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A novel route to fully substituted cyanoallenes from three components, ketones, chloromethyl *p*-tolyl sulfoxide, and nitriles, via α-bromocyclopropyl *p*-tolyl sulfoxides

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Abstract—Treatment of 1-chlorovinyl *p*-tolyl sulfoxides, which were derived from ketones and chloromethyl *p*-tolyl sulfoxide in high yields, with lithium α-carbanion of nitriles gave the adducts in quantitative yields. The adducts were converted to α-bromocyclopropyl *p*-tolyl sulfoxides in two steps in good yields. Finally, the sulfoxides were treated with excess lithium carbanion of isobutyronitrile to afford fully substituted cyanoallenes in high to quantitative yields via sulfoxide–lithium exchange reaction. This procedure offers a novel synthetic method for fully substituted cyanoallenes with coupling of three components (ketones, chloromethyl *p*-tolyl sulfoxide, and nitriles) in good overall yields.

Allenes are very interesting and highly important compounds in organic and synthetic organic chemistry.[1] Moreover, the allenyl structure is frequently found in natural products and pharmaceuticals.[2] In view of the importance of allenes, a large number of studies have been reported on their chemistry and synthesis.[1,2] The general methods for the synthesis of allenes are, for example, isomerization of acetylenes,[3] ring-opening of cyclopropylidenes,[4] the reaction of propargylic derivatives with organocopper reagents,[5] and β-elimination of olefins.[6] We recently reported a novel method for synthesis of allenes by the reaction of magnesium alkylidene carbenoids with lithium α-sulfonyl carbanions.[7] Although many methods for the preparation of allenes have appeared as above, it is still difficult to synthesize fully substituted (tetra-substituted) allenes having several functional groups.

Previously, we reported a new method for synthesis of allenes from 1-chlorocyclopropyl phenyl sulfoxides via magnesium cyclopropylidenes.[8] Recently, we have been investigating the development of new synthetic methods with 1-chlorovinyl *p*-tolyl sulfoxides with nitriles.[9] In continuation of our interest in the development of new synthetic method of allenes, we recently studied a combination of our two strategies described above and a novel synthetic method for fully substituted cyanoallenes from three components, ketones, chloromethyl *p*-tolyl sulfoxide, and nitriles was realized. The essence of this method is shown in Scheme 1.

Thus, 1-chlorovinyl *p*-tolyl sulfoxides **3** were synthesized from ketones **1** and chloromethyl *p*-tolyl sulfoxide **2** in three steps in over 90% overall yields.[10] Reaction of **3** with lithium α-carbanions of nitriles gave the adducts **4** in nearly quantitative yields. Treatment of the adducts **4** with *t*-BuOK in a mixture of THF–*t*-BuOH gave cyclopropyl sulfoxides, which were brominated with LDA–CBr_4 to afford α-bromocyclopropyl *p*-tolyl sulfoxides **5** in over 80% yields. Finally, sulfoxides **5** were treated with lithium α-carbanion of isobutyronitrile to give the fully substituted cyanoallenes **7** via lithium cyclopropylidene **6** in high yields.

The details of this investigation are described by using 1-chlorovinyl *p*-tolyl sulfoxide **8** as a representative example (Scheme 2). 1-Chlorovinyl *p*-tolyl sulfoxide **8** was synthesized from cyclopentadecanone in high overall yield.[10,11] Treatment of **8** with 2.5 equiv of lithium α-carbanion of propionitrile in THF at −78 °C for

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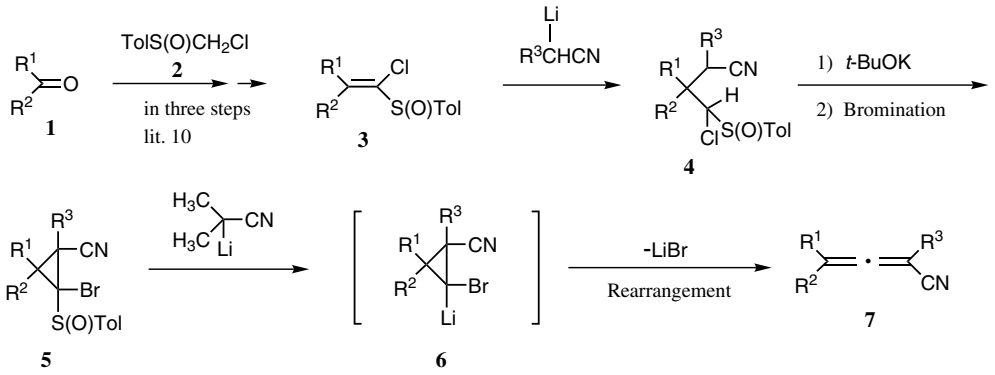
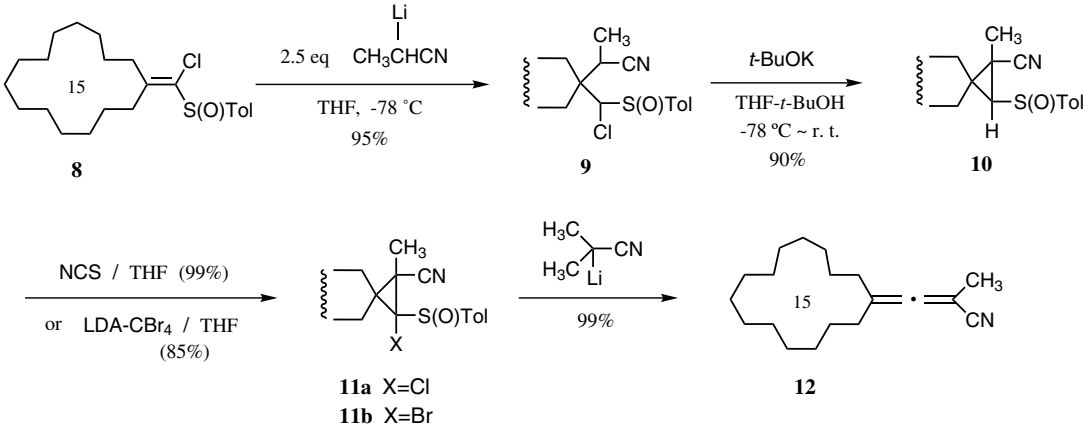


Scheme 1.

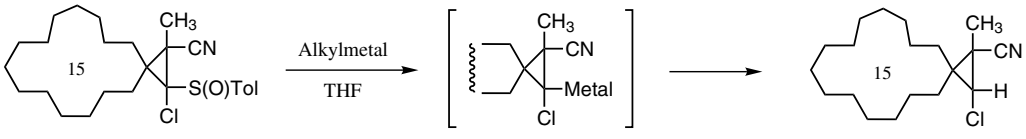


Scheme 2.

10 min afforded the adduct **9** in 95% yield as a mixture of two diastereomers. The adduct **9** was then treated with 5 equiv of *t*-BuOK in a mixture of THF–*t*-BuOH. The intramolecular S_N2 reaction took place to give the desired cyclopropane having *p*-tolyl sulfinyl group **10** in high yield. The cyclopropyl sulfoxide **10** was chlorinated with NCS[12] in THF to give the chloride **11a** in quantitative yield.

First, based on our experience with the synthesis of allenes from α-chlorocyclopropyl phenyl sulfoxides with Grignard reagent,[8] **11a** was treated with PhMgCl at 0 °C for 1 h (Scheme 3). All the starting materials **11a** disappeared to give a magnesium cyclopropylidene **13a**; however, no desired allene **12** was observed. Instead, chlorocyclopropane **14** was obtained in 65% yield. Treatment of **11a** with *t*-BuLi also gave **14** or a complex mixture without the desired allene **12** via a lithium cyclopropylidene **13b**.

The intermediate of these reactions is the magnesium cyclopropylidene **13a** or lithium cyclopropylidene **13b**.



Alkylmetal	Conditions	Yield of **14**
PhMgCl (2.5 eq)	-30 ~ 0 °C, 0 °C, 1 h	65%
t-BuLi (3 eq)	-80 °C, 1 h	50%
t-BuLi (3 eq)	-80 ~ 0 °C, 0 °C, 1 h	complex mixture

Scheme 3. Treatment of α-chlorocyclopropyl *p*-tolyl sulfoxide **11a** with alkylmetals.

In our previous letter,[8] magnesium cyclopropylidenes rearranged to allenes at above −60 °C; however, in this study, highly substituted cyclopropylidenes having a cyano group (**13a** and **13b**) were found to be quite stable and no rearrangement occurred.

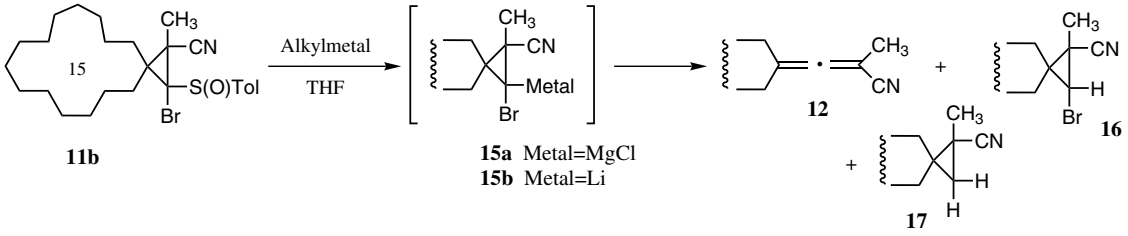
Next, the cyclopropyl sulfoxide **10** was brominated by treatment with LDA followed by carbon tetrabromide to give the bromide **11b** as a mixture of diastereomers in 85% yield (Scheme 2). This bromide was treated with Grignard reagent or alkyllithium and the results are summarized in Table 1. The bromide **11b** was treated with PhMgCl or *i*-PrMgBr (entries 1–3). Again, the main product was desulfinylated bromocyclopropane **16**. However, in these cases a trace amount of the desired allene **12** was observed. From these results, again, the magnesium cyclopropylidene **15a** appeared to be unexpectedly stable.

Next, the bromide **11b** was treated with *t*-BuLi (entries 4–7). The result shown in entry 4 is quite interesting. Treatment of the bromo-sulfoxide **15b** with *t*-BuLi at −78 °C gave cyclopropane **17** as a main product in 67% yield. This result implied that both sulfoxide-lithium exchange and bromine–lithium exchange reaction took place at the same time at −78 °C. Indeed, by treatment of **11b** with *t*-BuLi at −50 °C and −30 °C (entries 5 and 6) the yield of **17** was diminished and the yield of the desired allene **12** was increased. The yield of **12** was 44% when the reaction was conducted at room temperature (entry 7).

At this stage of our investigation, we thought that if a nucleophile (alkyllithim) that attacked only sulfoxide was used in this reaction, the desired allene **12** could be obtained in high yield. After some investigation we found that lithium α-carbanion of isobutyronitrile worked excellently. Excess of the anion, which was prepared from isobutyronitrile with *tert*-BuLi, was added to a solution of **11b** in THF portionwise at room temperature to give a quite clean reaction mixture, from which the desired allene **12** was obtained in quantitative yield (entry 8).[13]

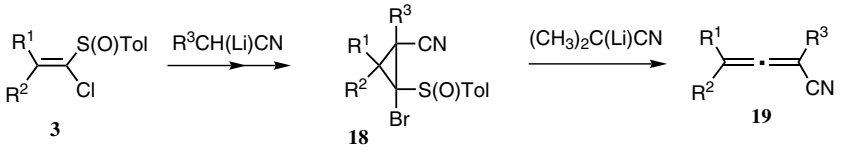
Finally, generality of this procedure was investigated and the results are summarized in Table 2. Entry 1

Table 1. Treatment of α-bromocyclopropyl *p*-tolyl sulfoxide **11b** with alkylmetals



Entry	Alkylmetal (equiv)	Conditions	**12** (%)	**16** (%)	**17** (%)
1	PhMgCl (2.5)	−50 to 0 °C, 0 °C, 0.5 h	Trace	66	0
2	PhMgCl (2.5)	−50 to rt, rt, 0.5 h	Trace	58	0
3	*i*-PrMgBr (2.5)	−50 to rt, rt, overnight	Trace	84	0
4	*t*-BuLi (2.5)	−78 to 0 °C, 0 °C, 2 h	Trace	29	67
5	*t*-BuLi (2.5)	−50 to rt, rt, 2 h	16	Trace	37
6	*t*-BuLi (2.5)	−30 to rt, rt, 2 h	34	13	16
7	*t*-BuLi (2.5)	rt, 2 h	44	13	10
8	**$(CH_3)_2C(Li)CN$ (10)**	**rt, overnight**	**99**	**0**	**0**

Table 2. Synthesis of fully substituted cyanoallenes **19** from 1-chlorovinyl *p*-tolyl sulfoxides **3** through α-bromocyclopropyl *p*-tolyl sulfoxides **18** with lithium α-carbanion of isobutyronitrile



Entry	**3**		R^3	**18**	**19**
	R^1	R^2		Yield[a] (%)	Yield (%)
1	$-(CH_2)_{14}-$		CH_3	72	**12** (99)
2	$-(CH_2)_{14}-$		$CH_2CH_2CH_2CH_3$	65	**19a** (99)
3	$-(CH_2)_9-$		CH_3	67	**19b** (89)
4	$-(CH_2)_5-$		$CH_2CH_2CH_2CH_3$	85	**19c** (76)
5	CH_3	CH_2CH_2Ph	$CH_2CH_2CH_2CH_3$	89	**19d** (96)

[a] Three-step overall yield from 1-chlorovinyl *p*-tolyl sulfoxide **3**.

showed the result described above with the overall yield for the synthesis of the bromocyclopropyl *p*-tolyl sulfoxide from **8**. Entry 2 shows the result using hexanenitrile as the nitrile to give the *tetra*-substituted allene **19a** in good overall yield. The fully substituted cyanoallenes were synthesized from cyclodecanone (entry 3) and cyclohexanone (entry 4) with propionitrile or hexanenitrile. By using 4-phenyl-2-butanone and hexanenitrile in this procedure, the fully substituted allene **19d** was obtained in high overall yield. It is interesting to note that all the substituents of the allene **19d** are different, butyl, cyano, methyl, and 2-phenylethyl groups.

Acknowledgements

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13. Experiment for the synthesis of allene **12**: *tert*-Butyllithium (0.89 mmol) was added dropwise to a solution of isobutyronitrile (0.07 mL, 0.81 mmol) in 16 mL of dry THF at −78 °C and the reaction mixture was stirred at the temperature for 1 h. In another flask at room temperature, about one-tenth of the solution of lithium α-carbanion of isobutyronitrile, described above, was added to a solution of bromide **11b** (40 mg, 0.08 mmol) in 16 mL of THF portionwise in every 10 min. After the addition, the reaction mixture was stirred at room temperature for 12 h. The reaction was quenched by adding satd aq NH_4Cl solution and the whole was extracted with CH_2Cl_2. The product was purified by silica gel column chromatography to afford 22.2 mg (99%) of allene **12** as a colorless oil. IR (neat) 2929, 2857, 2217 (CN), 1954 (allene), 1460 cm^{-1}; ^1H NMR δ 1.26–1.39 (20H, m), 1.45–1.52 (4H, m), 1.89 (3H, s), 2.08 (4H, m). MS *m*/*z* (%) 273 (M^+, 51), 146 (25), 120 (53), 107 (100). Calcd for $C_{19}H_{31}N$: M, 273.2457. Found: *m*/*z* 273.2456.