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# Synthesis of β-substituted α-iodo cycloalkanones by the CuI-mediated conjugate addition of Grignard reagents to α-iodo cycloalkenones

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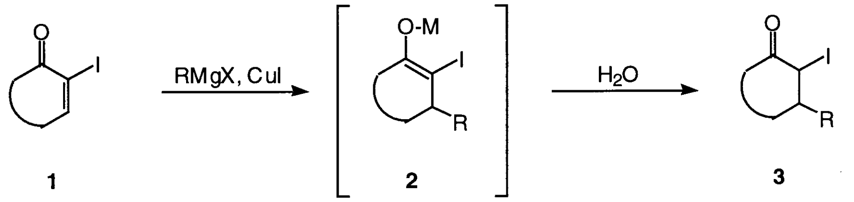
**Abstract**—CuI-mediated conjugate addition of Grignard reagents to α-iodo cycloalkenones afforded β-substituted α-iodo cycloalkanones in good to excellent yields. © 2001 Elsevier Science Ltd. All rights reserved.

β-Substituted α-iodo ketones **3** are versatile intermediates in organic synthesis. Although various methods to prepare α-iodo ketones from olefins,[1] epoxides,[2] ketones,[3] enol esters[4] and silyl enol ethers[4,5] have been reported, with a few exceptions[3,4b] these methods have serious limitations, such as use of toxic reagents or the difficult purification of silyl enol ethers. Moreover, these methods are generally not adaptable for the regioselective synthesis of β-substituted α-iodo ketones. During work on α-carbonyl radical cyclization, we discovered a facile method for the preparation of β-substituted α-iodo ketones.[6] We applied that method in total synthesis of several natural products, e.g. (+)-modhephene,[6] (−)-dendrobine,[7] (−)-5-oxosilphiperfol-6-ene,[8] dimethyl gloiosiphone A[9] and (−)-paniculatine,[10] but we later found that our method sometimes afforded β-substituted α-iodo ketones in only moderate yield, presumably due to the hydrolysis of TMS-enol-ether intermediates. Therefore, we became interested in developing a more efficient method to prepare β-substituted α-iodo ketones. We envisaged that conjugate addition of a Grignard reagent to α-iodo enone **1** would afford compound **3** (Scheme 1) directly, and thus could serve as an alternative entry to β-substituted α-iodo ketones.

To our knowledge the conjugate addition of a Grignard reagent to α-iodo enones has not been explored, probably because the vinyl iodide moiety in α-iodo enones is known to react readily with organometallic reagents.[11] In the related work, Normant and co-workers reported the conjugate addition of lithium dimethylcuprate to α-chloro or α-fluoro enones.[12] Vandewalle et al. performed 1,4-addition of a Grignard reagent to 4,4-dimethyl-2-bromocyclopentenone in a total synthesis of quadrone.[13] Paquette and Klemeyer described conjugate addition of allyllithium to an α-bromo enone.[14] In a alkylated cubane synthesis, Tsanaktsidis and co-workers preformed conjugate addition of methyl Grignard to a bicyclic α-bromo enone.[15]

Here we report results on conjugate addition of Grignard reagents to α-iodo cycloalkenones, which provides a new entry to β-substituted α-iodo cycloalkanones. Treatment of α-iodo cycloalkenones **4**–**10** with a mix-



**Scheme 1.**

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*Keywords*: α-iodo ketone; α-iodo enone; Grignard reagents; conjugate addition; α-carbonyl radical.

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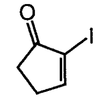
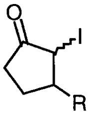
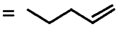
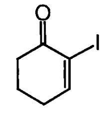
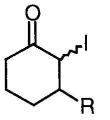
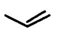
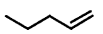
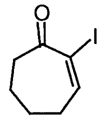
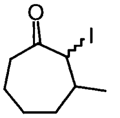
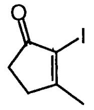
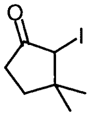
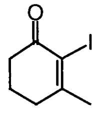
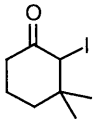
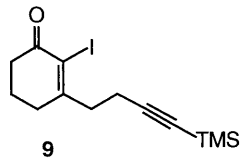
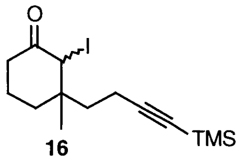
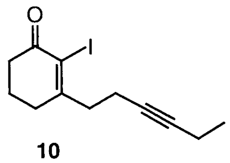
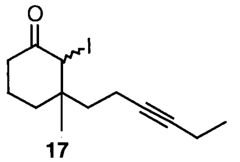
ture of a Grignard reagent (RMgCl or RMgBr) and CuI at 0°C, followed by quenching with saturated $NH_4Cl$ and extraction with $Et_2O$, gave β-substituted α-iodo cycloalkanones **11**–**17** in good to excellent yields;[16] the results are summarized in Table 1. This reaction succeeds presumably because of formation of enolate **2**, shown in Scheme 1, which can prevent further reaction of the Grignard reagent with the iodo group. The starting materials, α-iodo enones **4**–**6** are readily available on iodination of the corresponding cycloalkenones according to conventional methods.[17] β-Substituted α-iodo enones **7**–**10** were prepared according to our methods.[18] Various Grignard reagents such as alkyl, vinyl, and phenyl Grignard can be used. Use of CuI is necessary. Without its addition, both 1,2- and 1,4-addition products are obtained. β,β-Disubstituted α-iodocycloalkanones **14**–**17** can also be prepared in good yield. Products **11a**–**b**, **12a**–**e** and **13** are formed

**Table 1.** Conjugate addition of Grignard reagents to α-iodo cycloalkenones

| α-Iodo Cycloalkenones | β-Substituted α-Iodo Cycloalkanones | | Yields (*ratios*) [a] |
|---|---|---|---|
|  **4** |  | **11a** R = Me | 58 % (*cis* : *trans* = 1 : 1.6) |
| | | **11b** R =  | 64 % (*cis* : *trans* = 1 : 1.2) |
|  **5** |  | **12a** R = Me | 79 % (*cis* : *trans* = 1 : 2.2) |
| | | **12b** R = Bu | 61 % (*cis* : *trans* = 1 : 1.3) |
| | | **12c** R =  | 68 % (*cis* : *trans* = 1 : 1) |
| | | **12d** R = Ph | 66 % (*cis* : *trans* = 5.3 : 1) |
| | | **12e** R =  | 64 % (*cis* : *trans* = 5.8 : 1) |
| | | **12f** R =  | 60 % (*cis* only) |
|  **6** |  **13** | | 60 % (*cis* : *trans* = 13.4 : 1) |
|  **7** |  **14** | | 70 % |
|  **8** |  **15** | | 71 % |
|  **9** |  **16** | | 81 % (α : β = 1: 1) |
|  **10** |  **17** | | 72 % (α : β = 1: 1) |

a) The ratios were determined from the $^1H$ NMR integration of α and β protons of *cis* and *trans* isomers.

as mixtures of *cis* and *trans* isomers. Compounds **16** and **17** are obtained as a mixture of two diastereomers.

In summary, we have developed a new method to prepare β-substituted α-iodo cycloalkanones via conjugate addition of a Grignard reagent to α-iodocycloalkenones. This method is also useful for synthesis of β,β-disubstituted α-iodocycloalkanones. Application of this method for the preparation of α-iodo ketone intermediates in total synthesis of natural products is currently under investigation in our laboratory.

## Acknowledgements

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16. A representative procedure for conjugate addition: To a solution of CuI (385 mg, 2.02 mmol) in dry THF (3 mL) was added MeMgBr (2.7 M in $Et_2O$, 0.75 mL, 2.02 mmol) at 0°C. The mixture was stirred at the same temperature for 10 min. A solution of **5** (150 mg, 0.68 mmol) in dry THF (3 mL) was then added. The reaction mixture was stirred at 0°C for 1 h and then quenched with saturated $NH_4Cl$ (5 mL). The aqueous layer was extracted with $Et_2O$ (5 mL×3). The combined organic layers were washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL), and then dried over $MgSO_4$. Filtration, concentration and silica gel column chromatography (EtOAc–hexane, 1:15) gave **12a** as a colorless oil (127 mg, 79%): $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.50–4.49 (dd, $J=2.0$, 2.0 Hz, 0.38 H), 4.40–4.38 (dd, $J=7.0$, 0.8 Hz, 0.62 H), 3.36–3.28 (m, 0.38 H), 3.05–2.98 (m, 0.62 H), 2.34–1.48 (m, 6 H), 1.17–1.15 (d, $J=7.2$ Hz, 1.86 H), 1.01–0.99 (d, $J=6.0$ Hz, 1.14 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 205.3, 203.9, 45.2, 42.0, 41.9, 37.1, 37.0, 34.1, 29.8, 28.8, 24.9, 23.0, 22.7, 21.8; IR (neat): 2961, 1712, 1218 cm$^{-1}$; MS (EI): $m/z$ 238 (M+, 100), 111 (23); HRMS: $m/z$ calcd for $C_7H_{11}IO$: 237.9855, found 237.9859.
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