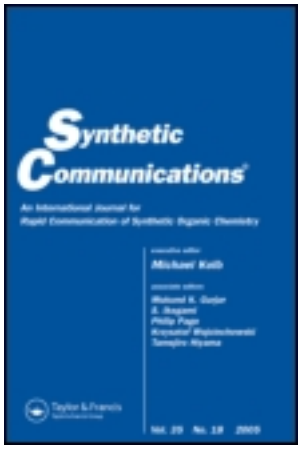

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Regioselective α-Bromination of Aralkyl Ketones Using N-Bromosuccinimide in the Presence of Montmorillonite K-10 Clay: A Simple and Efficient Method

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REGIOSELECTIVE α-BROMINATION OF ARALKYL KETONES USING N-BROMOSUCCINIMIDE IN THE PRESENCE OF MONTMORILLONITE K-10 CLAY: A SIMPLE AND EFFICIENT METHOD

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GRAPHICAL ABSTRACT

Abstract *A simple and more convenient method has been developed for regioselective α-bromination of various aralkyl ketones with N-bromosuccinimide (NBS) in the presence of Montmorillonite K-10 catalyst in methanol at 60–65 °C. The present procedure offers advantages of short reaction time, simple workup, good yields of products and reusability of the catalyst for four times without loss of activity.*

Supplemental materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *to view the free supplemental file.*

Keywords Aralkyl ketones; α-bromination; Montmorillonite K-10 clay; N-bromosuccinimide; regioselectivity

INTRODUCTION

Development of simple and efficient synthetic routes for widely used organic compounds from readily available reagents is one of the major challenges in organic synthesis. Organic bromides are regarded as important precursors for various transformations employed in organic and pharmaceutical synthesis. The bromination of aralkyl ketones may lead to side-chain α-bromination as well as ring bromination depending upon the conditions employed. The side-chain bromination has attracted attention because of the potential of the resulting bromoacetophenones as versatile building blocks in the synthesis of carbo- and heterocyclic compounds used in the

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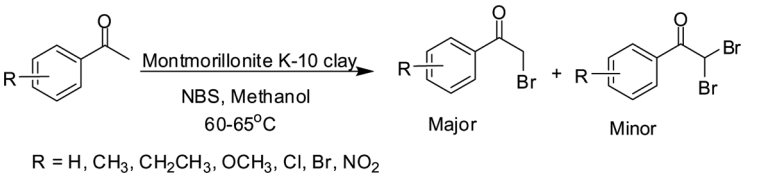
design of novel and highly effective pharmaceuticals with a broad spectrum of bioresponses and also as intermediates for a variety of biologically active compounds.[1] Arabaci et al. reported that α-bromoacetophenone derivatives actively participated in the inhibition of protein tyrosine phosphatase such as SHP-1 and PTP1B.[2]

Considerable efforts have been focused on the development of efficient bromination methods instead of conventional methods that require hazardous and toxic elemental bromine[3,4] in the presence of protic or Lewis acid.[5,6] A number of bromination protocols of carbonyl compounds have been developed, for example, use of cupric bromide,[7] dioxane, dibromide[8] and tetra-butyl ammonium tribromide.[9] In terms of user friendliness and availability, N-bromosuccinimide (NBS) is a superior brominating agent.[10,11] It has been reported that ketones are α-brominated using NBS catalyzed by $Mg(ClO_4)_2$,[12] NBS/sonochemical bromination,[13] NBS/NH_4OAc,[14] NBS/Amberlyst-15,[15] NBS/silica-supported $NaHSO_4$,[16] NBS/sulfonic acid functionalized silica,[17] NBS/ionic liquids,[18] NBS/solvent-free reaction conditions,[19] bromodimethyl sulfoniumbromide,[20] ethylene bis(N-methylimidazolium)ditribromide,[21] H_2O_2-HBr,[22] NBS/hυ,[23] trihaloisocyanuric acids,[24] pyridinium bromochromate,[25] and NH_4Br-oxone.[26]

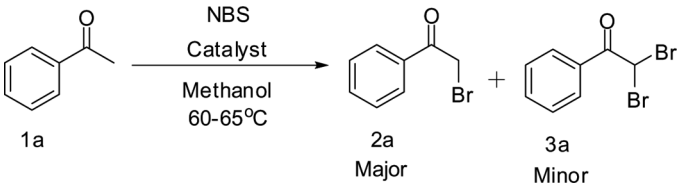
However, all these methods suffer from one or more disadvantages such as long reaction times, preparation of catalyst, use of hazardous chemicals, and intricate workup procedures. Hence, the development of a simple and efficient method for α-monobromination of aralkyl ketones remains a major challenge for synthetic organic chemists. Hence, a study has been undertaken using Montmorillonite K-10 clay as a catalyst for the conversion of aralkylketones to α-monobrominated aralkylketones with NBS in methanol. Montmorillonite K-10 clay has been used as catalyst for number of synthetic organic transformations and offers several advantages over classical acids, for example, strong acidity, noncorrosiveness, low cost, mild reaction conditions, good yields, selectivity, and ease of workup.[27]

Herein, we report a simple, more convenient, and regioselective method for the preparation of α-monobrominated aralkyl ketones in good yields by the reaction of various aralkyl ketones with N-bromosuccinimide (NBS) in the presence of Montmorillonite K-10 catalyst in methanol at 60–65 °C (Scheme 1).

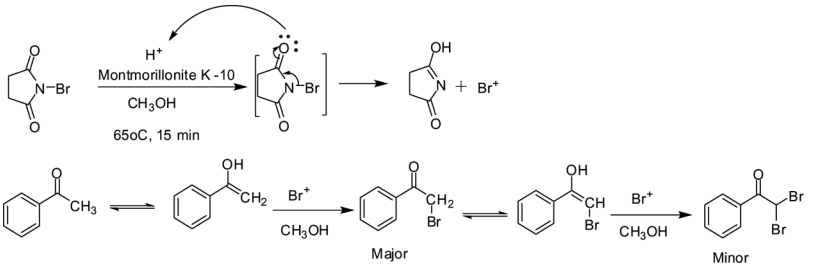
In the present study, our initial objective was to identify an appropriate catalyst or solvent for regioselective α-bromination of various aralkyl ketones with NBS. For this purpose, we choose to assess regioselective α-bromination of acetophenone (**1a**), and all the reaction parameters were optimized with respect to it. Acetophenone can undergo electrophilic ring bromination at the *m*-position as well as electrophilic α-bromination in the side chain. Electrophilic ring bromination using NBS in the



Scheme 1. Synthesis of α-brominated aralkyl ketones from aralkyl ketones using NBS in the presence of 10% Montmorillonite K-10 catalyst.



Scheme 2. α-Bromination of acetophenone using NBS in presence of 10% of Montmorillonite K-10 clay catalyst.



Scheme 3. Plausible mechanism for the preparation of 2-bromo-1-phenylethanone (major) from acetophenone.

presence of p-TsOH has been achieved.[4] In the present study, we have achieved the electrophilic α-bromination in the side chain using NBS in the presence of Montmorillonite K-10 clay (Scheme 2).

In the presence of an acidic catalyst such as Montmorillonite K-10, NBS may undergo protonation at the carbonyl oxygen resulting in the generation of the bromocation. The bromocation may directly attack at the aromatic ring or a potential nucleophilic center like the α-carbon atom of a ketone. Alternatively, the bromocation may react with a nucleophilic solvent such as methanol to form an electrophilic species, such as CH_3OBr, which can react with the enol form of the ketone to form α-bromo derivative as shown in Scheme 3.

RESULTS AND DISCUSSION

Different type of solvents, temperature, and mode of NBS addition were examined for their effect on the transformation of acetophenone (**1a**) into 2-bromo-1-phenylethanone (**2a**) by treatment with NBS in the presence of Montmorillonite K-10 catalyst, and the obtained results are discussed. Initially, α-bromination of acetophenone (**1a**) was carried out with NBS in methanol in the absence of the catalyst, and bromination was not observed even up to 24 h (entry 1, Table 1). In the presence of Montmorillonite K-10 catalyst, it afforded 68% yield of the desired product (**2a**) in 4.0 h at 30–35 °C (entry 2, Table 1), and the same reaction was completed within 18 min at 60–65 °C with 94% of isolated yield (entry 3, Table 1).

Later, optimization of the reaction conditions was scrutinized to increase the yield of the product. A variety of solvents were also examined. The results presented in Table 2 showed that solvents provided various and yields (entries 1–4, Table 2).

Table 1. Screening of catalyst for synthesis of 2-bromo-1-phenylethanone[a]

Entry	Catalyst	Temp. (°C)	Time (h)	Product(s)[b] **2a** and **2b**	Selectivity (%) **2a**:**3a**
1	—	30–35	24	—	0:0
2	Montmorillonite K-10	30–35	4.0	**2a** and **3a**	68:32
3	Montmorillonite K-10	60–65	0.3	**2a** and **3a**	94:06

[a]Reaction conditions: Acetophenone (10 mmol), NBS [10 (+2) mmol: portionwise addition], 10% Montmorillonite K-10, and methanol (20 ml).
[b]Scheme 2.

Solvents such as Et_2O and tetrahydrofuran (THF) gave product **2a** in lower yields (entries 1 and 2, Table 2). When ethanol was used as a solvent, moderate yield of the product (**2a**) was obtained (entry 4, Table 2). Solvents such as dimethylsulfoxide (DMSO), dimethylformamide (DMF), CH_2Cl_2, and CCl_4 were generally employed for NBS bromination.[28] However, we did not observe conversion in any of these solvents (entries 5–8, Table 2) at 30–35 °C. In this study, we found that methanol is the best solvent (entry 3, Table 2) for maximum isolated yield of the desired product (**2a**), especially at reflux temperature.

It is interesting to mention the effect of reaction temperature on the course of bromination in the presence of Montmorillonite K-10 catalyst, since at higher temperature (65 °C) regioselectivity would be changed. In the case of acetophenone substrate, with increasing temperature α-monobromination was increased instead of α-dibromination (entries 1–5, Table 3). α-Bromination was also predominant in the case of other substituted acetophenones and substituted acetonaphthones even at higher temperature (entries 1–14, Table 5). In this study, we found that the optimum temperature is 60–65 °C to obtain highest yields of the desired products within a short period of time.

To obtain some further insight into the bromination process, we investigated the effect of mode of NBS addition. Portionwise addition and one time addition of NBS had a significant effect on the isolated yield of the desired product (**2a**).

Table 2. Screening of solvents for synthesis of 2-bromo-1-phenylethanone[a]

Entry	Solvent	Time (h)	Yield (%)[b]
1	Et_2O	0.5	35 (63)[c]
2	THF	1.5	29 (45)[c]
3	CH_3OH	4.0	68 (94)[c]
4	CH_3CH_2OH	7.0	54 (69)[c]
5	DMF	24	0 (6)[c]
6	DMSO	24	0 (7)[c]
7	CH_2Cl_2	24	0 (10)
8	CCl_4	24	0 (5)

[a]Reaction conditions: Acetophenone (10 mmol), NBS (11 (+2) mmol: portionwise addition), 10% Montmorillonite K-10, methanol (20 ml), and temperature 30–35 °C.
[b]Isolated yield.
[c]Isolated yields were shown in parentheses, when the reactions were carried out under reflux temperature.

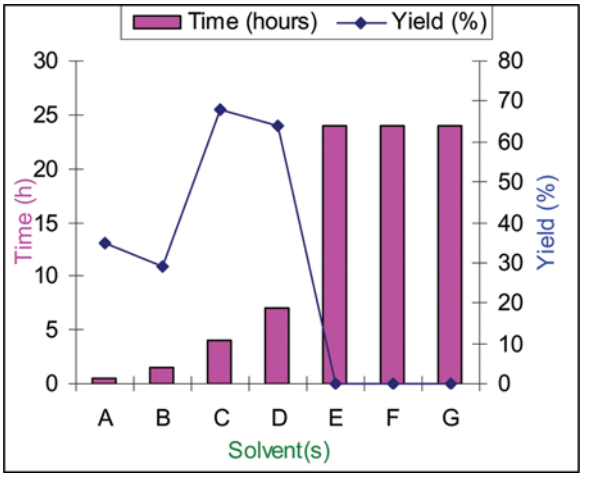


Figure 1. Solvents obtained yield of 2-bromo-1-phenylethanone. Solvents: A-Et_2O, B-THF, C-CH_3OH, D-CH_3CH_2OH, E-DMF, F-DMSO, G-CH_2Cl_2, and H-CCl_4. (Figure is provided in color online.)

For example, the isolated yield of the product (**2a**) was increased on addition of NBS in portion wise (entries 2–4, Table 4) when compared to one-time addition of NBS (entry 1, Table 4). From this study, we concluded that portionwise addition is the best option to obtain improved yields.

Table 3. Optimization of temperature for synthesis of 2-bromo-1-phenylethanone[a]

Entry	Time (h)	Temp. (°C)	Yield (%)[b]
1	6.0	20–30	51
2	4.0	30–40	68
3	2.5	40–50	75
4	1.0	50–60	82
5	0.3	60–65	94

[a]Reaction conditions: Acetophenone (10 mmol), NBS [10 (+2) mmol: portionwise addition], 10% Montmorillonite K-10, and methanol (20 ml).
[b]Isolated yield.

Table 4. Optimization of mode of N-bromosuccinimide addition[a]

Entry	Mode of NBS addition	Time (min)	Yield (%)[b]
1	Once	10	71
2	2 portions	12	78
3	4 portions	14	85
4	6 portions	18	94

[a]Reaction conditions: Acetophenone (10 mmol), NBS [10 (+2) mmol)], 10% Montmorillonite K-10, and methanol (20 ml) at 65 °C.
[b]Isolated yield.

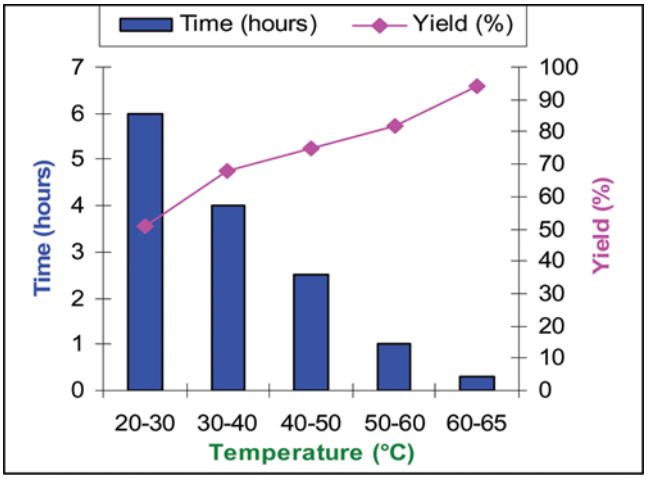


Figure 2. Temperature-dependent yield of 2-bromo-1-phenylethanone. (Figure is provided in color online.)

Finally, with intention of further investigation into the bromination process, we studied the effect of substituents present on the aromatic ring of aralkyl ketones. The Presence of electron-releasing and electron-withdrawing groups on substrates had significant effect on isolated yields of the products (entries 1–14, Table 5). In this study, we found that substrates, without substituents (entry 1, Table 5) or with electron releasing groups (entries 3–10, Table 5) or with extensive conjugation (entries 13 and 14) gave excellent isolated yields. In contrast to this, the substrates containing electron withdrawing groups (entries 11 and 12, Table 5) gave lower yields of the products.

Based on optimized conditions, a series of α-bromoketones were prepared by the reaction of aralkyl ketone (10 mmol) with N-bromosuccinimide (12 mmol) in

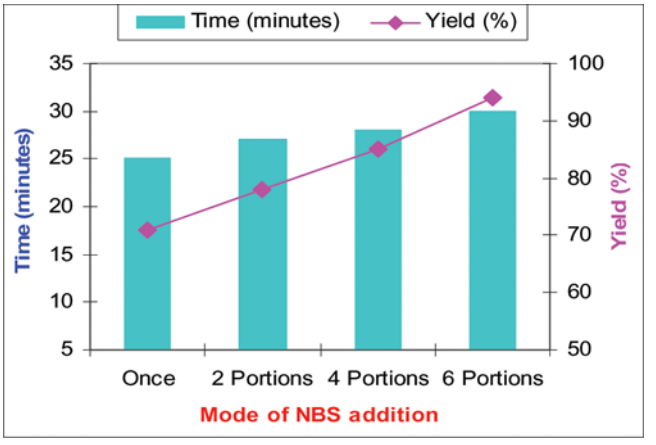
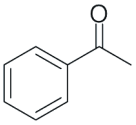
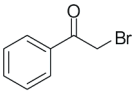
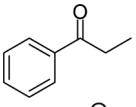
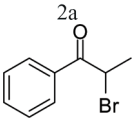
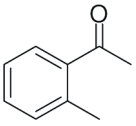
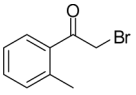
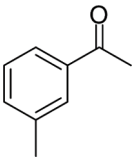
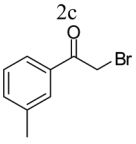
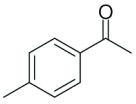
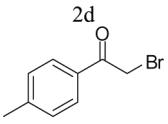
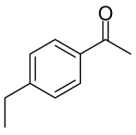
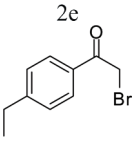
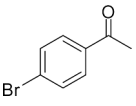
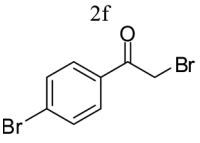
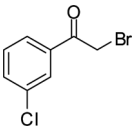
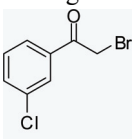


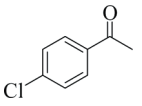
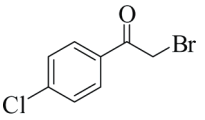
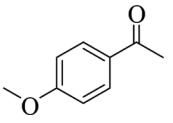
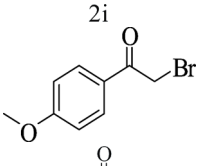
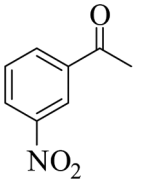
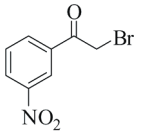
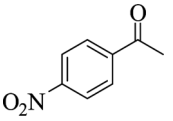
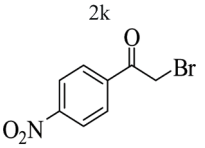
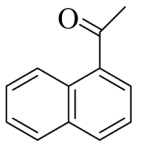
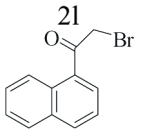
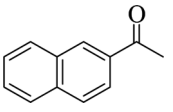
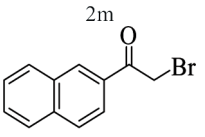
Figure 3. Mode of NBS addition–dependent yield of 2-bromo-1-phenylethanone. (Figure is provided in color online.)

Table 5. α-Bromination of aralkyl ketones using NBS in the presence of Montmorillonite K-10 in methanol[a]

Entry	Substrate	Product	Time (min)	Yield (%)	
				NBS in one portion	NBS in portions
1			18	74	94[29]
2		2a 	12	44	65[30]
3			15	82	92[31]
4		2c 	16	81	94[32]
5		2d 	12	85	96[29]
6		2e 	16	76	88[33]
7		2f 	13	79	95[29]
8		2g  2h	13	75	85[34]

(*Continued*)

Table 5. Continued

Entry	Substrate	Product	Time (min)	Yield (%) NBS in one portion	Yield (%) NBS in portions
9			11	79	92[34]
10		2i 	12	52	78[35]
11			20	24	45[36]
12		2k 	15	44	65[36]
13		2l 	11	65	88[37]
14		2m 	12	72	91[38]
		2n			

[a]Reaction conditions: Substrate (10 mmol), NBS 10 (+2) mmol added in either one or six portions, 10% Montmorillonite K-10 catalyst, methanol (20 ml), and temperature 60–65 °C.

20 ml of methanol containing 10% Montmorillonite K-10 catalyst, and the obtained results are listed in the Table 5. In the absence of catalyst, bromination was not observed.

In conclusion, we have developed an efficient methodology for α-bromination of aralkylketones by using a NBS/Montmorillonite K-10/methanol system within 20–30 min. Operational simplicity, good regioselectivity, rapid completion of the reactions, good yields of the products, and reusability of catalyst are the notable advantages of this method, which make it an attractive addition to the existing

literature. To broaden this methodology, further investigations on α-bromination of cyclic and acyclic ketones, amides, and β-ketoesters are under way.

EXPERIMENTAL

A mixture of aralkyl ketone (10 mmol), N-bromosuccinimide (12 mmol), 10% (w/w) Montmorillonite K-10 clay, and 20 ml of methanol were stirred at 60–65 °C up to the disappearance of the substrate. N-Bromosuccinimide was added portion-wise (six portions). The reaction mixture was filtered to collect catalyst, solvent was removed under reduced pressure, the crude product was added to aqueous sodium thiosulfate, and the product was extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The obtained crude was purified over silica gel using eluent of n-hexane and EtOAc (99:1 ratio).

Bulk-scale crude materials were purified using the recrystallization technique by dissolving in n-hexane EtOAc (9:1 ratio) at 40–45 °C and subsequent cooling to 0–5 °C. Then, the formed solid product was filtered and washed with cold n-hexane. The obtained pure product was dried in vacuum oven.

SUPPLEMENTARY INFORMATION

Supplementary information (experimental procedures, IR, ^{1}H NMR, and mass spectral data of compounds) associated with this article can be found in the online version.

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