Pergamon

Tetrahedron Letters 43 (2002) 3033–3036

TETRAHEDRON
LETTERS

A novel synthesis of carboxylic acid derivatives having a quaternary carbon at 3-position and functional groups at 4-position from 1-chlorovinyl *p*-tolyl sulfoxides and acetic acid esters

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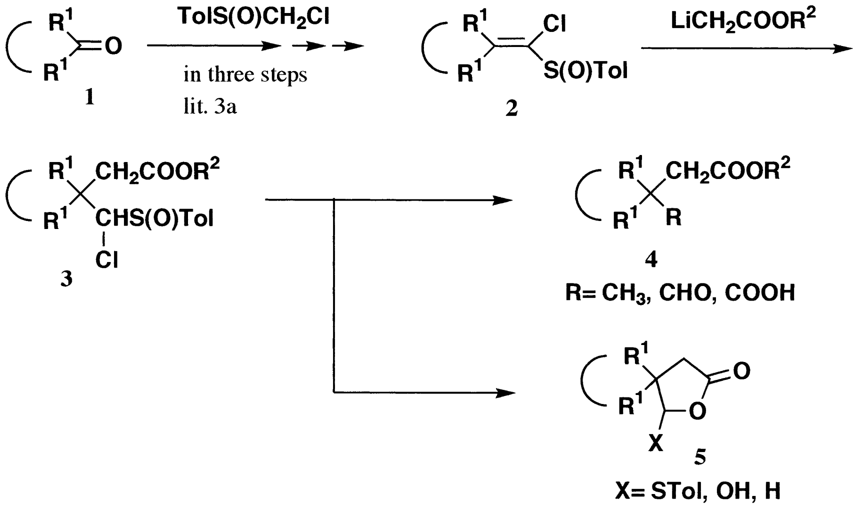
Received 25 January 2002; revised 15 February 2002; accepted 22 February 2002

Abstract—Addition of the lithium enolate of acetic acid esters to 1-chlorovinyl *p*-tolyl sulfoxides, which were derived from ketones and chloromethyl *p*-tolyl sulfoxide in three steps in good yields, gave carboxylic acid esters having a quaternary carbon at the 3-position, and chlorine and sulfinyl groups at the 4-position in high yields. Various kinds of functionalized carboxylic acid derivatives, including spiro-lactones, were derived from the adducts in good to high yields. © 2002 Elsevier Science Ltd. All rights reserved.

Carboxylic acids and their derivatives are obviously among the most important and fundamental compounds in organic and synthetic organic chemistry. Innumerable studies on the chemistry and synthesis of carboxylic acids and their derivatives have already been reported; however, in view of the importance of these compounds in organic chemistry, new synthetic methods are still eagerly sought.[1] On the other hand, construction of the quaternary carbon center has been a formidable task and a quite interesting challenge in synthetic organic chemistry.[2]

Recently, we reported several new synthetic methods starting from 1-chlorovinyl *p*-tolyl sulfoxides **2** derived from ketones **1** and chloromethyl *p*-tolyl sulfoxide.[3] In continuation of our studies for the development of a



Scheme 1.

Keywords: carboxylic acid; spiro-lactone; quaternary carbon; sulfoxide; 1-chlorovinyl aryl sulfoxide.

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PII: S0040-4039(02)00414-8

new synthetic method by using 1-chlorovinyl *p*-tolyl sulfoxides, herein we report a novel method for the synthesis of carboxylic acid derivatives having a quaternary carbon at the 3-position **4** and lactones **5** via the adduct of the vinyl sulfoxide **2** with acetic acid esters (Scheme 1).

In previous studies, we have found that cyanomethyllithium (lithium carbanion of acetonitrile) added to the 1-chlorovinyl *p*-tolyl sulfoxides **2** in high yields.[3b–d] We further investigated the reaction of **2** with nucleophiles, and the lithium enolate of acetic acid esters was found to work excellently. The results are summarized in Table 1.

The reaction was conducted simply by adding a solution of **2** to a solution of the lithium enolate of *tert*-butyl acetate derived from the acetate with LDA at −75°C.[4] The addition reaction was quite fast and found to be completed within 5 min (entries 1, 3, and 4). The yields of **3** were quantitative in all three cases. The result of the reaction with the lithium enolate of ethyl acetate was quite interesting (entry 2). In this case, the reaction with vinyl sulfoxide at −75°C did not take place at all. However, using 3 equivalents of the carbanion and allowing the temperature of the reaction to warm to 0°C, the desired adduct **3b** was obtained in 80% yield. We have no idea for the difference in reactivity of ethyl acetate and *tert*-butyl acetate at present. The adducts **3a–d** have two chiral centers and theoretically two diastereomers should be produced. In these reactions, only one case (entry 3) gave a mixture of the diastereomers.

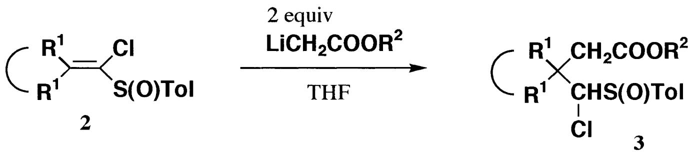
The adducts **3** are very interesting compounds in organic chemistry. First, the adducts **3** have a quaternary carbon at the 3-position. Second, they have a highly functionalized carbon at the 4-position. By chemical modification of the carbon, the adducts **3** would be converted to various kinds of carboxylic acid derivatives. Based on this expectation, we investigated the chemistry of **3**, and quite interesting results were obtained (Scheme 2).

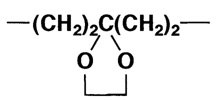
At first, transformation of the carbon having a chlorine atom and a sulfinyl group to a methyl group was investigated. Reduction of the chlorine atom of **3a** was successfully carried out under radical dehalogenation conditions[5] to give a sulfoxide **6** in high yield. Reduction of the sulfinyl group of **6** was easily carried out with Raney nickel W-2[6] in refluxing ethanol to afford the desired product **7** having the methyl group in quantitative yield.

Next, we investigated the transformation of the carbon having the sulfinyl group to aldehyde. As we have recognized that α-chlorinated sulfoxides are quite stable to an acid or a base, we tried to reduce the sulfoxide to sulfide. In some known reactions for the reduction of sulfoxide,[7] we tried to reduce **3a** with trifluoroacetic anhydride (TFAA) in the presence of NaI in acetone.[7c] Quite a clean reaction took place to afford the unexpected spiro-γ-lactone **8**, having a tolylthio group at the 4-position, in high yield.

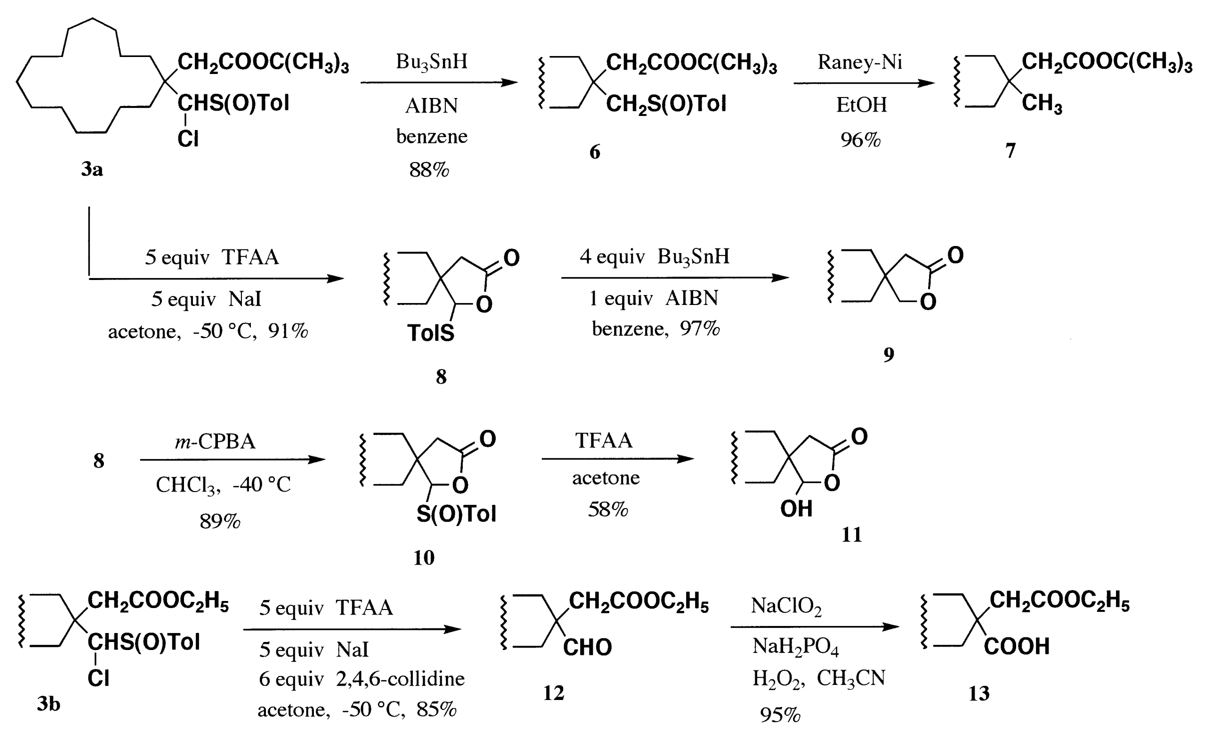
The presumed mechanism of this quite interesting reaction is shown in Scheme 3. First, the reaction of the sulfoxide **3a** gives an acyloxysulfonium ion.[8] At the same time, the *tert*-butyl ester is eliminated by trifluoroacetic acid to give carboxylic acid **14**. The iodide anion then attacks the chlorine atom to give thionium ion **15**. The oxygen of the carboxylic acid attacks intramolecularly the thionium ion to afford the spirolactone **8**.

Table 1. Addition of lithium enolate of acetic acid esters to 1-chlorovinyl *p*-tolyl sulfoxides **2**

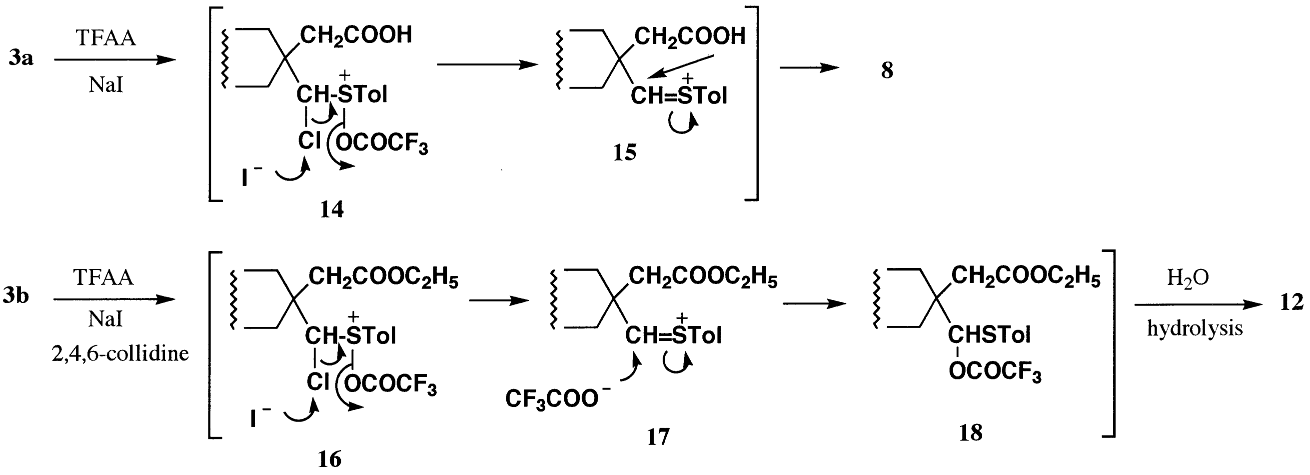


Entry	2		R^2	Conditions	3
	R^1	R^1			Yield / %
1	—$(CH_2)_{14}$—		$C(CH_3)_3$	-75 °C, 5 min	**3a** 98
2	—$(CH_2)_{14}$—		CH_2CH_3	-75 ~ 0 °C, 1 h[a)]	**3b** 80
3	 $—(CH_2)_2C(CH_2)_2—$ with C bearing OCH_2CH_2O		$C(CH_3)_3$	-75 °C, 5 min[b)]	**3c** 99
4	CH_3	CH_3	$C(CH_3)_3$	-75 °C, 5 min	**3d** 99

a) 3 equivalents of lithium enolate of ethyl acetate was used. b) The adduct **3c** was a mixture of two diastereomers; the ratio was 83:16. All other adducts **3a**, **3b**, and **3d** were a single product.



Scheme 2. Synthesis of various carboxylic acid derivatives from the adducts **3a** and **3b**.



Scheme 3. A plausible mechanism for the formation of lactone **8** and aldehyde **12** by treatment of **3a** and **3b** with TFAA.

Desulfurizaion of the tolylthio group of **8** was successfully carried out with Bu_3SnH in the presence of 2,2′-azobisisobutyronitrile (AIBN)[9] to give the spiro-lactone **9** in quantitative yield. The spiro-lactone of the higher oxidation state (**11**) than **9** was synthesized from **8** via the sulfoxide **10**. Thus, the sulfide **8** was oxidized with *m*-chloroperbenzoic acid at −40°C to give the sulfoxide **10** in good yield. Treatment of the sulfoxide with TFAA in acetone gave the desired lactone having an hydroxyl group at the 4-position **11** through the Pummerer rearrangement.

Finally, we investigated conversion of the carbon bearing the chlorine and the sulfinyl group to an aldehyde group (Scheme 2). As mentioned above, as the *tert*-butyl ester is easily eliminated by TFAA, we used the ethyl ester **3b**. Treatment of the ethyl ester **3b** with TFAA–NaI in the absence of a base gave the desired **12** in 60% yield; however, about 20% of the lactone **8** was still present. We further investigated this reaction and found that excess organic base worked to give the desired aldehyde **12** in 85% yield without the lactone **8**.

The mechanism of this reaction was presumed as shown in Scheme 3. By the same reaction as above, **3b** gave thionium ion **17** through **16**. As this reaction was carried out in the presence of excess organic base, and the ethyl ester was used, the ester remained intact by TFAA. Trifluoroacetic acid was added to the thionium ion **17** to afford the sulfide having a trifluoroacetoxy group on the same carbon, which was hydrolyzed in the work-up process to give the aldehyde **12**. Oxidation of this aldehyde **12** to carboxylic acid was carried out with $NaClO_2$[10] to give the desired carboxylic acid **13** in quantitative yield.

In conclusion, we have developed a novel and versatile procedure for a synthesis of carboxylic acid derivatives having a quaternary carbon on the 3-position from 1-chlorovinyl *p*-tolyl sulfoxides. These carboxylic acid derivatives, in addition, have various kinds of functional groups with a different oxidation state at the 4-position.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research No. 11640545 from the Ministry of Education, Culture, Sports, Science and Technology, Japan, which is gratefully acknowledged.

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