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A novel synthesis of 2,4,4-trisubstituted 2-cyclopentenones by consecutive reaction of 1-chlorovinyl *p*-tolyl sulfoxides with acetonitrile and its homologues

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Abstract—1-Chlorovinyl *p*-tolyl sulfoxides were synthesized from several kinds of ketones and chloromethyl *p*-tolyl sulfoxide in three steps in high overall yields. Treatment of the 1-chlorovinyl *p*-tolyl sulfoxides with cyanomethyllithium (lithium α -carbanion of acetonitrile) at low temperature gave the adducts in almost quantitative yields. The adducts were then treated with LDA followed by excess lithium α -carbanion of the homologues of acetonitrile to afford 3,5,5-trisubstituted cyclopentadienyl enaminonitriles, which were hydrolyzed and heated under acidic conditions to give 2,4,4-trisubstituted 2-cyclopentenones in good overall yields.

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The 2-cyclopentenone ring system is obviously one of the most widely found carbon structures in natural and unnatural organic compounds. In addition, 2-cyclopentenones are quite important intermediates in synthetic organic chemistry.¹ Many methods, including the Nazarov cyclization² and the Pauson–Khand reaction,³ have already been reported for the construction of 2-cyclopentenones; however, in view of the importance of 2-cyclopentenone derivatives in organic synthesis, new methods are still very important and welcome.

Recently, we reported a new method for the synthesis, including asymmetric synthesis, of 4,4-disubstituted 2-cyclopentenones $4.^4$ The method starts from ketones 1

and chloromethyl *p*-tolyl sulfoxide to give 1-chlorovinyl *p*-tolyl sulfoxides **2**, which are treated with excess cyanomethyllithium to afford cyclopentadienyl enaminonitriles **3**. The enaminonitriles **3** are heated with H_3PO_4 in acetic acid to give 4,4-disubstituted 2-cyclopentenones **4** in high overall yields (Scheme 1).

As this method is quite useful for the synthesis of substituted 2-cyclopentenones, we further investigated the reaction of **2** with several lithium α -carbanions of the homologues of acetonitrile. However, for example, the reaction of **2** with lithium α -carbanion of propionitrile gave only a complex mixture. Finally, we found a quite interesting and versatile method for the synthesis



Scheme 1.

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Scheme 2.

of 2,4,4-trisubstituted 2-cyclopentenones **8**. The essence of the reaction is as follows. First, 1-chlorovinyl *p*-tolyl sulfoxides **2** are treated with cyanomethyllithium at -78° C to give the adducts **5** in near quantitative yields. After purification, **5** are again treated with LDA followed by excess lithium α -carbanion of homologues of acetonitrile **6** to afford the cyclopentadienyl enaminonitriles **7**, which are heated with H₃PO₄ to afford the 2,4,4-trisubstituted 2-cyclopentenones **8** in good overall yields from **2** (Scheme 1).

A representative example is described for the synthesis of 2,4,4-trisubstituted 2-cyclopentenones 12 from 1chlorovinyl *p*-tolyl sulfoxide 9 and acetonitrile, propionitrile, and butyronitrile as shown in Scheme 2. A THF solution of 1-chlorovinyl p-tolyl sulfoxide 9, derived from cyclopentadecanone and chloromethyl ptolyl sulfoxide,⁵ was added to a solution of three equivalents of cyanomethyllithium in THF at -78°C and the reaction mixture was stirred for 10 min. This reaction gave the adduct 10 as a mixture of two diastereomers in 97% yield after silica gel column chromatography. A solution of 10 was added to a solution of LDA (3 equiv.) at -78°C and the reaction mixture was stirred for 30 min. To this was added lithium α -carbanion of propionitrile (4 equiv.), which was generated from propionitrile and *n*-BuLi at -78° C, through a cannula and the whole was slowly allowed to warm to room temperature over 2.5 h. This treatment gave the desired cyclopentadienyl enaminonitrile 11a in 80% yield. The same treatment of 10 with butyronitrile afforded 11b in a similar yield.

The presumed mechanism of this reaction is illustrated in Scheme 3. Treatment of the adduct 5 with LDA gives the lithium α -sulfinyl carbanion 13. Elimination of lithium chloride from the carbanion 13 results in the formation of the α -sulfinyl carbenoid 14 upon warming of the reaction mixture. Lithium α -carbanion of the homologues of the acetonitrile 6 adds to the electrophilic carbon of the carbenoid 14 to give the α -sulfinyl carbanion of dinitrile 15. Finally, this dinitrile 15 cyclizes under highly basic conditions (the Thorpe– Ziegler reaction)⁶ with concomitant elimination of the *p*-toluenesulfenyl anion to give the enaminonitrile 7.

The enaminonitriles **11a** and **11b** were heated under reflux in acetic acid containing H_3PO_4 and a small

amount of water for about 30 h to afford the desired 2,4,4-trisubstituted-2-cyclopentenones **12a** and **12b** in 93 and 83% yields, respectively (Scheme 2).

To ascertain the generality of this procedure, we synthesized two 1-chlorovinyl *p*-tolyl sulfoxides from 1,4cyclohexanedione mono-ethylene ketal and benzophenone and reacted them first with cyanomethyllithium (Table 1). As shown in Table 1, the adducts were obtained in 99 and 93% yields, respectively. With these adducts, α -carbanions of propionitrile (entries 1 and 5) and butyronitrile (entries 2 and 6) were reacted. The desired enaminonitriles were obtained in 55 ~ 76% yield. The enaminonitriles were converted to the desired 2,4,4-trisubstituted 2-cyclopentenones under the abovementioned conditions without any problem in 72 ~ 89% yield.

Interestingly, (4-methoxyphenyl)acetonitrile (entries 4 and 7) gave the aromatic ring-substituted 2-cyclopentenones in good overall yields; especially in entry 4, the two-step overall yield was 89%. The result in entry 3 is much more interesting; by our method a highly hindered triphenylmethyl group can be introduced at the 2-position of the 2-cyclopentenone by using 3,3,3triphenylpropionitrle. The generality of this reaction was confirmed by these results.

Table 2 shows the results for the reaction of the adduct **10** and various kinds of the homologues of acetonitrile. A long carbon chain can be introduced at the 2-position of the cyclopentenone to give **12c** in good overall yield (entry 1). 3-Methylbutyronitrile gave isopropyl group-substituted 2-cyclopentenone **12d** without any



Scheme 3.

 Table 1. Synthesis of 2,4,4-trisubstituted 2-cyclopentenones from 1-chlorovinyl p-tolyl sulfoxides via the cyclopentadienyl enaminonitriles



a) 3,3,3-Triphenylpropionitrile was synthesized by dehydration of 3,3,3-triphenylpropionic amide with trifluoromethanesulfonic anhydride and triethylamine. See lit. 8.

Table 2. Synthesis of various kinds of 2,4,4-trisubstituted 2-cyclopentenones 12 from 1-chlorovinyl p-tolyl sulfoxides derived from cyclopentadecanone via the cyclopentadienyl enaminonitriles 11

10 10	CH ₂ CN ^{1) LDA} CHS(O)Tol ²⁾ R ³ CHCN CI Li		N NH ₂ R ³	H ⁺		
Entry	R ³ CH₂CN	Enaminonitrile		2-Cyclopentenone 12		
		Yield / %			Yield / %	
1	C ₆ H ₁₃ CN	72	120	€ {\0 C₅H ₁₁	87	
2	(CH ₃) ₂ CHCH ₂ CN	79	12d		91	
3	(Ph) ₃ CCH ₂ CN	46	12e		51	
4	CH ₃ CH=CHCH ₂ CN	76	12f	XIO	24	
5	CH3O-CH2CN	64	12g		93 -OCH₃	

problem in good overall yield (entry 2). As shown in entry 3, a highly hindered substituent, triphenylmethyl group, again could be introduced by this reaction; however, in this case the yield of **12e** was shown to be somewhat lower than that in Table 1, entry 3.

Entry 4 shows that the cyclopentadienyl enaminonitrile having a conjugated olefin could be obtained without problem; however, the acidic treatment gave only 24% yield of **12f**. Aromatic group-substituted 2-cyclopentenone **12g** was again obtained without problem in good overall yield.

In conclusion, we have presented herein a new, relatively short, and quite versatile procedure for synthesis of 2,4,4-trisubstituted 2-cyclopentenones. As it has been recognized that the transformation of 2-cyclopentenones to 2-substituted 2-cyclopentenones is no easy task,⁷ this procedure will become a quite important method for the synthesis of 2,4,4-trisubstituted 2-cyclopentenones.

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