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An efficient, rapid and regioselective nuclear bromination of aromatics and heteroaromatics with NBS using sulfonic-acid-functionalized silica as a heterogeneous recyclable catalyst☆

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Abstract—A simple, efficient and rapid method has been developed for high-yielding regioselective nuclear monobromination of aromatic and heteroaromatic compounds using NBS in the presence of sulfonic-acid-functionalized silica at room temperature. The catalyst works under heterogeneous conditions and can be recycled.

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The bromination of aromatic and heteroaromatic compounds is an important reaction in synthetic organic chemistry.[1] Brominated arenes and heteroarenes are useful as pharmaceuticals, agrochemicals, flame retardants and specialty chemicals.[2] Several aryl and heteroaryl bromides are potential antitumour, antibacterial and antioxidant agents.[3] They are also capable of undergoing C–C bond formation via transmetalation reactions such as Heck, Stille and Suzuki reactions.[4] The direct bromination of aromatic and heteroaromatic compounds using bromine generates toxic and corrosive HBr, which causes environmental pollution.[5] The reaction is also generally unselective forming mixtures of mono and polybrominated products. A variety of brominating agents such as tetrabromocyclohexadienone,[6a] tetraalkylammonium tribromide,[6b] NBS along with a supporter or a catalyst,[6c] DBU hydrobromide perbromide,[6g] hexamethylenetetramine tribromide,[6h] Me_2SBr_2,[6i] $KBr–NaBO_3·4H_2O$,[6j] $HBr–H_2O_2$,[6k] $HBr–O_2–NaNO_2$[6l] and RBr–NaH in DMSO[6m] have been developed for the monobromination of aromatic and heteroaromatic compounds. However, in terms of ease of handling and availability, NBS is a superior brominating agent. Earlier methods involving the utilization of NBS are associated with several drawbacks including long reaction times ($NBS–SiO_2$),[6c] high temperatures (NBS–TBAB and NBS–HZSM-5)[6d,e] and a complex experimental procedure ($NBS–HBF_4·Et_2O$).[6f] Thus it is desirable to develop suitable convenient methods to utilize NBS efficiently for nuclear bromination of aromatic and heteroaromatic compounds under mild reaction conditions.

In continuation of our work[7] on the application of heterogeneous catalysts for the development of useful synthetic methodologies we have now shown that activated arenes can easily be brominated with NBS in the presence of sulfonic-acid-functionalized silica (Fig. 1) at room temperature.[8]

Initially we attempted the bromination of *p*-cresol with NBS using various heterogeneous catalysts (Table 1). The bromination required 15 h (yield 78%) in the presence of only silica gel.[6c] NBS in the presence of $H_2SO_4·SiO_2$ or $HClO_4·SiO_2$ was found to complete the bromin-

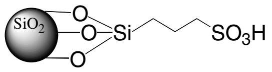

Figure 1. Sulfonic-acid-functionalized silica.

Keywords: Aromatic and heteroaromatic compounds; Nuclear bromination; NBS; Sulfonic-acid-functionalized silica; Regioselectivity; Heterogeneous recyclable catalyst.

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Table 1. Catalyst screen[a]

Entry	Catalyst	Time	Product	Isolated yield (%)
a	Silica gel	15 h	2-Bromo-*p*-cresol	78
b	Silica chloride	4 h	2-Bromo-*p*-cresol	89
c	$NaHSO_4{\cdot}SiO_2$	3 h	2-Bromo-*p*-cresol	91
d	$H_2SO_4{\cdot}SiO_2$	10 min	2-Bromo-*p*-cresol	70
			2,6-dibromo-*p*-cresol	14
e	$ClSO_3H{\cdot}SiO_2$ (wet)	30 min	2-Bromo-*p*-cresol	87
f	PTSA·SiO_2	20 min	2-Bromo-*p*-cresol	72
			2,6-Dibromo-*p*-cresol	13
g	Sulfonic-acid-functionalized silica	10 min	2-Bromo-*p*-cresol	99
h	Amberlyst-15	2.5 h	2-Bromo-*p*-cresol	89
i	Sulfated Zirconia	15 min	2-Bromo-*p*-cresol	61
			2,6-Dibromo-*p*-cresol	17
j	$HClO_4{\cdot}SiO_2$	10 min	2-Bromo-*p*-cresol	52
			2,6-Dibromo-*p*-cresol	23

[a] All reactions were performed using *p*-cresol (1 mmol) and different catalysts (50 mg in each case) in $CH_3CN–Et_2O$ (1:3) (5 mL) at room temperature.

ation of *p*-cresol in 10 min, but a mixture of mono and dibrominated products was obtained. Considering the reaction time (10 min) and yield of monobrominated product (99%), sulfonic-acid-functionalized silica was found to be the best catalyst. It was subsequently utilized for bromination of various aromatics with NBS. A series of phenols, alkoxy arenes and anilines were converted into the corresponding monobromo compounds in high yields and in short reaction times (Table 2). Most of the anilines underwent the conversion immediately.

The present conversion is highly regioselective. Activated arenes showed *para*-selectivity in the formation of the corresponding monobromo compounds. However, when the *para*-position of a substrate was blocked with a substituent the *ortho*-brominated product was obtained.

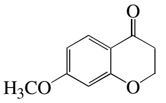
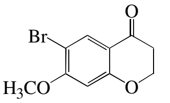
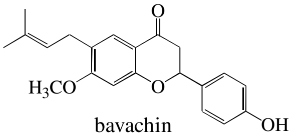
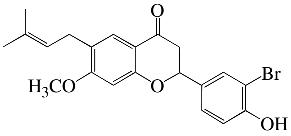
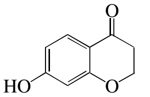
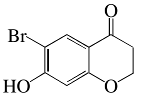
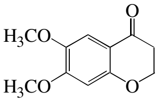
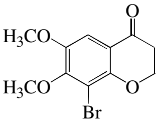
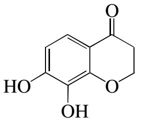
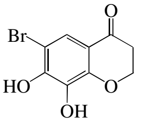
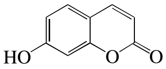
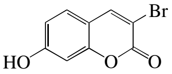
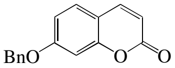
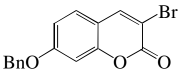
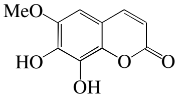
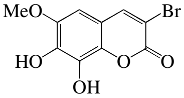
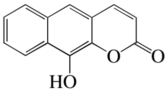
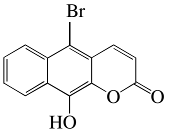
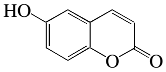
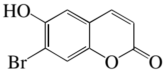
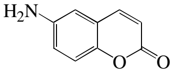
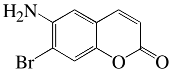
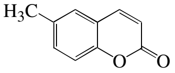
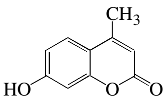
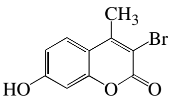
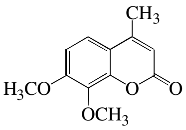
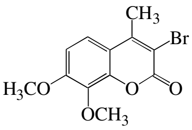
The present method is also suitable for the selective bromination of heteroaromatic compounds, such as chromanones, flavanoids and coumarins (Table 3). Some of these compounds (such as bavachin, fraxetin and oxyanin-B; Table 3, entries b, h and q, respectively) are naturally occurring. Several brominated derivatives of these compounds are known to possess various biological properties.[9] 4-Chromanones and flavanoids underwent bromination at the *ortho*/*para*-positions with respect to the hydroxyl and alkoxy groups. However,

Table 2. Bromination of aromatic compounds using sulfonic-acid-functionalized silica[a]

Entry	Substrate **1**	Time (min)	Product **2**	Isolated yield (%)
a	Aniline	30	4-Bromoaniline	89
b	4-Bromoaniline	1.0	2,4-Dibromoaniline	98
c	*N*,*N*-Dimethylaniline	1.0	4-Bromo-*N*,*N*-dimethylaniline	99
d	*o*-Toluidine	5.0	4-Bromo-*o*-toluidine	98
e	*p*-Toluidine	1.0	2-Bromo-*p*-toluidine	99
f	2-Nitroaniline	180	4-Bromo-2-nitroaniline	91
g	4-Nitroaniline	180	2-Bromo-4-nitroaniline	94
h	4-Chloroaniline	2.0	2-Bromo-4-chloroaniline	98
i	4-*N*,*N*-Dimethylaminobenzaldehyde	1.0	3-Bromo-4-*N*,*N*-dimethylaminobenzaldehyde	98
j	2-Aminoacetophenone	30	2-Amino-5-bromoacetophenone	86
k	2-Aminobenzophenone	30	2-Amino-5-bromobenzophenone	83
l	2-Naphthylamine	1.0	1-Bromo-2-naphthylamine	99
m	1-Naphthylamine	5.0	2-Bromo-1-naphthylamine	92
n	Phenol	30	4-Bromophenol	83
o	*o*-Cresol	10	4-Bromo-*o*-cresol	98
p	*m*-Cresol	15	4-Bromo-*m*-cresol	
q	*p*-Cresol	10	2-Bromo-*p*-cresol	99
r	Anisole	45	4-Bromoanisole	98
s	Salicylaldehyde	95	5-Bromo salicylaldehyde	87
t	Vanillin	180	5-Bromovanillin	73
u	2-Hydroxyacetophenone	120	5-Bromo-2-hydroxyacetophenone	80
v	2,4-Dihydroxyacetophenone	30	5-Bromo-2,4-dihydroxyacetophenone	71
w	4-Methoxyacetophenone	180	3-Bromo-4-methoxy acetophenone	75
x	2-Naphthol	1.0	1-Bromo-2-naphthol	99
y	1-Naphthol	5.0	2-Bromo-1-naphthol	89

[a] The structures of the products were determined from spectral (^1H and ^{13}C NMR and MS) and elemental analysis data.

Table 3. Bromination of heteroaromatic compounds using sulfonic-acid-functionalized silica[a]

Entry	Substrate **3**	Time (h)	Product **4**	Isolated yield (%)
a		0.1		95
b		0.25		69
c		0.25		67
d		1.0		85
e		1.75[b]		73
f		2.0[b]		75
g		0.5		98
h	 fraxetin	2.0[b]		70
i		0.5		97
j		2.0		73
k		2.0		76
l		5.0	No reaction	
m		1.5		93
n		3.0		89

(*continued on next page*)

Table 3 (*continued*)

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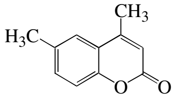
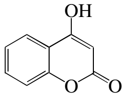
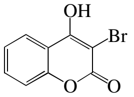
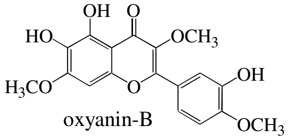
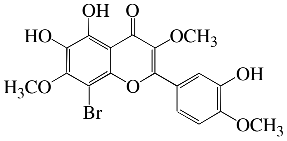
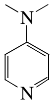
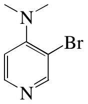
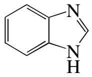
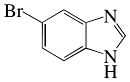
o		5.0	No reaction	
p		2.0		78
q	 oxyanin-B	3.0[b]		72
r		0.5		91
s		3.0		77

[a] The structures of the products were determined from spectral (^{1}H and ^{13}C NMR and MS) and elemental analysis data.

[b] $CH_3OH–CH_3CN$ (1:3) was used as a solvent.

with coumarins, the bromination occurred mainly at C-3. Nitrogen heterocycles, DMAP (Table 3, entry r) and benzimidazole (entry s) also afforded monobromo products in high yields. The structures of products were settled from their spectral (^{1}H and ^{13}C NMR and MS) and elemental analysis data.[8]

Sulfonic-acid-functionalized silica[10] acts as an organic–inorganic hybrid (interphase) catalyst wherein a Brønsted acid site has been selectively created. It works under heterogeneous conditions but its reaction centres are highly mobile, as in a homogeneous catalyst. The catalyst was prepared[10b] by immobilization of propyl thiol on silica using 3-mercaptopropyltrimethoxysilane followed by the selective oxidation of the thiol groups by aqueous H_2O_2 to the sulfonic acid groups. It was recycled consecutively three times without the loss of its activity.

In conclusion, we have developed an efficient and versatile method for the nuclear monobromination of aromatics and some heteroaromatics using NBS in the presence of sulfonic-acid-functionalized silica as a heterogeneous catalyst. The method is highly regioselective offering potential in various synthetic applications. The mild reaction conditions, simple experimental procedure, rapid conversion, excellent yields and reusability of the catalyst are notable advantages of the method.

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References and notes

1. Larock, J. R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Protection*; Wiley-VCH: New York, 1997.
2. Taylor, R. *Electrophilic Aromatic Substitution*; Wiley: New York, 1990.
3. Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937–1944.
4. *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998.
5. De la Mare, P. B. *Electrophilic Halogenation*; Cambridge University Press: Cambridge, 1997; Chapter 5.
6. (a) Cram, D. J.; Dicker, I. B.; Lauer, M.; Knobler, C. B.; Trueblood, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7150–7167; (b) Kajigaeshi, S.; Kakinami, T.; Okamoto, T.; Nakamura, H.; Fujikawa, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4187–4189; (c) Konishi, H.; Aritomi, K.; Okano, T.; Kiji, J. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 591–593; (d) Ganguly, N. C.; De, P.; Dutta, S. *Synthesis* **2005**, 1103–1105; (e) Paul, V.; Sudalai, A.; Daniel, T.; Srinivasan, K. V. *Tetrahedron Lett.* **1994**, *35*, 7055–7056; (f) Oberhauser, T. *J. Org. Chem.* **1997**, *62*, 4504–4506; (g) Muathen, H. A. *J. Org. Chem.* **1992**, *57*, 2740–2741; (h) Bisarya, S. C.; Rao, R. *Synth. Commun.* **1993**, *23*, 779–788; (i) Majetich, G.; Hicks, R.; Reister, S. *J. Org. Chem.* **1997**, *62*, 4321–4326; (j) Roche, D.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2000**, *41*, 2083–2085; (k) Vyas, P. V.; Bhatt, A. K.; Ramachandraiah, G.; Bedekar, A. V. *Tetrahedron Lett.* **2003**, *44*, 4085–4088; (l) Zhang, G.; Liu, R.; Xu, Q.; Ma, L.; Liang, X. *Adv. Synth. Catal.* **2006**, *348*, 862–866; (m) Guo, M.; Varady, L.; Fokas, D.; Baldino, C.; Yu, L. *Tetrahedron Lett.* **2006**, *47*, 3889–3892.
7. (a) Das, B.; Ramu, R.; Ravikanth, B.; Reddy, K. R. *Tetrahedron Lett.* **2006**, *47*, 779–782; (b) Das, B.; Thirupathi, P.; Mahender, I.; Reddy, V. S.; Rao, Y. K. *J. Mol. Catal. A: Chem.* **2006**, *247*, 233–239; (c) Das, B.; Ravi-

kanth, B.; Ramu, R.; Rao, B. V. *Chem. Pharm. Bull.* **2006**, *54*, 1044–1045; (d) Das, B.; Reddy, K. R.; Thirupathi, P. *Tetrahedron Lett.* **2006**, *47*, 5855–5857.

8. General experimental procedure: To a mixture of an arene/heteroarene (1 mmol) and sulfonic-acid-functionalized silica (15 mg) in CH_3CN–Et_2O (1:3) (5 mL) NBS (1.05 mmol) was added. The mixture was stirred at room temperature and the reaction was followed by TLC. After completion, the mixture was filtered. The catalyst was washed with $CHCl_3$ (2 × 5 mL), EtOH (2 × 5 mL) and Et_2O (2 × 5 mL) and subsequently dried at 80 °C for reuse. The filtrate was concentrated and the residue was subjected to column chromatography (silica gel, hexane–EtOAc) to obtain pure brominated arene/heteroarene.

   The recovered catalyst was used three more times for the bromination of *p*-cresol following the above procedure for 10 min in each case to furnish the corresponding brominated product with yields of 98%, 96% and 95%.

   The spectral (^{1}H and ^{13}C NMR and MS) and elemental analysis data of some representative heterocycles are given below:

   6-Bromo-7-methoxychroman-4-one **4a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.02 (1H, s), 6.42 (1H, s), 4.51 (2H, t, $J = 7.0$ Hz), 3.94 (3H, s), 2.72 (2H, t, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 189.4, 163.5, 162.2, 131.8, 116.1, 106.3, 100.8, 68.2, 56.8, 32.3; EIMS: *m/z* 258, 256 [$M^{+\cdot}$]. Anal. Calcd for $C_{10}H_9BrO_3$: C, 46.69; H, 3.50. Found: C, 46.61; H, 3.56.

   3-Bromo-7-hydroxy-4-methylcoumarin **4m**: ^{1}H NMR (200 MHz, $CDCl_3 + DMSO\text{-}d_6$): δ 10.21 (1H, br s), 7.48 (1H, dd, $J = 8.0$, 2.0 Hz), 6.78 (1H, dd, $J = 8.0$, 2.0 Hz), 6.78 (1H, d, $J = 2.0$ Hz), 2.58 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3 + DMSO\text{-}d_6$): δ 161.8, 156.7, 153.2, 150.8, 125.6, 114.2, 112.3, 107.5, 102.2, 19.4; EIMS: *m/z* 256, 254 [$M^{+\cdot}$]. Anal. Calcd for $C_{10}H_7BrO_3$: C, 47.06; H, 2.75. Found: C, 47.14; H, 2.71.

   8-Bromo-3′,5,6-trihydroxy-3,4′,7-trimethoxyflavone **4q**: ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): δ 12.80 (1H, br s), 8.84–8.65 (2H, br s), 7.86 (1H, d, $J = 2.0$ Hz), 7.78 (1H, dd, $J = 8.0$, 2.0 Hz), 6.98 (1H, d, $J = 8.0$ Hz), 4.05 (3H, s), 3.88 (3H, s), 3.82 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3 + CD_3OD$): δ 178.8, 157.2, 156.4, 152.2, 148.5, 148.1, 144.5, 138.2, 136.5, 122.0, 121.7, 115.4, 115.0, 108.2, 93.4, 61.5, 60.8, 59.6; EIMS: *m/z* 440, 438 [$M^{+\cdot}$]. Anal. Calcd for $C_{18}H_{15}BrO_8$: C, 49.20; H, 3.42. Found: C, 49.26; H, 3.38.

9. Bovicelli, P.; Bernini, R.; Antonioletti, R.; Mincione, E. *Tetrahedron Lett.* **2002**, *43*, 5563–5567.
10. (a) Shylesh, A.; Sharma, S.; Mirajkar, S. P.; Sing, A. P. *J. Mol. Catal. A: Chem.* **2004**, *212*, 219–228; (b) Karimi, B.; Khalkhali, M. *J. Mol. Catal. A: Chem.* **2005**, *232*, 113–117.