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Silver-Catalyzed Ring-Opening Bromination of Unstrained Cycloalkanols.

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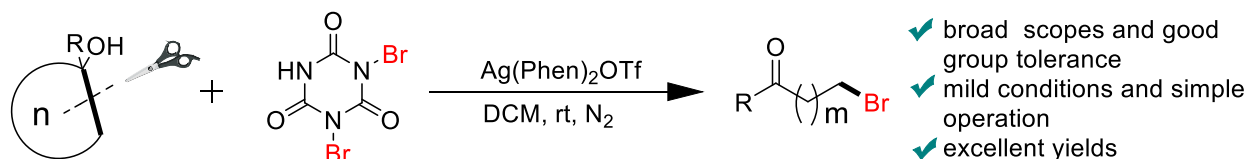
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Abstract: A new method for the bromination of unstrained cycloalkanols through silver catalysis has been reported. Using $\text{Ag(Phen)}_2\text{OTf}$ as the catalyst and dibromoisocyanuric acid as the brominating reagent, the unstrained cycloalkanols undergo a ring-opening bromination reaction under mild conditions, yielding the corresponding alkyl bromides. The method is operationally simple, affords excellent yields, and exhibits good functional group tolerance.

Keywords: silver catalysis; dibromoisocyanuric acid; distal brominated ketones; ring-opening reaction; unstrained cycloalkanols

Introduction

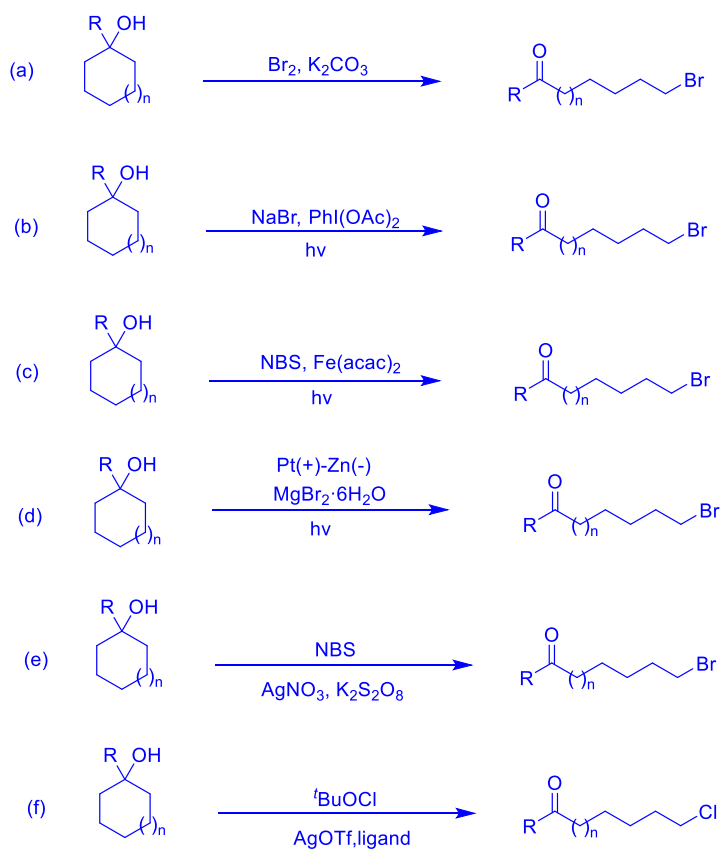
As important building blocks in organic synthesis, alkyl bromides containing carbonyl groups have been widely applied in the field of synthetic chemistry due to their excellent reactivity. These compounds, with their diverse reactivity and transformation potential, have become key intermediates for constructing complex molecular structures.[1-4] For example, remote unsaturated ketone compounds that widely distributed in various natural substances and medicinal components [5-7] could be directly prepared from the corresponding alkyl bromides. Due to extensive and inexpensive of cycloalkanols existed in organic synthesis.[8-16] It is important to establish ring-opening bromination reaction of cycloalkanols, through the ring-opening and crosscoupling strategy.[17]

In recent years, significant progress has been made in the research on the synthesis of distal brominated ketones through the ring-opening reaction of strained cycloalkanols.[18-19] Nevertheless, such methods are depended on the ring strain characteristics of the substrates, so their applicability is relatively limited. In contrast, unstrained cycloalkanols, as potential ketone alkylating reagents, not only enable selective control at the distal position by adjusting the ring

size but also introduce various different functional groups, providing new synthons for the synthesis of distal brominated unsaturated ketones.[20-23] However, due to the higher stability of the carbon rings in non-strained cycloalkanols, their ring-opening reactions pose greater challenges. In 2000, pioneering work was first reported in Li group that cycloalkanols could undergo ring-opening bromination under the presence of liquid Br₂ and K₂CO₃ (**Scheme 1a**).[24] Even though the protocol could be applied to both strained and unstrained cycloalkanols, the method suffered from poor substrate scope since liquid Br₂ had poor compatibility with most of the other functional groups, let alone the toxicity, corrosivity and inconvenience of handling the reagent. Thereafter, Wang group, Zeng group and Onomura group independently developed a photo-promoted strategy for ring-opening bromination of cycloalkanols, which provided a practical and straightforward way to obtain distal brominated ketones.[25-27] However, light condition was not friendly to the desired brominated products since they were readily to decompose under light irradiation, especially for tertiary bromides (**Scheme 1b-1d**).[25-27] Recently, the Zhu group developed a silver-catalyzed ring-opening bromination of cycloalkanols under photoredox catalysis (PC) with hypervalent iodine reagents, using NBS as the bromine source (**Scheme 1e**).[28] The method avoided the light-induced decomposition disadvantage aforementioned but still had drawbacks such as external oxidant K₂S₂O₈ was needed. Hence, considering the importance of distal brominated ketones, a more practical and effective protocol to accomplish the goal of ring-opening bromination of cycloalkanols under mild conditions with good functional group compatibility was in highly desirable. Recently, Zhang' s group developed a protocol for chlorination of cycloalkanols using ^tBuOCl as both oxidant and Cl source (**Scheme 1f**).[29] Herein, we describe a new approach to synthesize distal brominated ketones through silver-catalyzed ring-opening bromination of cycloalkanols, which uses

dibromoisocyanuric acid (DBI) as both oxidant and Br source (**Scheme 1g**). This method has broad substrate scope and excellent functional group compatibility, which can build remote brominated aliphatic ketones in one step.

previous work



this work



Scheme 1 The ring-opening halogenation of cycloalkanols

Results and Discussion

To commence the study, 1-phenylcyclohexanol **1a** was used as the model substrate for optimizing the reaction conditions (**Table 1**). Firstly, the brominating reagents were screened with Ag(Phen)₂OTf as the catalyst (**entries 1-3, Table 1**). The results showed that when dibromoisocyanuric acid (DBI) was used as the brominating reagent, the expected product **2a** was obtained in a yield of 88%. However, no reaction occurred when NBS (N-bromosuccinimide) was used, and similarly, no product was observed with NBA (N-bromoacetamide) as the brominating reagent. Secondly, the effects of different silver catalysts were compared using DBI as the brominating reagent (**entries 1 and 4-5, Table 1**). When AgOTf was used as the catalyst, the reaction did not occur, which might be due to the insolubility of AgOTf in DCM. Subsequently, when the Ag(Phen)₂NO₃ was employed as the catalyst, the product yield decreased to 46%. When the amount of DBI was reduced to 0.8 equiv, the product yield dropped to 72%, whereas increasing the DBI amount to 1.5 equiv. resulted in a yield of 78% (**entries 6-7, Table 1**). When the amount of Ag(Phen)₂OTf decreased from 10 mol% to 5 mol%, the yield decreased to 48% (**entry 8, Table 1**). Increasing the amount of Ag(Phen)₂OTf to 20 mol%, the product yield slightly increased to 89% (**entry 9, Table 1**). Finally, the solvents were screened and DCM was proved to be the optimal (**entries 10-15, Table 1**). Furthermore, the control experiment confirmed the catalytic effect of Ag(Phen)₂OTf (**entry 16, Table 1**).

Table 1. Optimization of the Reaction Conditions.

Entry ^a	Catalyst (mol %)	[Br] (equiv.)	Solvent	Yield ^b (%)
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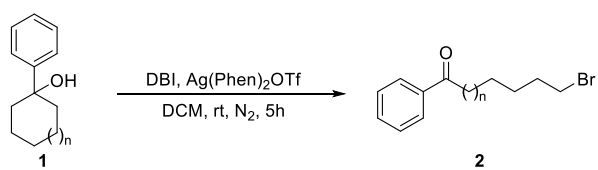
1	Ag(Phen) ₂ OTf (10)	DBI (1.0)	DCM	88 (80 ^c)
2	Ag(Phen) ₂ OTf (10)	NBS (1.0)	DCM	0
3	Ag(Phen) ₂ OTf (10)	NBA (1.0)	DCM	0
4	AgOTf (10)	DBI (1.0)	DCM	0
5	Ag(Phen) ₂ NO ₃ (10)	DBI (1.0)	DCM	46
6	Ag(Phen) ₂ OTf (10)	DBI (0.8)	DCM	72
7	Ag(Phen) ₂ OTf (10)	DBI (1.5)	DCM	78
8	Ag(Phen) ₂ OTf (5)	DBI (1.0)	DCM	48
9	Ag(Phen) ₂ OTf (20)	DBI (1.0)	DCM	89
10	Ag(Phen) ₂ OTf (10)	DBI (1.0)	CH ₃ CN	72
11	Ag(Phen) ₂ OTf (10)	DBI (1.0)	CH ₃ CN/H ₂ O	40
12	Ag(Phen) ₂ OTf (10)	DBI (1.0)	Acetone	48
13	Ag(Phen) ₂ OTf (10)	DBI (1.0)	Acetone/H ₂ O	20
14	Ag(Phen) ₂ OTf (10)	DBI (1.0)	THF	17
15	Ag(Phen) ₂ OTf (10)	DBI (1.0)	MeOH	trace
16	none	DBI (1.0)	DCM	0

^a Standard Conditions: **1a** (0.2 mmol), [Br] reagent, catalyst, solvent (2.0 mL), at room temperature under N₂ for 5 h. ^b Isolated yields based on **1a**. ^c Scale-up Reaction: **1a** (1 mmol), [Br] reagent, catalyst, solvent (10.0 mL), at room temperature under N₂ for 5 h, and the isolated yield was 80%

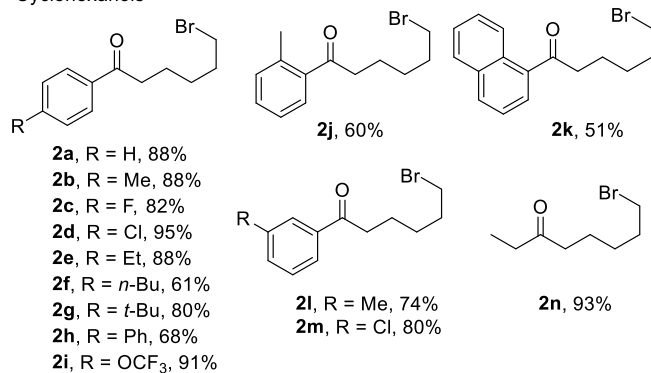
After obtaining the optimal reaction conditions, the applicability of the substrate was investigated (**Table 2**). Initially, the ring-opening bromination reactions of various cyclohexanols were investigated with different substituents. Aryl-substituted substrates containing electron-withdrawing or electron-donating groups generally afforded the desired products **2a-2m** in good to excellent yields (51%-95%). The position of the substituent on the aromatic ring had no

significant effect on the reaction efficiency. The naphthalene derivative was successfully transformed to the corresponding product in a moderate yield. Besides the aryl-substituted cyclohexanol, the alkyl-substituted 1-ethylcyclohexanol was also suitable substrates for this transformation, providing distal bromodifatty ketones **2n** in good yield. Next, the ring-opening bromination reactions of cyclopentanols containing different substituents were investigated. The results demonstrated that both aryl- and alkyl-substituted cyclopentanols proceeded smoothly to give the corresponding products **2o-2y** in excellent yields (63%-96%). Furthermore, the ring-opening bromination of cyclobutanols, cycloheptanols, and cyclooctanols with various functional groups also reacted efficiently, affording the corresponding distally brominated ketones **2z-2af**, **2ah-2ai** in 60%-92% yields. Notably, even macrocyclic substrates such as cyclododecanols also could effectively transferred through the ring-opening reaction into the distally brominated aliphatic ketone **2ag** in 71% yield-a product that was very challenging to synthesize using conventional methods. Scale-up reaction using **1a** still could provide a good yield (**Table 1**, **footnote c**).

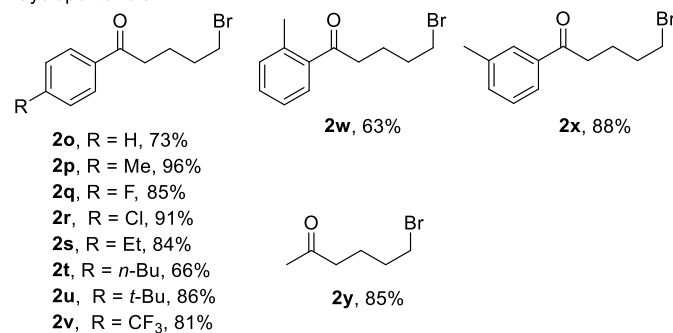
Table 2. Substrate scope



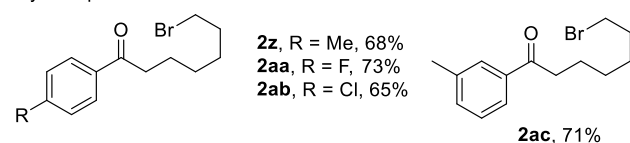
Cyclohexanols



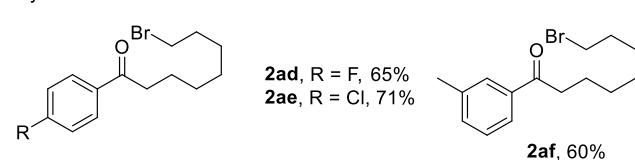
Cyclopentanols



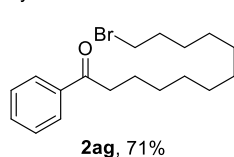
Cycloheptanols



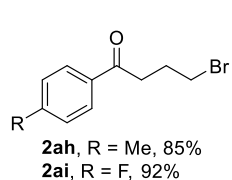
Cyclooctanols



Cyclododecanols



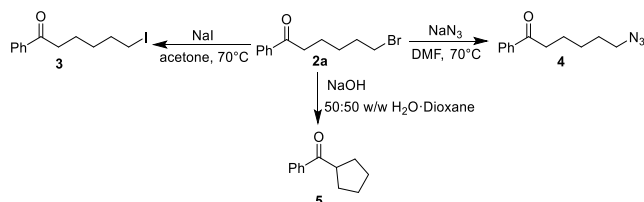
Cyclobutanols



Standard Conditions: **1a** (0.2 mmol, 1 equiv.), [Br] reagent, catalyst (10 mol%), solvent (2.0 mL), at room temperature under N₂ for 5 h.

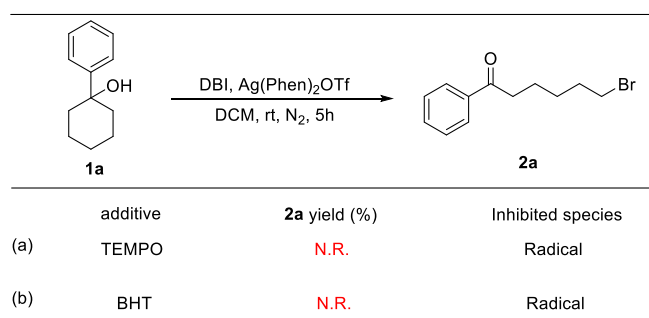
To demonstrate the applicability of this method, the products were converted into other valuable molecules through halogen exchange reactions, nucleophilic substitutions and cyclization reactions (**Scheme 2**). First, via the halogen exchange reaction, **2a** was readily

transformed into the alkyl iodide **3** in 86% yield.[30] Then, **2a** could be easily substituted by an azide to form the C–N bond **4** in 87% yield.[31] Furthermore, **2a** was successfully converted into benzoylcyclopentane **5** through a cyclization reaction in a yield of 80%.[32]



Scheme 2. Transformations of Products

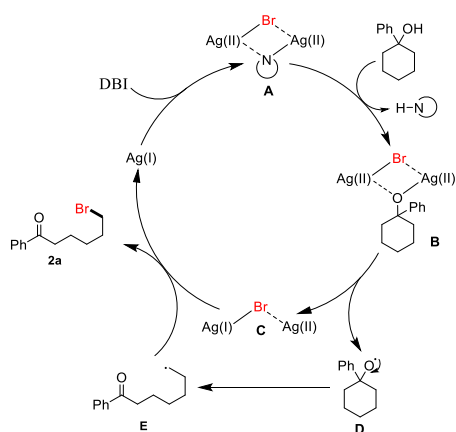
To investigate the reaction mechanism, two control experiments were conducted under standard conditions using the radical scavengers 2,2,6,6-tetramethyl-1-piperidinyloxy (**TEMPO**) and butylated hydroxytoluene (2,6-di-tert-butyl-4-methylphenol) (**BHT**). The results showed that the reactions were completely inhibited in both cases (**Schemes 3a and 3b**), suggesting that the transformation may proceed via a radical pathway.



Scheme 3. Control Experiments

Based on the above results and literature reports, a possible mechanism was proposed (**Scheme 4**).[29,33] Firstly, the complex of Ag(I) species reacts with DBI to form the Ag(II) intermediate complex **A**. Then, **A** undergoes ligand exchange with alcohol to obtain intermediate

B. Intermediate **B** undergoes homolytic cleavage to yield Ag(I) species **C** and alkoxy radical **D**. The alkoxy radical **D** rearranges to produce a carbon-centered radical **E**. Finally, radical **E** reacts with **C** to afford the target product **2a**, while the silver species is reduced from divalent back to monovalent, completing the catalytic cycle. In this reaction, DBI serves a dual role as both the oxidant and the bromine source simultaneously, demonstrating the advantage of atomic economy in this reaction.



Scheme 4. Plausible Mechanism

Conclusion

In general, we have developed a silver-catalyzed ring-opening bromination reaction of unstrained cycloalkanols. This conversion employs commercially available dibromoisocyanuric acid as the bromine source and requires no additional oxidant. This reaction features mild conditions and excellent yields which enables one-step construction of distally brominated aliphatic ketones, demonstrating significant synthetic value and high application potential.

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Author Contributions

All authors contributed to the preparation of this manuscript.

Notes

The authors declare no competing financial interests.

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