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Regioselective side-chain as well as nuclear monobromination of aromatic substrates with *N*-bromosuccinimide using phosphotungstic acid supported on zirconia as a heterogeneous catalyst

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Abstract

Regioselective monobromination of aromatic substrates with *N*-bromosuccinimide has been achieved in excellent isolated yields (84–98%) using phosphotungstic acid supported on zirconia as a novel heterogeneous catalyst. The catalyst has been characterized by means of X-ray diffraction (XRD), scanning electron microscopy (SEM), surface area and acidity measurements. Remarkably, the new catalyst system described brought about the side-chain bromination of aromatics to afford bromomethyl arenes in excellent yields (86–98%) without the need for a radical initiator. Recovery and recylability of the catalyst have been well established.

Keywords: Bromination; *N*-Bromosuccinimide; Phosphotungstic acid; Zirconia; Regioselective

1. Introduction

Brominated arenes are versatile intermediates in the synthesis of a wide variety of biologically active compounds [1]. They are widely used for the preparation of products of commercial importance such as pharmaceuticals, agrochemicals, synthetic colorants and performance chemicals. A popular and inexpensive reagent often used for aromatic bromination is *N*-bromosuccinimide (NBS) in CCl_4 [2]. A variety of methods for bromination of aromatics with NBS have been reported in the literature ranging from NBS-H_2SO_4 [3], NBS-SiO_2 [4], NBS-*p*TSA [5], NBS-amberlyst [6], NBS-NaOH [7], and NBS-HBF_4/Et_2O [8]. In recent times, we have reported the use of NBS-HZSM-5 [9], NBS-ultrasound [10] and NBS-ionic liquid [11] for this methodology. In continuation, this paper reports for the first time, regioselective high yielding nuclear and more particularly side-chain bromination of activated aromatic substrates with NBS in the presence of phosphotungstic acid impregnated on zirconia (PTZ) as a new heterogeneous catalyst using methanol as solvent (Scheme 1).

2. Experimental

2.1. Materials and equipment

All the chemicals, reagents and solvents were of LR grade procured from Merck and Lancaster, and used as such.

Infra-red spectra were recorded with ATI MATT-SON RS-1 FTIR spectrometer. Proton NMR spectra were recorded on Bruker AC-200 machine in $CDCl_3$ with TMS as an internal standard. Mass spectra were obtained with Finnigen MAT mass spectrometer. The diffractogram of X-ray powder diffraction pattern was recorded on a Rigaku diffractometer model D/max. IIIVC with N-filtered Cu Kα radiation. Determination of surface area was carried out by Brunner–Emmett–Teller (BET) N_2 adsorption using a Omnisorp 100CX apparatus.

2.2. Synthesis of the catalyst

2.2.1. Synthesis of zirconium hydroxide, $Zr(OH)_4$

Aqueous ammonia (28%) (100 ml) was added dropwise into a clear solution of zirconyl oxy chloride ($ZrOCl_2\cdot 8H_2O$) (100 g) dissolved in distilled water (1000 ml). The white precipitate (pH 10) was stirred at room temperature for 2 h. The precipitate was filtered and washed with distilled water

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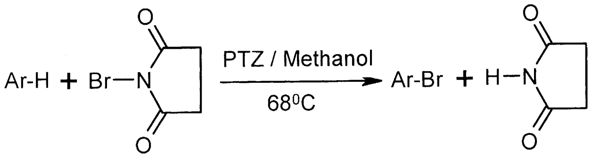

Scheme 1.

until chloride free (silver nitrate test). The solid was dried at 100 °C under static air for 12 h to obtain 40 g of pure and amorphous zirconium hydroxide (surface area 140 m^2/g).

2.2.2. *Synthesis of PTZ catalyst*

Methanolic solutions of 5, 10, 12 and 15% by weight of phosphotungstic acid (PTA) calculated with respect to zirconium hydroxide were prepared in which 1 wt.% of concentrated phosphoric acid was added. To this mixture dried zirconium hydroxide powder was added, keeping methanol:zirconium hydroxide ratio 10:1 and stirred for 1 h. Methanol was evaporated under reduced pressure and the resulting powder was dried at 120 °C for 12 h to afford the PTZ catalyst for the bromination reaction. The catalyst was activated by calcinating at 750 °C for 4 h.

2.3. *A typical procedure for bromination*

A mixture of aromatic substrate (0.018 mol), NBS (0.018 mol) and PTZ (5% (w/w)) in methanol (10 ml) was refluxed for 2 h under vigorous stirring. The completion of the reaction was followed by TLC using petroleum ether: ethyl acetate (10:1) as eluent. The reaction mixture was filtered to recover the PTZ catalyst. The catalyst was washed with methanol and dried at 100 °C for 2 h. The dried catalyst could be reused at least three times without loss of activity.

The filtrate was subjected to distillation under reduced pressure to remove methanol. The residue was diluted with water (10 ml). The mixture was then extracted with ethyl acetate (2 × 10 ml). The combined organic layer was separated, dried over anhydrous sodium sulphate and the ethyl acetate was distilled off to afford the TLC pure bromoarenes in almost all the cases except for catechol and hydraquinone. For catechol and hydroquinone, the pure products were isolated by column chromatogarphy.

3. Results and discussion

Sulphated metal oxides constitute super acidic catalytic systems. Hetero-polyacids are highly crystalline solids with large surface areas and possessing strong acid properties in solid phase and solution. The present catalytic system (PTZ) was generated by a combination of the two by supporting phosphotungstic acid on amorphous zirconium hydroxide in the presence of phosphoric acid by the wetness impregnation technique.

Table 1
Surface area of PTZ catalyst with different PTA loading

PTA loading (%)	Surface area (m^2/g)
0	32
5	65
10	78
12	91
15	84

PTZ catalyst with 5, 10, 12 and 15 wt.% loading of phosphotungstic acid on zirconia were prepared and characterized.

3.1. *Characterization of the catalyst*

3.1.1. *Surface area measurements*

The samples were activated at 573 K for 3 h in high vacuum (10^{-5} mm). After the treatment, the anhydrous weights of the samples were recorded. The samples were then cooled to 77 K in liquid nitrogen and allowed to adsorb nitrogen gas. Table 1 shows the BET surface area of PTZ series catalysts. First entry, i.e. simple zirconia calcined at 750 °C showed a surface area of 32 m^2/g. At 12% loading of PTA, the surface area increased by almost three times and was found to reach a maximum area of 91 m^2/g. This particular PTZ catalyst with 12% loading of PTA afforded the optimum results for the bromination reaction.

3.1.2. *X-ray diffraction (XRD)*

The X-ray diffraction (XRD) patterns of PTZ catalysts with different PTA loading calcined at different temperatures are shown in Figs. 1–3. The patterns were recorded in the region, 10–80° 2θ at a scanning rate of 4° min^{-1}. All the

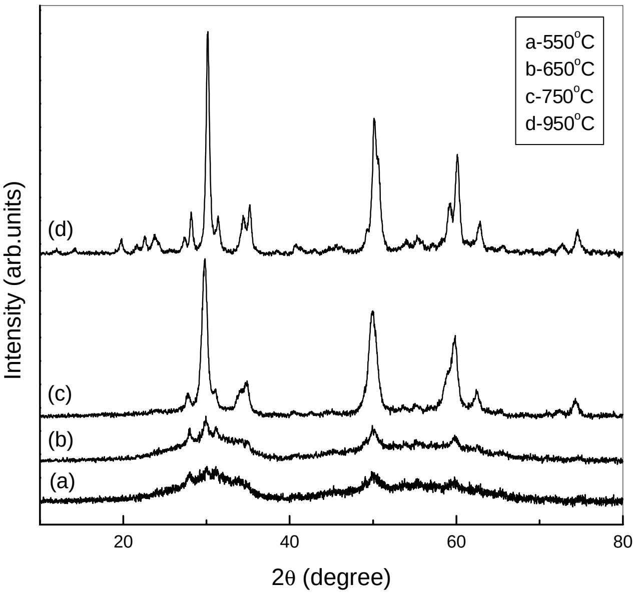

Fig. 1. Five percent PTA loading.

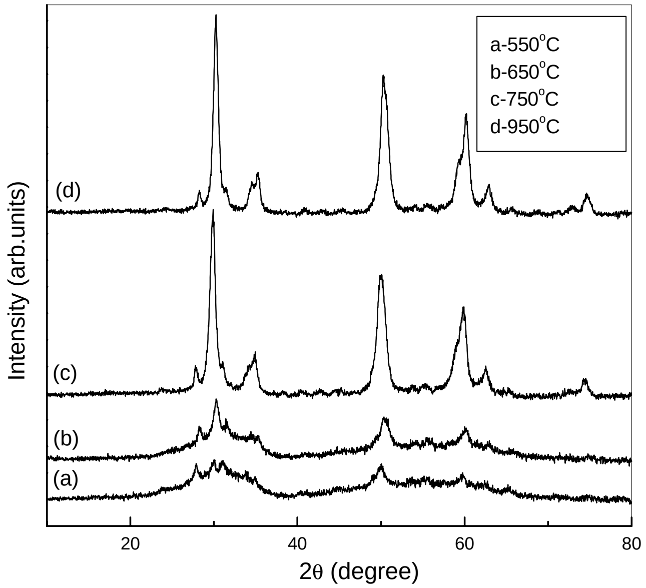

Fig. 2. 12% PTA loading.

peak positions were corrected with respect to silicon ($2\theta = 28.4^\circ$), which was used as internal standard. In all the cases the crystallization of zirconia was complete when the calcination temperature was 750 °C and almost pure tetragonal phase resulted as indicated by the peak at $2\theta = 30^\circ$. When the calcination temperature was 950 °C, monoclinic phase begins to appear but in a very low percentage.

There is no indication of crystalline phase related to bulk PTA which comes as a very strong peak at $2\theta = 10^\circ$ and small peaks at $2\theta = 15$, 17 and 22° even at a PTA loading of 15%. The reason may be that PTA particles are too small and/or too well dispersed on zirconia surface, which may be undetectable by XRD. It is well documented that the XRD pattern of PTA impregnated on freshly prepared SiO_2 and calcined at 400 °C showed characteristic peaks of PTA [12]. Hence, it can be concluded that PTA is well dispersed on zirconia surface. Moreover, PTA may have strong interaction with zirconia on the surface. Small peaks of monoclinic WO_3 were observed in 12% sample activated at 950 °C. These may be due to the breaking up of Keggin hetero-polyanion. From the calcination temperature required for crystallization of zirconia, it can be concluded that PTA and phosphoric acid help to stabilize the catalytically active tetragonal phase of zirconia and also it retard the formation of monoclinic phase.

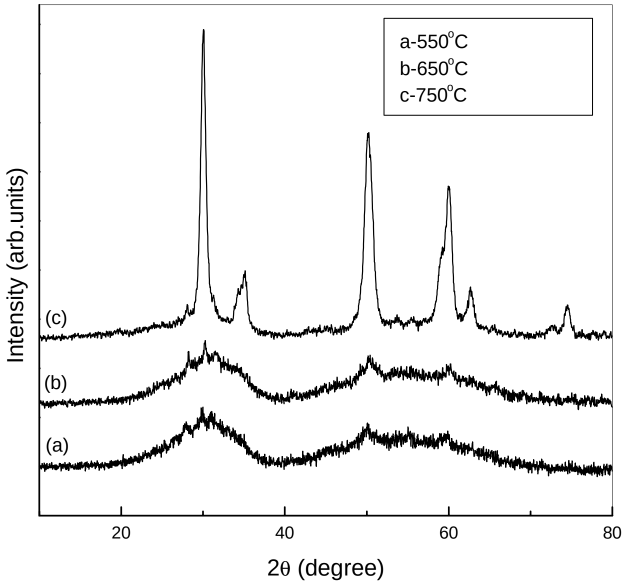

Fig. 3. 15% PTA loading.

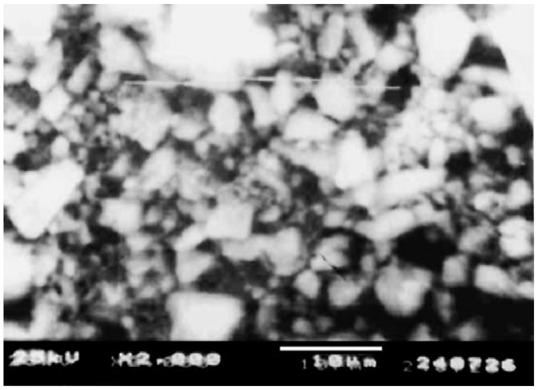

Fig. 4. SEM image of ZrO_2 calcined at 750 °C.

3.1.3. Scanning electron microscopy

Fig. 4 shows the scanning electron microscopic (SEM) image of zirconia calcined at 750 °C. It shows crystalline particles having average size of 10 nm of monoclinic zirconia. The PTA impregnated sample calcined at 750 °C resulted in some voids in the structure morphology (Fig. 5). The tetragonal zirconia (confirmed by XRD) has been seen as particles of 10 nm. These voids may have resulted from the phosphation and dehydration of PTA at high calcination temperature.

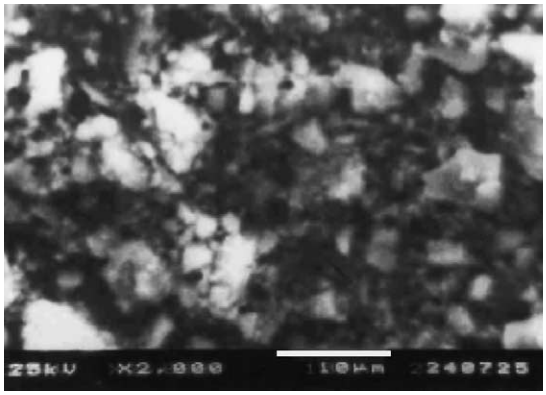

Fig. 5. SEM image of 12% PTZ.

Table 2
Bromination of toluene and anisole using PTZ with different loadings of PTA

Catalyst	Substrate	Product	Time (h)	Yield[a] (%)
5% PTA	Toluene	Benzyl bromide	9	97
	Anisole	4-Bromoanisole	10	96
10% PTA	Toluene	Benzyl bromide	6	97
	Anisole	4-Bromoanisole	8	96
12%PTA	Toluene	Benzyl bromide	1.3	98
	Anisole	4-Bromoanisole	1.5	97
15% PTA	Toluene	Benzyl bromide	3.5	98
	Anisole	4-Bromoanisole	5	98

[a] Isolated yields.

3.1.4. Acidity

The acidity of catalyst was measured using the reported Hammet indicator method [13,14]. This was carried out by exposing a slurry of catalyst (100 mg) in benzene (10 ml) to a dilute solution of anthraquinone in benzene (1% (w/v)), the latter being the Hammett indicator. A colour change from colourless to yellow was observed. It can be concluded that the acidity of the catalyst has an approximate pK_a value of -8.2.

3.2. Bromination reaction

The catalysts with different loadings of PTZ were tested by performing the side-chain bromination of toluene and nuclear bromination of anisole, respectively with NBS. The reactions were taken to completion as monitored by TLC. The time for complete conversion and isolated yields of the bromoarenes are recorded in Table 2.

It can be observed that the PTZ catalyst with 12% PTA loading afforded the best results. It may also be noted that this is the catalyst which exhibited the maximum surface area.

Consequently, a variety of activated aromatic substrates were reacted with NBS in the presence of PTZ with 12 wt.% loading of PTA. The time for complete conversion and the isolated yields of the bromoarenes are recorded in Table 3. As is evident, the monobromoarenes were obtained in excellent isolated yields. All the bromoarenes isolated are known compounds reported in literature. Their identities were confirmed by IR, ^{1}H NMR and mass spectral analyses. Their melting points agreed with those reported in literature. The efficiency of the catalyst system is clearly demonstrated as can be seen from Table 3, wherein the yields for the catalyzed reaction is significantly higher in comparison to the uncatalyzed one. Benzene, naphthalene, thiophene and chlorobenzene failed to undergo bromination under the reaction conditions. The catalyst PTZ was recovered by a simple filtration, and after drying at 100 °C for 2 h could be recycled at least three times without loss of activity (Table 4). In all the recycle batches, the catalyst could be recovered completely without any loss in weight.

It was remarkable to observe that the present catalyst system promoted the regiospecific side-chain bromination.of a variety of aromatic substrates (entries 1–7) to afford the respective bromomethyl arenes in excellent isolated yields without the need for the addition of a radical initiator. Normally, the side-chain bromination of such substrates with NBS require the use of a radical initiator such as benzoyl peroxide. In all these cases, only the monobrominated product could be obtained even if a 2–3 molar excess of NBS

Table 3
PTZ catalyzed bromination of aromatic substrates with NBS

Entry	Substrate	Product	Time (h)	Yield[a] (%)	
				Catalyst	No catalyst
1	Toluene	Benzyl bromide	1.3	98	10
2	*o*-Xylene	2-Bromomethyltoluene	1.5	89	41
3	*m*-Xylene	3-Bromomethyltoluene	1.5	87	11
4	1-Methylnapthalene	1-Bromomethylnapthalene	2.0	86[b]	13
5	BHT[c]	4-Bromo BHT	2.0	98	8
6	4-Tolualdehyde	4-Bromomethylbenzaldehyde	2.0	92	10
7	Acetophenone	2-Bromo-1-phenyl-ethanone	2.0	93	14
8	Anisole	4-Bromoanisole	1.5	98	28
9	*m*-Cresol	4-Bromo-3-methyl phenol	2.0	92	31
10	Catechol	4-Bromo catechol	2.0	86[d]	33
11	Hydroquinone	2-Bromo-4-hydroxy phenol	2.0	87[d]	23
12	2,6-Dimethyl aniline	4-Bromo-2,6-dimethyl aniline	2.0	84	30
13	2-Methyl anisole	4-Bromo-2-methylanisole	2.0	87	14
14	1-Napthol	4-Bromo-1-hydroxynapthalene	2.0	95	27
15	2-Napthol	1-Bromo-2-hydroxynapthalene	2.0	94	23
16	2-Methoxy naphthalene	1-Bromo-2-methoxynapthalene	2.0	96	57

[a] Isolated yields unless indicated otherwise.
[b] Estimated by GC analysis.
[c] 2,6-di-*tert*-Butyl-4-methyl-phenol.
[d] Isolated yields after column chromatography.

Table 4
Bromination of toluene and anisole with recovered PTZ catalyst[a]

Entry	Substrate	Product	Time (h)	Yield[b] (%)		
				Recycle I	Recycle II	Recycle III
1	Toluene	Benzyl bromide	1.3	98	97	97
2	Anisole	4-Bromoanisole	1.5	98	97	97

[a] In all recycle batches, the catalyst recovery was 100%.
[b] Isolated yields.

was employed in the reaction. All other substrates (entries 8–16) underwent nuclear bromination to afford the corresponding bromoarenes in high regioselectivity and excellent isolated yields.

Interestingly, there was no reaction when toluene was brominated under the reaction conditions in the presence of a radical quencher such as α,α-azobisiso-butyronitrile (AIBN). Further work is in progress to ascertain the mechanistic pathways for the brominations using this new catalyst system.

4. Conclusion

In conclusion, the present study demonstrates the efficacy of a new heterogeneous catalyst system consisting of phosphotungstic acid supported on zirconia exercising a unique regioselectivity in the side-chain as well as nuclear bromination of activated aromatics. Remarkably, the formation of bromomethyl arenes in excellent yields for a variety of substrates adds to the synthetic potential of the method. The recyclability of the catalyst and the easy work up procedure makes this an environmentally safer methodology amenable for scale-up operations.

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