Tetrahedron Letters 53 (2012) 4405–4408

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient tandem aldol condensation-thia-Michael addition process

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ARTICLE INFO

Article history:
Received 22 April 2012
Revised 26 May 2012
Accepted 8 June 2012
Available online 17 June 2012

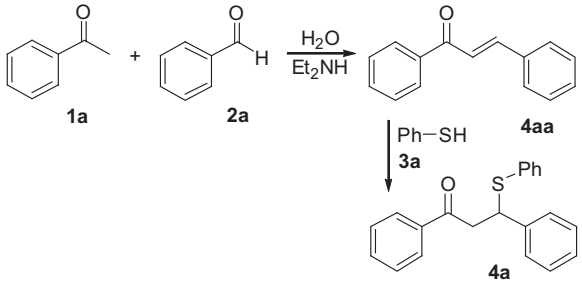
Keywords:
Tandem
Aldol condensation
Michael addition
Aqueous medium

ABSTRACT

An efficient synthesis of β-aryl-β-mercapto ketones is achieved via a tandem aldol condensation-thia-Michael addition process using an aqueous medium and diethylamine. Addition of different thiols to α,β-unsaturated ketones, formed in situ from the condensation of acetophenone derivatives with aldehydes, led to a rapid and high yielding synthesis of the products under very mild conditions using no expensive additive or catalyst. Products which precipitated spontaneously in the reaction mixtures were separated by simple filtration and purified by recrystallization.

The thia-Michael conjugate addition is an important process in organic chemistry and has versatile applications in biosynthesis[1] and in the construction of bioactive compounds.[2–4] The process is an effective route for the synthesis of β-sulfido derivatives,[5–7] which are precursors to synthetic equivalents of β-acylvinyl cations[8] and homoenolates.[9] Moreover, the thia-Michael addition to α,β-unsaturated carbonyl compounds provides a practical strategy for the selective protection of C=C bonds of conjugated enones, because regeneration of the double bond can be achieved conveniently by removal of the sulfur moiety.[3,10] In this regard, many catalytic systems have been developed for the conjugate addition of thiols to α,β-unsaturated carbonyl compounds including Lewis acids,[11–13] solid supports,[14,15] and ionic liquids.[16–18] However, several of these systems are limited because of the long reaction times, relatively harsh conditions, the use of expensive or noncommercial catalysts, and relatively low yields of products. In addition, the conjugated enones themselves require a separate preparation. These difficulties call for new methodologies and approaches to expand the synthetic scope of thia-Michael conjugate addition chemistry.

A tandem process is a sequence of reactions going through reactive intermediates. The process usually leads to the selective formation of products incorporating all of the starting materials and allows the synthesis of complex organic molecules and libraries of compounds from simple reactants without the separation and purification of intermediates.[19,20] Thus, tandem reactions are important from operational, economical, and environmental points of view.[21] In continuation of our studies on the development of environmentally friendly aqueous procedures,[22–24] and on the basis of our studies on aldol condensation reactions,[25–27] we herein report a novel tandem aldol condensation-thia-Michael addition process using an aqueous medium and Et_2NH, which under very mild conditions results in the efficient synthesis of β-aryl-β-mercapto ketones in one-pot from aldehydes, acetophenones, and thiols (Scheme 1). A search of the literature revealed the existence of a single related example, reported by Kumar and Akanksha on a multicomponent synthesis of β-aryl-β-mercapto ketones under $ZrCl_4$ catalysis.[28] For other closely related approaches, see the investigations by Wang's group on enantioselective organocatalyzed tandem Michael–aldol[29] and double Michael addition reactions.[30]



Scheme 1. Three-component synthesis of β-aryl-β-mercapto ketones.

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http://dx.doi.org/10.1016/j.tetlet.2012.06.040

Table 1
Effect of different amines on the synthesis of **4a**

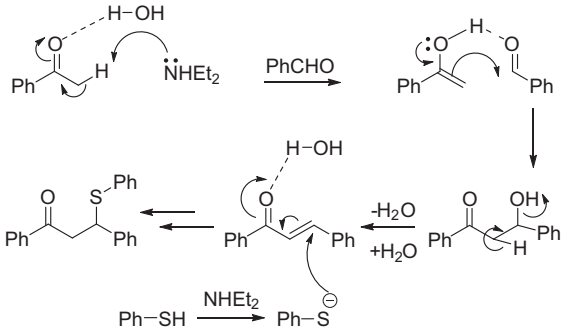
Entry	Conditions	Time (h)	Yield[a] (%)
1	H_2O/Et_2NH	4	93
2	H_2O	10	0
3	Et_2NH	10	15
4	H_2O/pyrrolidine	4	85
5	H_2O/piperidine	4	80
6	H_2O/DBU	4	95
7	H_2O/aniline	4	5
8	H_2O/hexylamine	4	23
9	H_2O/DABCO	4	25
10	H_2O/Et_3N	4	49

[a] GC yields.

Table 2
A study of the effect of additives on the synthesis of **4a**

Entry	Additive	Yield[a,b] (%)
1	H_2O/Et_2NH	40
2	Et_2NH	5
3	NaCl (1.5 M)/Et_2NH	7
4	NaCl (3.0 M)/Et_2NH	4
5	LiCl (1.5 M)/Et_2NH	20
6	LiCl (3.0 M)/Et_2NH	12
7	KCl (1.5 M)/Et_2NH	18
8	KCl (3.0 M)/Et_2NH	13
9	$LiClO_4$ (1.5 M)/Et_2NH	61
10	$LiClO_4$ (3.0 M)/Et_2NH	64

[a] GC yields.
[b] Reactions were stopped after 2 hours.



Scheme 2. A possible mechanistic pathway.

Initially, we optimized the conditions using the reaction of acetophenone (**1a**) with benzaldehyde (**2a**) and thiophenol (**3a**) at ambient temperature, as shown in Table 1. When **1a** and **2a** were mixed in aqueous Et_2NH, TLC showed the maximum formation of **4aa** after 3 hours. Addition of **3a** to the mixture at this point led to quantitative consumption of the reactants within a few minutes and the formation of **4a** in 93% yield (entry 1). In the absence of amine (entry 2) or water (entry 3), the reaction was either halted completely or proceeded very slowly illustrating the combined promoting effects of both H_2O and Et_2NH. Other secondary amines behaved similarly (entries 4–6), while both primary (entries 6–8) and tertiary (entries 8–10) amines showed much lower efficiency. This can be attributed to differences in the basicity and solubility of amines. All the secondary amines employed have comparably high basicities and are miscible with water, while the other amines have lower aqueous solubilities and/or weaker basicities.[31]

For organic reactions conducted in aqueous media, it is known that either the repulsive hydrophobic interactions of the reactants with water,[32,33] or hydrogen bonding activation of functional groups by water,[34,35] is responsible for the rate of the reaction. To shed light on the mechanism of the present process, several parallel reactions of **1a** with **2a** and **3a** were conducted, as summarized in Table 2. For a meaningful comparison of the results, the reactions were stopped before all the reactants had been consumed. Entry 1 shows the results for the reaction conducted under optimized H_2O/Et_2NH conditions after 2 hours. In the absence of water, a dramatic rate decrease was observed which highlights the crucial role of the aqueous medium (entry 2). The use of NaCl (entries 3 and 4), LiCl (entries 5 and 6), and KCl (entries 7 and 8) solutions also reduced the yields of the process. Rate retardation was clearly observed at higher concentrations of NaCl and LiCl disfavoring the 'salting-out'[36,37] effect and excluded hydrophobic interactions as being the driving force. Conversely, a rate acceleration was seen for the reactions performed in $LiClO_4$ solutions (entries 9 and 10). Therefore, a favorable hydrogen-bonded association of the reactants can be assumed which lowers the energy profile of the whole process similar to a Lewis acid mediated reaction (Scheme 2).[38–40]

To support the proposed mechanism, the reaction was stopped before the addition of the thiol and after TLC showed complete consumption of benzaldehyde and acetophenone. Analysis of the reaction mixture showed the presence of the single product **4aa** in 95% yield. The isolated product was subjected to reaction with **3a** under the same conditions and produced a high yield of **4a** within a few minutes.

Table 3
Acetophenone derived β-aryl-β-mercapto ketones synthesized under the optimum conditions

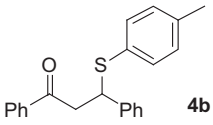
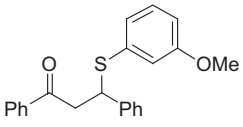
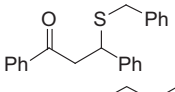
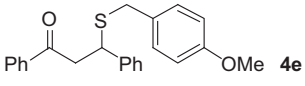
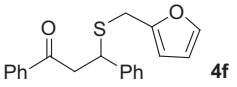
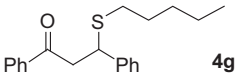
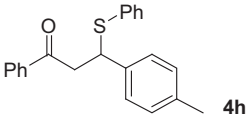
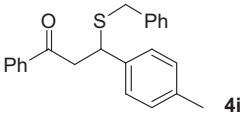
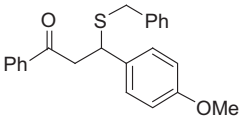
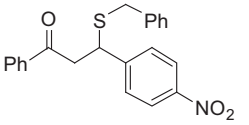
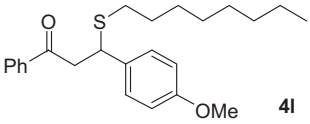
Entry	Aldehyde + thiol	Product	Time (h)	Yield[a] (%)
1	PhCHO + 4-MeC_6H_4SH	 **4b**	3	95
2	PhCHO + 3-$MeOC_6H_4SH$	 **4c**	4	96
3	PhCHO + $PhCH_2SH$	 **4d**	4	98
4	PhCHO + 4-$MeOC_6H_4SH$	 **4e**	5	95

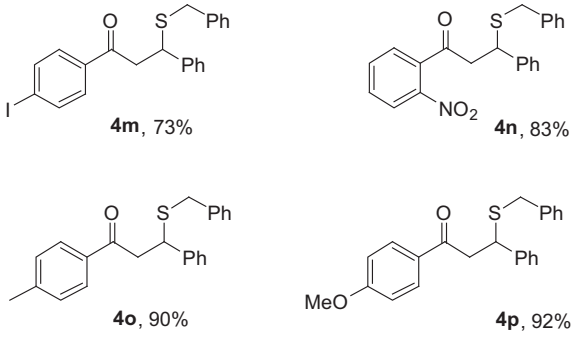
Table 3 (*continued*)

Entry	Aldehyde + thiol	Product	Time (h)	Yield[a] (%)
5	PhCHO + 2-furyl-CH_2SH	 **4f**	5	98
6	C_6H_5CHO + $Me(CH_2)_4SH$	 **4g**	5	95
7	4-MeC_6H_4CHO + PhSH	 **4h**	4	90
8	4-MeC_6H_4CHO + $PhCH_2SH$	 **4i**	4	96
9	4-$MeOC_6H_4CHO$ + $PhCH_2SH$	 **4j**	4	92
10	4-$O_2NC_6H_4CHO$ + $PhCH_2SH$	 **4k**	5	98
11	4-$MeOC_6H_4CHO$ + $Me(CH_2)_7SH$	 **4l**	5	95

[a] Isolated yield.

To show the generality of the process, we applied the conditions to reactions of **1a** with a variety of other aldehydes and thiols (Table 3).[41] When mixtures of **1a** and **2a** were reacted with different thiols bearing electron-releasing (entry 1) or electron-withdrawing (entry 2) substituents, products **4b** and **4c** were obtained in high yields, respectively. Similarly the same reactions with benzylic (entries 3–5) and aliphatic thiols (entry 6) gave high yields of products.

The scope of the procedure was expanded by variation of the aldehyde component. Various aldehydes with different electronic characters reacted under the optimized conditions to produce β-aryl-β-mercapto ketones in high yields (entries 7–10). Finally, to show the generality of the procedure, we subjected acetophenone derivatives bearing electron-withdrawing or electron-releasing groups to the reaction conditions: again high yields of products were obtained, as shown in Scheme 3.



Scheme 3. Products of combination of $PhCH_2SH$ and PhCHO with substituted acetophenones.

In summary, a very convenient procedure has been developed for the synthesis of β-aryl-β-mercapto ketones at ambient temperature. The reactions gave high yields of products in short times. The generality of the reaction and its efficient combination of two traditional steps into a one-pot process make it an interesting and useful addition to present methods. Additional in situ reactions of chalcone intermediates with other nucleophiles and reactants are under investigation in our laboratory.

Acknowledgements

Authors would like to thank the Iranian National Science Foundation (INSF-88002449) for financial support of this work.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.040. These data include MOL files and InChiKeys of the most important compounds described in this article.

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41. *Typical procedure:* A mixture of aldehyde (3 mmol), acetophenone (3 mmol), and Et_2NH (3 mmol) in 3 mL of degassed H_2O was stirred at room temperature for 3–5 hours until TLC showed complete disappearance of the reactants. The thiol (3 mmol) was added to this mixture and stirring was continued for another 4–6 min until TLC showed completion of the reaction. The product precipitated and the mixture was filtered and the solid portion was recrystallized from a mixture of petroleum ether and EtOAc to obtain the pure product. The identity of known compounds **4a**,**b**,**d**,**g**,**i**,**j** was confirmed by comparison of their physical and spectroscopic data with those reported in the literature. *Compound* **4c**: Mp 75–77 °C; IR (KBr, cm^{-1}) 1678, 1448, 1255; ^1H NMR ($CDCl_3$) δ 3.63 (dd, J = 6.0, 17.0 Hz, 1H), 3.68 (dd, J = 8.0, 17.0 Hz, 1H), 3.73 (s, 3H), 5.04 (dd, J = 6.0, 8.0 Hz, 1H), 6.79 (dd, J = 1.5, 8.2 Hz, 1H), 6.88 (dd, J = 1.5, 1.5 Hz, 1H), 7.00 (dd, J = 1.5, 7.6 Hz, 1H), 7.19 (dd, J = 7.9, 8.0 Hz, 1H), 7.24–7.26 (m, 1H), 7.29–7.32 (m, 2H), 7.42 (d, J = 7.5 Hz, 2H), 7.46 (dd, J = 7.5, 8.0 Hz, 2H), 7.56–7.59 (m, 1H), 7.92 (d, J = 7.2 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 45.2, 48.5, 55.6, 114.3, 117.8, 125.1, 127.8, 128.3, 128.5, 128.9, 129.1, 130.1, 133.7, 135.9, 137.2, 141.7, 160.1, 197.4 ppm; MS (70 eV): m/z 348 (M^+), 207, 140, 105; Anal. Calcd for $C_{22}H_{20}O_2S$: C, 75.83; H, 5.79. Found: C, 75.43; H, 5.64. *Compound* **4e**: Mp 68–70 °C; IR (KBr, cm^{-1}) 1680, 1465, 1242; ^1H NMR ($CDCl_3$) δ 3.52–3.62 (m, 4H), 3.84 (s, 3H), 4.54 (dd, J = 6.9, 7.3 Hz, 1H), 6.87 (d, J = 8.5, Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 7.29 (dd, J = 7.0, 7.5 Hz, 1H), 7.38 (dd, J = 7.5, 8.0 Hz, 2H), 7.45–7.48 (m, 4H), 7.58 (dd, J = 7.0, 7.5 Hz, 1H), 7.91 (d, J = 7.5 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 35.8, 44.6, 45.8, 55.7, 114.3, 127.7, 128.5, 129.0, 129.1, 130.3, 130.5, 133.6, 137.2, 142.4, 159.1, 197.2 ppm; MS (70 eV): m/z 362 (M^+), 207, 152, 121, 105; Anal. Calcd for $C_{23}H_{22}O_2S$: C, 76.21; H, 6.12. Found: C, 76.49; H, 6.31.