Pergamon

Tetrahedron Letters 43 (2002) 7521–7523

TETRAHEDRON LETTERS

Regioselective Michael addition of thiols to tertiary fumaric amide esters

Akio Kamimura,[a,*] Norikazu Murakami,[a] Kakuteru Yokota,[a] Masashi Shirai[b] and Hiroaki Okamoto[c]

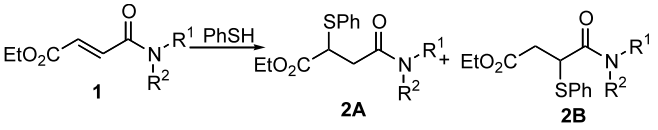
[a]*Department of Applied Chemistry, Faculty of Engineering, Yamaguchi University, Ube 755-8611, Japan*
[b]*Ube Laboratory, Ube Industries Ltd., Ube 755-8633, Japan*
[c]*Department of Advance Materials Science and Engineering, Faculty of Engineering, Yamaguchi University, Ube 755-8611, Japan*

Received 24 July 2002; revised 21 August 2002; accepted 23 August 2002

Abstract—The regiochemistry of the Michael addition of thiols to tertiary fumaric amide esters was efficiently controlled in the presence or absence of base; either of the two isomers was prepared in a highly selective way. © 2002 Elsevier Science Ltd. All rights reserved.

The Michael addition is the most important reaction in organic synthesis.[1] Thiols are known as a good nucleophile for the reaction. Existence of two activating groups usually enhances the reactivity of the acceptor alkenes but gives rise to a problem on regioselectivity that is not always easily solved.[2] Recently, we have demonstrated that the regiochemistry of the Michael addition of thiols to an unsymmetrical fumaric ester is efficiently controlled by the presence of lithium cation in non-coordinative solvent and one of the regioisomer is formed predominantly.[3] In this paper we report that the regiochemistry of the Michael addition to fumaric tertiary amide ester was nicely controlled in the presence or absence of base and either of the two regioisomers was prepared in a highly regioselective manner.

We first examined the Michael addition to fumaric amide ester **1** under the conventional base-catalyzed conditions (Scheme 1). The results are summarized in Table 1.



Scheme 1. *Reagents and conditions*: (X) Et_3N (0.1 equiv.), C_2H_5CN, rt, 6 h; (Y) CH_2Cl_2, rt, 48 h.

The Michael addition to **1** smoothly proceeded in the presence of catalytic amounts of base, condition X, to give the adduct **2a** in 85% yield (entry 1). The ratio of the two regioisomers was found to be 10/90 and regioisomer B was formed as the major component. We then examined various reaction conditions in order to change or improve the regioselectivity. The reaction proceeded without base even though the reaction rate became very slow, and **1a** disappeared within 24 h. After solvent was removed, adduct **2a** was obtained in 86% yield (entry 2). To our surprise, the crude adduct contained only a single isomer of **2a** which was found to be **2aA**, the opposite regioisomer to the product of the conventional Michael addition reaction. This change in regioselectivity was also observed in the reaction performed in C_2H_5CN. Other tertiary amide esters **1b**, **1c** and **1d** also gave adduct **2** in a similar manner; the base-catalyzed Michael addition (condition X) led to the formation of regioisomer **B** preferentially, while the reaction without base (condition Y) gave regioisomer **A** selectively (entries 3–8). It was interesting that the latter selectivity was very high and the minor isomer **B** was not observed in NMR spectra of the crude adducts. The same tendency was observed in the reaction with secondary amide, while the reaction rate under non-basic conditions became very slow; the yield of the adduct was poor, but the selectivity was high (entries 9 and 10).[4] To enhance the reaction rate for secondary amides under non-basic conditions, *N*-benzyloxyamide was used. Good yield and **A**-selective addition were achieved under non-basic addition conditions (entry 12), while a mixture of the two regioiso-

Keywords: Michael reactions; regiocontrol; thiols.
* Corresponding author.

0040-4039/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(02)01824-5

Table 1. Regioselective conjugate addition of thiols to fumaric amide ester **1**

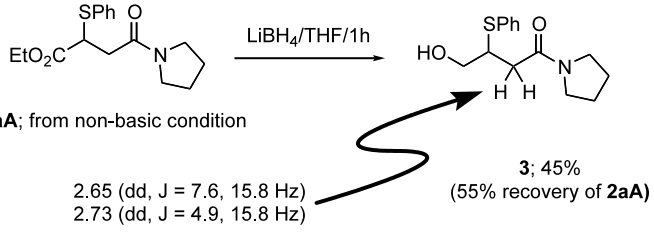
Entry	R^1	R^2	Conditions[a]	**2**	Yield (%)[b]	**A**/**B**[c]
1	$-(CH_2)_4-$		X	**2a**	85	10/90
2	$-(CH_2)_4-$		Y	**2a**	86	>99/1
3	$-(CH_2)_5-$		X	**2b**	87	7/93
4	$-(CH_2)_5-$		Y	**2b**	80	>98/2
5	Bn	Bn	X	**2c**	46	13/87
6	Bn	Bn	Y	**2c**	91	>98/2
7	$-CH_2CH=CH_2$	$-CH_2CH=CH_2$	X	**2d**	61	16/84
8	$-CH_2CH=CH_2$	$-CH_2CH=CH_2$	Y	**2d**	52	>98/2
9	Bn	H	X	**2e**	77	2/98
10	Bn	H	Y	**2e**	20	83/17[d]
11	OBn	H	X	**2f**	93	55/45
12	OBn	H	Y	**2f**	70	82/18

[a] X: Et_3N (0.1 equiv.), C_2H_5CN, rt, 6 h; Y: CH_2Cl_2, rt, 48 h.
[b] Isolated yield.
[c] Determined by HPLC or NMR analyses.
[d] Before chromatographic purification. See Ref. 4.

mers **A** and **B** was obtained in the reaction performed in the presence of base (entry 11). Use of Lewis acid such as $BF_3{\cdot}OEt_2$ failed to progress the reaction and desired Michael adduct **2** was not obtained. This is probably because the Lewis acid preferred to make a direct complex with thiophenol which is then deactivated to the Michael addition.

The structure of the adducts was determined in the following way (Scheme 2): compound **2aA**, for example, was reduced by treatment with $LiBH_4$ to give the corresponding amidealcohol **3** in 45% yield. The NMR spectrum of **3** indicated that the α-protons of the amide unit appeared as an ABX pattern around at 2.7 ppm. This result supported the structure of compound **3** in which the phenylthio group attached to the β-carbon of the amide unit so that we concluded the structure **2aA** as shown in Scheme 2. In addition, in the regioisomer series **2A**, the methyl group in the ethyl ester unit always appeared around 1.15 ppm, which is slightly upfield than the proton in regioisomer series **2B**. This observation was quite useful to determine the regiochemistry of the adducts. The regiochemistry for other adducts **2** was elucidated on the basis of these results.

The present results showed that nucleophilic attack of the thiol prefers the β-carbon to the ester group under the conventional basic conditions, while the attack occurred predominantly from the β-carbon to the amide group in the reaction in the absence of base. Our

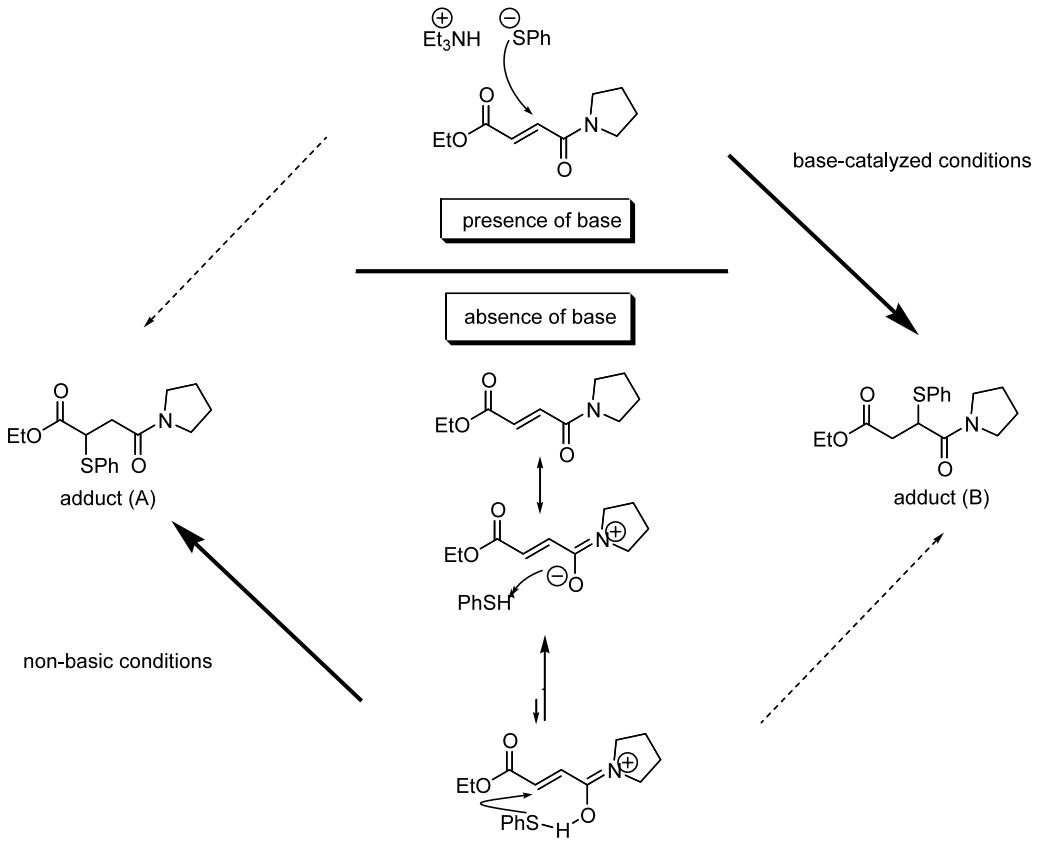


Scheme 2.

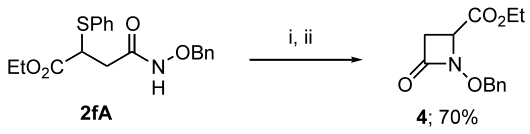
assumption for the change of the selectivity is summarized in Scheme 3. The ester group usually acts as a much stronger electron withdrawing group than the amide group so that the β-carbon to the ester group should be much activated toward the nucleophilic attack. The conventional basic conditions efficiently generate a nucleophilic thiolate anion that prefers to attack from this side to give regioisomer **B** in a regioselective manner. Due to high nucleophilicity of the thiolate anion, the reaction rate is quite fast and it finishes within an hour. This situation, however, is changed if the reaction is carried out without base; the concentration of the thiolate anion becomes small and the direct attack of the thiolate to the fumaric amide ester must be suppressed. In fact, the reaction rate became very slow and took several hours until the reaction was complete. The thiol proton, in turn, serves as an acid that can coordinate to the much basic amide carbonyl to form iminium ion intermediate when tertiary amide is used. Then the amide group is activated toward the nucleophilic attack and the β-carbon to the amide unit now becomes a much more electrophilic site than the β-carbon to the ester. The Michael addition occurs from this side to give regioisomer **A** predominantly. The secondary amide, however, should not form the iminium intermediate efficiently so that the reaction rate becomes very slow. Use of *N*-benzyloxyamide improved the yield probably because of the electron withdrawing property of the amide group. In fact, the conventional basic conditions resulted in the formation of a mixture of the two regioisomers.

To show a synthetic application, we attempted to convert the adduct **2** to β-lactam **4**.[5] Exposure of compound **2fA**, for example, to MeI in the presence of $AgClO_4$ gave sulfonium intermediate. Subsequent basic treatment afforded β-lactam **4** in good yield through the intramolecular S_N2 reaction (Scheme 4).[6]

The regiochemistry of the Michael addition of thiol to tertiary fumaric amide esters was efficiently controlled by the presence or absence of base. Further application



Scheme 3.



Scheme 4. *Reagents and conditions*: (i) MeI, $AgClO_4$, MeCN, rt; (ii) K_2CO_3, acetone, reflux, 4 h.

of this methodology is now underway in our laboratory.

References

1. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992.
2. (a) Zaderenko, P.; López, M. C.; Ballestros, P. *J. Org. Chem.* **1996**, *61*, 6825; (b) Allen, N. E.; Boyd, D. B.; Campbell, J. B.; Deeter, J. B.; Elzey, T. K.; Foster, B. J.; Hatfield, L. D.; Hobbs, J. N., Jr.; Hornback, W. J. *Tetrahedron* **1989**, *45*, 1905.
3. Kamimura, A.; Kawahara, F.; Omata, Y.; Murakami, N.; Morita, R.; Otake, H.; Mitsudera, H.; Shirai, M.; Kakehi, A. *Tetrahedron Lett.* **2001**, *42*, 8497.
4. It should be remarked that adduct **2e-A** isomerized to **2e-B** during the silica gel chromatographic purification. This isomerization happened only for **2e-A**; no isomerization was observed in any other adducts **2**.
5. Miller, M. J.; Bajwa, J. S.; Mattingly, P. G.; Peterson, K. *J. Org. Chem.* **1982**, *47*, 4928.
6. Miyata, O.; Fujiwara, Y.; Ninomiya, I.; Naito, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2167.