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An improved preparation and a new application of trichloromethylcarbinols from enolizable ketones

Jing Li *, Brenden Derstine, Takahiro Itoh, Jaume Balsells *

Department of Process Chemistry, Merck Research Laboratories, 770 Sumneytown Pike, West Point, PA 19486, United States

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ABSTRACT

We report an improved method for the preparation of trichloromethylcarbinols from enolizable ketones. Trichloromethylcarbinols were obtained in good to excellent yields by using of a combination of $CHCl_3$, *n*-BuLi, and chlorotitanium (IV) triisopropoxide. Hydrolysis of the trichloromethylcarbinol to an α,β-unsaturated ester was also explored.

Introduction

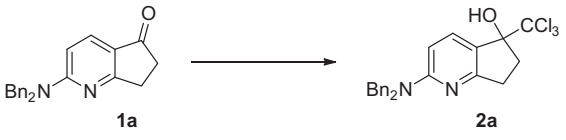
Trichloromethylcarbinols are very versatile intermediates in organic synthesis. It has been used for over a century to afford α-substituted carboxylic acids upon treatment with base and an appropriate nucleophile. Various nucleophiles have been explored in this Jocic-type process[1] such as hydroxide,[1] alcohol and phenol,[2] azide,[3] amine,[3i,4] fluoride,[2g,5] cyanide, [2g] hydride,[2f] and thiols.[2f] Other applications of trichloro-methylcarbinol include the formation of epoxides,[6] vinyl dichlorides[7], terminal alkynes,[8] and ring expanded ketones.[9]

The preparation of trichloromethylcarbinols usually involves base-promoted addition of chloroform to carbonyl compounds. Strong bases, such as *n*-BuLi, LiHMDS, potassium *tert*-butoxide in liquid ammonia, sodium in liquid ammonia, or powdered potassium hydroxide are commonly used.[10] Competing enolization is a major cause of low yield for enolizable ketone or aldehyde substrates. Although it has been reported that some mild amidine bases (like DBU) can promote the reaction between chloroform and carbonyl compounds, particularly aldehydes, this method has limited application on ketone substrates.[11] Corey's method of using decarboxylation of sodium trichloroacetate for addition reactions is also limited to aldehyde substrates.[12] $MgCl_2$ has been tried to suppress the ketone enolization. However, the poor solubility of $MgCl_2$ salts also introduced significant operational challenges, such as gumming and balling of salts and formation of emulsions during work up.[13] As an alternative, he developed an in situ formation of the otherwise difficult to handle trimethyl (trichloromethyl) silane and its application to the synthesis of TMS-protected trichloromethylcarbinols which, after deprotection, can provide trichloromethylcarbinols.[13]

In this Letter, we describe a simple and straightforward one-step method to synthesize trichloromethylcarbinols from sterically hindered and enolizable ketones by adding triisopropoxytitanium chloride. We also found further hydrolysis of the trichloromethylcarbinol moiety could lead to α,β-unsaturated esters, a new application for this versatile functional group.

Results

In the course of our research program, we were required to develop a scalable synthesis of trihalomethylcarbinol **2a** from ketone **1a** (Scheme 1). Several different conditions, such as $CHCl_3$/



Scheme 1. Initial substrate for ketone to trihalomethylcarbinol transformation.

* Corresponding authors. Tel.: +1 215 652 6603; fax: +1 215 652 7310 (J.L.); tel.: +1 215 652 6659; fax: +1 215 652 7310 (J.B.).
E-mail addresses: jing_li9@merck.com (J. Li), jaume_balsells@merck.com (J. Balsells).

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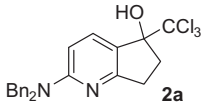
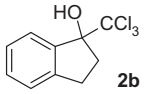
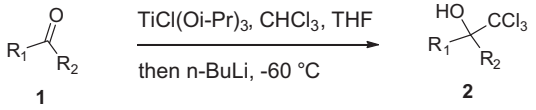
Table 1
Impact of $TiCl(OiPr)_3$ to $CHCl_3$/ketone addition reactions[a]

Product **2**	Assay yield[b] no additive (%)	Isolated yield[c] with $MgCl_2$ (%)	Isolated yield[c] with $TiCl(OiPr)_3$ (%)
 **2a**	0	—	91
 **2b**	28	41	78

[a] Reaction conditions: $CHCl_3$ (5 equiv), *n*-BuLi (5 equiv), $TiCl(OiPr)_3$ or $MgCl_2$ (0 equiv or 2 equiv), THF (0.5 M).
[b] Assay yield was determined by HPLC comparison with a standard solution of purified product.
[c] Purified by flash chromatography on silica gel.



1 **2**

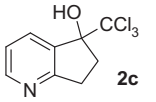
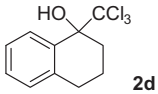
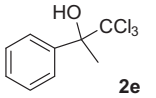
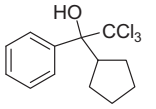
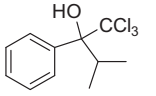
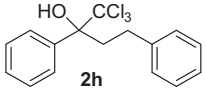
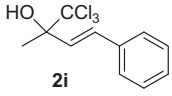
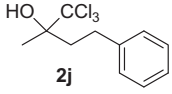
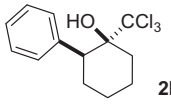
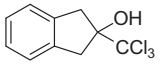
Scheme 2. Titanium promoted synthesis of trihalomethylcarbinol.

DBU, $CHBr_3$/LiOH, $CHBr_3$/LiHMDS, and $CHCl_3$/*n*-BuLi were investigated unsuccessfully. Most of the starting ketone remained unreacted under these conditions suggesting the reaction suffered from poor reactivity and stability of the chloroform carbanion as well as ketone enolization, which was apparent in the case of $CHBr_3$/LiHMDS, where trace amounts of α-bromination were observed as a byproduct of the reaction.

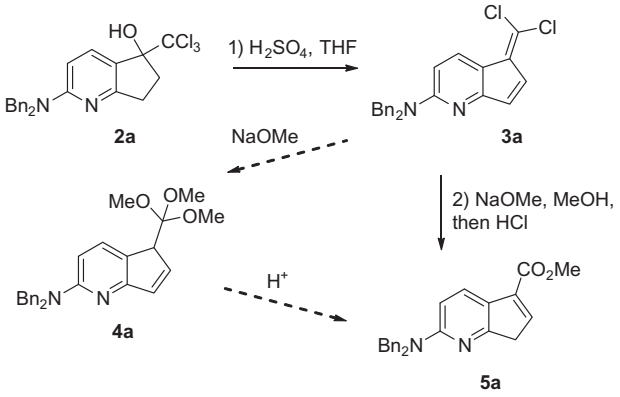
Scouting for an experimentally simple solution to suppress the enolization problem that would be amenable to the generation of multiple and diverse analogs, we turned our attention to the use of organotitanium reagents. Organotitanium reagents have been shown to be superior to traditional Grignard reagents for additions to sterically hindered and/or enolizable ketones.[14] Treatment of chloroform carbanion with $TiCl(OiPr)_3$ at a low temperature (−60 °C) followed by addition of the ketone starting material **1a** led to a clean conversion to the desired trihalomethyl-carbinol **2a**. Looking for the simplest possible experimental procedure, we explored the order of addition of the reagents and found that simply combining the ketone, $CHCl_3$, and $TiCl(OiPr)_3$ in cold THF and adding *n*-BuLi slowly provided a similar result. The drastic improvement on substrate **1a** encouraged us to explore the scope of this transformation. We started by carrying out the same comparison of reaction conditions on indanone **1b**. By comparison, the reaction without any additive only gave 28% assay yield, the reaction with 2 equiv $MgCl_2$ gave 41% isolated yield, while the reaction with 2 equiv $TiCl(OiPr)_3$ provided 83% assay yield and 78% isolated yield (Table 1).

The success of these experiments prompted us to examine the improved reaction conditions on a variety of other enolizable ketones (Scheme 2). The results summarized in Table 2 indicate that the titanium-promoted addition reaction works well on a number of ketones, including alkyl-aryl (entries 1–6), bisalkyl (entries 8–9), and α,β-unsaturated ketones (entry 7), to give the expected products in satisfactory yields. The presence of more sterically demanding branched alkyl groups (entries 4, 5, and 9) had no effect on the product formation as high yields were achieved in all of these examples. This protocol was also applied to a highly enolizable substrate, 2-indanone, to give desired trichloromethyl-carbinol in moderate yield (entry 10).

Table 2
Chlorotitanium (IV) triisopropoxide promoted addition of chloroform to ketones[a]

Entry	Ketones	Products	Isolated yield[b] (%)
1	**1c**	 **2c**	95
2	**1d**	 **2d**	93
3	**1e**	 **2e**	91
4	**1f**	 **2f**	84
5	**1g**	 **2g**	93
6	**1h**	 **2h**	88
7	**1i**	 **2i**	96
8	**1j**	 **2j**	71
9	**1k**	 **2k**	83[c]
10	**1l**	 **2l**	45

[a] Reaction conditions: $CHCl_3$(5 equiv), *n*-BuLi (5 equiv), $TiCl(OiPr)_3$ (2 equiv), THF (0.5 M).
[b] Purified by flash chromatography on silica gel.
[c] Relative stereochemistry determined by comparision of ^1H NMR with literature data[9b] (dr > 9:1 by ^1H NMR).



Scheme 3. Dehydration and hydrolysis of trihalomethylcarbinol. Reagents and conditions: (1) H_2SO_4, THF, 70 °C; (2) NaOMe, MeOH, 60 °C, then aq HCl, 80% for two steps.

It is reported that trihalomethylcarbinols can be reductively eliminated to vinyl dihalides by a reducing metal halide.[15] Under non-reductive acidic condition, $SOCl_2$ can dehydrate a trihalomethylcarbinol into a mixture of isomeric forms, such as vinyl trichloromethyl- and chloro- vinyl dichloride.[16] We wondered whether under more forceful acidic conditions we could drive the reaction into a more thermodynamically stable isomer and then through basic hydrolysis to provide and α,β-unsaturated ester. To test this idea, we treated trichloromethylcarbinol **2a** with excess sulfuric acid in warm THF. A major product **3a** was formed after a few hours of heating as determined by LCMS. After work up, the crude product **3a** was directly subjected to NaOMe in MeOH. Based on LCMS data, trimethoxy analog **4a** was gradually formed upon heating. Upon acidic work up, α,β-unsaturated ester **5a** was formed and isolated in 80% overall yield from **2a**. α,β-Unsaturated esters are a substrate for asymmetric hydrogenation, making this synthetic approach a potential route for enantioselective carbon homologation of ketones (Scheme 3).

Summary and conclusions

In summary, chlorotitanium (IV) triisopropoxide mediated addition of chloroform to enolizable ketones offers a facile, convenient, and efficient method for the synthesis of trichloromethylcarbinols.[17] We also demonstrated the conversion of trihalomethylcarbinol **2a** to provide an α,β-unsaturated ester.[18]

Acknowledgments

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Supplementary data

Supplementary data (spectroscopic data of selected entries from Table 1 and Table 2) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.118.

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17. *General procedure for the preparation of trihalomethylcarbinols:* A 50 mL round bottomed dry flask containing 2,3-dihydro-1*H*-inden-1-one (**1b**, 200 mg, 1.5 mmol), $CHCl_3$ (0.61 mL, 7.8 mmol), chlorotitanium (IV) triisopropoxide (790 mg, 3.0 mmol), and THF (3.0 mL) was cooled with dry ice acetone bath (internal temperature about −60 °C). *n*-BuLi (2.5 M in hexane, 3.0 mL, 7.5 mmol) was added slowly over 20 min. The reaction was stirred cold for four hours before quenching with saturated NH_4Cl (3 mL) and water (5 mL). After warm to room temperature, the mixture was extracted with EtOAc (10 mL × 3). The combined organics were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude oil was purified by ISCO silica gel chromatography (EtOAC/Hexane, 0–10% gradient) to give product **2b** as a colorless oil (298 mg, 78% yield).
18. *Conversion of trihalomethylcarbinol* **2a** *to* α,β*-unsaturated ester* **5a***:* A mixture of 2-(dibenzylamino)-5-(trichloromethyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-5-ol (**2a**, 5.6 g, 12.5 mmol) and concentrated sulfuric acid (21.0 mL, 375 mmol) in THF (56.0 mL) was heated at 70 °C for 15 h. The mixture was cooled to room temperature, the pH was adjusted to ~10 with 5 N NaOH, and extracted with EtOAc. The EtOAc layer was stirred with anhydrous $MgSO_4$ and activated charcoal (Darco KB-B) for one hour at room temperature before being filtered and concentrated. The orange solid **3a** (6.6 g) was taken up in MeOH (168 mL) and DMF (56 mL) and added NaOMe (20.2 g, 375 mmol). The mixture was stirred at 60 °C for one hour, and added slowly into a mixture of EtOAc, concd. HCl (35 ml), and water. The separated aqueous layer was extracted again with EtOAc and the combined organic layer was concentrated and purified by ISCO silica gel chromatography (EtOAC/Hexane, 0–60% gradient) to give the final product **5a** (3.7 g, 80% yield).