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Original article

# Silica gel catalyzed α-bromination of ketones using *N*-bromosuccinimide: An easy and rapid method

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ABSTRACT

An easy and rapid method for the α-bromination of ketones using N-bromosuccinimide (NBS) catalyzed by silica gel in methanol under reflux conditions was developed. The expected products were formed in excellent isolated yields within a short period of time (5–20 min). Major advantages of the present procedure include use of inexpensive and readily available catalyst, exclusion of pre- and post-chemical treatment of catalyst and use of methanol as solvent instead of ethers and chlorinated solvents.

## 1. Introduction

The α-bromination of ketones has attracted much attention because the resulting α-bromination of ketones are the key intermediates in organic synthesis [1,2]. Accordingly, a number of protocols have been developed which include cupric bromide [3], dioxane dibromide [4], tetra-butyl ammonium tribromide [5], $H_2O_2$–HBr [6], bromodimethyl sulfoniumbromide [7], ethylene bis(*N*-methyl imidazolium) ditribromide [8], trihaloisocyanuric acids [9], pyridinium bromochromate [10] and $NH_4Br$–oxone [11]. Moreover, owing to user friendliness and availability, N-bromosuccinimide has been extensively used as brominating agent: transformations can be modulated under various reaction conditions, for example: (i) using different types of catalysts such as $Mg(ClO_4)_2$ [12], $NH_4OAc$ [13], Amberlyst-15 [14], silica-supported $NaHSO_4$ [15], silica supported $NaHCO_3$ [16], sulfonic acid functionalized silica [17] and $FeCl_3$ [18]; (ii) ionic liquids [19], (iii) photochemical bromination [20]; (iv) sonochemical bromination [21] and (v) solvent free reaction conditions (SFRC) [22].

An extensive literature search revealed that bromination with NBS depends on the catalyst used and this encouraged researchers to develop a number of catalysts to make the bromination process easier and more efficient. Silica gel is known as a good catalyst in many synthetic applications [23,24] and also for ring bromination [25–27]; However, no reports were found on the investigation of silica gel as catalyst for the α-bromination of ketones using NBS. As a part of continuing agenda to explore the use of inorganic materials in the synthesis of organic compounds, we found that silica gel is an efficient catalyst for the α-bromination of ketones when N-bromosuccinimide in methanol is used under reflux conditions (Scheme 1).

## 2. Experimental

Ketones were purchased from Acros, Merck and S.D. Fine Chemicals Ltd., Mumbai, India. N-bromosuccinimide and silica gel (60–120 mesh) were procured from Merck, India. Methanol (99.0%) and ethyl acetate were purchased from Finar Chemicals Ltd., India. Double distilled water was used for work-up. Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The $^1$H NMR spectra were recorded on a Varian 300 MHz. Chemical shifts were expressed in parts per million (ppm). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br (broad). Mass spectra (MS) were recorded on Agilent, model-6410, triple quad LCMS. Thin-layer chromatography was performed using 0.25 mm Merck silica gel plates (60F-254) and visualized with UV light. Column chromatography was performed on silica gel of 60–120 mesh, Merck).

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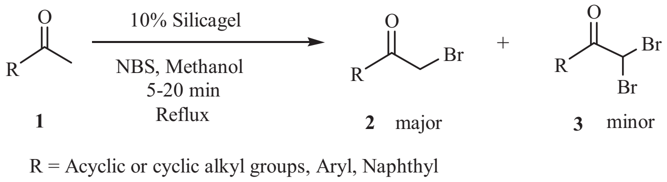


**Scheme 1.** The α-bromination of ketones using NBS in presence of silica gel in methanol.

Column chromatographic grade silica gel (60–120 mesh) supplied by Merck, India was employed in the present investigation. The pH value of 10% aqueous suspension of silica gel is $\sim$6.5–7.5. Silica gel catalyst was used as it is, without any activation or any further treatment or chemical modifications.

### 2.1. *Typical experimental procedure*

The α-bromination reaction was carried out using acetophenone (1200 mg, 10 mmol), N-bromosuccinimide (2136 mg, 12 mmol), 10% (w/w) silica gel (120 mg) in 10 mL of methanol at reflux conditions until the disappearance of the substrate. (Note: 2136 mg of N-bromosuccinimide was added portion wise *i.e.* 356 mg for each time in six portions). The progress of the reaction was monitored by TLC. The reaction mass was filtered after the completion of the reaction as per TLC and the catalyst was collected for reuse. The filtrate was concentrated under vacuum. Double distilled water was added to the reaction mixture and quenched with aqueous sodium thiosulfate and the product extracted with dichloromethane (Caution: Severe burning sensation of eyes was observed during the work-up process). The layers were separated and the organic layer was collected and washed thrice with distilled water (3 × 50 mL). The collected organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated. The obtained crude product was purified by column chromatography over silica gel (60–120 mesh) using *n*-hexane–EtOAc (99:1 ratio).

With the aim of studying the recycling of the catalyst, the isolated catalyst was washed with ethyl acetate (5 mL) after its filtration from the reaction medium, collected and dried in vacuum at 70 °C to a constant weight. Subsequently it was reused for the α-bromination of acetophenone and achieved 95%, 86% and 83% yields of product (**2a**) for first, second and third reuse of catalyst respectively. All products gave spectroscopic data in agreement with the literature [15,21,27–30].

The method is also very practical for scale up in process development. We attempted large scale (100 gram scale) synthesis of 2-bromo-1-phenylethanone **2a** and obtained fruitful results with isolated yields ranging from 93% to 96%.

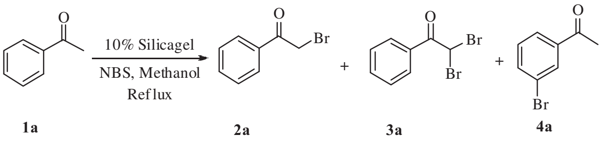
### 2.2. *General experimental procedure for large scale (100 g scale) preparation*

The α-bromination reaction was carried out using acetophenone (100 g, 0.832 mol), N-bromosuccinimide (213.6 g, 1.2 mol), 10% (w/w) silica gel (10 g) in 1 L of methanol under reflux conditions until the disappearance of the substrate (Note: 213.6 g of N-bromosuccinimide was added portion wise *i.e.* 35.6 g for each time in six portions). Excess N-bromosuccinimide (+0.1 mol) was added to complete the reaction as per TLC. The reaction mass was filtered, after the completion of the reaction as per TLC and the catalyst was collected for reuse. The solvent was removed and double distilled water was added to the reaction mixture and was quenched with aqueous sodium thiosulfate. The product was extracted with dichloromethane. (Caution: Severe burning sensation of eyes was observed during the work-up process). The layers were separated and the organic layer was collected and it was washed with distilled water for three times (3 × 1 L). The collected organic layer was dried over anhydrous $Na_2SO_4$ and filtered, concentrated and purified by recrystallization using *n*-hexane (300 mL). The resulting yield of pure α-brominated ketone, *i.e.* 2-bromo-1-phenylethanone (**2a**) was 94%. The same experiment was repeated twice and the yields were 93% and 96%, respectively. The reproducibility of the protocol was thus confirmed with the consistent isolated yields of desired product 2-bromo-1-phenylethanone (**2a**).

## 3. Results and discussion

To study the effect of solvents and temperature on the α-bromination of ketones, we carried out a reaction with acetophenone using N-bromosuccinimide in methanol in presence of silica gel at room temperature. However a low yield (56%, Table 1 entry 1) of the product 2-bromo-1-phenylethanone (**2a**) was obtained after 4 h. When the same reaction was carried out under reflux conditions (Table 1, entry 1), the yield was 95% within 18 min. Other solvents such as $Et_2O$, THF, $CH_3CN$, $CH_2Cl_2$ and $CHCl_3$ were also studied, but lower yields of the desired products were obtained (10–35%) as shown in Table 1. With $Et_2O$, THF, 1,4-dioxane and acetonitrile, lower yields of the product **2a** was formed, along with very low amounts of the α, α′-dibrominated

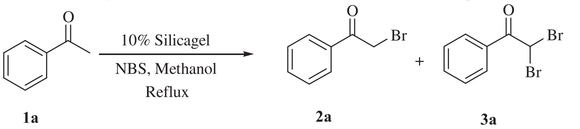
**Table 1**
Effect of solvent and temperature on the formation of α-brominated product (**2a**).[a]



| Entry | Solvent | Time (min) | Major product | Yield (%)[b] | Yield (%)[c] | Selectivity (**2a**:**3a**:**4a**) |
|---|---|---|---|---|---|---|
| 1 | MeOH | 18 | **2a** | 95 | 56 | 95:03:00 |
| 2 | $Et_2O$ | 15 | **4a** | 24 | 18 | 24:04:50 |
| 3 | THF | 18 | **4a** | 18 | 15 | 18:03:45 |
| 4 | 1,4-Dioxane | 28 | **4a** | 16 | 14 | 16:05:42 |
| 5 | $CH_3CN$ | 180 | **2a** | 35 | 22 | 35:14:28 |
| 6 | $CH_2Cl_2$ | 1500 | **2a** | 12 | 8 | 12:01:00 |
| 7 | $CHCl_3$ | 1500 | **2a** | 14 | 7 | 14:04:00 |
| 8[d] | MeOH | 1500 | – | 0 | 0 | 0 |

[a] Reactions were conducted with acetophenone (10 mmol); NBS (12 mmol), 10% (w/w) silica gel, solvent (10 mL) under reflux conditions.
[b] Isolated yields under reflux condition.
[c] Isolated yields at room temperature.
[d] Reaction carried out without catalyst.

**Table 2**
Role of catalyst load on the formation of α-brominated product (**2a**).[a]



| Entry | Catalyst (w/w %) | Time (min) | Major Product | Yield (%)[b] | Selectivity (%) (**2a**:**3a**) |
|---|---|---|---|---|---|
| 1 | 1 | 90 | **2a** | 41 | 41:03 |
| 2 | 5 | 60 | **2a** | 65 | 65:02 |
| 3 | 10 | 18 | **2a** | 95 | 95:03 |
| 4 | 15 | 20 | **2a** | 82 | 82:14 |
| 5 | 20 | 15 | **2a** | 74 | 74:18 |
| 6 | 30 | 11 | **2a** | 67 | 67:21 |

[a] Reactions were conducted with acetophenone (10 mmol); NBS (12 mmol), 10% (w/w) silica gel, methanol (10 mL) under reflux conditions.
[b] Isolated yields.