol, acetic acid and 2-methoxyethanol:

Mixture of different aromatic compounds (50 mmol), iodine (20 mmol) dissolved in 5 mL of 2-methoxyethanol and iodic acid (10 mmol) dissolved in water (1 mL) was added with shaking and refluxed for 3-8 minutes (tables 1-4). On cooling reaction mixture, crystalline solid product separated out (reaction monitored on TLC).

Obtained solid product was filtered through Buchner funnel. Physical data is given in Tables 1-4. For synthesis of di-iodo product 40 mmol of iodine and 20 mmol of iodic acid with 50 mmol of substrate was used.

Similar procedure was carried out by using 25 mL of ethanol or 20 mL of acetic acid. Results obtained by these procedures are shown in tables 1-4.

Spectral data of some selected compounds

4-Hydroxy-3,5-diiodo-benzaldehyde: IR (cm^{-1}): 2852 (C-H *stretch of* CHO),

Table 1. Physical data of iodo hydroxy benzaldehydes

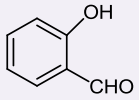
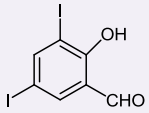
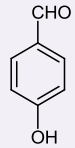
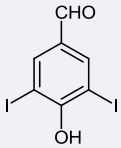
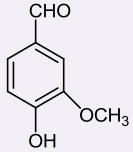
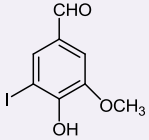
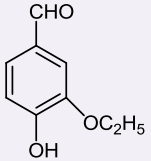
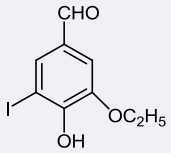
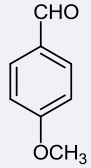
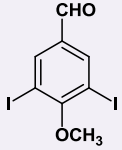
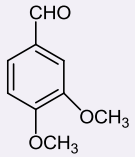
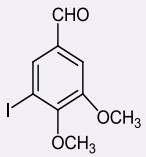
Entry No.	Substrate	Product	M.P. (^{0}C) Found (Reported)	Effect of solvent on iodination of hydroxy aldehydes					
				Ethanol		Acetic acid		2-Methoxyethanol	
				Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
1			110 (110) [19]	05	82	18	58	03	96
2			194 (195) [18]	07	80	20	62	05	88
3			184 (185) [18]	09	85	22	50	05	90
4			185 (185) [19]	05	80	17	63	04	86
5			105 (107) [19]	08	80	21	55	05	92
6			70 (69-72) [19]	10	80	23	68	05	85

Table 2. Physical data of iodo hydroxy acetophenones

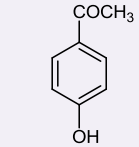
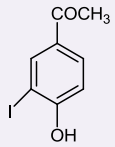
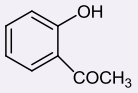
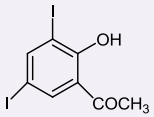
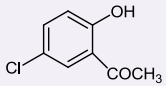
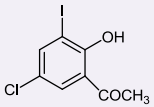
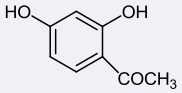
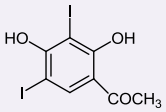
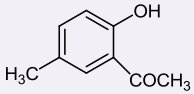
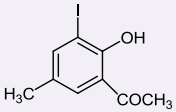
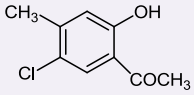
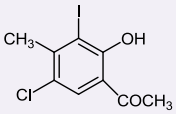
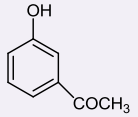
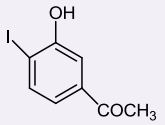
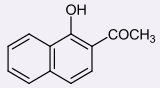
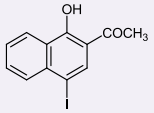
Entry No.	Substrate	Product	M.P.(^{0}C) Found (Reported)	Effect of solvent on iodination of hydroxy acetophenones					
				Ethanol		Acetic acid		2-Methoxyethanol	
				Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
1			164 (162) [19]	05	80	18	58	05	87
2			132 (132) [18]	08	85	22	64	06	92
3			89 (90) [19]	05	84	17	60	04	95
4			177 (178) [18	09	85	24	62	05	90
5			90 (90) [19]	05	82	18	50	03	85
6			78 (76) [19]	06	85	25	70	05	88
7			156 (155) [19]	07	82	19	62	04	90
8			156 (156) [19]	05	79	16	55	05	96

Table 3. Physical data of iodo anilines

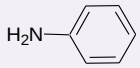
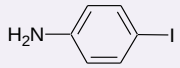
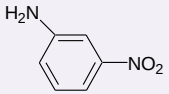
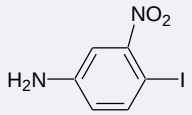
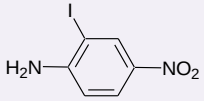
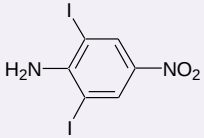
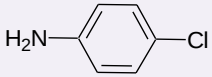
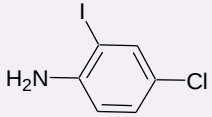
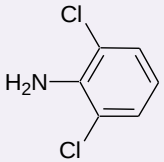
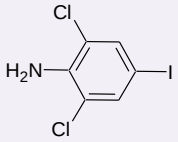
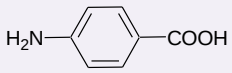
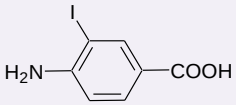
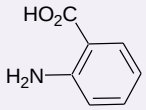
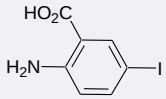
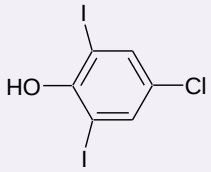
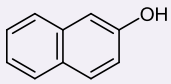
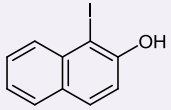
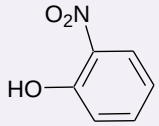
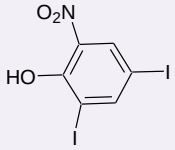
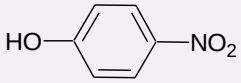
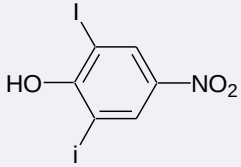
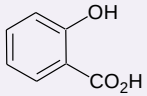
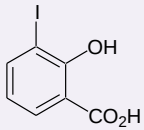
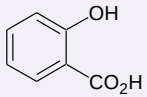
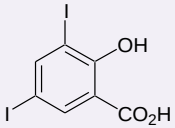
Entry No.	Substrate	Product	M.P.(^{0}C) Found (Reported)	Effect of solvent on iodination of anilines					
				Ethanol		Acetic acid		2-Methoxyethanol	
				Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
1			62 (62-63) [20]	10	80	25	62	05	88
2			120 (122) [20]	05	75	17	54	03	84
3			115 (116) [19]	06	80	19	60	07	82
4			252 (251-253) [19]	09	75	23	50	08	90
5			40 (39-41) [19]	07	75	21	58	05	94
6			85 (80) [19]	05	80	17	60	08	86
7			255 (258) [19]	10	70	28	48	06	82
8			222 (220-225) [19]	06	60	25	42	08	85

Table 4. Physical data of iodo phenols

Entry No.	Substrate	Product	M.P (^{0}C) Found (Reported)	Effect of solvent on iodination of Phenols					
				Ethanol		Acetic acid		2-Methoxyethanol	
				Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
1			105 (107) [21]	10	82	27	52	08	88
2			108 (108-110) [19]	06	80	22	60	05	92
3			95 (93) [22]	12	85	30	66	04	90
4			150 (152) [19]	13	80	28	52	07	82
5			185 (190) [19]	09	80	25	60	05	85
6			220 (220) [19]	12	80	27	52	08	86

1660 (C=O), 1558 (C=C stretch). ^{1}H NMR ($CDCl_3$): δ 7.72 (s, 2H, Ar-H), 8.42 (s, 1H, OH), 10.02 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSOd_6, δ,ppm):: 91.12 (C *of two* Ar-I), 131.64 (C of Ar-C), 139.42 (C *of two* Ar-H), 182.21 (C *of* Ar-OH), 191.37 (C *of* CHO). MS m/z: 374 (M^+). Anal. calcd. for: $C_7H_4O_2I_2$: C, 22.45; H, 1.06; I, 67.91. Found: C, 22.49; H, 1.09; I, 67.94.

3,5-Diiodo-4-methoxy-benzaldehyde: IR (cm^{-1}): 2845 (C-H *stretch of* CHO), 1652 (C=O), 1548 (C=C stretch). ^{1}H NMR ($CDCl_3$): δ 3.27 (s, 3H, OCH_3), 7.85 (s, 2H, Ar-H), 9.97 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSOd_6, δ,ppm): 190.78 (C=O), 137.60, 88.23 (*C of Aromatic ring*), 60.92 (OCH_3). MS m/z: 388 (M^+). Anal.calcd. for: $C_8H_6O_2I_2$: C, 24.74; H, 1.54; I, 65.46. Found: C, 24.68; H, 1.51; I, 65.42.

2,4-Dihydroxy-3,5-diiodoacetophenone: IR (cm^{-1}): 3428 (OH), 1660 (C=O), 1555 (C=C stretch). ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H, CH_3), 7.90 (s, 1H, Ar-H), 12.62 (s, 1H, OH), 8.92 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSOd_6, δ,ppm): 24.17 (C *of methyl group*) 76.14 (C *of two* Ar-I), 141.29 (C of Ar-H), 178.24 (C *of two* Ar-OH), 197.68 (C *of carbonyl group*). MS m/z: 404 (M^+). Anal.calcd. for: $C_8H_6O_3I_2$: 23.76; H, 1.48; I, 62.87. Found: C, 23.80; H, 1.51; I, 62.93.

1-(1-Hydroxy-4-iodo-naphthalen-2-yl)-ethanone: IR (cm^{-1}): 3438 (OH), 1664 (C=O), 1560 (C=C stretch). ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, CH_3), 6.25-7.91 (m, 5H, Ar-H), 14.12 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSOd_6, δ, ppm): 200.37 (C=O), 164.95, 135.29, 133.20, 130.73, 127.28, 124.62, 122.47, 91.82(*C of Aromatic ring*), 26.62 (CH_3). MS m/z: 312 (M^+). Anal.calcd for: $C_{12}H_9O_2I$: C, 46.15; H, 2.88; I, 40.70. Found: C, 46.10; H, 2.86; I, 40.67.

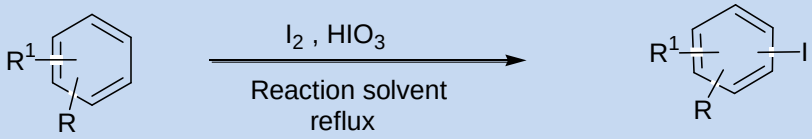
2,6-diiodo-4-nitroaniline: IR (cm^{-1}): 3348 (NH), 1553 (C=C), 1368 (NO_2). ^{1}H NMR ($CDCl_3$): δ 4.08 (s, 2H, NH_2), 7.89 (s, 2H, Ar-H). ^{13}C NMR (75 MHz, DMSOd_6, δ, ppm): 156.20, 145.89, 135.33, 86.90 (*C of Aromatic ring*). MS m/z: 390 (M^+). Anal.calcd. for: $C_6H_4N_2O_2I_2$: C, 18.46; H, 1.02; I, 65.12. Found: C, 18.52; H, 1.05; I, 65.17.

2,6-diiodo-4-nitrophenol: IR (cm^{-1}): 3442 (OH), 1557 (C=C), 1352 (NO_2). ^{1}H NMR ($CDCl_3$): δ 7.82 (s, 2H, Ar-H). ^{13}C NMR (75 MHz, DMSOd_6, δ, ppm): 161.86, 140.18, 134.70, 90.85. MS m/z: 391 (M^+). Anal.calcd. for: $C_6H_3O_3I_2$: C, 18.41; H, 0.76; I, 64.96. Found: C, 18.38; H, 0.75; I, 64.92.

Results and Discussion

2-methoxyethanol is non-halogenated, inexpensive and water soluble which facilitate its removal from reaction product. In view of this observation it was thought worthwhile to carry out iodination of reactive aromatics using iodine and iodic acid as

iodinating agent in 2-methoxyethanol as an efficient and alternative reaction solvent (Scheme-**1**).



Reaction solvent: **A**: ethanol; **B**: acetic acid; **C**: 2-methoxyethanol
R = CHO, $COCH_3$, NH_2, OH;
R_1 = OH, OCH_3, OC_2H_5, Cl, CH_3, NO_2, COOH

Scheme 1. Iodination of reactive aromatics

In order to optimize the reaction conditions in terms of solubility, clean reaction conditions, isolation of product, time required for completion of reaction, yield and purity of product, we carried out the above reaction in ethanol and acetic acid and our results summarized in Table:**1-4**. We found that 2-methoxyethanol is remarkably effective reaction solvent consuming shorter reaction time besides increasing yield of product (Table.**1-4**). Encouraged by the results, we turned our attention towards variety substituted reactive aromatics. In all cases, the reaction proceeded smoothly in high yields at 120°C using 2-methoxyethanol as an attractive reaction solvent for iodination reaction.

Conclusion

We reported remarkably efficient reaction medium for modified practical procedure for iodination of aromatics using iodine-iodic acid in 2-methoxyethanol. Present method, offer additional advantages such as comparatively least requirement of amount of solvent, simple reaction conditions, no need of catalyst, economical process with easier setup and workup procedure giving high yields of desired product.

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