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Novel Chlorotrimethylsilane Catalyzed Stereoselective Deconjugation of β -Bromo (or Iodo) Substituted α,β -Unsaturated Acyclic Ketone

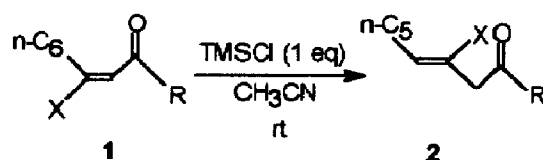
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Abstract: TMSCl catalyzed stereoselective isomerization (deconjugation) of β -substituted α,β -unsaturated ketones to the corresponding (Z)- β,γ -unsaturated ketones and its mechanism studies are described

While investigating the reaction of 2-alkyn-1-ones with TMSI¹, we discovered that TMSCl² can catalyze the isomerization of β -substituted enones to the corresponding β,γ -unsaturated enones with high stereoselectivities. Most of the earlier known methods for isomerization or deconjugation of α,β -unsaturated carbonyl compounds involved a base,³⁻⁵ or has been done under photochemical conditions.⁶ To the best of our knowledge, this kind of stereoselective isomerization or deconjugation has not been carried out chemically under neutral and very mild conditions. Initially, stoichiometric amount of TMSCl was used to promote the deconjugation experiments and the results are summarized in **Table I**

It is clearly shown in the Table that even catalytic amount of TMSCl is enough in a longer reaction time to isomerize both β -iodo- or bromo-substituted enones to the corresponding deconjugated products in good yields and with $\geq 98\%$ stereoselectivities while the β -chloro-substituted compounds (entries 8 and 9) gave very poor yields of the desired products even with longer reaction time. We also observed that only acyclic α,β -unsaturated ketones underwent deconjugation with TMSCl. For example, when we treated 3-iodo-2-cyclohexenone with 1 equiv of TMSCl in CH₃CN at rt, only the halogen exchanged product 3-chloro-2-cyclohexenone (21%) and starting material were recovered. While under the same conditions, 3-bromo-2-cyclohexenone gave 3-chloro-2-cyclohexenone (24%) and 3-bromophenol (42%). Other carboxylic acid derivatives such as (Z)-3-iodo-2-nonenic acid, N,N-dimethyl (Z)-3-iodo-2-nonenic amide, and methyl (Z)-3-iodo-2-nonenate remain unchanged under the same reaction conditions. Moreover, we also found that the β -phenyl enone (entry 12) gave low yield even after 12h. While the corresponding β -methyl enone did not give any rearranged product under the same reaction conditions (entry 13). Attempts were then made to increase the yield of deconjugation of β -alkyl or aryl substituted enones by using TMSI. Yields of the deconjugated products improved when the reaction of β -phenyl enone was carried out with TMSI (entry 14). While the β -methyl enone gave only 20% yield of the deconjugated products (Z/E = 2/1) and 72% of the starting material after 24h at rt (entry 15). Attempts to add the same amount of Et₃N⁷ as TMSCl in the reaction to help us to observe the expected silyl dienol ether intermediate by ¹H-NMR were fail. Thus, the starting material was totally recovered when used 1 equiv of Et₃N and TMSCl. Probably, Et₃N may form a complex with TMSCl to deactivate TMSCl so as to retard the isomerization process. Actually, no matter how carefully we mixed Et₃N and TMSCl under nitrogen atmosphere, there is always an unidentified white fume was formed. However, used 0.5 equiv of Et₃N and 1 equiv of TMSCl still gave 86% yield of the

Table I. Reaction of 3-Substituted-2-alken-1-ones with TMSCl.

Entry	Geometry of 1	R	X	Reaction time (h)	Yield of 2 (%) ^a
1	E	CH ₃	I	3	92
2	Z	CH ₃	I	3	92
3 ^b	E	CH ₃	I	3	10
4 ^b	E	CH ₃	I	12	90
5 ^b	E	CH ₃	Br	12	88
6	E	CH ₃	Br	3	91
7	Z	CH ₃	Br	3	90
8 ^c	E	CH ₃	Cl	3	<5
9 ^c	Z	CH ₃	Cl	3	<5
10	Z	Ph	I	12	89
11	Z	n-C ₅	I	3	88
12	Z	CH ₃	Ph	12	31
13	Z	CH ₃	CH ₃	12	—
14 ^d	Z	CH ₃	Ph	12	62
15 ^d	Z	CH ₃	CH ₃	24	20 ^e

^a All new compounds were characterized by their spectral data. The stereochemistry was determined by 2D-NOESY ¹H-NMR spectra.

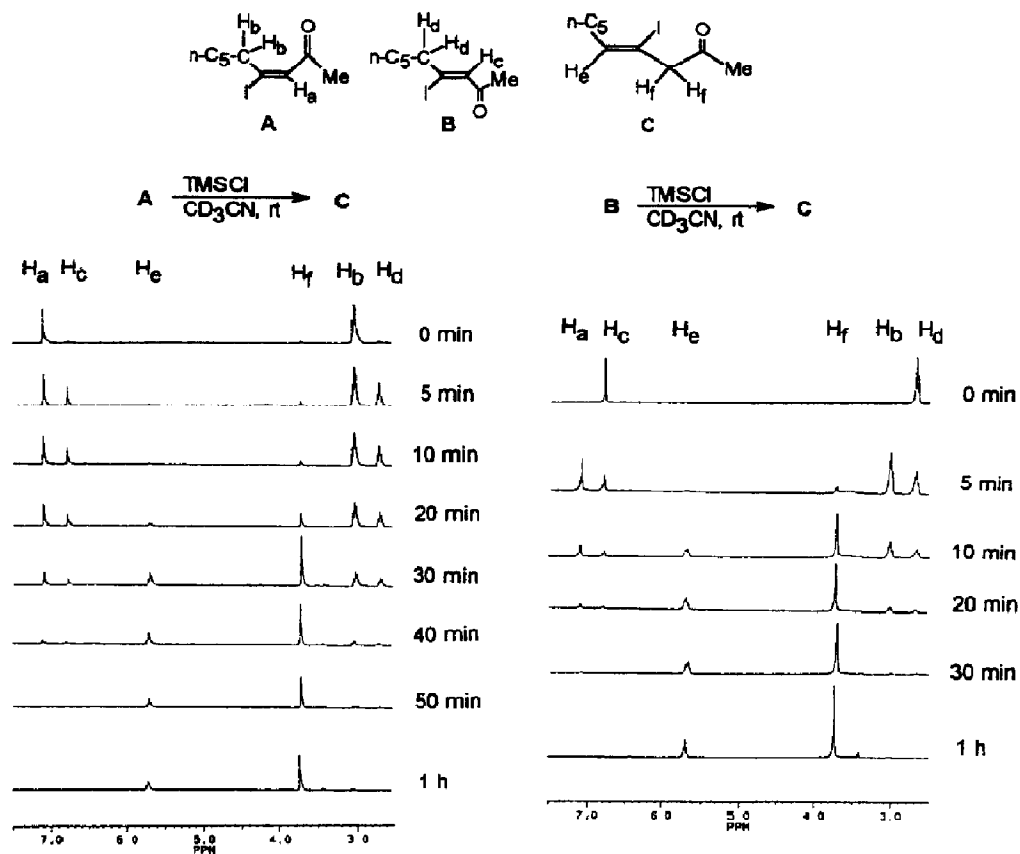
^b Reaction was carried out with catalytic amount (0.1 eq) of TMSCl.

^c There was no change in product yield when the reaction time was increased to 12h.

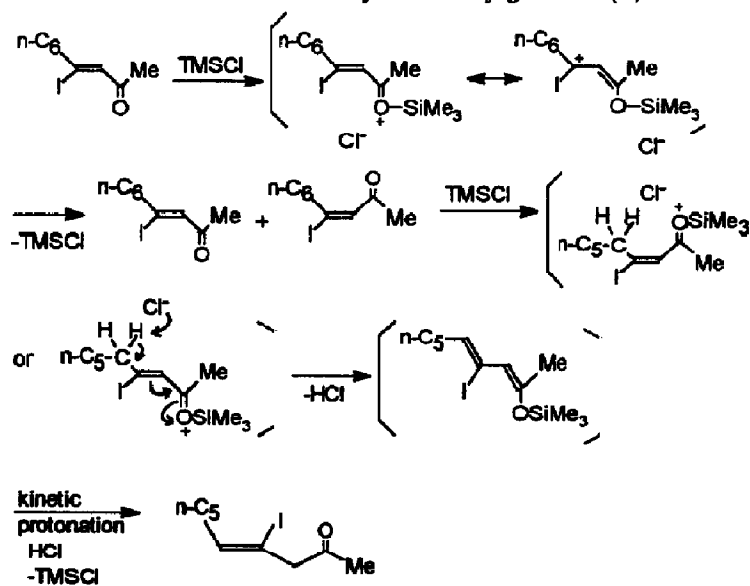
^d Reaction was carried out with 1 equiv of TMSI. ^e Z/E ratio is 2/1.

expected deconjugated product. We also observed that while the reaction of (E)-4-iodo-3-decen-2-one with 1 equiv of TMSCl can be finished in 1h, under the same concentration and conditions the corresponding (Z)-isomer can be deconjugated completely in 30 min. When we used ¹H-NMR to monitor the above reactions (Fig. 1), we observed that both isomers gave almost the same mixture of (Z)- and (E)-4-iodo-3-decen-2-one with a ratio of about 1 to 2 in 3 to 5 min. After prolonging the reaction time, both isomers were isomerized completely to the same product in 30 min to 1h. We then proposed the reaction mechanism for this reaction

Fig. I. $^1\text{H-NMR}$ Spectra Changes with Time for TMSCl -Promoted Deconjugation of (E)- and (Z)-4-Iodo-3-decen-2-one to Form (Z)-4-Iodo-4-decen-2-one



Scheme I. Plausible Mechanism for the TMSCl -Catalyzed Deconjugation of (Z)-4-Iodo-3-decen-2-one



as follows (**Scheme 1**): TMSCl acts as a Lewis acid to activate both (E)- and (Z)-enone to form silyl enol ether allylic cation intermediate. This equilibrium of (Z)- and (E)-isomers can be reached very fast when TMSCl was regenerated. TMSCl can also act as a Lewis acid to activate both enones. At this stage, the chloride anion acts as a base to abstract one of the allylic protons to form HCl and the silyl dienol ether intermediate. Since the allylic protons in the (Z)-isomer has less steric hindrance than that of the (E)-isomer, they are more easily to be accessed than that in the (E)-isomer by the chloride anion. Thus, the process of deconjugation for the (Z)-isomer was faster than the (E)-isomer. Since the coexistence of HCl and the silyl dienol ether are inevitable and the following kinetic protonation⁸ of the silyl dienol ether with HCl to form the deconjugated product and TMSCl is also very fast, we can not observe the expected silyl dienol ether intermediate by ¹H-NMR spectral analysis even at -40°C. Since the n-pentyl group and the iodo substituent are on the syn position of the C-C single bond, the proton abstraction and the following double bond migration and protonation should give (Z)-form of the deconjugated product. One may think that using either HCl or HI in catalytic or stoichiometric amount may undergo the same reaction process. However, we observed that none of them gave the same results as we used TMSCl in the above deconjugation reaction. Both 10 mol % of HCl (37% aq. solution) and HI (47% aq. solution) reacted with (E)-4-iodo-3-decen-2-one to give major the mixture of C-C double bond isomerized products (53-93%, E/Z = 2/1) after 48h at rt. Used 1 equiv of HCl gave both (Z)-4-iodo- and (Z)-4-chloro-4-decen-2-one in 81% total yield with 1 to 1 ratio after 72h at rt. While using 1 equiv of HI gave 7 to 1 ratio of (Z)- and (E)-4-iodo-4-decen-2-one with 77% total yield in both 9 and 96h at rt.

The following procedures for the preparation of (Z)-4-iodo-4-decen-2-one is representative. To (E)-4-iodo-3-decen-2-one (1.40 g, 5 mmol) in CH₃CN⁹ (10 mL) was added TMSCl (0.55 g, 5 mmol) under nitrogen atmosphere and the reaction mixture stirred at rt for 3h. Concentration followed by purification by column chromatography (silica gel, hexane/ether = 5/1) gave 1.28 g of **2** (R = Me) in 92% yield.

In conclusion, TMSCl and TMSI are mild reagents for the isomerization of β-substituted enones especially β-iodo or β-bromo enones. Efforts are now underway to extend this method to other substrates with various functional groups.

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References and Notes

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2. The freshly distilled TMSCl from quinoline was used in all these reactions.
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7. The freshly distilled Et₃N from P₂O₅ was stored with molecular sieve 4Å before use.
8. Based on INSIGHT I. program calculation, a bulkier group such as iodide or bromide at β-position makes conjugated double bonds noncoplanar; thus the kinetic protonation process was more readily achieved.
9. CH₃CN and CD₃CN were distilled over CaH₂ and stored with molecular sieve 4A before use.

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