# Synthesis of Chiral 5-Substituted Cyclohex-2-enones from 5-Trimethylsilylcyclohex-2-enone

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Optically active and racemic 5-substituted cyclohex-2-enones were synthesized from 5-trimethylsilylcyclohex-2-enone.

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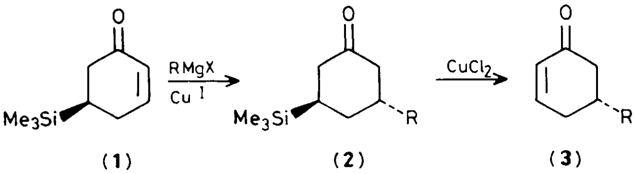
In connection with our continuing study[1] on the utilization of 5-trimethylsilylcyclohex-2-enone (**1**) in natural product synthesis, we have examined the two-step access to 5-substituted cyclohex-2-enones from (**1**) [Scheme 1, (**1**) → (**2**) → (**3**)]. Cyclohexenone derivatives are useful intermediates for the syntheses of a wide variety of natural products;[2] furthermore, the availability of such compounds with optical activity would prove useful in chiral natural product synthesis.

1,4-Addition of Grignard reagents to (**1**) catalysed by $Cu^I$ proceeded smoothly to give the corresponding *trans*-adduct (**2**) in high yield as the exclusive product, which was then treated with $CuCl_2$ to eliminate the $SiMe_3$ group. Under almost all the oxidative reaction conditions reported by Fleming *et al.* in similar systems,[3] attempted elimination of the $SiMe_3$ group from (**2a**) (R = Ph) resulted in disappointing results (some are shown in Table 1, entries 1—3). The yields could not be increased by optimization of reaction conditions. After many trials, treatment of (**2a**) (R = Ph) with anhydrous $CuCl_2$ (3 equiv.) in commercial grade dimethylformamide



Scheme 1

**Table 1.** Synthesis of 5-substituted cyclohex-2-enones (**3**).

| Entry | R | Yield (**2**), % | Method[a] | Yield (**3**),[b] % | | E.e., % |
|---|---|---|---|---|---|---|
| 1 | Ph | 90 | A[c] | (**3a**) | 26 | — |
| 2 | Ph | | B[d] | | 45[g] | — |
| 3 | Ph | | C[e] | | 63[g] | — |
| 4 | Ph | | D[f] | | 84 | — |
| 5 | $p$-$MeC_6H_4$ | 92 | D | (**3b**) | 91 | — |
| 6 | $p$-$MeOC_6H_4$ | 92 | D | (**3c**) | 85 | — |
| 7 | $Bu^t$ | 95 | D | (**3d**) | 84 | — |
| 8 | $PhCH_2CH_2$ | 92 | D | (**3e**) | 82 | — |
| 9[h] | Ph | 94 | D | (−)-(**3a**) | 82 | 98 (*R*) |
| 10[h] | $p$-$MeC_6H_4$ | 96 | D | (−)-(**3b**) | 83 | 98 (*R*) |
| 11[h] | $Bu^t$ | 86 | D | (−)-(**3d**) | 92 | 96 (*R*) |

[a] Method in the second step (**2**) → (**3**). [b] Based on (**2**). [c] $CuBr_2$ (2 equiv.), $CHCl_3$–AcOEt, reflux 1 h. [d] $PhNMe_3Br_3$, tetrahydrofuran (THF), 0 °C, 1 h. [e] $C_5H_5NHBr_3$, THF, 0 °C, 10 min. [f] $CuCl_2$ (3 equiv.), dimethylformamide (DMF), 60 °C, 25—90 min. [g] Contaminated with a small amount of by-product. [h] Optically pure (*R*)-(−)-(**1**) was used.

(DMF) at 60 °C for 40 min was found to be effective for this conversion (entry 4). Starting from (±)-(**1**), five racemic enones (**3a**—**e**) were synthesized in 75—84% overall yields (entries 4–8).

Highly optically active compounds (*R*)-(**3**) [96—98% enantiomeric excess (e.e.)] were also synthesized starting from (*R*)-(−)-(**1**). Optically pure samples of (−)-(**3a**) and (−)-(**3b**) were obtained by recrystallization of the products and the specific rotation values, $[\alpha]_D^{23}$ −46.4° (*c* 5.00, $CHCl_3$) and $[\alpha]_D^{20}$ −44.5° (*c* 1.70, $CHCl_3$), were used to calculate the e.e. values.† In the case of (−)-(**3d**), the enone was converted into 3-t-butylcyclohexanone, $[\alpha]_D^{22}$ +23.1° (*c* 2.80, $CHCl_3$), by hydrogenation, and the e.e. value was calculated based on the value $[\alpha]_D$ +24.1°.[4]

In conclusion, this method provides the first straightforward route to synthesize highly optically active 5-substituted cyclohex-2-enones from a common starting material.

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† In the case of (**3a**), the optically pure samples, (−)- and (+)-(**3a**), were also obtained by the direct resolution of (±)-(**3a**), *i.e.* recrystallization of (±)-(**3a**) from pentane gave a racemic mixture (conglomerate) which was isolated by mechanical separation.