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Regioselective conjugate addition of thiols to unsymmetric fumaric esters in the presence of a lithium cation

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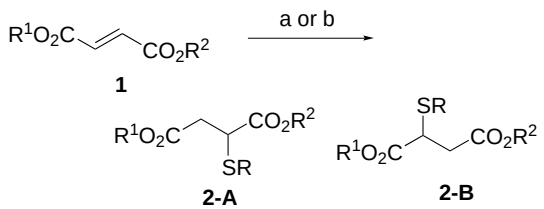
Abstract—Unsymmetrically substituted fumaric esters underwent highly regioselective conjugate addition of thiols in the presence of a lithium cation in non-coordinative media.

The Michael addition is recognized a very useful tool to construct carbon backbones.[1] The existence of two electron-withdrawing groups attaching to each side of an olefin enhances its reactivity to the Michael addition, but incurs a problem of regioselectivity unless the two groups are identical. One example of such case is the conjugate addition to unsymmetric fumaric esters, in which control of the orientation is rather difficult because the electronic and steric differences between the two ester groups are small. As a result, this simple but inherent problem has remained unsolved so far. To the best of our knowledge, there has only been one report so far, in which a mixture of the two regioisomers was formed in poor regioselectivity.[2] Otherwise, conjugate adducts have been prepared in a different way that involved several steps.[3] In this paper, we report an excellent solution to the problem. The Michael addition of thiols to unsymmetric fumaric esters was effectively controlled, and the presence of a lithium cation in an uncoordinative solvent enhanced the selectivity to a practically useful level, in which a single regioisomer of the adducts was obtained in high diastereomeric purity.[4]



Scheme 1. Michael addition of thiols to unsymmetric fumaric esters. *Reagents and conditions*: (a) PhSH, base (0.1 equiv.), −50°C; (b) $PhSSiMe_3$, TBAF (1 equiv.), −50°C.

The Michael addition of thiol to unsymmetric fumaric ester **1** was examined under various conditions (Scheme 1).[5] The results are summarized in Table 1. Ethyl methyl fumarate **1a**, an unsymmetric fumaric ester, underwent conjugate addition of benzenethiol in the presence of a catalytic amount of a base to give Michael adduct **2a** in good yield (Scheme 1, Table 1 entry 1). As expected, the adduct contained two regioisomers, **2a**–**A** and **2a**–**B**, in a 1.51:1 ratio so that the addition took place almost non-selectively. The product ratio in the addition to **1a** did not change very much under various reaction conditions (entries 2 and 3). The Michael addition to *tert*-butyl ethyl fumarate **1b** also occurred smoothly under similar basic conditions at −50°C. To our surprise, one of the regioisomers, **2b**–**A**, was formed preferentially in over 11.8:1 ratio (entry 4). The fluoride anion-catalyzed Michael addition also gave a mixture of **2b**–**A** and **2b**–**B** in about 10:1 ratio (entry 5). The presence of catalytic amounts of a lithium thiolate in THF or DME also gave the adduct **2b** in good yields, but the regioselectivity remained at a similar level (entries 6 and 7). The selectivity was greatly improved when the reaction was carried out in CH_2Cl_2; **2b**–**A** was obtained in 28:1 ratio (entry 8). Use of toluene as the reaction solvent furnished slightly better regioselectivity, but the yield of **2b**

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Table 1. Regioselective Michael addition of thiols to unsymmetric fumaric esters

Entry	R^1	R^2	R	Time (h)	Conditions	**2**	Yield (%)[a]	**A**/**B**[b]
1	Me	Et	Ph	1.5	Et_3N/C_2H_5CN	**2a**	91 (7)	1.51
2	Me	Et	Ph	1.5	BuLi/THF	**2a**	96 (3)	1.49
3	Me	Et	Ph	1.5	$BuLi/CH_2Cl_2$	**2a**	99 (0)	1.46
4	Et	*t*Bu	Ph	4.5	Et_3N/C_2H_5CN	**2b**	77 (2)	11.8
5	Et	*t*Bu	Ph	2.5	Bu_4NF/CH_2Cl_2[c]	**2b**	12 (–)[d]	10.1
6	Et	*t*Bu	Ph	12	BuLi/THF	**2b**	75 (0)	11.5
7	Et	*t*Bu	Ph	2	BuLi/DME	**2b**	82 (0)	11.2
8	Et	*t*Bu	Ph	12	$BuLi/CH_2Cl_2$	**2b**	84 (0)	28.4
9	Et	*t*Bu	Ph	24	BuLi/toluene	**2b**	42 (42)	15.7
10	Et	*t*Bu	*o*-MeC_6H_4-	2.5	$BuLi/CH_2Cl_2$	**2c**	92 (0)	41.1
11	Et	*t*Bu	*p*-MeC_6H_4-	12	$BuLi/CH_2Cl_2$	**2d**	87 (0)	22.4
12	Et	*t*Bu	Et	12	$BuLi/CH_2Cl_2$	**2e**	75 (0)	8.06
13	Et	*t*Bu	$HOCH_2CH_2$-	1.5	$BuLi/CH_2Cl_2$	**2f**	86 (0)	6.22
14	Et	*t*Bu	*o*-$MeOC_6H_4$-	42	$BuLi/CH_2Cl_2$	**2g**	0 (100)	–

[a] Isolated yield. Recovery of the starting fumaric ester is in parentheses.
[b] Determined by ^1H NMR analyses.
[c] $PhSSiMe_3$ was used instead of PhSH.
[d] Not determined.

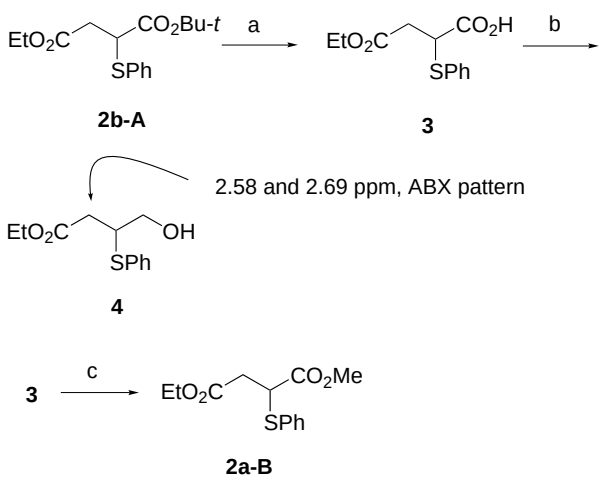
decreased to 42% due to precipitation of most of the lithium thiolate in toluene (entry 9). No other counter cations such as sodium, potassium, magnesium or aluminum were effective for the smooth progress of the Michael addition. The best regioselectivity was observed in the addition of *o*-thiocresol, the reaction of which gave **2c**–**A** in 41.1:1 selectivity (entry 10). These reaction conditions also promoted the addition of aliphatic thiol to **1b** in a regioselective manner (entry 12), while the selectivity decreased for the addition of oxy-substituted thiols (entries 13 and 14).

The structure of the adducts was determined by chemical conversion of **2** followed by NMR analyses (Scheme 2). The major adduct of the reaction **2b**–**A**, for example, was converted to carboxylate **3**, which was reduced by BH_3·THF to give **4**.[6] The α-protons to the ethoxycarbonyl group in **4** appeared at 2.58 and 2.69 ppm in an ABX pattern which unambiguously supported the structure of **4** shown in Scheme 2. Treatment of **3** with MeI and DBU afforded a methyl ester,[7] which was identical to **2a**–**B**, the minor isomer formed in the Michael addition to **1a**.

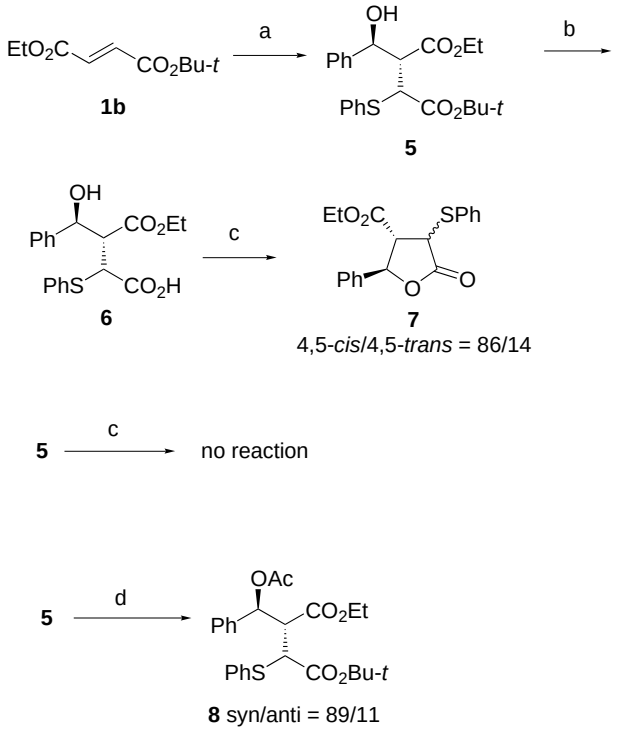
This high regiocontrol in unsymmetric fumaric esters was applied to a tandem Michael/aldol reaction (Scheme 3).[8] Treatment of **1b** in the presence of lithium thiolate and benzaldehyde, for example, resulted in the formation of tandem Michael/aldol adduct **5** as a mixture of four diastereoisomers. To determine the diastereomeric ratio, **5** was converted to the corresponding acetate **8** in 80% yield and NMR analysis of the mixture indicated that the diastereomeric ratio of the four isomers in **8** was 66:23:6:5. It should be mentioned that no γ-butyrolactones such as **7** were found in the reaction mixture; this was in contrast to the reaction starting from diethyl fumarate that gave considerable amounts of lactone **7** in the same tandem procedure.[8] This result suggests that the tandem reaction took place in a highly regioselective manner to give **5** exclusively; i.e. no regioisomer of **5** should be formed.

In fact, treatment of **5** with PPTS in refluxing benzene resulted in complete recovery of **5**, whereas acidic treatment followed by heating in the presence of PPTS gave 4,5-*cis* lactone **7** in 86:14 ratio, in which all the ethoxycarbonyl group survived during the conversion. Thus, in the tandem reaction, thiolate attacked the *tert*-butoxycarbonyl-attached carbon exclusively, giving **5** in regiochemically pure form. The configuration of the two major isomers of **7** was unambiguously determined to be 4,5-*cis* on the basis of their X-ray crystallographic study and NOE experiments,[9] although very slight stereochemical isomerization during the later treatment might occur. Hence, we conclude that the tandem reaction takes place in a completely regioselective and highly *anti*-aldol-selective manner.

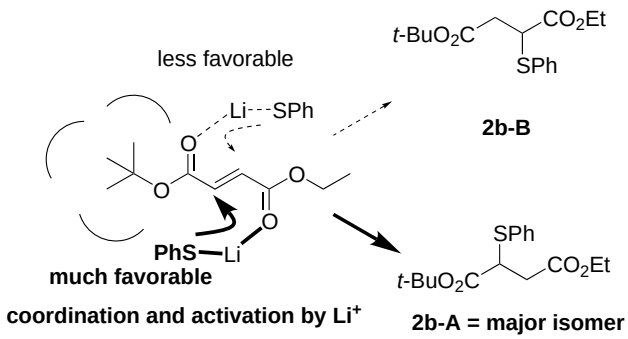
We assume the following reaction mechanism that accomplishes the present high regioselectivity (Scheme 4). In all cases, lithium thiolate selectively attacked the



Scheme 2. Determination of the regiochemistry of **2**. *Reagents and conditions*: (a) TFA, thioanisole, rt, 98%; (b) BH_3·THF, THF, −10°C to rt, 48%; (c) MeI, DBU, toluene, rt, 74%.



Scheme 3. Michael/aldol tandem reaction to an unsymmetric fumaric ester. *Reagents and conditions*: (a) PhSLi, PhCHO, CH_2Cl_2, −50°C, 15 h, 83%; (b) TFA, thioanisole, rt; (c) PPTS, toluene, 110°C, 89% from **5**; (d) Ac_2O, DMAP, pyridine, rt, 2 h, 80%.



Scheme 4. Supposed reaction mechanism.

tert-butoxycarbonyl site of the unsymmetric fumaric ester **1b**. The selectivity was enhanced when lithium thiolate was used in a non-coordinating solvent such as CH_2Cl_2. It may seem strange that the thiolate prefers to attack the much bulky *tert*-butoxycarbonyl side of the acceptor. This can be rationalized, however, if the activation of an ester group by the coordination of the lithium cation is a significant factor in the Michael addition process. Thus, the lithium cation, which should not be solvated in CH_2Cl_2, acts as a strong Lewis acid,[10] and likely coordinates to either of the carbonyl groups in fumaric ester **1b**. Due to steric bulkiness of the *tert*-butyl residue, the lithium cation should prefer the less bulky ethoxycarbonyl group, which is then activated. As a result, the Michael addition of thiolate mainly occurs on the β-carbon of the coordinated carbonyl group to give diastereomer A in a highly regioselective way. Further investigation and application of this reaction are now under way in our laboratory.

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