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A stereoselective Michael–imino aldol tandem reaction triggered by thiolate anions

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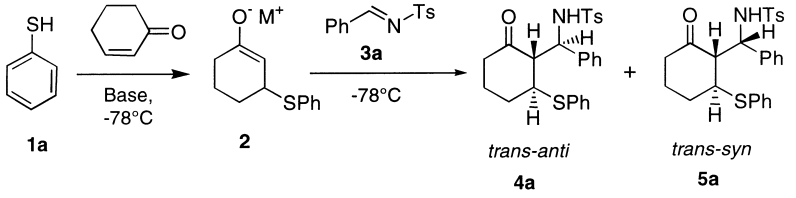
Abstract

The one-pot reaction of cyclohexenone, arylthiol and *N*-tosylimines provides Michael–imino aldol tandem reaction products in high yields and stereoselectivities.

The Michael–aldol reaction has been widely investigated, and many excellent results with high diastereoselectivity and enantioselectivity have been achieved over the past few years.[1] In this reaction various kinds of nucleophiles have been used,[2–4] but the electrophiles, which are used to capture the products of the Michael addition, are mainly aldehydes.[5] Although β-amino ketones or analogues, the useful intermediates in organic synthesis, will be obtained if imines are used as the electrophile, only a few reports of using imines as the electrophiles in these reactions have appeared.[6] In the course of studies of applications of imines in organic synthesis,[7] we studied the use of imines as electrophiles in tandem Michael–aldol reactions. Herein, we would like to report our results on tandem Michael–aza-aldol reactions with high *trans–anti*-stereoselectivity.

Reaction of thiolate **1** and cyclohexenone gives rise to enolate **2** which is trapped by imine **3** to afford the corresponding β-amino ketone **4** as the final product (Scheme 1). Various reaction conditions have been investigated and the results are summarized in Table 1.



1a **2** *trans-anti* **4a** *trans-syn* **5a**

Scheme 1.

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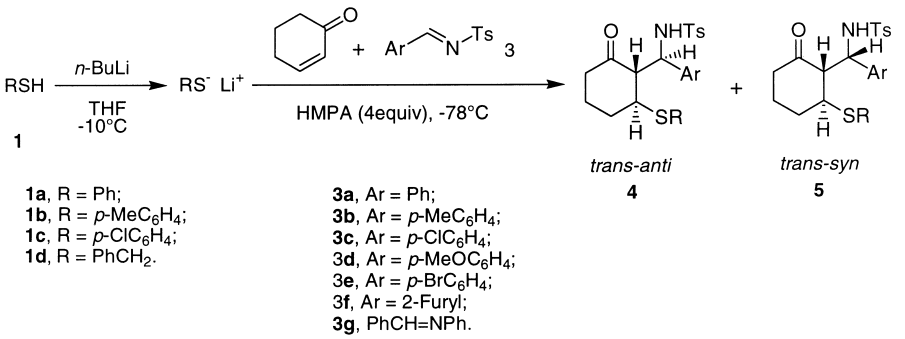
Table 1
The optimization of the three-component condensation of thiolate, cyclohexenone and imine[a]

Entry	Base	solvent	Additive (equiv)	Yield(%)[c]	**4a : 5a**[b]
1	*n*-BuLi	CH_2Cl_2	none	51	64 : 36
2	*n*-BuLi	Hexane	none	53	50 : 50
3	*n*-BuLi	THF	none	91	38 : 62
4	*n*-BuLi	THF	HMPA(2)	93	85 : 15
5	*n*-BuLi	THF	HMPA(4)	93	94 : 6
6	*n*-BuLi	THF	HMPA(10)	82	96 : 4
7	*n*-BuLi	THF	12-Crown-4 (1)	88	54 : 46
8	*n*-BuLi	THF	TMEDA(2)	90	55 : 45
9	NaH	THF	HMPA(4)	86	91 : 9
10	EtMgBr	THF	HMPA(4)	84	80 : 20

[a] The reaction was performed in the molar ratio of thiol : Base : enone : imine=1 : 1 : 1 : 1. [b] determined by 300MHz ^{1}H NMR .[c] isolated yields.

The reaction exhibits several interesting features. Firstly, it provides only two stereoisomers (two pairs of enantiomers), although four stereoisomers are possible. The configuration of the major stereoisomer was determined to be *trans–anti* **4a** by X-ray crystallography. To our surprise, the large α-aminobenzyl and phenylthio groups are axial with respect to the cyclohexenone, consistent with predominantly axial attack.[8] Secondly, it shows a dependence on the solvent used. The reaction gives more *trans–anti* product when it is run in CH_2Cl_2, but in THF more *trans–syn* product is obtained while 50:50 *trans–anti* and *trans–syn* products are afforded in hexane (Entries 1, 2 and 3). It is worthwhile to point out that a high yield of products is obtained when THF is used as solvent. This may be caused by the higher reactivity of the separated lithium enolate ion pair formed in ethereal solvents. Thirdly, the presence of hexamethylphosphoramide (HMPA) dramatically affects the stereochemistry of the reaction. The stereoisomer ratio of **4a**:**5a** was 38:62 when the reaction proceeded in THF without addition of HMPA. The ratio was changed to 85:15 when 2 equiv. of HMPA were added. The ratio was raised to 96:4 when 10 equiv. HMPA were used (Entry 6). Although HMPA is a strong cation-solvating reagent and favors the formation of separated ion pairs,[9] other cation-solvating reagents, such as 12-crown-4 and TMEDA, did not change the stereochemistry of reaction when used as additive (Entries 7 and 8). So HMPA plays not only the role of separating the lithium ion and enolate anion. In addition, it was found that the base used could affect the stereoselectivity (Entries 5, 9 and 10). Among these cases, butyllithium was the best.

On the basis of the above, various imines and thiolates were investigated (Scheme 2) and the results obtained are summarized in Table 2.[10,11] From Table 2, it was found that the inactivated imine **3g** did not give any product because of its low reactivity (Entry 10). However, the imines activated by a *p*-tolylsulfonyl group reacted well with the enolate intermediate **2** and provide Michael–aldol products **4** and **5** in high yields and stereoselectivities. The yields of the reactions decreased slightly with decreasing reactivity of the imine and the thiolates (Entries 4, 6 and 8). On the other hand, the stereoselectivities of the reactions increased with decreasing the reactivity of the thiol anions (Entries 1, 8 and 9). Possibly with the increasing reactivity of the thiol anions, the Michael addition intermediates **2** become more reactive and the stereoselectivities decreases.



Scheme 2.

Table 2
The three-component condensation of thiolate, cyclohexenone and imines[a]

Entry	Thiol	Imine	Yield(%)[c]	Product **4** and **5**	**4 : 5**[b]
1	**1a**	**3a**	93	**4a**, **5a**	16 : 1
2	**1a**	**3b**	92	**4b**, **5b**	16 : 1
3	**1a**	**3c**	92	**4c**, **5c**	17 : 1
4	**1a**	**3d**	83	**4d**, **5d**	9 : 1
5	**1a**	**3e**	91	**4e**, **5e**	16 : 1
6	**1a**	**3f**	82	**4f**, **5f**	23 : 1
7	**1b**	**3a**	96	**4g**, **5g**	16 : 1
8	**1c**	**3a**	82	**4h**, **5h**	22 : 1
9	**1d**	**3a**	96	**4i**, **5i**	4 : 1
10	**1a**	**3g**	—	—	—

[a] The reaction was performed in the molar ratio of thiol : Base : enone : imine: HMPA=1 : 1 : 1 : 1 : 4.
[b] Determined by 300MHz ^{1}H NMR .[c] Isolated yields.

In conclusion, we have demonstrated a one-pot Michael–imino aldol tandem reaction of three components, i.e. thiolates, cyclohexenone and imines, with high yields and stereoselectivities. Further investigations of this novel Michael–imino aldol tandem reaction using other nucleophiles and its asymmetric version are underway.

Acknowledgements

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10. **General procedure**: To a solution of thiophenol (110 mg, 1 mmol) in THF (6 mL) was added BuLi (0.62 mL, 1 mmol, 1.6 M in hexane) at –10°C. After stirring for 5 min, the mixture was cooled to –78°C (the additive was added if necessary and stirred for a further 5 min) and a solution of cyclohexenone (96 mg, 1 mmol) and imine **3** (1 mmol) in THF (4 mL) was added. The resulting mixture was stirred at this temperature to completion and monitored by TLC, then quenched with aqueous HCl solution (1 mL, 2N) at the same temperature. Water (10 mL) was added and the mixture was extracted with ethyl acetate (10 mL×3). The combined organic layer was washed with brine (15 mL) and dried with anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel to furnish the products **4** and **5**.
11. All new compounds give satisfactory analysis results.