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Thiol-mediated tandem Michael–aldol reaction: a convenient method for the synthesis of fused cyclopentenones

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ABSTRACT

A simple, convenient, one-pot synthetic approach towards substituted cyclopentenone derivatives via thiol-mediated tandem Michael–aldol reaction followed by acid-catalyzed thiol elimination and isomerization of 3-(2-formyl-3,4-dihydronapthalene 1-yl)-acrylic acid esters has been developed.

Functionalized cyclopentenones are versatile precursors for the synthesis of natural products and biologically active molecules,[1] some of which are shown in Figure 1.[2] Numerous methods have been reported for the synthesis of cyclopentenone derivatives. Amide classical methods, intramolecular aldol, Wittig reaction and Nazarov cyclization are noteworthy.[3] The Pauson–Khand reaction[4] has also emerged as a powerful tool to construct bicyclic cyclopentenone structure. Our group has synthesized some sesquiterpene precursors containing cyclopentenone subunit using intramolecular Heck reaction.[5]

There are several literature reports of intramolecular domino reactions in which one or more cycles are formed via metal and acid–base-catalyzed reactions.[6] Among them, the tandem Michael–aldol reaction represents a classical method of carbon–carbon bond formation that has been applied for the synthesis of carbocycles and heterocycles.[7] Thiol-mediated Mortia–Baylis–Hillman is one type of tandem Michael–aldol reaction that has also been reported in the literature.[8] Kiyoshi Tomiokga and his group have synthesized (−)-Neplanocin-A by using lithium thiolate-initiated Michael–aldol tandem cyclization reaction.[9]

In continuation of our efforts on C–C bond formation reaction,[10] herein we report a thiol-mediated tandem Michael–aldol reaction for the synthesis of cyclopentenone derivatives from 3-(2-formyl-3,4-dihydronapthalene 1-yl)-acrylic acid esters. In our previous reports[11] we had demonstrated the successful synthesis of furan, dihydrofuran and pyrrole derivatives from the same precursor using intramolecular Michael addition.

We anticipated that 3-(2-formyl-3,4-dihydronapthalene 1-yl)-acrylic acid derivative **2** could be more effective for tandem Michael followed by intramolecular aldol reaction because these substrates include both enone and formyl groups. The starting materials **2** were

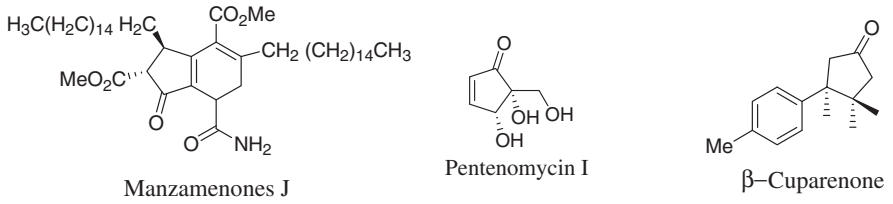

Figure 1. Some biologically active molecule.

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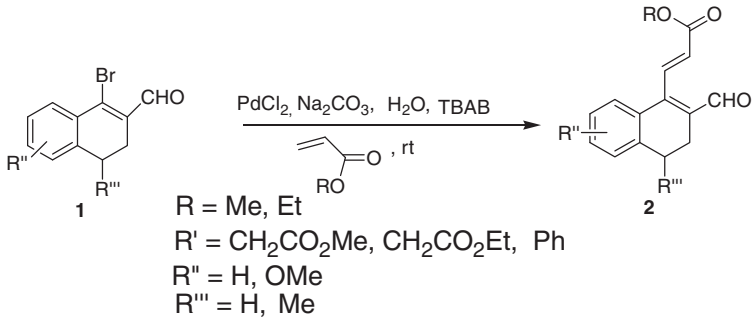
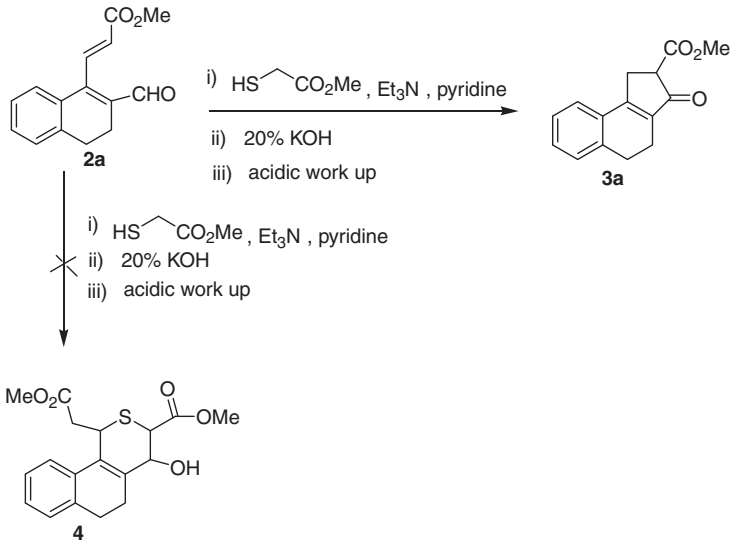
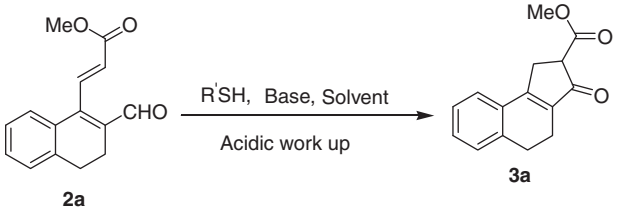


Scheme 1. Preparation of 3-(2-formyl-3,4-dihydronapthalene 1-yl)-acrylate ester.



Scheme 2. Synthesis of cyclopentenone derivative from the substrate **2a**.

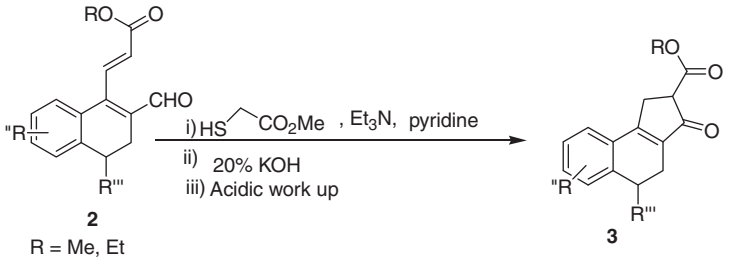
Table 1
Optimization of the reaction condition by using different types of bases and Michael donors[a]



Entry	Michael donor	Base	Solvent	Yield (%)
1	HS CO_2Me	Et_3N	Et_3N	Dec[b]
2	HS CO_2Me	Pyridine	Pyridine	NR[b]
3	HS CO_2Me	Et_3N	Pyridine	10[b]
4	HS CO_2Me	^tBuOK	Pyridine	NR[b]
5	HS CO_2Me	(i) Et_3N, (ii) 20% KOH	Pyridine	55
6	HS CO_2Et	(i) Et_3N, (ii) 20% KOH	Pyridine	50
7	PhSH	(i) Et_3N, (ii) 20% KOH	Pyridine	35
8	PPh_3	(i) Et_3N, (ii) 20% KOH	Pyridine	NR

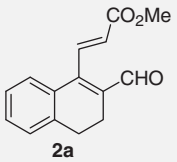
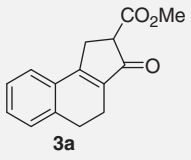
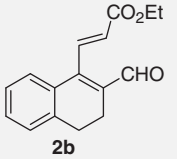
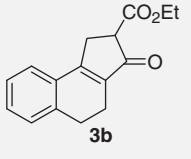
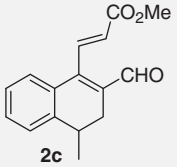
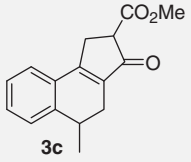
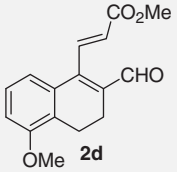
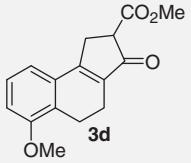
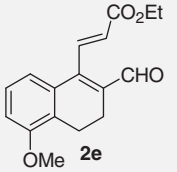
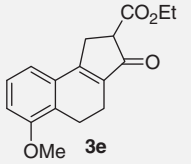
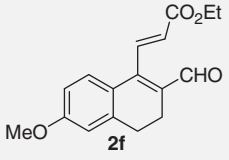
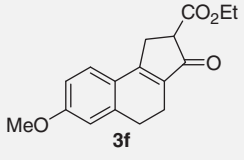
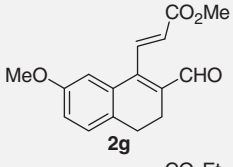
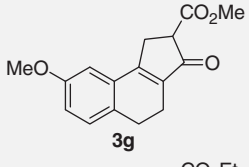
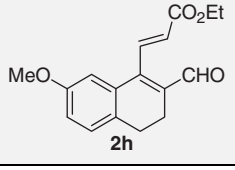
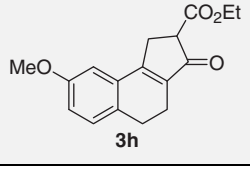
NR: no reaction.
Dec: Decomposition of the starting material.
[a] Reaction conditions: Substrate **2a** (1 mmol), Michael donor (1.2 mmol), base (1.2 mmol) and solvent (3 mL) at 70–80 °C for 2 h, 20% KOH (6 mL) at 0–5 °C for 20 min, acidic work up by 6(M) HCl.
[b] Without 20% KOH.

Table 2
Synthesis of cyclopentenone derivatives[a]

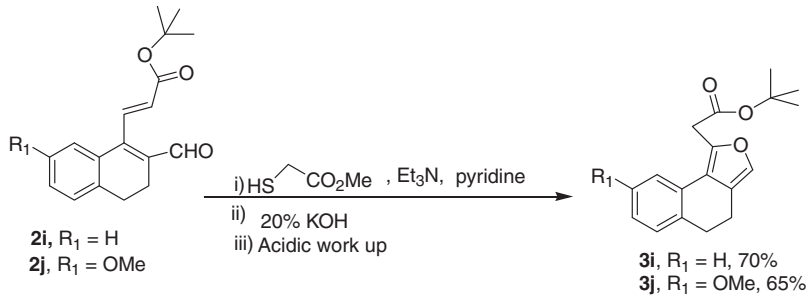


2
R = Me, Et
R" = H, OMe
R''' = H, Me

3

Entry	Substrate	Product	Yields (%)
1	 **2a**	 **3a**	55
2	 **2b**	 **3b**	60
3	 **2c**	 **3c**	45
4	 **2d**	 **3d**	48
5	 **2e**	 **3e**	50
6	 **2f**	 **3f**	40
7	 **2g**	 **3g**	50
8	 **2h**	 **3h**	52

[a] Substrate **2** (1 mmol), methyl thioglycolate (1.2 mmol), base (1.2 mmol) and solvent (3 mL) at 70–80 °C for 2 h, 20% KOH (6 mL) at 0–5 °C for 20 min, acidic work up by 6(M) HCl.



Scheme 3. Synthesis of fused furan derivative.

synthesized in good yields (80–90%) by our reported procedure where β-bromovinyl aldehydes **1** were treated with acrylate esters in the presence of palladium chloride, sodium carbonate and tetrabutylammonium bromide in water at room temperature (Scheme 1) for 2–3 h.

Our primary objective was to synthesize thiopyran derivative **4** (Scheme 2) from the substrate **2** employing methyl thioglycolate which was used to synthesize thiophene derivatives[12] from β-chlorovinyl aldehydes as reported by our group. When substrate **2a** was treated with the same reagent system,[12] cyclopentenone derivative **3a** was obtained unexpectedly.

Optimization of reaction condition was done with **2a** as the model substrate by changing different types of Michael donors and bases. When the reaction was carried out only with pyridine or triethylamine, we did not get any cyclized product. Compound **2a** on treatment with methyl thioglycolate and triethylamine in pyridine solvent at 70–80 °C followed by acidic work up afforded **3a** only in 10% yield. After a quick optimization of the reactant ratio (**2a**/thiol/Et_3N = 1.0:1.2:1.2), the product yield of **3a** was increased to 55% after the addition of 20% KOH (Table 1, entry 1).

Ethyl thioglycolate and thiophenol also gave successful results (Table 1, entries 6 and 7). The reaction did not take place with triphenyl phosphine (Table 1, entry 8).

With the optimized reaction condition [(i) reactant molar ratio **2**/thiol/Et_3N = 1.0:1.2:1.2; (ii) 20% KOH],[13] we examined the generality and substrate scope of this new cyclization reaction. As shown in Table 2, various 3-(2-formyl-3,4-dihydronapthalene 1-yl)-acrylate esters gave the corresponding cyclopentenone derivatives with moderate to good yields (entries 1–8).

In view of the absence of any supporting evidence, at this point, we are unable to produce any mechanistic explanation other than the account of the formation of the observed products.

The use of *t*-butyl ester derivatives **2i** and **2j** did not furnish the desired cyclopentenone derivatives, instead; they produced furan derivatives **3i** and **3j** (Scheme 3).

The formation of fused furan derivatives for the substrate **3i–j** can be explained by inhibition of intermolecular Michael addition due to steric interaction of adjacent tertiary butyl group. As reported earlier,[10] formation of furan derivative can be explained by attack of the thiol at the aldehyde followed by intramolecular Michael addition and subsequent elimination of thiol.

In conclusion, we have developed a novel methodology for the synthesis of cyclopentenone derivatives via thiol-initiated tandem Michael–aldol reaction. Application of this method to the synthesis of some sesquiterpine natural products is currently in progress and will be discussed in due course.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.142.

References and notes

1. (a) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671; (b) Singh, V.; Thomas, B. *Tetrahedron* **1998**, *54*, 3647; (c) Sugahara, T.; Ogasawara, K. *Tetrahedron Lett.* **1996**, *37*, 7403–7406; (d) Du, X.; Chu, H. V.; Kwon, O. *Tetrahedron Lett.* **2004**, *45*, 8843–8846; (e) Weaving, R.; Roulland, E.; Monneret, C.; Florent, J. C. *Tetrahedron Lett.* **2003**, *44*, 2579–2581.
2. (a) Takeuehi, S.; Kikuehi, T.; Tsukamoto, S.; Ishibashi, M.; Kobayashi, J. *Tetrahedron* **1995**, *51*, 5979–5986; (b) Gibson, S. E.; Lewis, S. E.; Mainolfi, N. *J. Organomet. Chem.* **2004**, *689*, 3873–3890; (c) Castro, J.; Moyano, A.; Pericas, M. A.; Riera, A.; Greene, A. E.; Larena, A. A.; Piniella, J. F. *J. Org. Chem.* **1996**, *61*, 9016–9020; (d) Srikrishna, A.; Sundarababu, G. *Tetrahedron* **1991**, *47*, 481–496.
3. (a) Briggs, M. E.; Qacemi, M. E.; Kalaï, C.; Zard, S. Z. *Tetrahedron Lett.* **2004**, *4*, 6017–6020; (b) Onofrio, D. F.; Piancatelli, G.; Nicoli, M. *Tetrahedron* **1995**, *51*, 4083–4088; (c) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479–6517.
4. Belanger, B. D.; O'Mahony, D. J. R.; Livinghouse, T. *Tetrahedron Lett.* **1998**, *39*, 7637–7640.
5. (a) Mal, S. K.; Ray, D.; Ray, J. K. *Tetrahedron Lett.* **2004**, *45*, 277–279; (b) Ray, D.; Mal, S. K.; Ray, J. K. *Synlett* **2005**, 2135–2140; (c) Ray, D.; Ray, J. K. *Org. Lett.* **2007**, *9*, 191–194; (d) Ray, D.; Paul, S.; Brahma, S.; Ray, J. K. *Tetrahedron Lett.* **2007**, *48*, 8005–8008.
6. (a) Kato, K.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 4915–4917; (b) Xi, Z.; Fan, H.-T.; Mito, S.; Takahashi, T. *J. Organomet. Chem.* **2003**, *682*, 108–112; (c) Barluenga, J.; Barrio, P.; Vicente, R.; López, L. A.; Tomás, M. *J. Organomet. Chem.* **2004**, *689*, 3793–3799.
7. (a) Kataoka, T.; Kinoshita, H.; Kinoshita, S.; Iwamura, T. *Tetrahedron Lett.* **2002**, *43*, 7039–7041; (b) Takasu, K.; Ueno, M.; Ihara, M. *J. Org. Chem.* **2001**, *66*, 4667–4672; (c) Yagi, K.; Turitani, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 3111–3114; (d) Davies, S. G.; Fenwick, D. R. *Chem. Commun.* **1997**, 565–566; (e) Fleming, I.; Kilburn, J. D. *J. Chem. Soc., Chem. Commun.* **1986**, 305–306; (f) Yamamoto, Y.; Asao, N.; Uyehara, T. *J. Am. Chem. Soc.* **1992**, *114*, 5429–5430.
8. (a) Richard, E. L.; Murphy, J. P.; Dinon, F.; Fratucello, S.; Brown, P. M.; Gelbrich, T.; Hursthouse, M. B. *Tetrahedron* **2001**, *57*, 7771–7784; (b) Dinon, F.; Richards, E.; Murphy, J. P.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A. *Tetrahedron Lett.* **1999**, *40*, 3279–3282; (c) Kamimura, A.; Mitsudera, H.; Asano, S.; Kakehi, A.; Noguchi, M. *Chem. Commun.* **1998**, 1095–1096; (d) Barrett, A. G. M.; Kamimura, A. *J. Chem. Soc., Chem. Commun.* **1995**, 1755–1756.
9. Ono, M.; Nishimura, K.; Tsubouchi, H.; Nagaoka, Y.; Tomioka, K. *J. Org. Chem.* **2001**, *66*, 8199–8203.
10. (a) Jana, R.; Samanta, S.; Ray, J. K. *Tetrahedron Lett.* **2008**, *49*, 851–854; (b) Samanta, S.; Mohapatra, H.; Jana, R.; Ray, J. K. *Tetrahedron Lett.* **2008**, *49*, 7153–7156; (c) Jana, R.; Chatterjee, I.; Samanta, S.; Ray, J. K. *Org. Lett.* **2008**, *10*, 4795–4797; (d) Nandi, S.; Ray, J. K. *Tetrahedron Lett.* **2009**, *50*, 6993–6997.
11. (a) Samanta, S.; Jana, R.; Ray, J. K. *Tetrahedron Lett.* **2009**, *50*, 6751–6754; (b) Yasmin, N.; Ray, J. K. *Synlett* **2010**, 924–930.
12. Ray, J. K.; Gupta, S.; Pan, D.; Kar, G. K. *Tetrahedron* **2001**, *57*, 7213.
13. *Typical experimental procedure for the synthesis of cyclopentenone*:[12]
To a stirred solution of **2** (1 mmol) and thiol derivative (1.2 mmol) in 3–4 mL pyridine at 0 °C triethylamine (1.2 mmol) was added dropwise. The reaction mixture was heated at 70–80 °C for 2 h. Then it was cooled to 0–5 °C and 6 ml 20% aq KOH was added to it. The stirring was further continued for 10 min. The reaction mixture was then poured into ice-water and extracted with dichloromethane. The organic layer was washed with 6 (M) HCl and water and then dried over anhydrous Na_2SO_4. Evaporation of solvent followed by purification with column chromatography afforded cyclopentenone derivative with 40–60% yield.
Spectral data of representative compounds:
Compound **3a**: yellow solid, mp 78–80 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ: 2.48 (t, 2H, J = 8 Hz), 2.85–2.94 (m, 2H), 3.01–3.14 (dd, 1H, J_{gem} = 18 Hz, J_{trans} = 7 Hz), 3.23–3.34 (dd, 1H, J_{gem} = 18 Hz, J_{cis} = 2.6 Hz), 3.61–3.66 (m, 1H), 3.76 (3H, s),

7.15–7.25 (m, 1H), 7.29–7.31 (m, 1H), 7.35–7.40 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.26, 27.68, 29.30, 52.01, 52.68, 124.47, 126.88, 128.26, 131.26, 131.32, 135.69, 138.74, 165.79, 169.83, 199.84. IR ν_{max} ($CHCl_3$): 2924.06, 1736.93, 1692.75, 1627.35, 1390.54, 1217.79, 1018.57, 771.43 cm^{-1}. HRMS calcd for $C_{15}H_{14}O_3$ [M$^+$+Na]: 265.0843; found: 265.0842.

Compound **3j**: Yellow liquid, ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.46 (s, 9H), 2.61–2.68 (m, 2H), 2.76–2.82 (m, 2H), 3.83 (s, 5H), 6.71–6.76 (m, 1H), 7.09–7.18 (m, 3H). ^{13}C ($CDCl_3$, 50 MHz) δ: 19.56, 28.04 (3C), 29.69, 35.70, 55.36, 81.72, 110.07, 111.84, 119.58, 123.02, 129.11, 129.39, 130.66, 135.33, 142.71, 158.57, 168.63. IR ν_{max} ($CHCl_3$): 2934.02, 1731.24, 1610.39, 1571.07, 1488.94, 1368.32, 1227.01, 1156.74, 1037.48, 867.63 cm^{-1}.