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Efficient construction of 1,2-dihydroquinoline and 1,2,3,4-tetrahydroquinoline rings using tandem Michael-aldol reaction

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Abstract—1,2-Dihydroquinolines and a 1,2,3,4-tetrahydroquinoline were efficiently constructed using tandem Michael-aldol reaction starting from *N*-protected *o*-aminobenzaldehydes and α,β-unsaturated carbonyl compounds in good yield.

1,2,3,4-Tetrahydroquinolines have shown a variety of biologically activities such as antiarrhythmic, antitumor, and immunosuppressant effects, and attract attention for their potential as medicines.[1] Recently, martinelline and martinellic acid bearing a synthetically interesting heterocyclic ring, a pyrroloquinoline skeleton, were isolated from the roots of the tropical plant, *Martinella iquitosensis*, as the first natural occurring nonpeptide bradykinin receptor antagonists (Fig. 1).[2] Their intriguing structures as well as biological activities have prompted us to investigate the synthesis of the pyrroloquinoline ring.[3,4] As a preliminary study we first investigated development of a new method for construction of the 1,2,3,4-tetrahydroquinoline ring. Although extensive synthetic work has been done to prepare the tetrahydroquinolines so far,[1] there is still a need for facile construction of the tetrahydroquinoline skeleton. We describe here a new method for one-step construction of the 1,2,3,4-tetrahydroquinoline and 1,2-dihydroquinoline rings using tandem Michael-aldol

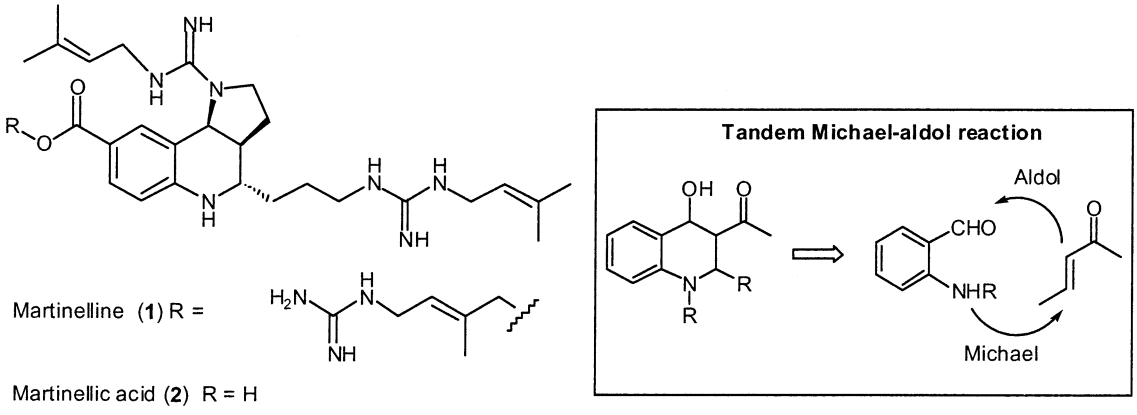

Figure 1.

Keywords: 1,2-dihydroquinoline; 1,2,3,4-tetrahydroquinoline; tandem Michael-aldol reaction.
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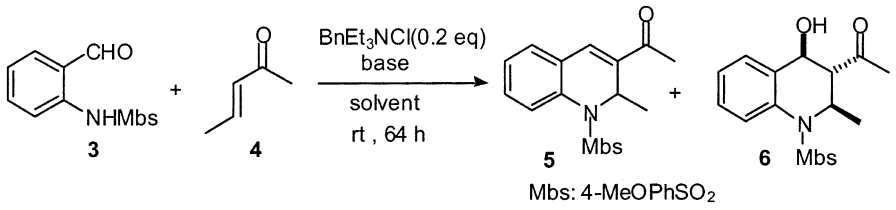
Table 1.



Condition	Base	Solvent	Yield (%)	
			5	**6**
A	4 M K_2CO_3	$CHCl_3$	84	0
B	$NaHCO_3$	THF	0	81

cyclization reaction[5,6] between *N*-protected *o*-aminobenzaldehydes[7] and α,β-unsaturated carbonyl compounds in the presence of a quaternary ammonium salt.[8] In this reaction shown in Figure 1, we expected that the anion of the sulfonamide would attack the β-position of the α,β-unsaturated carbonyl compound to generate the corresponding enolate which would be able to react intramolecularly with the aldehyde to produce the 1,2,3,4-terahydroquinoline.[9]

We investigated a model reaction using the *N*-protected *o*-aminobenzaldehyde and 3-penten-2-one as shown in Table 1. The reaction of 4-methoxybenzenesulfonamide **3** with the acceptor (3 equiv.) was carried out under biphasic liquid–liquid conditions using chloroform and 4 M aqueous potassium carbonate in the presence of benzyltriethylammonium chloride (BTEACl, 0.2 equiv.) (condition A). After stirring the mixture at 23°C for 64 h, 1,2-dihydroquinoline **5** was unexpectedly obtained in 84% yield.[10] Apparently under these reaction conditions base-catalyzed dehydration took place. In the absence of BTEACl, no reaction was observed. Our efforts for obtaining the tetrahydroquinolines found an alternative condition using sodium hydrogen carbonate as a base in tetrahydrofuran in the presence of BTEACl (condition B).[11] The biphasic liquid–solid reaction at 23°C proceeded to give after 72 h the tetrahydroquinoline **6** in 81% yield. Under 50% potassium hydroxide as a base desired reaction did not take place but the enone **4** was completely consumed. Use of a tosyl group as *N*-protection gave somewhat low yield due to incomplete conversion. The relative stereochemistry of **6** was elucidated by the value of coupling constants between H_a and H_b, and H_b and H_c, respectively (Fig. 2).

We next examined a new Michael-aldol reaction of the *N*-protected *o*-aminobenzaldehydes with some Michael acceptors to clarify the generality of these reaction conditions. The results are summarized in Table 2. First, under condition A several reactions were examined. The α,β-unsaturated aldehyde easily reacted with arylsulfonamide **3** (entries 4 and 5). The elongation of the alkyl chain and introduction of a functional group as a nitrile and urethane function were compatible with the reaction under the conditions (entries 3 and 5). In the case of entry 5, the intramolecular cyclization forming the pyrrolidine ring, a possible side reaction, was not observed but the desired intermolecular reaction proceeded in a quantitative yield. The ketone conjugated with an aromatic ring needed longer reaction time and higher temperature but the yield was excellent (entry 2). Unfortunately, cyclohexenone and β,β-disubstituted α,β-unsaturated carbonyl compounds did not react under the conditions. Next, under condition B the generality was examined. However, the reactions with Michael acceptors other than 3-penten-2-one were found to give the tetrahydroquinolines along with a considerable amount of the 1,2-dihydroquinolines. It was found that there was no reliability in the biphasic liquid–solid reaction under condition B due to base-sensitivity of the terahydroquinolines.

A diastereoselective Michael-aldol reaction using a chiral Michael acceptor was also investigated. The reaction of **3** with the chiral acceptor **9**[12] in chloroform at 23°C for 14 h smoothly proceeded to afford a diastereomeric mixture of the cycloadducts (**10a** and **10b**) in a quantitative yield and in a ratio of 76:24 (Table 3). Stereochemical elucidation of the products by spectroscopic means was difficult. However, the esters (**11a** and **11b**) derived from the adducts in two steps were separable by column chromatography and the major **11a** was fortunately a nice crystalline.[13,14] Single-crystal X-ray analysis[15] of **11a** unambiguously disclosed the *R*-configuration of the newly formed stereocenter, the 2-position of the 1,2-dihydroquinoline (Fig. 3). The effect of the arenyl group at the sulfonamide was briefly investigated. Interestingly, the 2-naphthyl derivative **14** also gave the cycloadducts in a quantitative yield and was found to improve somewhat the diastereoselectivity to a ratio of 83:17.

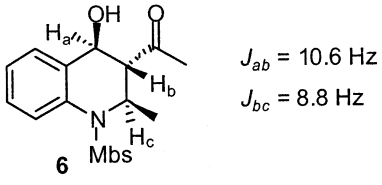
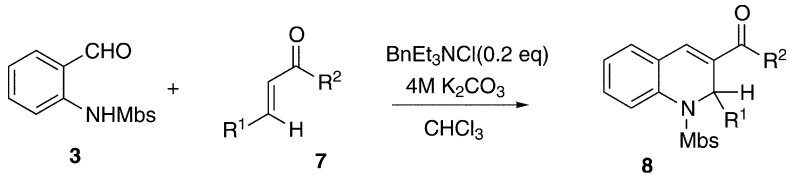


Figure 2.

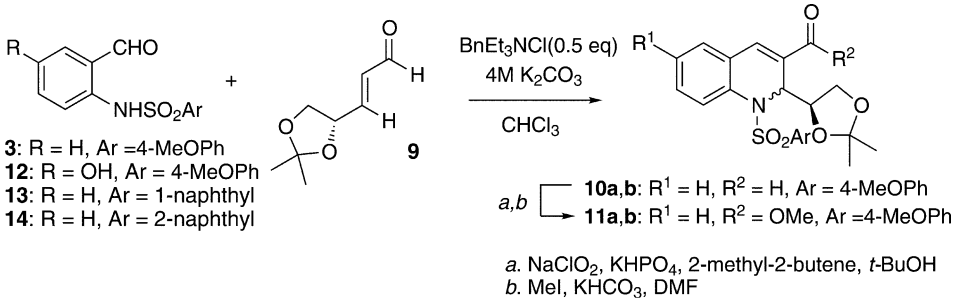
Table 2.



Entry[a]	R^1	R^2	Conditions	Yield (%)
1	Me	Me	rt, 64 h	84
2	Me	Ph	rt–45°C, 7 days	88 (94)[b]
3	$-(CH_2)_2$-CN	Me	rt, 68 h	92 (97)[b]
4	Me	H	rt, 27 h	73
5	$-(CH_2)_3$-NHBoc	H	rt, 68 h	82 (98)[b]

[a] All reactions were performed using **3** (0.24 mmol) and acceptor **7** (0.72 mmol, 3 equiv.).
[b] The yields in parentheses are based on consumed starting materials.

Table 3.



Entry	Sulfonamide	Conditions	Yield	Ratio
1	**3**	rt, 14 h	Quant.	76:24
2	**12**	rt, 15 h	Quant.	60:40
3	**13**	rt, 16.5 h; 50°C, 21 h	Quant.	77:23
4	**14**	rt, 16.5 h; 50°C, 21 h	Quant.	83:17

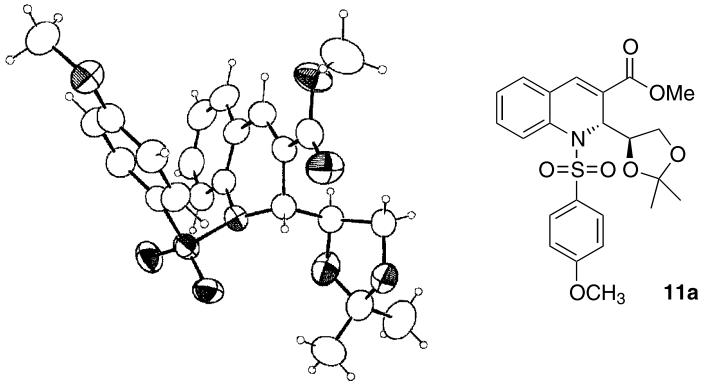


Figure 3.

In summary, a new efficient method for the synthesis of 1,2-dihydroquinolines and 1,2,3,4-tetrahydroquinoline from *N*-protected *o*-aminobenzaldehydes and α,β-unsaturated carbonyl compounds by tandem Michael-aldol reaction has been developed. It is demonstrated that the method can be also used for diastereoselective construction of 1,2-dihydroquinolines. Further investigation directed towards total synthesis of martinelline is now ongoing according to this procedure.

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10. *Typical procedure for condition A*: To a mixture of 2-(4-methoxybenzenesulfonylamino)benzaldehyde **3** (70 mg, 0.24 mmol), enone **4** (0.72 mmol), and $BnEt_3NCl$ (10 mg, 0.04 mmol) in $CHCl_3$ (1 mL) was added 4 M aq. K_2CO_3 (1 mL) at 23°C under an argon atmosphere. After stirring the mixture for 64 h at 23°C, the mixture was diluted with EtOAc. The organic layer was washed with H_2O and saturated aqueous NaCl, and dried over Na_2SO_4. After removal of the solvent, the residue was purified with column chromatography. The product was eluted with EtOAc–*n*-hexane (1:2) to give the 1,2-dihydroquinoline as solids in 84% yield: mp 142–143°C (EtOAc–*n*-hexane); IR (KBr) 2969, 2928, 1660, 1595 1260, 1163 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (d, 3H, $J=7$ Hz), 2.12 (s, 3H), 3.79 (s, 3H), 5.50 (q, 1H, $J=6.9$ Hz), 6.71 (d, 2H, $J=9.2$ Hz), 6.82 (s, 1H), 7.1 (dd, 1H, $J=7.6$ Hz, 1.5 Hz), 7.23 (d, 2H, $J=9.0$ Hz) 7.30 (dt, 1H, $J=7.5$Hz, 1.1 Hz), 7.46 (dd, 1H, $J=8.1$ Hz, 1.6 Hz), 7.79 (d, 1H, $J=8.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 19.0, 24.9, 48.8, 55.5, 113.5, 126.7, 127.1, 128.4, 128.5, 128.9, 130.4, 130.9, 131.9, 134.2, 138.5, 162.9, 195.2; MS (FAB, NBA) 358 ($M+H^+$). Anal. calcd for $C_{19}H_{19}NO_4S$: C, 63.85; H, 5.36; N, 3.92. Found: C, 63.9; H, 5.24; N, 3.86.
11. *Typical procedure for condition B*: The reaction was carried out by using sodium hydrogen carbonate as a base and tetrahydrofuran as a solvent instead of 4 M K_2CO_3 and $CHCl_3$ according to condition A. Chromatography of the crude material using EtOAc–*n*-hexane (1:1) as an eluant gave the tetrahydroquinoline in 81% yield: IR (neat) 3492, 2969, 2925, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (3H, d, $J=6.4$ Hz), 2.24 (3H, s), 2.55 (1H, dd, $J=8.8$, 10.6 Hz), 3.61 (1H, d, $J=10.6$ Hz), 3.83 (3H, s), 4.42 (1H, dq, $J=6.4$, 8.8 Hz), 6.85 (2H, d, $J=9.0$ Hz), 7.28–7.43 (5H, m), 7.66 (1H, d, $J=7.7$ Hz); ^{13}C NMR ($CDCl_3$) δ 24.3, 32.2, 53.2, 55.5, 66.0, 67.8, 114.1, 122.4, 126.8, 127.9, 128.2, 129.0, 130.3, 133.1, 137.1, 163.0; HRMS (FAB) calcd for $C_{19}H_{22}NO_5S$ 376.1219 ($M+H^+$), found 376.1246.
12. The chiral acceptor was prepared from the known (4*S*)-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)acrylic acid ethyl ester in two steps: (1) reduction of the ester with diisobutylaluminum hydride in methylene chloride in 66% yield and (2) oxidation of the allyl alcohol with activated manganese dioxide in 93% yield.

13. The esters **11a** and **11b** were prepared from a mixture of **10a** and **10b** in two steps: (1) oxidation of the aldehyde to the carboxylic acid using $NaClO_2$ in aqueous *t*-BuOH in the presence of KH_2PO_4 and 2-methyl-2-butene in a quantitative yield and (2) esterification using iodomethane in dimethylformamide in the presence of $KHCO_3$ in 77% yield.
14. **11a**: mp 146–147°C $[\alpha]_D^{22} = +431.3$ (*c* 0.62, $CHCl_3$); IR (KBr) 2979, 1706, 1595, 1312, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (3H, s), 1.14 (3H, s), 3.77 (3H, s), 3.78 (3H, s), 3.94–4.02 (1H, m), 4.18–4.25 (2H, m), 5.34 (1H, d, $J = 3.1$ Hz), 6.68–6.72 (2H, m), 7.11 (1H, dd, $J = 7.6$, 1.5 Hz), 7.16 (3H, s), 7.20 (1H, dt, $J = 7.5$, 1.1 Hz), 7.24–7.28 (2H, m), 7.36–7.40 (1H, m), 7.81 (1H, d, $J = 8.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 24.3, 25.0, 52.0, 54.5, 55.5, 64.7, 76.7, 109.2, 113.6, 124.7, 126.4, 127.2, 127.6, 128.3, 129.0, 129.9, 130.4, 134.9, 135.9, 163.2, 165.1. Anal. calcd for $C_{23}H_{25}NO_7S$: C, 60.12; H, 5.48; N, 3.05. Found: C, 60.14; H, 5.41; N, 3.01
15. Crystallographic data for **11a**: formula $C_{23}H_{25}NO_7S$, FW = 459.5, orthorhombic, space group $P2_12_12_1$, $a = 8.337(1)$, $b = 12.901(1)$, $c = 21.389(1)$ Å, $V = 2300.4(6)$ $Å^3$, $Z = 8$, Nonius Kappa CCD, Mo Kα, $R = 0.047$, $Rw = 0.046$. CCDC 218556 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).