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## Simple and Efficient System for the α-Bromination of a β-Ketoester by Using N-Bromosuccinimide in the Presence of Silica-Supported NaHCO<sub>3</sub> as the Heterogeneous Catalyst: An Environmentally Benevolent Approach

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# SIMPLE AND EFFICIENT SYSTEM FOR THE $\alpha$ -BROMINATION OF A $\beta$ -KETOESTER BY USING N-BROMOSUCCINIMIDE IN THE PRESENCE OF SILICA-SUPPORTED NaHCO<sub>3</sub> AS THE HETEROGENEOUS CATALYST: AN ENVIRONMENTALLY BENEVOLENT APPROACH

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#### **GRAPHICAL ABSTRACT**



**Abstract** Selective and efficient  $\alpha$ -bromination of  $\beta$ -ketoesters and cyclic and acyclic ketones is achieved by reaction with N-bromosuccinimide (NBS) catalyzed by silica-supported sodium bicarbonate (NaHCO<sub>3</sub> · SiO<sub>2</sub>) under mild reaction conditions and with short reaction times. With 100% selectivity with all substrates, after 45 min at room temperature  $(20 \pm 2 \,^{\circ} C)$ , conversions for ethylacetoacetate were 67% and for acetophenone, cyclohexanone, and cycloheptanone were 58, 50, and 55%, respectively. Acetyl acetone recorded 65% conversion with 100% selectivity. Although cyclopentanone and toluene had only 20% conversion, both reactions showed 100% selectivity toward  $\alpha$ -bromination. The catalysts exhibit activity and reusability.

Keywords Acyclic ketones;  $\alpha$ -bromination;  $\beta$ -ketoesters; NaHCO<sub>3</sub>-SiO<sub>2</sub> catalyst; NBS (N-bromosuccinimide)

#### INTRODUCTION

 $\alpha$ -Monobromination of  $\beta$ -ketoesters and carbonyl compounds is a significant transformation in organic synthesis as the  $\alpha$ -bromintaed products are frequently used as synthetic intermediates.<sup>[1,2]</sup>  $\alpha$ -Monobromination of  $\beta$ -ketoesters without  $\alpha$ -substituents has been a challenging problem, because the monosubstituted product

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is always accompanied by a small amount of disubstituted product. The majority of reagents include bromine,<sup>[3]</sup> copper(II) bromide,<sup>[4]</sup> and N-bromosuccinimide (NBS).<sup>[5]</sup> In the presence of protic and Lewis acids, bromine is generally used for α-bromination of carbonyl compounds.<sup>[1]</sup> In terms of accessibility and ease of handling, N-bromosuccinimide is economical and a better brominating reagent. The major advantage of the use of NBS is that the reaction by-product, succinimide, can be recovered effortlessly. With NBS,  $\alpha$ -bromination of ketones is well known to proceed via a radical process promoted by initiators such as azo-bis-isobutyronitrile (AIBN) and dibenzoyl peroxide (BPO) in refluxing CCl<sub>4</sub>.<sup>[6]</sup> The Lewis acid, Mg(ClO<sub>4</sub>)<sub>2</sub>, is employed to promote 2-halogenation of 1,3-dicarbonyl compounds.<sup>[7]</sup> Recently, the bromination of β-ketoesters using NBS catalyzed by NH<sub>4</sub>OAc.<sup>[8]</sup> Amberlyst-15,<sup>[9]</sup> and NaHSO<sub>4</sub> adsorbed on silica gel<sup>[10,11]</sup> were reported. Togni et al. reported the use of the Ti(TADDO-Lato) complex to catalyze enantioselective α-halogenation of  $\alpha$ -substituted  $\beta$ -ketoesters with limited selectivity,<sup>[12]</sup> where TADDO stands for tetraaryl-1,3-dioxolane-4,5-dimethanols. While several methods have been developed for the 2-chlorination<sup>[13]</sup> and 2-iodination<sup>[14]</sup> of 1,3-dicarbonyl compounds using N-chlorosuccinimide and N-iodiosuccinimide, respectively, very few of these methods were successful in monohalogenation of  $\beta$ -ketoesters. A number of reported methods were practically inconvenient because of either harsh reaction conditions or the dihalogenated products formed.<sup>[13,14]</sup> Researchers have reported 100% selective reactions using silica-supported catalysts in organic synthesis.<sup>[15,16]</sup> Earlier, we have reported use of NiSiO<sub>2</sub> catalysts for reduction of various nitro aromatics to aromatic amines with 100% selectivity and good conversions.<sup>[17]</sup> In this manuscript, we report a method for the selective and efficient bromination of  $\beta$ -ketoesters and cyclic and acyclic ketones, which is achieved via treatment with NBS and catalyzed by NaHCO<sub>3</sub> on silica. It provides an alternative route for the fast and highly selective monobromination of cyclic and acyclic ketones and  $\beta$ -ketoesters with good conversions under moderate conditions.

#### **EXPERIMENTAL**

#### Materials

All chemicals were synthesis-grade reagents available from Merck.

#### **Preparation of Catalysts**

The catalysts were prepared by the impregnation method. This involved dissolving sodium bicarbonate (2.47 g) in distilled water (20.0 ml) and adding to it silica gel (5.0 g). The mixture was stirred for 2 h with a magnetic stirrer at room temperature ( $20 \pm 1$  °C) and aged at room temperature overnight. The excess water was removed by heating the mixture in a water bath and using a rotavapor under mild vacuum to evaporate the water. The catalyst material was dried in an oven at 100 °C for 12 h.<sup>[17]</sup>

#### **Typical Reaction Procedure**

NBS (1.2 mmol) was added to ethyl acetoacetate (1.0 mmol) together with 10.0 mL ether as solvent and 200 mg of catalyst. The reaction mixture was stirred at

room temperature, and the reaction progress was monitored by thin-layer chromatography (TLC) and gas chromatography (GC). At the end of the reaction, the reaction mixture was filtered, washed with sodium metabisulfite solution, and extracted with ethyl acetate. The ethyl acetate extract was washed twice with deionized water. The extract was dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvent was evaporated on a rotavapor to give the crude product of monosubstituted bromo ester, which was then subjected to column chromatography to afford the pure product. The final product was characterized by IR (neat): 1718, 1462, 1227 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  4.67 (1H, s), 4.28 (2H, q, J = 7.0 Hz), 2.43 (3H, s), 1.32 (3H, t, J = 7.0 Hz); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$  197.6, 167.3, 6.8, 54.6, 27.1, 14.2. <sup>1</sup>H and <sup>13</sup>C NMR (400 MHz, Bruker).

#### **RESULTS AND DISCUSSION**

The solid catalysts offer many advantages in organic synthesis, such as operational simplicity, environmental compatibility, nontoxicity, reusability, and low cost. Hence, suitable heterogeneous catalysts are in great demand both in academic research and industry. Several heterogeneous materials are thus finding increasing applications in the field of catalysis.<sup>[13,14]</sup> A tremendous upsurge of interest in various chemical transformation processes by catalysts under heterogeneous conditions has occurred. The factors that influence the physicochemical, surface, and catalytic properties of the catalytic material include the preparation conditions, thermal treatment, and nature of the support, doping with certain foreign oxides, and treatment with ionizing radiation. The properties of the support material depend also on its preparation method, concentration of reagents, precursor of the support, and the nature of gas atmosphere used in calcination. All these parameters affect the behavior of the catalytic material toward certain catalytic reactions. The synthesis of  $\alpha$ -monobromo products of  $\alpha$ -unsubstituted  $\beta$ -ketoesters is difficult because bromo compounds are unstable and undergo disproportionation to dibrominated and debrominated products.

Initially, we explored the possibility of using the Ni-loaded silica catalysts for selective  $\alpha$ -monobromination of  $\beta$ -ketoesters using NBS. Choosing the ethylacetoace-tate as a model substrate, the activity of 5%, 10%, and 15% Ni loaded SiO<sub>2</sub> catalysts were studied. Although even after 120 min of reaction time, the conversions were poor but interesting enough the selectivity was 100%. While 5% Ni silica gave 45% conversion, 10% Ni gave 50% and 15% Ni gave 55%. Ni-supported silica catalysts were observed to be less active because of the weak interaction between Ni and silica, multilayer nickel on the support, or formation of the thick Ni particles.

As long reaction durations were demanded with the nickel silica catalysts, we investigated the scope of use of NaHCO<sub>3</sub> on SiO<sub>2</sub> support as catalyst for the title reactions, and inspiring results were obtained. Table 1 presents the results for the bromination of a  $\beta$ -ketoester as the model substrate with a series of catalysts. The 15% NaHCO<sub>3</sub> loaded SiO<sub>2</sub> exhibited greater activity relative to the 5% and 10% NaHCO<sub>3</sub> loadings. With the 5% NaHCO<sub>3</sub> on SiO<sub>2</sub>, conversion was 58%, while with 10% and 15% NaHCO<sub>3</sub> loadings, the conversions increased to 60% and 67% respectively. Furthermore, the reaction duration decreased with increased NaHCO<sub>3</sub> loading on silica. With reactions with great loading of NaHCO<sub>3</sub> (i.e., with 20% NaHCO<sub>3</sub> on SiO<sub>2</sub>), interestingly the conversion decreased from 67% to 55%. The observed lower activity of the catalyst with higher bicarbonate loading could be due to excessive loading of

Support/loading	Loading (%)	Reaction time (min)	Conversion (%)	Selectivity (%)
SiO <sub>2</sub> -Ni	5	120	45	100
	10	120	50	100
	15	120	55	100
SiO <sub>2</sub> -NaHCO <sub>3</sub>	5	60	58	100
	10	50	60	100
	15	45	67	100

**Table 1.** Bromination of  $\beta$ -ketoester using N-bromosuccinimide and supported catalyst in ether or CCl<sub>4</sub><sup>*a*</sup>

*Notes.* Ethylacetoacetate, 1.0 mmol; NBS, 1.2 mmol; catalyst, 200 mg. Temperature,  $20 \pm 2$  °C. <sup>*a*</sup>Mean of duplicate runs.

 $NaHCO_3$  on the silica surface, restricting the simultaneous access for reactants to active sites on silica.

Thus, identifying 15% of bicarbonate loading on silica as the optimal, the efficiency of the catalyst material in transformation of selected keto compounds was investigated. Of the three cyclic ketones, namely cyclohexanone, cyclopentanone, and cycloheptanone, all had 100% selectivity. After 45 min, cyclohexanone was converted to 2-bromocylcohexanone with 55% conversion, while cycloheptanone had 50% conversion and cyclopentanone had 20%. Acetophenone, the aromatic ketone, had 58% conversion, and acetylacetone, an aliphatic ketone, showed 65% conversion. Toluene, an alkyl aromatic gave poor conversion to 2-bromotoluene (20%) but still retained 100% selectivity. Table 2 summarizes the reaction conditions, conversion, and product selectivity of the different substrates studied. Sodium bicarbonate loaded on silica proved to be an extremely active catalyst for the quick and selective bromination of the selected ketones with good conversions under moderate reaction conditions, because of the mild basic nature of the reaction on the metal surface. Neither silica nor sodium bicarbonate alone could give any conversions under otherwise identical conditions.

#### Catalyst Characterization: 15% NaHCO<sub>3</sub>

Silica catalysts were characterized by x-ray diffraction (XRD), infrared (IR) techniques, and Si NMR spectroscopy. The XRD spectra (Phillip-PW 1830XRD

No	Substrate	Product	Conversion (%)	Selectivity (%)
1	Ethylacetoacetate	2-Bromo ethyl Acetoacetate	67	100
2	Acetophenone	1-Bromo-methylene Acetophenone	58	100
3	Cyclohexanone	1-Bromo cyclohexanone	55	100
4	Cycloheptanone	1-Bromo cycloheptanone	50	100
5	Cyclopentanone	1-Bromo cyclopentanone	20	100
6	Acetyl acetone	2-Bromoacetyl acetone	65	100
7	Toluene	2-Bromotoluene	20	100

**Table 2.** Bromination of  $\beta$ -ketoester and cyclic ketones using N-bromosuccinimide and 15% NaHCO<sub>3</sub>-SiO<sub>2</sub> in Ether or CCl<sub>4</sub>.<sup>*a*</sup>

*Notes.* Substrate, 1.0 mmol; NBS, 1.2 mmol, and catalyst, 200 mg. Reaction duration, 45 min. Temperature,  $20 \pm 2$  °C.

<sup>a</sup>Mean duplicate runs.



Figure 1. XRD data of NaHCO<sub>3</sub>-SiO<sub>2</sub> catalysts: A, 15%; B, 10%; C, 5%; and D, 20%.

diffraction spectrometer) showed strong reflections at  $2\theta - 25^{\circ}$ , which may be associated with those usually observed in amorphous silicates between  $24^{\circ}$  and  $31^{\circ}$  in 5%, 10%, 15%, and 20% NaHCO<sub>3</sub>-SiO<sub>2</sub>.<sup>[18,19]</sup> (See Fig. 1.) The smaller broad peak occurred at  $2\theta = 12.0^{\circ}$  for this sample. This peak may be associated with an interlayer spacing in silicates, broadened by stacking disorder observed in 5%, 10%, and 20% NaHCO<sub>3</sub>-SiO<sub>2</sub>, whereas with 15% NaHCO<sub>3</sub>-SiO<sub>2</sub>, the broad peak is less observed. Similar basal reflections were already observed.<sup>[20]</sup> There are also narrow reflections, indicating the presence of some crystalline phases. The majority of these reflections were attributed to sodium sesquicarbonate.<sup>[21,22]</sup> Occassionally, some traces



Figure 2. IR spectra of 15% NaHCO<sub>3</sub>-silica catalysts.

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of trydimite or quartz may appear in some samples. During the identification process of these crystallike reflections other carbonates, such as  $Na_2CO_3$ , its hydrates, and  $Na_2SiO_3 \cdot 5H_2O$ , were considered.

The examination of IR spectra (Perkin-Elmer FT-IR spectrometer) of 15% NaHCO<sub>3</sub>-SiO<sub>2</sub> fresh catalysts showed that the observed bands agree with the literature data. (See Fig. 2.) Many bands are associated with the amorphous silica: Asymmetric stretching Si-O (1154 and 1037 cm<sup>-1</sup> respectively), stretching of Si-O-X, where x = K or Na (953 cm<sup>-1</sup>), symmetric stretching of O-Si-O (457–600 cm<sup>-1</sup>).<sup>[23–28]</sup> The presence of molecular water is revealed by the band from 1642 to 1660 cm<sup>-1</sup> (bending of H<sub>2</sub>O). Also, the broad band extending from 2300 to 3700 cm<sup>-1</sup> is associated with stretching of X-OH, with x<sup>+</sup>H or Si, indicating the presence of a substantial amount of OH- groups in the silica matrix.<sup>[29,30]</sup> On the other hand, the band at 1470 cm<sup>-1</sup> corresponds to CO<sub>3</sub><sup>2-</sup> anions, indicating the presence of carbonates in these samples in agreement with XRD experiments.<sup>[31–34]</sup> This shows that the NaHCO<sub>3</sub> is as active species in association with silica for the activation of n-bromosuccinimide, which initiated the bromination of  $\beta$ -ketoester and cyclic ketones. These results conclusively demonstrate that 15% NaHCO<sub>3</sub>-silica catalyst is ideally suited for the selective bromination of  $\beta$ -ketoester and cyclic ketones and acetophenone 1-bromo compounds with good conversion and selectivity.

#### Si NMR Spectroscopy

The <sup>29</sup>Si MAS-NMR spectra of the sample shows few broad peaks, a typical distribution of isotropic chemical shift values caused by structural disordered distribution. These can be identified with the reported literature data for different tetrahedral  $Q^n$  environments for Si in silicates.<sup>[35]</sup> As usual, the symbol,  $Q^n$  identifies the connectivity of silicate tetrahedron, n being the number of bridging oxygens (Si-O-Si). The population of each Q<sup>n</sup> species observed in the <sup>29</sup>Si NMR spectrum of sample can be obtained from the least-square fitting of Gaussian function observed peaks. In the analysis, the Gaussian distributions centered about -79 ppm, -88 ppm, -97 ppm and -106 ppm were attributed to Q<sup>1</sup>, Q<sup>2</sup>, Q<sup>3</sup>, and Q<sup>4</sup> units respectively. The most shielded resonance centered at an isotropic shifts of -106 ppm can be attributed unambiguously to Q<sup>4</sup> units, while the others show a remarkably close resemblance with the progressive 10 ppm deshielding expected from each additional non-bridging oxygen.<sup>[36]</sup> All the observed lines, with the exception of the narrow  $Q^4$  line centered at -107 ppm in sample D, correspond to silicon sites in the disordered sample. The chemical shift of additional  $Q^4$  line in sample agrees well with the crystalline quartz (-107.4 ppm,)<sup>[37]</sup> indicating the presence of nonreactive, or at least less reactive, silica in this kind of samples.

#### Effect of Solvent Medium

Further, to understand the influence of solvent on conversion efficiency, reactions were conducted in different solvent systems, employing ethyl acetoacetate as substrate and 15% NaHCO<sub>3</sub>-SiO<sub>2</sub> as catalyst. While all solvents retained the 100% selectivity, both CCl<sub>4</sub> and ether could give 67% conversion after 45 min. Reactions were slow with the other solvents. After 180 min, while CHCl<sub>3</sub> gave 60% conversion, CH<sub>2</sub>Cl<sub>2</sub> (50%), CH<sub>3</sub>CN (45%), and MeOH recorded only 20% conversions. Thus, both ether

and carbon tetrachloride proved to be the ideal solvents. While nickel loaded on silica was a good and selective catalyst for  $\alpha$ -monobromination of various ketones, bicarbonate-supported silica proved to be a superior basic catalyst for this transformation. The NaHCO<sub>3</sub> silica catalyst could be easily separated by simple filtration, and the recovered catalyst could be reused. The NaHCO<sub>3</sub> on silica catalysts can be prepared with ease from the environmentally friendly reagents, NaHCO<sub>3</sub> and silica gel. The bromination of  $\beta$ -keto esters is known to pass through an enol formation, and such transformation is accelerated by the availability of suitable acid and base proton donors and acceptors. A literature survey shows that cocatalyst loaded on silica can promote the acidic nature of silanol groups on a silica surface behaving as proton donors.<sup>[32,33]</sup>

#### Mechanism

A probable mechanism involves the enolization of ketone through an initial hydrogen bonding to silanol group. Subsequently, because of its activation by the presence of a cocatalyst, bicarbonate in its vicinity, Si-OH provides the proton to substrate. Possibly the reactivity of NBS also gets enhanced by the acquired acid character of silanol groups, which leads to the desired product. The bicarbonate on the silica surface readily accepts the proton from the enol, facilitating the reaction. Hence, it can be concluded that combination of both bicarbonate and silica activities lead to increased efficiency in conversion. Even distribution of bicarbonate on silica surface manifested by the characterization of the catalyst using XRD and IR studies support the hypothesis.

SiO<sub>2</sub> is an amorphous solid, and its surface has the aggregated primary particles, which are noncrystalline (hence the term *silica gel*). The most reactive groups are the -OH groups (silanol groups) that terminate the primary particles; these results are confirmed by measurements of the number of adsorbed pyridiunium ions, which are acidic in character (Brønsted acid sites).<sup>[39]</sup> The NaHCO<sub>3</sub>, which is supported on SiO<sub>2</sub>, is basic in character. In conclusion, we can say that bicarbonate and silica provide the combination of basic and acidic properties needed for the efficient catalytic process.<sup>[39]</sup>

The comparison of efficiency of Ni and NaHCO<sub>3</sub> supported on silica shows that NaHCO<sub>3</sub> has superior activity. Loading of bicarbonate on the silica support has a positive effect on the rate of bromination reaction compared to Ni on silica. Lower conversion efficiencies observed with 5%, 10%, and 20% of sodium bicarbonate on SiO<sub>2</sub> points to 15% loading as ideal for good conversions. The swift reactions achieved at 15% of NaHCO<sub>3</sub> loading can be attributed to the need for surface OH groups to provide the necessary Brønsted acid site needed for fast reactions. These results show the variables available in the design of solid catalysts (loading) can be used for selective bromination of  $\beta$ -ketoester initiated by surface sites.

#### CONCLUSIONS

In conclusion, an efficient and highly selective method for  $\alpha$ -monobromination of  $\beta$ -ketoesters by treatment with NBS and catalyzed by NaHCO<sub>3</sub> · SiO<sub>2</sub> is developed. This method demonstrates simplicity, high selectivity, shorter reaction times ,and good yields with recyclable and economically viable catalyst. The characterization of NaHCO<sub>3</sub>-SiO<sub>2</sub> catalysts with XRD, IR, and <sup>29</sup>Si NMR conclusively demonstrates that silica and carbonate species are present on the matrix of the supported system and are active species for  $\alpha$ -bromination of  $\beta$ -ketoesters and cyclic ketones. The simple experimental procedure, good yields of monobrominated products, atom economy, ecofreindly nature, reusability, short reaction times, and application of heterogeneous catalysts are advantages of the proposed procedure.

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