Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 1899–1902
Tetrahedron Letters

Organocatalytic highly enantioselective tandem Michael–Knoevenagel reaction for the synthesis of substituted thiochromanes

Rajasekhar Dodda, Tanmay Mandal, Cong-Gui Zhao *

Department of Chemistry, University of Texas at San Antonio, One UTSA Circle, San Antonio, TX 78249-0698, USA

Received 27 December 2007; revised 24 January 2008; accepted 25 January 2008
Available online 31 January 2008

Abstract

Enantioenriched tetrasubstituted thiochromanes have been synthesized using a tandem Michael addition–Knoevenagel reaction between 2-mercaptobenzaldehydes and benzylidenemalonates with a 9-*epi*-aminoquinine thiourea derivative as the catalyst. Steric and electron effects were found to affect profoundly the enantioselectivity and diastereoselectivity of the reaction.

Thiochromanes, the sulfur analogues of chromanes, have been reported to possess important biological activities.[1] There are also reports that the replacement of oxygen atom in chromanes with a sulfur atom results in enhanced bioactivities.[1e,g] Owing to their biological relevance, several asymmetric synthetic methods[2] have been developed; nonetheless, these methods are either not catalytic or they use special reagents. Most recently, there is considerable interest in developing catalytic asymmetric synthesis of these derivatives using organocatalysis.[3] For example, Wang and co-workers reported an enantioselective synthesis on the basis of a tandem Michael-aldol reaction using a quinine thiourea catalyst.[3c]

As part of our on going effort in developing novel organocatalytic reactions,[4] we recently discovered[3e] a novel synthesis of trisubstituted thiochromanes on the basis of a tandem[5] Michael–Henry reaction catalyzed by cupreine. During the course of this study, we envisioned that Wang's approach toward thiochromanes may be improved by using readily available benzylidenemalonates as the substrates.

As shown in Fig. 1, *trans*-*N*-cinnamoyl-2-oxazolidinone derivatives were used as the substrates in Wang's approach. The purpose of introducing the oxazolidinone moiety into the substrate is to achieve proper hydrogen-bonding between the substrate and the thiourea moiety of the catalyst (Fig. 1, left),[3c] which is essential for achieving the desired stereoselectivity. It is our conviction that benzylidenemalonates should also be good substrates for this catalytic system, because similar hydrogen-bonding may be readily achieved with these compounds (Fig. 1, right). The major advantage of using benzylidenemalonates as the substrates lies in that these compounds are readily available through the Knoevenagel condensation[6] of malonates and aldehydes. Moreover, instead of a tandem Michael-aldol reaction, the synthesis will be a tandem Michael–Knoevenagel reaction.[7] For the latter, to the best of our knowledge, an organocatalytic example has not yet been established in the literature. Herein, we wish to report our preliminary results on the synthesis of substituted

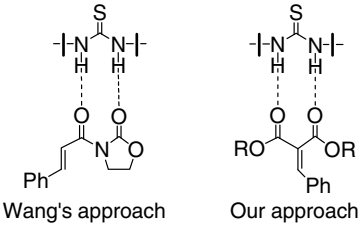


Fig. 1. Proposed hydrogen-bonding between the catalyst and the substrates.

* Corresponding author. Tel.: +1 210 458 5432; fax: +1 210 458 7428.
E-mail address: cong.zhao@utsa.edu (C.-G. Zhao).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.01.113

thiochromanes using this tandem Michael–Knoevenagel reaction.

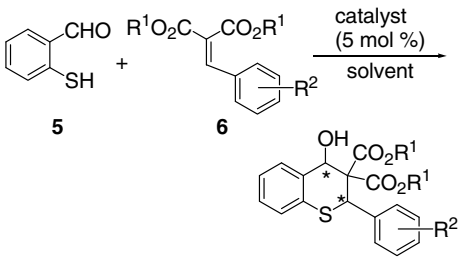
By using 2-mercaptobenzaldehyde (**5**) and diethyl 2-benzylidenemalonate (**6a**) as the model compounds, we initially studied the tandem Michael–Knoevenagel reaction in CH_2Cl_2 using 5 mol % of 9-*epi*-aminoquinine thiourea catalyst **1** (Fig. 2) at room temperature (Table 1, entry 1). We were pleased to find that the reaction completed in just 30 min and an excellent yield (94%) of the desired thiochromane **7a** was obtained. According to the ^{1}H NMR analysis of the crude product, the two diastereomers were obtained in a ratio of 70:30. The ee value of the major diastereomer was determined to be 80% (entry 1). However, further screening some similar alkaloid catalysts (**2**–**4**, Fig. 2) that do not have the thiourea moiety all led to poor ee values of the major diastereomer, although the diastereoselectivities obtained remained almost the same for these catalysts (Table 1, entries 2–4). These results again testified that a proper hydrogen-bonding between the substrate and the catalyst is essential for the enantioselectivity and that the diastereoselectivity of this reaction is quite independent of the catalyst structure.[3c]

The reaction conditions were further optimized using catalyst **1**. As shown in Table 1, common organic solvents such as ether (entry 5), toluene (entry 6), and EtOAc (entry 7) all produce worse enantioselectivities of the product as compared to CH_2Cl_2 (entry 1). EtOAc is a particularly bad solvent, and an almost racemic product was obtained (8% ee), most likely because it competes with the substrate for hydrogen-bonding. Gratifyingly, it was found that the enantioselectivity may be improved by carrying out the reaction at subambient temperatures. For example, an ee value of 86% was obtained for the major diastereomer at 0 °C (entry 8). The highest ee value of 90% (for both diastereomers) was obtained when the reaction was conducted at −40 °C (entry 9). However, although lowering temperature is effective in improving the enantioselectivity of this reaction, it does not increase the diastereoselectivity at all (entries 1, 8, and 9).

To get better diastereoselectivity, we further evaluated the effects of the size of the ester alkyl groups on the reaction. As is evident from Table 1, the smaller methyl ester (**6b**, entry 10) actually led to worse diastereoselectivity (60:40) than the ethyl ester. In contrast, although the larger isopropyl ester (**6c**) produced slightly higher diastereoselectivity (75:25) of the product, the enantioselectivity obtained was slightly lower (87% ee). These conflicting effects left us with limited options for further optimization in this direction. The effects of substituents on the phenyl ring were then studied, and it was found that diethyl 2-(2-methoxybenzylidene)malonate (**6d**) yielded the desired thiochromanes **7d** in excellent diastereoselectivity (93:7) and enantiomeric excess (94% ee, entry 12). Nevertheless, with diethyl 2-(4-methoxybenzylidene)malonate (**6e**), the diastereoselectivity obtained for the product again falls to 70:30 (entry 12), although the ee values of the products are similar to that of their 2-methoxy counterpart. These results indicate that the diastereoselectivity increase in the case of **6d** was mainly due to steric factors instead of electronic effects. It is also worth noting that, within error limits, the enantioselectivities obtained for the minor diastereomers are almost the same as those of the major ones in all of the above cases (entries 9–12, values in the parentheses).

To understand the scope of this reaction, various substituted diethyl methylenemalonates and some substituted

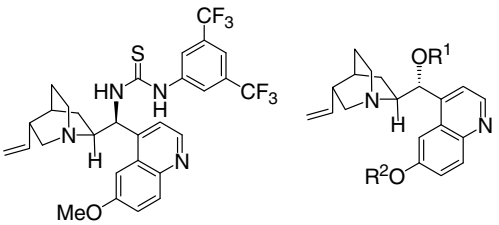
Table 1
Catalyst screening and reaction condition optimizations[a]



5 6 7

Entry	Catalyst	R^1	R^2	Yield[b] (%)	dr[c]	ee[d] (%)
1	**1**	Et	H	**7a**, 94	70:30	80
2	**2**	Et	H	**7a**, 86	65:35	23
3	**3**	Et	H	**7a**, 90	70:30	14
4	**4**	Et	H	**7a**, 81	70:30	6
5[e]	**1**	Et	H	**7a**, 96	65:35	43
6[f]	**1**	Et	H	**7a**, 88	60:40	47
7[g]	**1**	Et	H	**7a**, 86	72:28	8
8[h]	**1**	Et	H	**7a**, 92	70:30	86
9[i]	**1**	Et	H	**7a**, 95	70:30	90(90)
10[i]	**1**	Me	H	**7b**, 90	60:40	87(88)
11[i]	**1**	*i*-Pr	H	**7c**, 87	75:25	87(84)
12[i]	**1**	Et	2-OMe	**7d**, 94	93:7	94(94)
13[i]	**1**	Et	4-OMe	**7e**, 93	70:30	91(93)

[a] Unless otherwise indicated, all reactions were conducted at room temperature with **5** (0.11 mmol), **6** (0.10 mmol) and the catalyst (5 mol %) in CH_2Cl_2 (1.0 mL) for 30 min.
[b] Yield of isolated product after flash column chromatography.
[c] Determined by ^{1}H NMR analyses of the crude product.
[d] Enantiomeric excess was determined by HPLC analysis on a Chiralpak AD-H and/or a Chiralpak OJ-H column; values in the parentheses are those of the minor diastereomers.
[e] Ether (1.0 mL) as the solvent.
[f] Toluene (1.0 mL) as the solvent.
[g] EtOAc (1.0 mL) as the solvent.
[h] Reaction was performed at 0 °C for 1 h.
[i] Reaction was performed at −40 °C for 2 h.



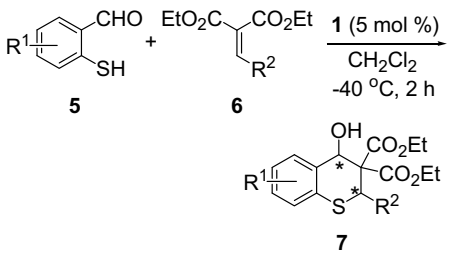
1

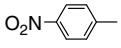
2. R^1 = H; R^2 = Me
3. R^1 = R^2 = H
4. R^1 = OBn; R^2 = H

Fig. 2. Catalysts screened for the tandem Michael–Knoevenagel reaction.

2-mercaptobenzaldehydes[8] were studied as the substrates.[9] The results are compiled in Table 2.

Table 2
Enantioselective tandem Michael–Knoevenagel reaction[a]



Entry	R^1	R^2	Yield[b] (%)	dr[c]	ee[d] (%)
1	H		**7d**, 94	93:7	94
2	H		**7f**, 96	95:5	94
3	H		**7g**, 92	90:10	93
4	H		**7h**, 90	90:10	93
5	H		**7i**, 91	90:10	94
6	H		**7j**, 95	90:10	96
7	H		**7k**, 95	75:25	92[e]
8	H		**7l**, 93	90:10	88
9	H		**7m**, 90	92:8	70
10	H		**7n**, 93	70:30	72(72)[f]
11	4-OMe		**7o**, 93	90:10	91
12	4-Cl		**7p**, 90	92:8	90
13	H	*i*-Pr	**7q**, 92	75:25	49(46)[f]
14	H	*c*-C_6H_{11}	**7r**, 88	77:23	(60)[f,g]

[a] All reactions were conducted at −40 °C with **5** (0.11 mmol), **6** (0.10 mmol) and catalyst **1** (5 mol %) in CH_2Cl_2 (1.0 mL) for 2 h.
[b] Combined yield of isolated product after flash column chromatography.
[c] Determined by ^1H NMR analyses of the crude product.
[d] Enantiomeric excess was determined by HPLC analysis on a Chiralpak AD-H column.
[e] The minor diastereomer is not separable on HPLC columns.
[f] Numbers in the parentheses are the ee values of the minor diastereomers.
[g] The major diastereomer is not separable on HPLC columns.

As shown in Table 2, for benzylidenemalonates, besides 2-methoxy group (**6d**, entry 1), other substituents at the 2-position also lead to good results. For example, 2-benzyloxy (**6f**, entry 2), 2-ethyl (**6g**, entry 3), and 2-phenyl (**6h**, entry 4) substituted diethyl benzylidenemalonates all react with 2-mercaptobenzaldehyde to generate the corresponding thiochromanes in excellent yields, diastereoselectivities and enantioselectivities. Diethyl 2-(naphthalen-1-yl)-methylenemalonate derivatives **6i** and **6j** are also excellent substrates for this reaction (entries 5 and 6). In contrast, although diethyl 2-(naphthalen-2-yl)methylenemalonate (**6k**) gave the desired thiochromane **7k** in excellent ee value (92%, entry 7), the diastereoselectivity dropped again to 75:25. Electron-withdrawing groups at the *ortho* position also generate high diastereoselectivities. For example, both 2-bromo (**6l**, entry 8) and 2-nitro (**6m**, entry 9) substituted diethyl benzylidenemalonates yield dr over 90:10 for the products. Nonetheless, the enantioselectivities obtained are lower as compared to their electron-donating counterparts. The above results indicate that the diastereoselectivity of this reaction is sensitive mainly toward the steric factors at the *ortho* position of the phenyl ring, but the enantioselectivity outcome is influenced by the electronic effects of the substituent on the aromatic ring. Thus, it is not surprising that diethyl 2-(4-nitrobenzylidene)malonate (**6n**) leads to the poorest results in stereoselectivities (entry 10), because it has a strong electron-withdrawing group on the phenyl ring but no substituent at the *ortho* position. On the other hand, subsituents on the 2-mercaptobenzaldehyde ring has minimum effects on the reaction. For example, the reaction of 2-mercapto-4-methoxybenzaldehyde (**7o**, entry 11) and 4-chloro-2-mercaptobenzaldehyde (**7p**, entry 12) with diethyl 2-(2-methoxybenzylidene)malonate both give similar diastereoselectivities and enantioselectivities as the unsubstituted 2-mercaptobenzaldehyde (**7d**, entry 1). In contrast to aryl-substituted methylenemalonates, alkyl-substituted methylenemalonates lead to poor diastereoselectivities and enantioselectivities of the products. For example, the reaction of 2-mercaptobenzaldehyde and diethyl isobutylidenemalonate produces the expected thiochromane with a diastereomeric ratio of 75:25 and a poor 49% ee for the major product (**7q**, entry 13). Similar results were also obtained for the product of diethyl cyclohexylmethylenemalonate (**7r**, entry 14).

In summary, we have developed a tandem Michael–Knoevenagel reaction of 2-mercaptobenzaldehydes and benzylidenemalonates for the synthesis of enantioenriched tetrasubstituted thiochromanes using a quinine thiourea catalyst **1**. The diastereoselectivity of the reaction increases if there is a substituent at the *ortho* position of the phenyl ring of the benzylidene moiety, while the enantioselectivity decreases if the phenyl ring is substituted with an electron-withdrawing group. Chiral tetrasubstituted thiochroman-4-ols may be synthesized in high enantioselectivities (up to 96% ee) and diastereoselectivities (up to 95:5) if these two factors are taken into account during the synthesis.

Acknowledgments

Generous financial support of this project from the Welch foundation (Grant No. AX-1593) and the NIH-MBRS program (Grant No. S06 08194) is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.113.

References and notes

1. For examples, see: (a) Castro, M. E.; Harrison, P. J.; Pazos, A.; Sharp, T. *J. Neurochem.* **2000**, *75*, 755–762; (b) Lejuene, F.; Rivet, J.-M.; Gobert, A.; Canton, H.; Millan, M. J. *Eur. J. Pharmacol.* **1993**, *240*, 307–310; (c) Bolognesi, M. L.; Bortolini, M.; Cavalli, A.; Andrisano, V.; Rosini, M.; Minarini, A.; Melchiorre, C. *J. Med. Chem.* **2004**, *47*, 5945–5952; (d) Jolas, T.; Haj-Dahmane, S.; Lanfumey, L.; Fattaccini, C. M.; Kidd, E. J.; Adrien, H.; Hamon, M. *Arch. Pharmacol.* **1993**, *347*, 453–463; (e) Vliet, L. A. V.; Rodenhuis, N.; Dijkstra, D.; Wikstrom, H.; Pugsley, T. A.; Serpa, K. A.; Meltzer, L. T.; Heffner, T. G.; Wise, L. D.; Lajiness, M. E.; Huff, R. M.; Svensson, K.; Sundell, S.; Lundmark, M. *J. Med. Chem.* **2000**, *43*, 2871–2882; (f) Xia, P.; Yin, Z.-J.; Chen, Y.; Zhang, Q.; Zhang, B.; Xia, Y.; Yang, Z.-Y.; Kilgore, N.; Wild, C.; Morris-Natschke, S. L.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3341–3343; (g) Spruce, L. W.; Rajadhyaksha, S. N.; Berlin, K. D.; Gale, J. B.; Miranda, E. T.; Ford, W. T.; Blossey, E. C.; Verma, A. K.; Hossain, M. B.; Helm, D. V. D.; Breitman, T. R. *J. Med. Chem.* **1987**, *30*, 1474–1482.
2. (a) Ursini, C. V.; Dias, G. H. M.; Rodrigues, J. A. R. *J. Organomet. Chem.* **2005**, *690*, 3176–3186; (b) Micskei, K.; Hajdu, C.; Wessjohann, L. A.; Mercs, L.; Kiss-Szikszai, A.; Patonay, T. *Tetrahedron: Asymmetry* **2004**, *15*, 1735–1744; (c) Evans, D. A.; Michael, F. E.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 3534–3543; (d) Zhang, X.; Taketomi, T.; Yoshizumi, T.; Kumobayashi, H.; Akutagawa, S.; Mashima, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 3318–3319; (e) Quallich, G. J.; Woodall, T. M. *Tetrahedron Lett.* **1993**, *34*, 785–788; (f) Xie, J.-W.; Chen, W.; Li, R.; Zheng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 389–392; (g) Xue, D.; Chen, Y.-C.; Wang, Q.-W.; Cun, L.-F.; Zhu, J.; Deng, J.-G. *Org. Lett.* **2005**, *7*, 5293–5296.
3. (a) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354–10355; (b) Rios, R.; Sunden, H.; Ibrahem, I.; Zhao, G.-L.; Cordova, A. *Tetrahedron Lett.* **2006**, *47*, 8679–8682; (c) Zu, L.; Wang, J.; Li, H.; Xie, H.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036–1037; (d) Rios, R.; Sunden, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Cordova, A. *Tetrahedron Lett.* **2006**, *47*, 8547–8551; (e) Dodda, R.; Goldman, J. J.; Mandal, T.; Zhao, C.-G.; Broker, G. A.; Tiekink, E. R. T. *Adv. Synth. Catal.*, in press.
4. (a) Mandal, T.; Samanta, S.; Zhao, C.-G. *Org. Lett.* **2007**, *9*, 943–945; (b) Mandal, T.; Zhao, C.-G. *Tetrahedron Lett.* **2007**, *48*, 5803–5806; (c) Samanta, S.; Krause, J.; Mandal, T.; Zhao, C.-G. *Org. Lett.* **2007**, *9*, 2745–2748; (d) Samanta, S.; Zhao, C.-G. *J. Am. Chem. Soc.* **2006**, *128*, 7442–7443; (e) Dodda, R.; Zhao, C.-G. *Org. Lett.* **2006**, *8*, 4911–4914; (f) Jakka, K.; Zhao, C.-G. *Org. Lett.* **2006**, *8*, 3013–3015.
5. For selected examples on organocatalytic tandem reactions, see: (a) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2003**, *42*, 4233–4237; (b) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962–5963; (c) Brandau, S.; Maerten, E.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986–14991; (d) Enders, D.; Huttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861–863; (e) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 371–374; (f) Kotkar, S.; Chavan, V. B.; Vilas, B.; Sudalai, A. *Org. Lett.* **2007**, *9*, 1001–1004; (g) Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun.* **2007**, 507–509.
6. For reviews, see: (a) Jones, G. *Org. React.* **1967**, *15*, 204–599; (b) Li, J.-T.; Wang, S.-X.; Chen, G.-F.; Li, T.-S. *Curr. Org. Synth.* **2005**, *2*, 415–436.
7. For an example of tandem Michael–Knoevenagel reaction, see: Obrecht, D.; Gerber, F.; Sprenger, D.; Masquelin, T. *Helv. Chim. Acta* **1997**, *80*, 531–537: For examples of Michael addition of mercaptans to methylenemalonate derivatives, see: (a) Delepine, J.-L.; Pecquet, P.; Betton, M.-C.; Huet, F. *Synth. Commun.* **1996**, *26*, 2819–2829; (b) Ohno, S.; Mizukoshi, K.; Izumi, K.; Kato, K.; Hori, M. *Chem. Pharm. Bull.* **1988**, *36*, 551–562; (c) Danishefsky, S.; Rovnyak, G. *J. Org. Chem.* **1974**, *39*, 2924–2925; (d) Stewart, J. M.; Olsen, D. R. *J. Org. Chem.* **1966**, *33*, 4534–4536.
8. 2-Mercaptobenzaldehydes were synthesized according to: Gallagher, T.; Pardoe, D. A.; Porter, R. A. *Tetrahedron Lett.* **2000**, *41*, 5415–5418.
9. For the experimental details, please see the Supplementary Data.