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Synthesis of γ-halogenated ketones via the Ce(IV)-mediated oxidative coupling of cyclobutanols and inorganic halides

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Abstract

A straightforward method for the synthesis of γ-halo-substituted ketones formed via the CAN-initiated oxidative addition of halides to 1-substituted cyclobutanols has been developed. This method has short reaction times, and provides access to a range of bromo and iodo γ-substituted ketones in good to excellent yields.

Keywords

CAN; Cyclobutanol; γ-Substituted ketone; Oxidative coupling

1. Introduction

Ketones with γ-halo substitutions are useful starting materials for the synthesis of biologically active compounds. The γ-substituted ketone moieties in neurological agents such as spiperidol and haldol (Fig. 1) are incorporated by utilizing γ-chloro ketones in particular as starting materials.[1,2] Ketones with γ-chloro substitutions have been used also in the synthesis of antagonists for the melanin-concentrating hormone (MCH_1) receptor.[3] The ability to efficiently generate starting materials containing γ-halo ketone subunits has the potential to greatly impact the synthesis of novel, pharmaceutically active compounds.

Although γ-substituted ketone functionalities have been incorporated into molecules traditionally through γ-chloro ketones, the use of other γ-halo ketones such as γ-iodo or bromo ketones may be synthetically beneficial since these halides are better leaving groups than chloride. However, the synthetic approaches to structurally diverse γ-halo ketones have been limited to only a handful of synthetic routes for γ-chloro and a few γ-bromo ketones. While there is no general method for producing γ-chloro ketones, both aryl- and aliphatic γ-chloro ketones can be synthesized via Friedel–Crafts or Grignard reactions.[4] Typically, γ-iodo and bromo ketones are produced by refluxing γ-chloro ketones in the presence of either iodide or bromide. While useful, these conversions typically require long reaction times and superstoichiometric amounts of the desired halide.[5] The development of a general and direct route to γ-iodo and bromo ketones would be of interest.

Cerium(IV) reagents, namely cerium(IV) ammonium nitrate (CAN), have been used extensively by organic chemists as single-electron oxidants.[6] CAN has proven to be a cost-effective, versatile reagent that is capable of mediating novel carbon–carbon and carbon–

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Supplementary data
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heteroatom bonds.7,8 Previous research from our group has shown that β-substituted ketones are accessible through the use of CAN.9 By selectively oxidizing an inorganic anion in the presence of a 1-substituted cyclopropanol with CAN, the generated inorganic radical was added to the cyclopropanol resulting in ring opening. After a subsequent oxidation of the radical intermediate and deprotonation, β-substituted ketones were produced in very good to excellent yields. In addition to quick reaction times, these reactions worked for both 1-aryl- and 1-alkyl-cyclopropanols as well as a variety of inorganic anions. Based on this precedent, we sought to examine whether this method could be extended to 1-substituted cyclobutanols thereby providing access to γ-substituted ketones. The results of these studies are presented herein.

2. Results and discussion

To examine the breadth of γ-substituted compounds that could be achieved from the oxidation of inorganic anions with CAN, both 1-aryl- and 1-alkyl-cyclobutanols were synthesized. These starting materials were generated via the reaction of cyclobutanone, or 2-ethyl-cyclobutanone for **1f**, with a variety of Grignard reagents.[10,11] The reactions produced acceptable product yields, and were purified by nonchromatographic methods. The 1-phenyl-cyclobutanol (**1a**) was purified by recrystallization from *n*-pentane at reduced temperature (−20 °C). Substrates **1c,f** were synthesized quantitatively and required no additional purification. For all other starting materials (**1b,d** and **e**), short-path distillations at reduced pressure were used to purify gram quantities of the desired compounds.

In an initial study, sodium iodide (NaI) was oxidized with CAN in the presence of substrate **1a** using reaction conditions [20% H_2O/acetonitrile (MeCN)] previously employed for the oxidative addition of inorganic anions to 1-substituted cyclopropanols.[9] While γ-iodo ketone **2a** was generated as the major product, multiple side products were observed by ^{1}H NMR analysis of the crude reaction mixture. Since changes in solvent often times can impact the chemoselectivity of reactions initiated by CAN, several solvent systems were examined to determine if the reaction yield could be improved.[12] Among the solvent systems screened, ^{1}H NMR analysis showed that 20% H_2O/1,2-dimethoxyethane (DME) generated **2a** almost exclusively. As a result, this solvent system was utilized for the other unsubstituted substrates. As shown in Table 1, γ-iodo ketones **2a–e** were obtained in good to very good isolated yields for both 1-aryl- and 1-alkyl-cyclobutanols.

To examine the regioselectivity of the ring opening, **1f** was subjected to the same reaction conditions. While product **2f** was formed exclusively, the reaction mixture contained unreacted starting material. After scanning a series of solvent and reaction conditions, optimal yields of **2f** were obtained in 20% H_2O/MeCN at 0 °C.

Next, the synthesis of γ-bromo ketones was examined. In previous work on the synthesis of β-substituted ketones, the oxidation of bromide anion by CAN was shown to be relatively slow compared to the oxidation of iodide. In order to avoid the possibility of direct oxidation of **1a–f** by CAN, these brominations were performed in a two-phase solvent system of 50% H_2O/methylene chloride (CH_2Cl_2).[14] In an initial experiment, the bromination of **1a** using potassium bromide (KBr) as the bromide anion source provided **3a** in an 87% isolated yield (Table 2). Under similar experimental conditions, the bromination of aryl substrates **1b–c** produced **3b–c** in good to excellent yields. While complete conversion to **3f** was not achieved even at reduced temperatures, bromination of **1f** exhibited the same regioselectivity as the iodination. Surprisingly, reactions of 1-alkyl-cyclobutanols **1d–e** produced **3d–e** in yields of less than 20%. Examination of GC–MS and ^{1}H NMR data showed that brominations of **1d–e** resulted in a mixture of starting material, desired γ-bromo ketone and α,γ-dibrominated ketones.

The presence of α-brominated products suggests formation of molecular bromine during the course of the reaction. A series of experiments were performed to determine if this supposition was correct (Table 3). Ketone **4** was used in these experiments since it is structurally similar to the starting material **1d** and product **3d**. Initially, 1 equiv of **4** was reacted with 0.5 equiv of molecular bromine (entry 1). In a subsequent experiment, substrate **4** was reacted with an equivalent of both CAN and KBr, which should generate an equal amount of molecular bromine if bromine atom homocoupling occurs following oxidation. Experiments contained in entries 1 and 2 show identical ratios of **5**:**4**, a finding consistent with in situ formation of molecular bromine. Interestingly, the yield of **5** was increased by the addition of excess CAN (entry 3), an observation which is indicative of a larger mechanistic role of cerium beyond oxidation, presumably through Lewis acid activation.

From the data obtained, the mechanistic pathway shown in Scheme 1 is proposed. Initially, bromine anion is oxidized by CAN to bromine radical, which adds to the 1-substituted cyclobutanol **1d**. Bromine atom addition to cyclobutanols is supported by the observation that no γ-substituted products were obtained when **1d** was treated with molecular bromine. The intermediate **1d′** generated from the ring opening of **1d** is less stable than the corresponding benzylic radicals of 1-aryl-cyclobutanols **1a–c**. As a result, 1-alkyl-cyclobutanols are expected to be less reactive allowing homocoupling of bromine atoms to become a competitive pathway. Following a second oxidation by CAN of **1d′** and deprotonation, molecular bromine adds α to the carbonyl of **3d** producing the α,γ-dibrominated ketone **3d′**.

Since bromination was only successful in the case of 1-aryl-substituted cyclobutanols, other oxidants were examined to determine whether the desired products could be obtained. Iodinations and brominations with NaI and KBr were performed with Cu-ClO_4·$6H_2O$ in MeCN.[16] However, only a complex mixture of reactions products was obtained, none being the γ-haloketone. The use of ferrocenium hexafluorophosphate in CH_2Cl_2 provided only unreacted starting material in all cases.[17]

Due to the rapid evolution and applications of ‘click chemistry’, direct routes to incorporation of azide into molecules would be very useful in synthesis. The extension of this approach to the oxidative addition of azide to 1-substituted cyclobutanols was examined. Unfortunately, oxidative addition of azide anions to 1-substituted-cyclobutanols has been disappointing thus far. When 1 equiv of sodium azide (NaN_3) was oxidized by CAN in the presence of 1 equiv of **1a–e**, evolution of nitrogen gas was observed even at reduced temperatures providing only starting material after reaction work-up. Even though azide anion is oxidized much faster than **1a–e** by CAN, the homocoupling of azide radicals and subsequent decomposition to evolve N_2 gas are favoured over radical addition to cyclobutanols. When 5 equiv excesses of NaN_3 and CAN were used with 1 equiv of **1a**, equal amounts of the desired γ-azido product and the γ-nitrato compound were generated with isolated yields of less than 20%. Although the synthesis of γ-azido ketones using this method was inefficient, subsequent transformations using the accessible γ-iodo and bromo products can produce other substrates including azides and nitriles.[18,19]

Since CAN is a versatile single-electron oxidant capable of oxidizing a variety of functional groups, this Ce-mediated protocol may appear to be incompatible with more complex substrates. However, rate studies performed by our research group have shown that the oxidation of inorganic anions by CAN is extremely fast indicating that these reagents are oxidized preferentially to other functional groups. Additionally, previous studies on the relative rates of oxidation of substrates and functional groups have shown that selective oxidations can be achieved using CAN.[9,20] As a result, this protocol should be applicable to

complex molecules providing that substrates do not contain functional groups with rates of oxidation similar to inorganic anions.

3. Conclusions

An alternative route to both γ-iodo and γ-bromo ketones has been developed. The synthesis of γ-iodo ketones from 1-substituted cyclobutanols is general producing both aryl- and alkyl-γ-iodo ketones in good to very good yields. While the synthesis of aliphatic γ-bromo ketones proved to be more difficult, 1-aryl-γ-bromo ketones were obtained in good to excellent yields. In both cases, the halide was shown to add selectively to the least hindered carbon of the cyclobutanol. This method has short reaction times, and provides access to a range of structurally diverse γ-halo ketones that can be used as starting materials for the synthesis of more complex compounds containing γ-substituted ketones.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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11. *General procedure for the synthesis of 1-substituted cyclobutanols:* All glassware was flame-dried before use. Cyclobutanone (13.4 mmol) was dissolved in 25 mL of diethyl ether and purged with N_2. The temperature was reduced to 0 °C. The appropriate Grignard reagent (14.7 mmol) was added dropwise with stirring. The reaction was allowed to stir for an additional 3 h. Water was added slowly to quench the reaction. The organic layer was removed, and the aqueous layer was extracted three times with ether. The organic layers were combined, dried with $MgSO_4$, filtered and concentrated. Pure 1-substituted cyclobutanols were then obtained by recrystallization from *n*-pentane at −20 °C (**1a**) or short-path, low pressure distillation (**1b,d** and **e**). Compounds **1c,f** were produced in quantitative yields and required no additional purification. ^{1}H NMR and ^{13}C NMR were used to assess purity, and are included in the Supplementary data. Tabulated experimental details and product yields are also included in the Supplementary data.
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13. *General procedure for the synthesis of γ-iodo ketones:* Sodium iodide (0.33 mmol) was dissolved in 1 mL of H_2O, and was added to the 1-substituted cyclobutanol (0.33 mmol) in 2 mL of DME. The reaction was then purged with N_2. CAN (0.67 mmol) was dissolved in 2 mL of DME, and was added dropwise via syringe with stirring. After stirring for 30 min, the volatiles were removed from the reaction via rotary evaporation. Water was added, and then extracted three times with diethyl ether. The organic layers were combined, dried with $MgSO_4$, filtered and concentrated. The γ-iodo ketones **2a**–**f** were purified further by flash chromatography using a 15% ethyl acetate/hexanes solution as the eluting solvent. ^{1}H NMR and ^{13}C NMR were used to assess purity, and are included in the Supplementary data.

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15. *General procedure for the synthesis of γ-bromo ketones:* Potassium bromide (0.33 mmol) was dissolved in 1vmL H_2O, and was added to the 1-substituted cyclobutanol (0.33 mmol) in 3 mL of CH_2Cl_2. The reaction was then purged with N_2. CAN (0.67 mmol) was dissolved in 2 mL H_2O, and was added dropwise via syringe with stirring. After stirring for 30 min, the volatiles were removed from the reaction via rotary evaporation. Water was added, and then extracted three times with diethyl ether. The organic layers were combined, dried with $MgSO_4$, filtered and concentrated. The γ-bromo ketones **3a**–**c** were purified further by flash chromatography using a 15% ethyl acetate:hexanes solution as the eluting solvent. ^{1}H NMR and ^{13}C NMR were used to assess purity, and are included in the Supplementary data.

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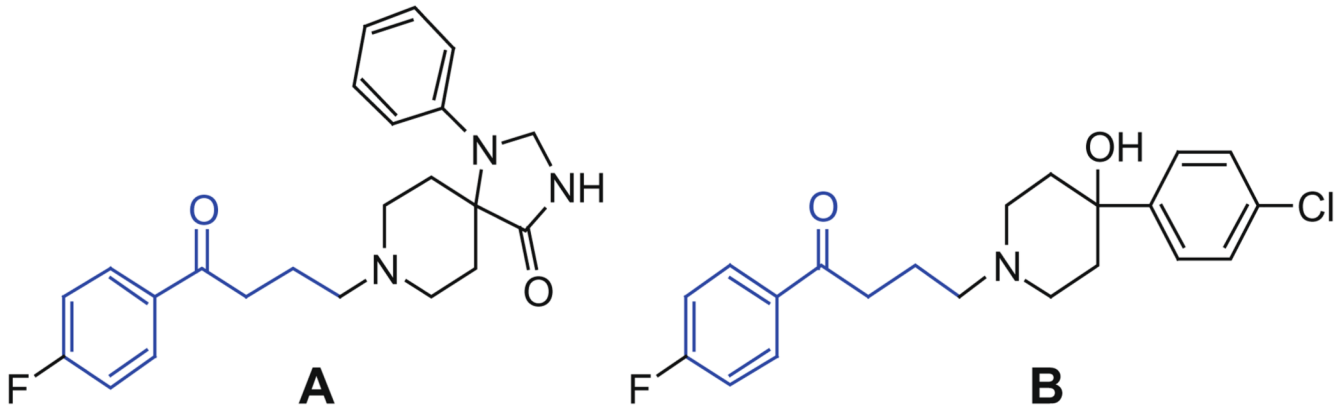
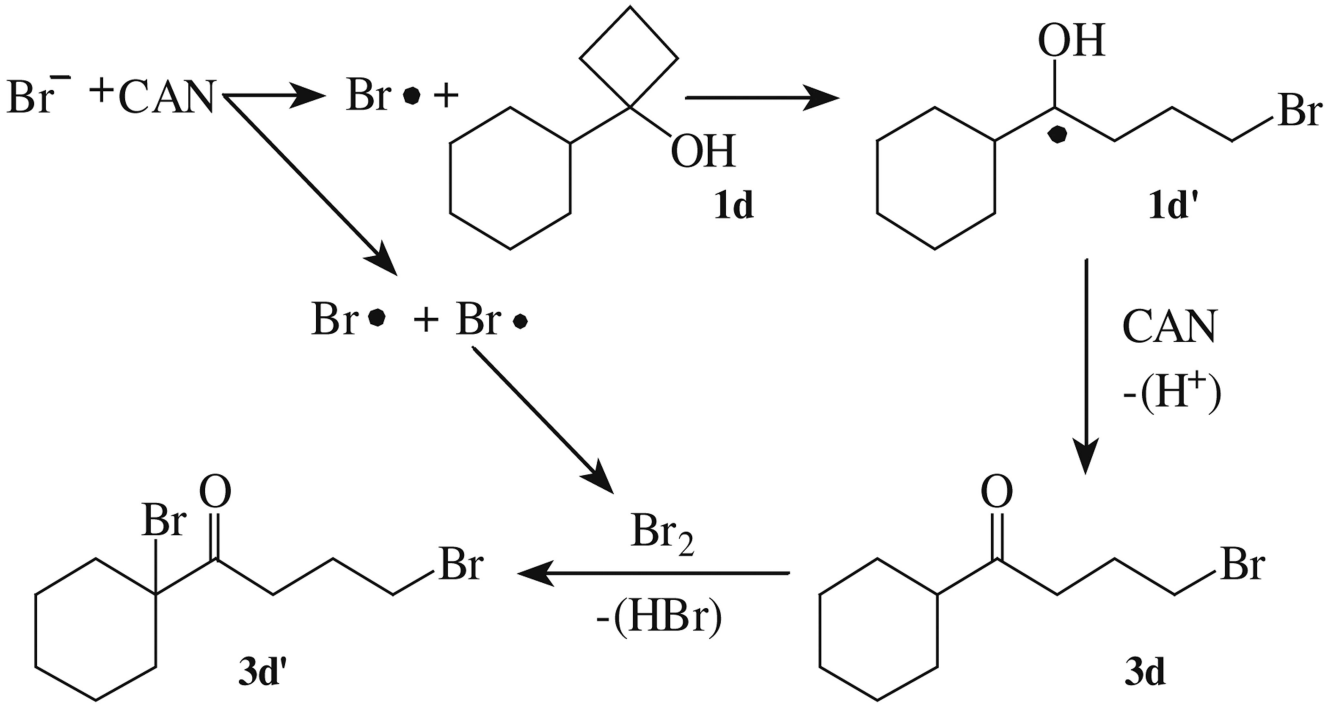


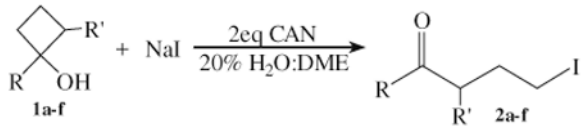
Figure 1.
Structures of spiperidol (**A**) and haldol (**B**).



Scheme 1.
Proposed pathway to dibrominated ketones.

Table 1

Synthesis of γ-iodo ketones[13]



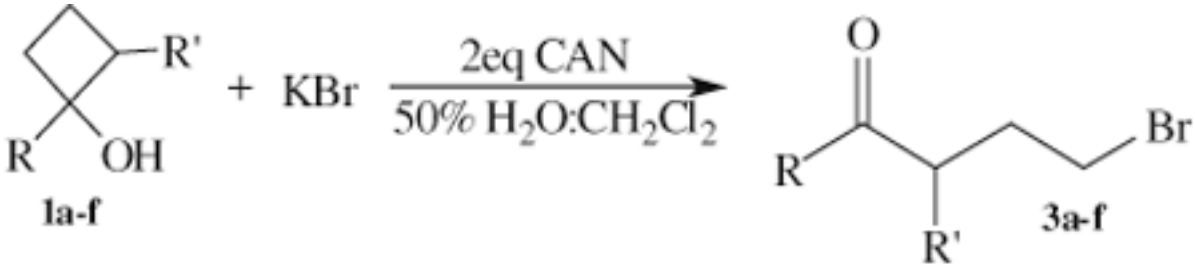
Substrate	Product	R	R′	Yield[a] (%)
1a	**2a**	Ph	H	79
1b	**2b**	*p*-CH_3O-Ph	H	67
1c	**2c**	*p*-F-Ph	H	79
1d	**2d**	Cyclohexyl	H	64
1e	**2e**	*n*-hexyl	H	80
1f	**2f**[b]	*p*-F-Ph	Et	80

[a] Isolated yield.

[b] Conditions: Reaction run at 0 °C in 20% H_2O/MeCN.

Table 2

Synthesis of γ-bromo ketones[15]



Substrate	Product	R	R′	Yield (%)
1a	**3a**	Ph	H	87[a]
1b	**3b**	*p*-CH_3O-Ph	H	70[a]
1c	**3c**	*p*-F-Ph	H	95[a]
1d	**3d**	Cyclohexyl	H	ND[b]
1e	**3e**	*n*-hexyl	H	ND[b]
1f	**3f**	*p*-F-Ph	Et	37[c]

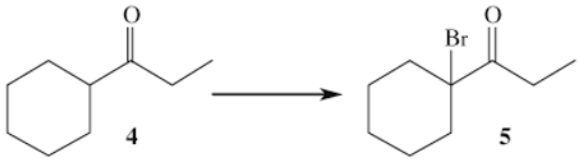
[a] Isolated yield.

[b] Mixture of 1-alkyl-cyclobutanol, γ-bromo ketone and α,γ-dibrominated ketones.

[c] Determined by ^1H NMR.

Table 3

α-Bromination of aliphatic substrates



Entry	Conditions[a]	Ratio (5:4)[b]
1	**4** (0.33 mmol), Br_2 (0.17 mmol)	3:1
2	**4** (0.33 mmol), KBr (0.33 mmol), CAN (0.66 mmol)	3:1
3	**4** (0.33 mmol), KBr (0.33 mmol), CAN (0.83 mmol)	9:1

[a] 50% H_2O/CH_2Cl_2.

[b] Ratios determined by GC.