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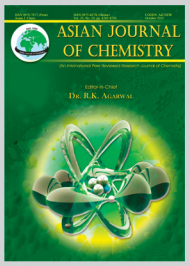

NOTE

Synthesis of 5-Bromo-2-furfural under Solvent-Free Conditions Using 1-Butyl-3-Methylimidazolium Tribromide as Brominating Agent

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The development of a facile and general method for the preparation of 5-bromo-2-furfural is described. An excellent yield of high regioselectivity came out of the bromination reaction of 2-furfural with 1-butyl-3-methylimidazolium tribromide under solvent-free conditions.

Key Words: Selective bromination, 5-Bromo-2-furfural, 1-Butyl-3-methylimidazolium tribromide, 2-Furfural.

5-Bromo-2-furfural is key intermediate in the preparation of important biologically active compounds[1-5], pharmaceutical[6-12] and agrochemical[13-15]. In previous reports 5-bromo-2-furfural was generally synthesized using 2-furfural as starting material, which was subjected to bromination with equivalents of bromine either in a solvent or solely in the presence of aluminum chloride[16-19]. Molecular bromide, the simplest brominating agent, which has high atom utilization and widely application in large-scale industrial production though, suffers from several drawbacks of hazardous and difficult to handle, especially from poor regioselectivity. These reactions in many cases result in a mixture of mono and dibrominated products. In spite of the present methodologies, there is still a desire to explore a mild, efficient and environmentally benign route for the highly selective preparation of 5-bromo-2-furfural.

Reaction in solvent-free and ionic liquids medium is attracting increasing interest for good selectivity, enhanced reaction rate, manipulative simplicity and friendly environment as an alternative to classical molecular solvents in synthetic organic chemistry[20-23]. Herein, an efficient synthetic process of high selectivity for the monobromination of 2-furfural using 1-butyl-3-methylimidazolium tribromide ([bmim]Br_3) as brominating agent as compared with other brominating agents.

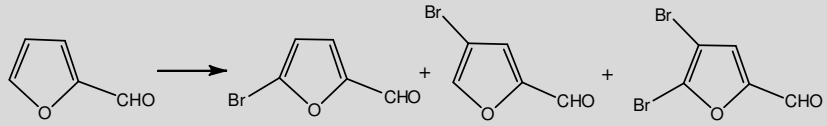
Melting points were determined on digital melting point apparatus and were uncorrected. TLC analyses were carried out on silica gel 60 GF254 precoated aluminum sheets using UV light for detection. HPLC (Shimadzu LC-10 Avp Plus using 30 volume of distilled water to 70 volume of methanol as eluent.) was utilized to determine product compositions and substrate conversions using *n*-dodecane as internal standard. IR spectra were recorded in cm^{-1} (KBr) (Hitachi IR meter 260-10). ^1H NMR spectra were recorded on a Bruker 400 MHz spectrometer using the indicated solvents.

Preparation of 1-butyl-3-methylimidazolium bromide ([bmim]Br): A three-necked 50 mL round bottom flask was charged with *N*-methylimidazole (0.10 mol) followed by dropwise addition of 1-bromobutane (0.11 mol) at 70 ºC. After the addition was completed, the resulting mixture was stirred at 140 ºC for 1.5 h. The combined organic layer was washed three times by ethyl acetate and vacuum-dried overnight at 70 ºC.

Preparation of 1-butyl-3-methylimidazolium tribromide ([bmim]Br_3): Bromine (0.10 mol) was added in dropwise to stirred 1-butyl-3-methylimidazolium bromide (0.10 mol), which obtained by the above experiment. After the addition was completed, the resulting mixture was stirred for 2 h at room temperature and washed by ethyl acetate (30 mL × 3). The residue was vacuum-dried overnight at 70 ºC.

A typical preparation of 5-bromo-2-furfural: A three-necked 50 mL round bottom flask was charged with [bmim]Br_3 (20 mmol) followed by dropwise addition of freshly distilled 2-furfural (20 mmol) over a period of 0.5 h and the reaction mixture was stirred for at 40 ºC 2.5 h under nitrogen atmosphere. The mixture was extracted with petroleum ether (30 mL × 3), the organic layer was washed with water, dried (sodium sulfate) and concentrated. The crude product was purified by distillation and recrystallization with 10 % ethyl acetate-ether solution. 5-Bromo-2-furfural of yellowish crystal in 88 % yield was obtained. Mp. 82-85 ºC, ^1H NMR ($CDCl_3$), δ: 9.55 (s, 1H), 7.25 (s, 1H), 6.57 (s, 1H).

TABLE-1
BROMINATION OF 2-FURFURAL WITH DIFFERENT BROMINATING AGENT[a]



Entry	Brominating agent	Solvent	Additive	Reaction time (h)	Reaction temp. (ºC)	Conversion (%)	Yield (%)	Product compositions (%)[b]		
								5-Bromo	4-Bromo	4,5-Bromo
1	Br_2	CH_2Cl_2	HQ[c]	8	60	88.3	45.4	84.6	11.7	3.7
2	Br_2	CH_2Cl_2	$AlCl_3$	14	0	67.6	10.9	20.4	10.5	69.1
3	Br_2	$ClCH_2CH_2Cl$	$AlCl_3$	16	0	85.9	8.4	11.4	2.5	86.1
4	Br_2	$ClCH_2CH_2Cl$	HQ[c]	8	80	89.5	55.2	79.8	17.5	2.7
4	NBS	DMF	–	6	80	95.1	64.2	86.3	9.4	4.3
5	NBS	DMF	–	18	–15	93.8	17.9	38.6	54.1	7.3
6	NBS	CCl_4	–	5	70	90.7	58.5	83.7	12.9	3.4
7	NBS	CCl_4	–	22	–5	82.1	18.6	48.6	44.6	6.8
8	$[Bmim]Br_3$	–	–	3	40	96.6	88.1	94.8	5.2	–
9	$[Bmim]Br_3$	–	–	10	0	20.8	5.9	53.3	46.7	–

[a]All reactions were carried out using 2g of 2-furfural; [b]Final product composition determined by HPLC, calculated from HPLC peak areas; [c]HQ means hydroquinone

Bromination of 2-furfural involving substrate amounts, solvents types, reaction time and temperature *etc*., was discussed in detail. Some results are summarized in Table -1.

Initially, we experienced very low yields. Close examination revealed that one of the main factors that contributed to low yield was the occurrence of a polymerization reaction with formation of a black tar. Any attempts to minimize polymerization found that it is rather important to the addition manner of 2-furfural in slowly and dropwise.

The reaction of Br_2 and 2-furfural at 0 ºC in the presence of $AlCl_3$ is in favour of the double bromine of 2-furfural to synthesis 4,5-dibromo-2-furfural (entry 3).

Using N-bromosuccinimide (NBS) as brominating agent, product ratio dramatically changed depending on reaction temperature. While the ratio of 5-bromo and 4-bromo was 86:9 at 80 ºC (entry 4), it was 39:54 at -15 ºC (entry 5). When using CCl_4 as a solvent, we obtained the same results (entrys 6 and 7).

The reaction of 5-bromo-2-furfural synthesized in a high yield of 88.1 % occurred easily at 40 ºC within 3 h of nearly completed conversion of substrate by employing $[bmim]Br_3$ as a brominating agent (entry 8).

After the reaction was completed and work-up carried out as described above, the ionic liquid [Bmim]Br could be reused without any loss of original activity after washed with ether and dried at vacuum. Even after five times usage, there was observed little change in the numerical values as to the yield (Table-2).

TABLE-2
EFFICACY OF RECYCLED $[Bmim]Br_3$ [a]

$[Bmim]Br + Br_2 \xrightarrow{2h,r.t} [Bmim]Br_3$

Entry	Conversion (%)	Yield (%)	Isomer proportion (%)[b]	
			5-Bromid	4-Bromid
1	96.6	88.3	94.8	5.2
2	97.3	85.8	93.5	6.5
3	95.7	86.9	93.9	6.1
4	95.6	85.7	94.3	5.7
5	96.4	86.5	94.7	5.3

[a]All reaction conditions were the same as those given in Table-1; [b]Final product composition determined by HPLC, calculated from HPLC peak areas

Conclusion

The bromination of 2-furfural with $[Bmim]Br_3$, could occur rapidly under solvent-free conditions at 40 ºC and completed within 3 h with high yield. 1-Butyl-3-methylimidazolium tribromide ($[Bmim]Br_3$), is an important alternative to the use of traditional brominating agents for its simplicity, high selectivity, high reactivity and environmentally more benign.

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