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Ball-Milling Promoted Monobromination Reactions: One-pot Regioselective Synthesis of Aryl Bromides and α-Bromoketones by NBS and Recyclable MCM-41-SO_3H at Room Temperature

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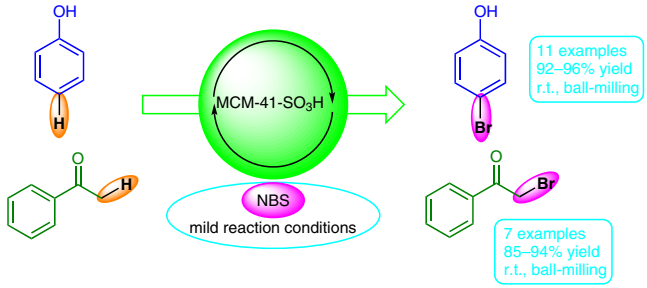

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Abstract An effective approach to monobromination reactions utilizing room temperature ball-milling is introduced for the synthesis of aryl bromides and bromoketones with *N*-bromosuccinimide (NBS) and MCM-41-SO_3H. Advantages of this technique are short reaction times and high regioselectivity. In contrast to other techniques using microwaves, ultrasound, or ionic liquids, handling of sensitive materials is possible and furthermore, this method has advantages over other solvent-free techniques that require a higher reaction temperature for high yield of products.

Key words ball-mill, monobromination, regioselectivity, MCM-41-SO_3H, NBS

Halogenated compounds have diverse applications in various fields such as pharmaceuticals and agrochemicals.[1] Aromatic halides are the key fragments of coupling reactions such as Heck, Suzuki, Sonogashira, and hetero coupling reactions.[2–5]

For the synthesis of brominated aromatic compounds, Br_2 is the traditional reagent, but results in the production of HBr and procedures often require careful control of temperature and amount of Br_2. As a result, improved mild brominating agents have been developed,[6–13] but a fundamental disadvantage for many of these methods is unwanted oxidation of sensitive functional groups.

To eliminate such problems, NBS has been used for brominating aromatic compounds[14] and several reaction conditions in organic solvents have been reported to activate the halogenating ability of NBS.[15–17]

There are some reports that describe halogenations in the presence acidic catalyst, such as trihaloisocyanuric acid for halogenation of β-dicarbonyl compounds,[18a] sodium hypochlorite for the halogenation of β-dicarbonyl compounds,[18b] and NBS in the presence of acidic catalyst.[16]

It became clear to us that combining an acidic catalyst and NBS leads to more efficient bromination reactions. In addition, using heterogeneous acidic nanocatalysts can be advantageous over homogeneous catalysts as a result of their high surface area, recyclability and simplified work-up.

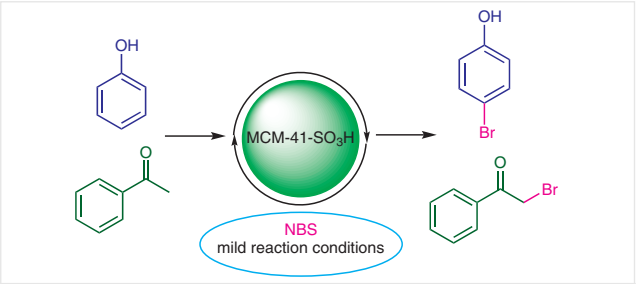
A specific example of a silica material with ordered structure, narrow pore-size distribution (1.5–10 nm) and very high surface area (more than 1500 $m^2\ g^{-1}$) that can be used as a heterogeneous nanocatalyst is MCM-41. Modification of its surface can result in a solid acid with high uniformity, modified by covalent anchoring of different organic moieties in a well-ordered mesoporous material. Thus, nanoparticulate MCM-41-SO_3H with covalently bound sulfonic acid was selected for investigation as a heterogeneous acidic nanocatalyst.

It has been said that 'the best solvent is no solvent', but to obtain high yields under solvent-free conditions frequently involves high temperatures that are not suitable for materials that are temperature sensitive such as terminal alkynes.[19]

One solution can be found in 'mechanochemistry',[20] which involves induction of a chemical reaction by the direct absorption of mechanical energy.[1] In mechanochemistry, mechanical energy in the solid state is used for bond breaking (as compared to microwave and sonication in which thermal activation is used for bond breaking).[21] Intramolecular bonds can be mechanically broken and this is then followed by further chemical reactions.[19,22] Mechanochemistry is now conducted using ball-mills under solvent-free conditions.[23–27] Ball-milling is an emerging field with

applications in the synthesis of metal complexes, the formation of metal–organic frameworks, the synthesis of catalysts, and the assembly of co-crystals between pharmacologically active compounds.[28–32] Examples of ball-milling applications in organic synthesis include C–H bond-functionalization, C–N coupling, and the formation of pyrazoles and indoles.[33,34]

In this study, ball-milling was examined for bromination reactions with NBS in the presence of MCM-41-SO_3H as a co-catalyst.[35] It was found that using NBS without any co-catalyst led to extended reaction times (Table 1), but reaction in the presence of MCM-41-SO_3H under ball-milling conditions afforded the corresponding brominated products of aryl alcohols in 1–10 min and ketones in 4–20 min in 85–96% product yields. In this manuscript, we thus present the mechanochemical monobromination of activated aromatic and aliphatic substrates as a novel protocol (Scheme 1).[34b,34c] In conclusion, we have developed an efficient technique for monobromination reaction, and, in comparison to other solvent-free techniques that require high temperature, this method is highly effective.



Scheme 1 Monobromination of aryl and aliphatic compounds

Bromination was examined using ball-milling (a Retsch Mixer Mill MM 400) with NBS with and without MCM-41-SO_3H and the results showed that the time required without MCM-41-SO_3H co-catalyst was twice as long as reaction with the presence of the MCM-41-SO_3H (Table 1). In the presence of NBS and MCM-41-SO_3H in ethanol, the desired products were obtained in 1 h, whereas in the presence of other co-catalysts, much longer times were required (Table 2, entries 3 and 5).

Table 1 Bromination Reaction with and without Co-catalyst[a]

Substrate	NBS	NBS and MCM-41-SO_3H
Naphthalen-2-ol	10 min, 75%	5 min, 95%
Acetophenone	30 min, 70%	15 min, 87%

[a] Ball-milling at room temperature.

To optimize the amount of catalyst, 0.01 g catalyst for each mmol of substrate was initially used, but starting material remained. When the amount of catalyst was increased to 0.02 g the yields of reaction were optimal. When the amount of catalyst was increased to 0.03 and 0.04 g, dibrominated products were produced. Various solvent systems were investigated, but the best yields were gained when ball-milling alone was used.

The vibrational frequency of the ball-milling device was 3–30 Hz, and the grinding jars were stainless steel with a volume of 10 mL. The size of the milling balls was 10 mm. Initial studies used a rotational frequency of 20 Hz at room temperature for a total of 11 minutes for bromination of 2-chlorophenol. Increasing the rotational frequency from 20 to 30 Hz led to increased product yield, along with a 10 minute decrease in the reaction time. The highest yield of 96% of 4-bromo-2-chlorophenol was obtained at a rotational frequency of 30 Hz within 1 minute (Table 3, entry 4).

Table 2 Comparison with Other Catalytic Systems[a]

Entry	Catalyst	Time	Solvent	Temp. (°C)	Yield (%)	Ref.
1	NH4Br-oxone	7 h	MeOH	r.t.	81	[36]
2	H_2O_2-HBr	3 h	H_2O	r.t.	60	[37]
3	NBS-pTSA	30 min	CH_3CN	80	46	[38]
4	HBr	10 h	DMSO	40	69	[39]
5	*p*-TsOH·H_2O-NBS	9 h	CH_3Cl	r.t.	92	[40]
6	MCM41-SO_3H	15 min	solvent free	r.t.	87	

[a] Bromination reaction of acetophenone.

A range of bromination reactions was investigated using this protocol and the results are shown in Table 3 and Table 4. All the substrates treated with 0.01 g of NBS and 0.02 g of MCM-41-SO_3H for each mmole of substrate at room temperature afforded the corresponding brominated products in high yield with high regioselectivity. Worthy of note, the reaction of NBS and benzaldehyde in the presence of 0.02 g MCM-41-SO_3H did not give the expected direction of substitution and 4-bromo benzaldehyde was obtained instead.[48–50]

Table 3 Bromination of Aromatic Compounds[a]

Entry	Substrates	Products	Time (min)	Yield (%)	Mp lit/found
1	phenol	4-bromophenol	1	96	65–66[41]/63–65
2	2,4-dichlorophenol	2-bromo-2,4-dichlorophenol	1	94	68[42]/68
3	benzaldehyde	4-bromobenzaldehyde	1	96	liquid
4	2-chlorophenol	4-bromo-2-chlorophenol	1	96	49–50[41]/50–53
5	2-nitrophenol	4-bromo-2-nitrophenol	2	92	91–93[41]/91–93
6	2-hydroxybenzaldehyde	4-bromo-2-hydroxybenzaldehyde	2	94	102–104[43]/103–104
7	resorcinol	2-bromo-1,3-diol	4	95	99–101[43]/98–101
8	naphthalen-1-ol	4-bromo-1-naphthol	4	93	44–46[44]/130–133
9	naphthalen-2-ol	1-bromo-2-naphthol	5	95	83–84[43]/81–83
10	2-bromo-4-chlorophenol	2,6-dibromo-4-chlorophenol	5	95	92[41]/32–33
11	2,5-dimethylphenol	4-bromo-2,5-dimethylphenol	10	94	86–88[41]/88–90

[a] All reactions were carried out in a ball-mill at r.t.

Table 4 α-Bromination of Carbonyl Compounds[a]

Entry	Substrates	Products	Time (min)	Yield (%)	Mp lit/found
1	methyl-3 oxobutanoate	methyl-2-bromo-3 oxobutanoate	4	93	liquid
2	ethyl-3 oxobutanoate	ethyl-2-bromo-3 oxobutanoate	5	94	liquid
3	cyclohexane-1,3-dione	2-bromo-cyclohexane-1,3-dione	8	90	159–161[45]/157–160
4	5,5-dimethylcyclohexane-1,3-dione	2-bromo-5,5-dimethylcyclohexane-1,3-dione	10	89	158–160[45]/160–162
5	acetophenone	2-bromoacetophenone	15	87	49–51[46]/48–50
6	4-nitro-acetophenone	2-bromo-1-(4-nitrophenyl)ethanone	15	88	95–98[36]/100–101
7	4-methyl-acetophenone	2-bromo-1-(4-methoxyphenyl)ethanone	20	85	69–70[47]/70–72

[a] All reactions were carried out in a ball-mill at r.t.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590959.

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(48) **Preparation of MCM-41-SO_3H:** Diethylamine (2.7 g) was added to deionized water (42 mL) at room temperature. The mixture was stirred for 10 min, then cetyltrimethylammonium bromide (1.47 g) was added and the mixture was stirred for 30 min until a clear solution was obtained. To this mixture, tetraethoxysilane (2.1 g) was added dropwise and the pH of the reaction mixture was maintained at 8.5 by adding hydrochloric acid solution (1 M). After 2 h, the solid product was filtered, washed with deionized water, dried at 45 °C for 12 h, and then calcined at 550 °C for 5 h
(49) **Preparation of MCM-41-SO_3H:** Dichloromethane (5 mL) containing MCM-41 (1.0 g) was added to a flask equipped with a pressure equilibrating dropping funnel charged with chlorosulfonic acid (2 mL) and equipped with a gas inlet tube. The chlorosulfonic acid was added dropwise over 30 min at room temperature and HCl gas generated was swept from the reaction vessel. The mixture was then stirred for 30 min and the solvent was evaporated to obtain MCM-41-SO_3H
(50) **General bromination experimental procedure:** Substrate (1 mmol), NBS (0.1 g) and MCM-41-SO_3H (0.2 g) were added to a ball-mill jar. Reaction was conducted at a rotational frequency of 30 Hz at room temperature and the reaction was followed by TLC. After completion, the mixture was separated and MCM-41-SO_3H was recovered. The recovered MCM-41-SO_3H was reused five more times without any decrease in its catalytic ability