Synthesis of γ-Halogenated Ketones via the Ce(IV)-Mediated Oxidative Coupling of Cyclobutanols and Inorganic Halides

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Introduction

The γ-substituted ketone moiety is an important structural feature in several biologically active compounds such as the drugs spiperidol (**A**) and Haldol (**B**) as well as antagonists for the melanin-concentrating hormone (**C**). The incorporation of this moiety into molecules usually involves a γ-halo ketone precursor. The ability to efficiently generate a variety of starting materials containing γ-halo ketone subunits has the potential to greatly impact the synthesis of novel, pharmaceutically active compounds.

Synthesis

Based on previous work involving Ce(IV)-mediated oxidative addition of inorganic anions to 1-substituted cyclopropanols, we sought to examine whether this method could be extended to 1-substituted cyclobutanols thereby providing access to γ-substituted ketones. The following table summarizes the results of this research.

Substrate	Product	R	R'	MX	Conditions[a]	Yield (%)
1a	2a	Ph	H	NaI	A	79[b]
1b	2b	*p*-CH_3O-Ph	H	NaI	A	67[b]
1c	2c	*p*-F-Ph	H	NaI	A	79[b]
1d	2d	cyclohexyl	H	NaI	A	64[b]
1e	2e	*n*-hexyl	H	NaI	A	80[b]
1f	2f	*p*-F-Ph	Et	NaI	B	80[b]
1a	3a	Ph	H	KBr	C	87[b]
1b	3b	*p*-CH_3O-Ph	H	KBr	C	70[b]
1c	3c	*p*-F-Ph	H	KBr	C	95[b]
1d	**3d**	**cyclohexyl**	**H**	**KBr**	**C**	**ND[c]**
1e	**3e**	***n*-hexyl**	**H**	**KBr**	**C**	**ND[c]**
1f	3f	*p*-F-Ph	Et	KBr	C	37[d]

[a] Conditions: (A) 20% H_2O:DME, (B) 20% H_2O:MeCN at 0°C and (C) 50% H_2O:CH_2Cl_2
[b] Isolated yields
[c] Mixture of 1-alkyl-cyclobutanol, *γ*-bromo ketone and *α,γ*-dibrominated ketones
[d] Determined by ^{1}H-NMR

Molecular Bromine

The presence of α-brominated products (**3d**-**e**) suggests formation of molecular bromine during the course of the reaction. The following series of experiments was performed to determine if this supposition was correct.

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

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**), suggesting a larger mechanistic role of cerium beyond oxidation, presumably through Lewis acid activation.

Proposed Mechanism

From the experimental data obtained, the following mechanism is proposed:

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Conclusions

An alternative route to both γ-iodo and γ-bromo ketones has been developed. The synthesis of γ-iodo ketones 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 more difficult, 1-aryl-γ-bromo ketones were obtained in good to excellent yields. This method 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.

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