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Nonselective Bromination–Selective Debromination Strategy: Selective Bromination of Unsymmetrical Ketones on Singly Activated Carbon against Doubly Activated Carbon

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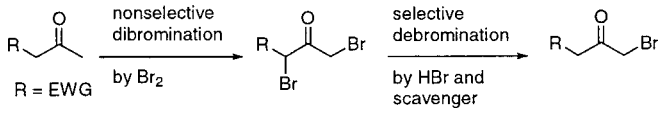
ABSTRACT



We have found a new synthetic method for the preparation of the α-bromoketones that are brominated in the less activated *terminal* position of unsymmetrical ketones. Brominations in short reaction times (kinetically controlled) provided internally brominated compounds as a major product. However, brominations in longer reaction times (thermodynamically controlled) gave more of the terminally brominated compound through the reversible reaction by Br_2 and produced hydrogen bromide. Several brominated compounds at the *terminal* position were successfully prepared through the new synthetic route.

Recently, we reported regio- and substituent-selective debromination reaction on activated aromatic bromine by hydrobromic acid and a scavenger.[1] Therein, the ipso-protonated compound **1** is the intermediate of the debromination reaction as shown in Figure 1. The protonated

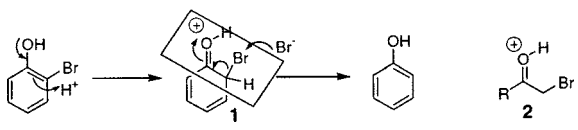
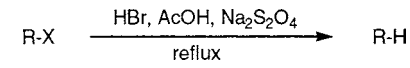


Figure 1. Mechanism of reductive debromination of bromophenol and the structure similarity between intermediate **1** and protonated α-bromoketone.

α-bromoketone **2** has the same scaffold as intermediate **1** shown boxed in Figure 1. We have checked whether or not α-bromoketones could also be reduced by the same reducing system (HBr/scavenger of Br_2).

Through this investigation, we could obtain debrominated products of α-bromocarbonyls in around 90% yield (Table 1). Although there were many reports on isomerization of

Table 1. Reductive Debromohydrogenation Reactions of α-Bromocompounds in Concentrated HBr/AcOH Conditions



entry	reactant	time[a] (h)	scavenger[b] (equiv)	yield (%)[c]
1	**3b**	4	1.15	**3a** (89)
2	**4b**	3	1.15	**4a** (92)

[a] At reflux. [b] $Na_2S_2O_4$. [c] Isolated yield.

α-bromoketones by HBr,[2] this is the first report where HBr is used as a reducing agent of α-bromoketone. During this

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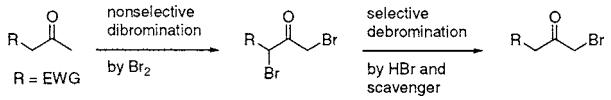
study of bromination and debromination processes of aliphatic ketones, we also have discovered the selective bromination of unsymmetrical ketones on singly activated carbon against doubly activated carbon, which will provide a new general synthetic route for the preparation of brominated unsymmetrical ketones in a less activated position (Scheme 1). Unsymmetrical ketones such as phenylacetone

Scheme 1. New Synthetic Strategy for the Selective Preparation of *Terminal* Bromoketones



(**5**) and 1-phenyl-1,3-butanedione (**6**) have a methylene group and a methyl group. In this report, the methylene carbon is in an *internal* position that is doubly activated by two electron-withdrawing groups (EWG): phenyl and carbonyl or two carbonyls. In addition, the methyl carbon is in a *terminal* position singly activated by only one carbonyl.

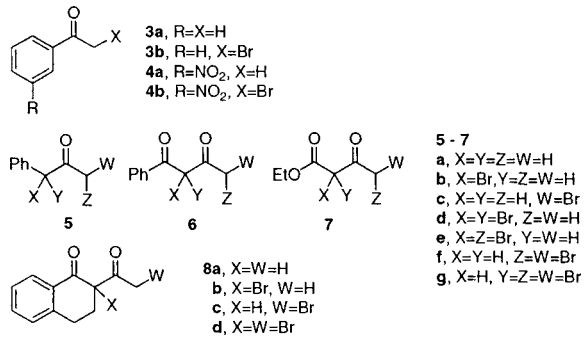


Figure 2. Compound list.

Many reagents for reduction of α-bromoketones have been developed: (i) reducing agents, e.g., zinc in acetic acid,[3] alkyltinhydride,[4] vanadium(II) chloride,[5] silicon hydride,[6] borohydride,[7] stannous chloride,[8] titanium(III) salts,[9] sodium bisulfite,[10] and benzimidazolines;[11] (ii) nucleophilic reducing agents, e.g., NaI/chlorotrimethylsilane,[12] organophosphine,[13] telluroates,[14] thiols,[15] selenols,[16] amines,[17] and anionic iron complex;[18] (iii) heterogeneous hydrogenation;[19] and (iv) homogeneous Pd-catalyzed hydrogenation.[20] However, to our knowledge, there has been no report on hydrobromic acid as a reducing agent of α-bromoketones.

During our research on the possibility of hydrobromic acid as a reducing agent, we found that the addition of hydrobromic acid causes reversible isomerization such as those published reports[2] and discovered that HBr causes irreversible debromination when added with a scavenger of bromine (*first discovery*). We also found that the doubly activated *internal* position is more rapidly brominated[21] and debrominated than the singly activated *terminal* position (*second discovery*).

In the case of bromination at the more activated α-position of unsymmetrical ketones, the required α-bromoketones can be obtained by direct bromination. However, there is a synthetic difficulty in the preparation of α-bromoketones brominated at the less activated α-position. There are some reports on synthetic methods of unsymmetrically brominated α-ketones: bromination of epoxides,[22] oxidation of olefins by sodium bromite,[23] bromodecarboxylations,[24] and bromodeacylations;[25] however, all of them have synthetic limits as general applications for the preparation of unsymmetrical α-bromoketones.

Table 2. Kinetic Bromination (Short Reaction Time)[a]

		time	product (%)[b]			
entry	reactant	(min)	reactant	internal	terminal	other
1	**5a**	10	**5a** (3)	**5b** (87)	**5c** (1)	**5e** (9)
2	**6a**	1	**6a** (6)	**6b** (80)	**6c** (5)	**6e** (9)
3	**7a**	1	**7a** (8)	**7b** (75)	**7c** (7)	**7d** (6)
4	**8a**	10	**8a** (0)	**8b** (100)	**8c** (0)	

[a] Reaction conditions: Br_2 (1.0 equiv) was added, and acetic acid was used as a solvent. [b] NMR integral ratio yield.

In this report, we have tried to discover a new synthetic method for the preparation of α-bromoketones that are brominated at the less activated *terminal* position of unsym-

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Table 3. Thermodynamic Bromination (Long Reaction Time)[a]

entry	reactant	time (h)	product (%)[b] reactant	internal	terminal	other
1	**5a**	24	**5a** (11)	**5b** (56)	**5c** (13)	**5e** (20)
2	**6a**	3	**6a** (19)	**6b** (0)	**6c** (62)	**6f** (19)
3	**7a**	3	**7a** (7)	**7b** (0)	**7c** (86)	**7f** (7)
4[c]	**8a**	3	**8a** (17)	**8b** (45)	**8c** (19)	**8d** (10)

[a] Reaction conditions: Br_2 (1.0 equiv) was added, and acetic acid was used as a solvent. [b] NMR integral ratio yield. [c] Yield of terminal product **8c** was increased by longer reaction times: after 16 h, **8a**:**8b**:**8c** = 3:3:2; in addition, the solution was darkened, and some decomposition occurred.

metrical ketones. As the first step, to investigate the reactivity of unsymmetrical ketones, two kinds of reaction conditions were tested as shown in Tables 2 and 3. Brominations in short reaction times (kinetically controlled) provided the internally brominated compounds as a major product (Table 2).[21] However, Table 3 shows that brominations in longer reaction times (thermodynamically controlled) gave the more terminally brominated compound through the reversible reaction by Br_2 and produced hydrogen bromide.[26] Although there were many reports on the rearrangement of α-bromoketones, there were no reports on the selective preparation of bromination in the less activated *terminal* position of unsymmetrical ketones using this bromine rearrangement. By controlling the reaction time, we could obtain **7c** in an acceptable yield, but the yields of the others (**5c**, **6c**, and **8c**) were not good.

Table 4. 1,3-Dibromination of Phenylacetone (**5a**)[a]

reactant	temp	time	product yield (%) **5b**	**5c**	**5e**	**5g**
5a	rt	5 min	7.4	1.5	73.7	13.3
5a	rt	24 h	3.9	0.8	77.2	15.4
5a	80 °C	30 min	6.2	1.5	76.8	15.3

[a] Reaction conditions: Br_2 (1.0 equiv) was added, and acetic acid was used as a solvent. [b] NMR integral ratio yield. [c] Yield of terminal product **8c** was increased by longer reaction times: after 16 h, **8a**:**8b**:**8c** = 3:3:2; in addition, the solution was darkened and some decomposition occurred.

From the conjunction of *the first* and *second discoveries*, we designed a new synthetic route for the selective preparation of *terminal* bromocompounds composed of nonselective bromination and selective debromination by hydrogen bromide and a scavenger as shown in Scheme 1. Table 4 shows

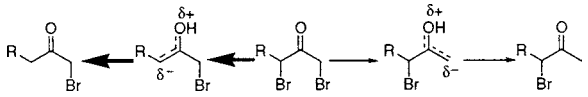
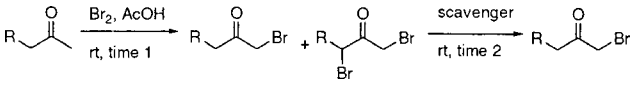


Figure 3. Irreversible debromination with scavenger.

the nonselective 1,3-dibromination of phenylacetone as a sample compound by 2 equiv of bromine, wherein **5e** was obtained as a major product and **5g** was obtained as a minor product, which also can be debrominated to **5c**.

Table 5. Selective Preparation of Various *Terminal* Bromo Compounds by the General Procedure, Including Nonselective Bromination−Selective Debromination



reactant/Br_2 (equiv)	time1/time 2 (h/h)	scavenger[a] (equiv)	isolated yield (%)[b] reactant	internal	terminal	other
5a (2.2)[c]	6/30	A	**5a** (5)	**5b** (3)	**5c** (85)	**5e** (3)
6a (1.3)	2/30	H (0.6)	**6a** (11)	**6b** (0)	**6c** (85)	**6f** (1)
7a (1.5)	0.5/1	H (1.3)	**7a** (3)	**7b** (0)	**7c** (90)	**7f** (3)
8a (2.0)[d]	3/0.5	A	**8a** (0)	**8b** (0)	**8c** (95)	**8d** (0)

[a] Scavenger A = acetone; scavenger H = 1,4-hydrobenzoquinone. [b] In cases where acetone was used as a scavenger, byproduct that is thought to be produced from bromoacetone makes separation by column chromatography difficult; therefore, byproduct was removed by keeping the mixture in vacuo for over 6 h. [c] Concentrated HBr was added. No addition of concentrated HBr increases the amount of **5a**. [d] Product **8c** is relatively stable in an acidic reaction medium; however, after extraction, decomposition was observed within 1 h.

Consequently, several brominated compounds at the *terminal* position were successfully prepared through the new synthetic route shown in Scheme 1, and the results are shown in Table 5. After 1,3-dibromination of the reactant by addition of around 2 equiv of bromine and stirring for a long time at room temperature, followed by addition of the scavengers, the *terminal* bromo compounds were produced through the irreversibly selective debromination on the *internal* bromides of the 1,3-dibromo compound as shown in Figure 3. The scavenger was added after confirmation of the disappearance of *internal* bromo compounds (**5b**, **6b**, **7b**, and **8b**), because (**5b**, **6b**, **7b**, and **8b**) revert to starting materials after debromination. In all of the cases, the *terminal* compounds were obtained in more than 85% yields. In the cases of **6a** and **7a**, *internal* bromo compounds (**6b** and **7b**) were not detected when less than 2 equiv of bromine were used.

In conclusion, we discovered a new reducing system of α-bromocarbonyl compounds using hydrobromic acid in the presence of a scavenger of generated bromine. Using the selective debromination, we could selectively prepare bromo compounds that are brominated on the less activated α-posi-

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tion of carbonyl from the mixture of polybrominated compounds. This new method, bromination and selective debromination, is useful because it is cheap and easy to use, providing the selectively brominated product in high yields. This method is useful for preparing 1-bromo-3-phenylacetone, which cannot be prepared by either kinetically or thermodynamically controlled reaction conditions and can only be prepared by bromination following selective debromination.

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Supporting Information Available: Experimental procedures including characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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