Stereoselective Michael/aldol tandem reaction triggered by thiolate anion or analogues

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A combination of a *tert*-butyl α,β-unsaturated ester, an aldehyde and lithium thiophenolate in CH_2Cl_2 undergoes a one-pot Michael/aldol tandem reaction to give a condensation adduct of the three components, an α-phenylthiomethyl-β-hydroxy ester, in good yield with high *syn*-selectivity.

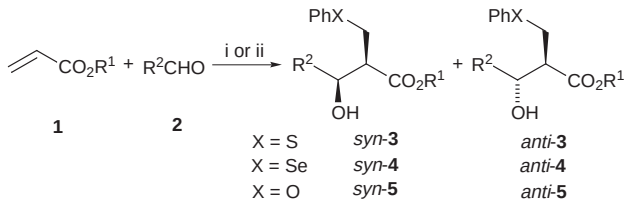
The Michael addition is one of the most powerful methodologies in organic synthesis.[1] Thiols are frequently used as good nucleophiles for the reaction with α,β-unsaturated esters, ketones or nitriles to give the corresponding Michael adducts quantitatively. The reaction is regarded as generating a β-thioenolate intermediate as a result of nucleophilic attack of the thiolate at the β-carbon of the Michael acceptor;[2] the intermediate is then protonated to give the Michael adduct. If the β-thioenolate intermediate was able to be used for the aldol reaction, a new Michael/aldol tandem reaction[3] could be developed and might provide a useful methodology for the construction of carbon skeleton since sulfur functionality is convenient for further transformation to other functional groups. There have been several similar examples of this type of reaction with carbon,[4] nitrogen[5] and silicon nucleophiles.[6] Although thiolate and its analogues have also been used in a similar way, good examples are limited to α,β-unsaturated ketones,[7] and the same sequence for α,β-unsaturated esters contains many problems.[7a,d,8] Additionally, the stereochemical outcome of the reaction with esters has not been clear so far. Here, we report a novel one-pot three-component condensation of thiolate, an α,β-unsaturated ester and an aldehyde with high *syn*-stereoselectivity.

The reaction procedure was quite simple; lithium thiophenolate was generated from thiophenol on treatment with butyllithium at −78 °C in CH_2Cl_2 to give a white precipitate, most of which remained undissolved following addition of acryrate esters at −78 °C. To the heterogeneous mixture, aldehyde was added at the same temperature; the reaction mixture then became a homogeneous pale yellow solution. The solution was maintained at −50 °C for 7 h and the three-component condensation adducts **3** were obtained (Scheme 1). To our surprise, no S_N2 product from CH_2Cl_2 and lithium thiolate was observed. The results are summarised in Table 1.‡

The reaction exhibited several interesting features. Firstly, choice of reaction solvent was quite important; CH_2Cl_2 or Et_2O were the only suitable solvents to perform the reaction. Other coordinative solvents such as THF or propiononitrile were not useful; only the simple Michael adduct of thiol and acrylate was formed. The counter cation was also important; use of lithium thiophenolate was essential. The reaction of methyl or ethyl acrylate gave the three component adducts **3a** or **3b** in 62 or 64% yield, respectively, but neither of their diastereomeric ratios were satisfactory (entries 1 and 2). The stereoselectivity was significantly improved when *tert*-butyl acrylate was used instead; the tandem adduct **3c** was obtained in 80% with 92 : 8 *syn*-selectivity (entry 3). The present stereoselectivity is much higher than the analogous aldol reaction of ester enolates generated from *tert*-butyl propionate with LDA, in which the reported *syn* : *anti* ratio was almost 1 : 1.[9] The tandem adducts **3**, starting from other aromatic and α,β-unsaturated aldehydes, were prepared in similar yields with high *syn*-selectivity (entries 4–6). Aliphatic aldehydes also gave the adduct in moderate yield, along with formation of the self-aldol product of the aldehyde (entry 7).

We also examined analogues of thiolate for the reaction. Lithium phenylselenolate,[10] which was generated from diphenyl diselenide and methyllithium,§ was found to be effective for the reaction; again the *syn*-enriched adduct **4a** was isolated in 63% (entry 8). The diastereoselectivity and yield of **4** for the reaction with aromatic aldehydes were slightly less than those for the reactions promoted by thiolate in CH_2Cl_2 (entries 8–10). The reaction with an aliphatic aldehyde, however, gave **4d** in only poor yield (entry 11). Phenoxide was too unreactive to promote the reaction (entry 12). We also tried to apply the present sequence to methyl vinyl ketone with thiolate and benzaldehyde, but only trace amounts of the corresponding tandem adduct were formed.

The stereochemistries of **3** and **4** were determined in the following way (Scheme 2); the phenylseleno group in compound **4a** was replaced by hydrogen on treatment with Bu_3SnH. Diastereomeric ratios of **4a** (85 : 15) and **6** (82 : 18) were almost the same within experimental error. The NMR spectrum of the

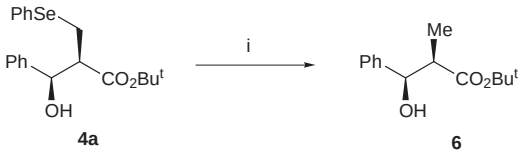


Scheme 1 *Reagents and conditions*: i, PhSLi, CH_2Cl_2, −78 °C, then −50 °C; ii, PhSeSePh, MeLi·LiBr, Et_2O, −78 °C, then room temp.

Table 1 The three-component condensation of thiolate, acrylate and aldehyde

Entry	R^1	R^2	X	Product	Yield (%)[a]	*syn* : *anti*[b]
1	Me	Ph	S	**3a**	62	71 : 29
2	Et	Ph	S	**3b**	64	66 : 34
3	Bu^t	Ph	S	**3c**	80	92 : 8
4	Bu^t	*p*-ClC_6H_4	S	**3d**	71	89 : 11
5	Bu^t	1-naphthyl	S	**3e**	92	88 : 12
6	Bu^t	PhCH=CH	S	**3f**	52	81 : 19
7	Bu^t	C_5H_{11}	S	**3g**	65	73 : 27
8	Bu^t	Ph	Se	**4a**	63	85 : 15
9	Bu^t	*p*-ClC_6H_4	Se	**4b**	52	81 : 19
10	Bu^t	2-naphthyl	Se	**4c**	64	84 : 16
11	Bu^t	C_9H_{19}	Se	**4d**	23	nd[c]
12	Bu^t	Ph	O	**5a**	0	—

[a] Isolated yield. [b] Determined by reversed phase HPLC analyses. [c] nd = not determined.

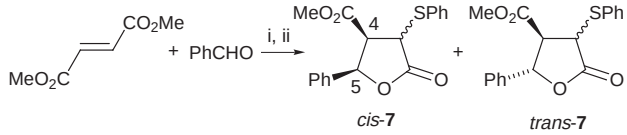


4a **6**

Scheme 2 *Reagents and conditions*: i, Bu_3SnH, AlBN, toluene, 110 °C (75%)

minor isomer of **6** was found to be identical to the known *anti*-diastereomer,[11] and we concluded that the major isomers of **4a** and **6** had *syn*-configuration. The stereochemistries of the other thio analogues **3** were determined on the basis of comparison of their ^{1}H NMR spectra and HPLC patterns.

The present methodology is useful for the preparation of γ-butyrolactone from lithium thiophenolate, fumarate ester and aldehyde. For example, reaction of the three components in CH_2Cl_2 at −50 °C for 5 h resulted in the formation of γ-butyrolactone **7** along with the β-hydroxy ester. The mixture was then treated with PPTS in refluxing toluene to give lactone **7** in 64% yield (Scheme 3). NOE measurements and HPLC analysis revealed that the 4,5-*cis* isomer was formed as the major isomer in an 80 : 20 ratio.



cis-**7** *trans*-**7**

64%; 4,5-*cis*:4,5-*trans* = 80:20

Scheme 3 *Reagents and conditions*: i, PhSLi, CH_2Cl_2, −78 °C, then −50 °C, 7 h; ii, PPTS, toluene, 110 °C, 2 h

Due to the heterogeneity of the mixture of acryrate and thiolate, the mechanism of the reaction and origin of the stereoselectivity are not clear; attempts to trap the β-thioenolate intermediate have so far been unsuccessful. Indeed, since most of the white precipitate of lithium thiophenolate in CH_2Cl_2 is undissolved in the presence of the acrylate esters, the concentration of the β-thioenolate intermediate in the absence of aldehyde should be very low. We assume that the active intermediate is formed with assistance due to coordination of the aldehyde to the lithium cation. Further investigation and application of the reaction will be reported in due course.

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Notes and References

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‡ All new compounds were fully characterised by spectroscopic analysis and microanalysis or HRMS.

§ Although lithium phenylselenolate should be generated from selenol and butyl lithium, we wished to avoid using the selenol formed from diselenide due to its toxicity and evil odour. After exploring several potential routes to lithium selenolate, we found that it was generated directly from a solution of diselenide *via* addition of methyl- or butyl-lithium. Although half of the selenium source is wasted as alkyl phenyl selenide, the present method was advantageous because anhydrous selenolate anion with no proton source was generated directly from commercially available diphenyl diselenide; the yellow colour of the diselenide disappeared when an equimolar amount of alkyllithium had been added.

1 M. E. Jung, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pargamon, Oxford, 1991, vol. 4, pp. 1–67.
2 O. Miyata, T. Shinada, I. Ninomiya, T. Naito, T. Date, K. Okamura and S. Inagaki, *J. Org. Chem.*, 1991, **56**, 6556; R. Clauss, W. Hinz and R Hunter, *Synlett*, 1997, 57.
3 For review for tandem reaction, see R. A. Bunce, *Tetrahedron*, 1995, **48**, 13 103.
4 J. F. G. A. Jansen and B. K. Feringa, *Tetrahedron Lett.*, 1991, **32**, 3239.
5 S. G. Davies and O. Ichihara, *J. Synth. Org. Chem. Jpn.*, 1997, **55**, 26 and references cited therein; S. G. Davies and D. R. Fenwick, *Chem. Commun.*, 1997, 565; N. Tsukada, T. Shimada, Y. S. Gyoung, N. Asao and Y. Yamamoto, *J. Org. Chem.*, 1995, **60**, 143; Y. Yamamoto, N. Asao and T. Yuehara, *J. Am. Chem. Soc.*, 1992, **114**, 5427; A. Hosomi, T. Yanagi and M. Hojo, *Tetrahedron Lett.*, 1991, **32**, 2371; N. Asao, T. Uyehara and Y. Yamamoto, *Tetrahedron*, 1990, **46**, 4563.
6 I. Fleming and J. D. Kilburn, *J. Chem. Soc., Chem. Commun.*, 1986, **305**; 1198; I. Fleming and A. K. Sarkar, *J. Chem. Soc., Chem. Commun.*, 1986, 1199.
7 (*a*) A. G. M. Barrett and A. Kamimura, *J. Chem. Soc., Chem. Commun.*, 1995, 1755; (*b*) T. Yura, N. Iwasawa and T. Mukaiyama, *Chem. Lett.*, 1986, 187; (*c*) M. Suzuki, T. Kawagishi and R. Noyori, *Tetrahedron Lett.*, 1981, **22**, 1809; (*d*) A. Itoh, S. Ozawa, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, 1980, **21**, 361.
8 J. I. Levin, *Synth. Commun*., 1992, 961.
9 C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn and J. Lampe, *J. Org. Chem*., 1980, **45**, 1066.
10 For generation of selenolate anion, see: C. Paulmier, *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon, Oxford, 1986, pp. 25–27 and references cited therein; D. Liotta, *Acc. Chem. Res.*, 1984, **17**, 28; D. L. J. Clive, *Tetrahedron*, 1978, **34**, 1049; H. Reich, *Acc. Chem. Res.*, 1979, **12**, 22.
11 E. J. Corey and S. S. Kim, *J. Am. Chem. Soc.*, 1990, **112**, 4976.

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