Synthesis of Hydroxylated 3,4-Dihydropyridine-2-ones from Intramolecular Nucleophilic Addition Reaction of Oxirane-Containing Tertiary Enamides

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Abstract: Catalyzed by *p*-toluenesulfonic acid in dry acetonitrile, oxirane-containing tertiary enamides underwent efficient cyclization via intramolecular addition to produce 3-hydroxy-3,4-dihydropyridin-2(1*H*)-one derivatives in moderate to good yields.

Key words: enamides, oxiranes, nucleophilic addition, cyclization, 3,4-dihydropyridin-2-ones

Pyridin-2-one derivatives and their partially reduced 3,4-dihydropyridin-2(1*H*)-one derivatives are important organic compounds. For example, while the former class of compounds finds wide applications in medicinal chemistry because of their diverse biological activities,[1] the latter occurs as natural products such as homoclausenamide.[2] 3,4-Dihydropyridin-2(1*H*)-ones also constitute useful scaffolds for the constrained amino acids.[3] In comparison with well-documented synthetic methods for pyridine-2-one derivatives,[4] the synthesis of 3,4-dihydropyridin-2-one compounds has remained largely unexplored.[4,5]

Enamines are very powerful intermediates in synthetic organic chemistry.[6] As the enamine variant, enamides are, however, stable and show diminished nucleophilic reactivity because of the electron-withdrawing effect of the *N*-acyl group which alleviates the delocalization of nitrogen lone-pair electrons to carbon–carbon double bond.[7] It has been shown in recent years that secondary enamides, the enamide species bear an N–H moiety, are able to react with different electron-deficient reactants in the presence of a Lewis acid catalyst.[8] These secondary enamides act actually as the aza-ene components to undergo the aza-ene reactions.[8a] The nucleophilic reactions of tertiary enamides have been rarely reported. Only very strong electrophiles such as acid chlorides, acid anhydrides, and Vilsmeier reagents are reported to react with tertiary enamides and enecarbamates.[7,9]

In the study of biomimetic synthesis of clausena alkaloids,[10] we have discovered that tertiary enamide behaves as a unique nucleophile to react intramolecularly with an oxirane moiety to give homoclausenamide.[10c] Very recently, tertiary enamides have been shown to undergo Lewis acid catalyzed intramolecular enaminic addition reaction to carbonyl groups, yielding quaternary carbon-containing hydroxylated pyrrol-2-one derivatives.[11] In order to continue our study in the exploration of reactivity of tertiary enamides and to synthesize 3-hydroxy-3,4-dihydropyridin-2-one derivatives, the analogues of naturally occurring homoclausenamide, we undertook the current investigation.

We started our study with the intramolecular cyclization reaction of oxiranecarboxamide-derived enamide **4a** (Table 1). When reaction of **4a** was conducted in boiling water, no cyclization product **5a** was obtained at all. Instead, 2-hydroxy-*N*-methyl-5-oxo-3,5-diphenylpentanamide (**6**)[12] was isolated in 68% yield (entry 1, Table 1). In the presence of two equivalents of *p*-toluenesulfonic acid, the reaction of **4a** at ambient temperature in acetonitrile (entry 2, Table 1) or at a lower temperature (from 0 °C to r.t.) in a mixture of acetonitrile and water (1:1, entry 3, Table 1) gave compound **6** in a lower yield. In the former case, a trace amount of the desired cyclization product **5a** was observed (entry 2, Table 1). Interestingly, when reaction was carried out in acetonitrile with a catalytic amount of *p*-toluenesulfonic acid (20 mol%), 3-hydroxy-1-methyl-4,6-diphenyl-3,4-dihydropyridin-2(1*H*)-one (**5a**) was produced efficiently as the major product in 78% yield (entry 4, Table 1). When dry acetonitrile was used as the solvent, the formation of **6** was prohibited and the desired N-heterocyclic compound **5a**[13] was yielded as the sole product (entry 5, Table 1). The employment of 4 Å MS, however, decreased the reaction rate (entry 6, Table 1). It should be noted that trifluoroacetic acid did not effect the intramolecular transformation of **4a** in nearly two days (entry 7, Table 1).

To examine the scope of the synthesis of 3,4-dihydropyridin-2(1*H*)-ones, a number of oxirane-containing enamides were prepared from the CuI-catalyzed cross-coupling reaction of 3-aryl-2-carboxamides with vinyl iodide **2** followed by N-alkylation reaction with alkyl halides in the presence of sodium hydride at 0 °C (Scheme 1). In all

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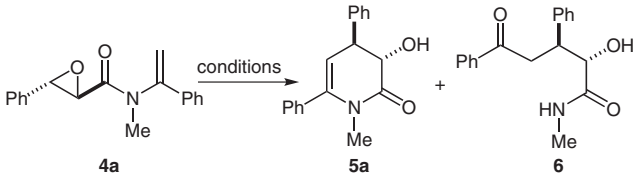
Table 1 Reaction of Tertiary Enamide **4a** under Different Reaction Conditions[a]

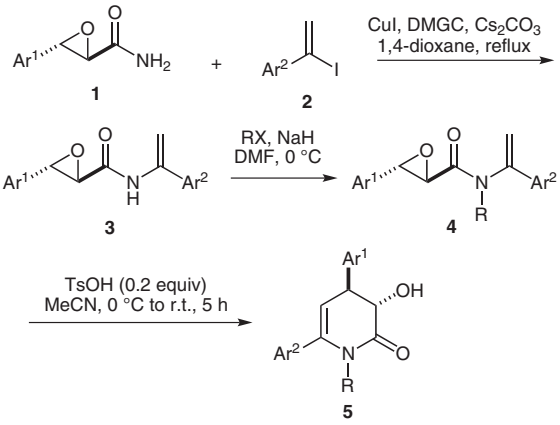


Entry	Catalyst (mmol)	Solvent	Additive	Temp (°C)	Time (h)	Yield of **5a** (%)[b]	Yield of **6** (%)[b]
1	–	H_2O	–	reflux	4	–	68
2	TsOH (200)	MeCN	–	r.t.	22	trace	43
3	TsOH (200)	MeCN–H_2O[c]	–	0 °C to r.t.	10	–	33
4	TsOH (20)	MeCN	–	0 °C to r.t.	5	78	trace
5	TsOH (20)	MeCN (dry)	–	0 °C to r.t.	5	78	–
6	TsOH (20)	MeCN (dry)	4 Å MS[d]	0 °C to r.t.	24	78	–
7	TFA (20)	MeCN (dry)	–	0 °C to r.t.	40	trace	–

[a] In the presence or absence of an acid, **4a** (0.4 mmol) was reacted in reaction media (12 mL) at different temperature.
[b] Isolated yield.
[c] Ratio of MeCN over H_2O was 1:1 in volume.
[d] 4 Å MS (100 mg) was used.

cases, the cross-coupling reaction gave moderate yields of **3** while N-alkylation generally afforded good to excellent yields of enamides **4** (Table 2).

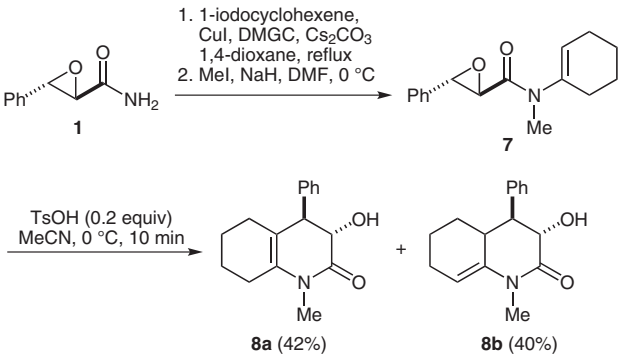
Under the optimized catalytic conditions, all enamides **4** tested underwent efficient intramolecular nucleophilic addition to epoxide moiety. For example, enamides **4a–e**, bearing either an electron-withdrawing group or an electron-donating group at both benzene rings, were converted into the corresponding 3,4-dihydropyridin-2(1*H*)-one derivatives **5a–e** in moderate to good chemical yields (41–84%, entries 1–5, Table 2). Substituents including an allyl (**4f**) and benzyl (**4g**) other than a methyl group (**4a–f**) on nitrogen atom led to equally efficient intramolecular cyclization reaction to afford the six-membered heterocyclic compounds **5f** and **5g** in 78% and 61%, respectively (entries 6 and 7, Table 2). When an enantiopure amide (2*R*,3*S*)-**1a** (ee >99.5%) was used, enantiopure product



Scheme 1 Synthesis of 3,4-dihydropyridin-2(1*H*)-ones **5** from tertiary enamides **4**

Table 2 Chemical Yields of Compounds **3–5**

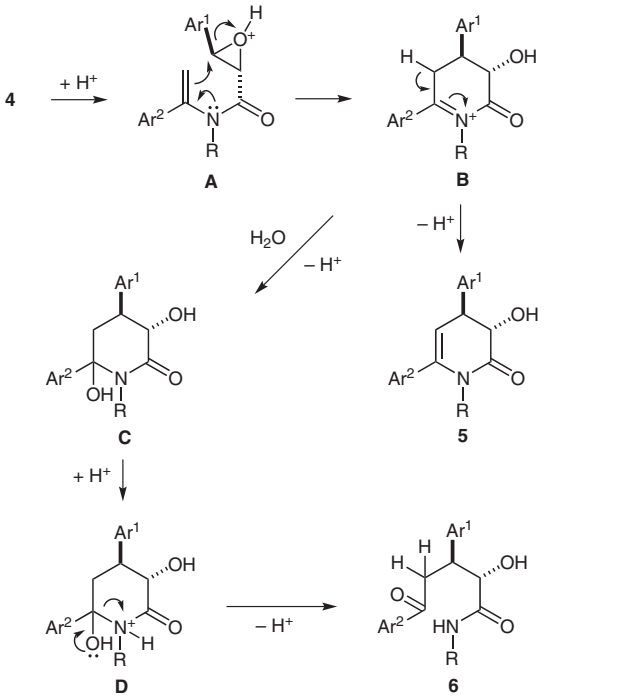
Entry	Product **3** (%)	Product **4** (%)	Product **5** (%)
1	**3a** $Ar^1 = Ar^2$ = Ph (68)	**4a** $Ar^1 = Ar^2$ = Ph, R = Me (100)	**5a** $Ar^1 = Ar^2$ = Ph, R = Me (78)
2	**3b** Ar^1 = 4-ClC_6H_4, Ar^2 = Ph (48)	**4b** Ar^1 = 4-ClC_6H_4, Ar^2 = Ph, R = Me (90)	**5b** Ar^1 = 4-ClC_6H_4, Ar^2 = Ph, R = Me (41)
3	**3c** Ar^1 = 4-MeC_6H_4, Ar^2 = Ph (47)	**4c** Ar^1 = 4-MeC_6H_4, Ar^2 = Ph, R = Me (83)	**5c** Ar^1 = 4-MeC_6H_4, Ar^2 = Ph, R = Me (77)
4	**3d** Ar^1 = Ph, Ar^2 = 4-BrC_6H_4 (50)	**4d** Ar^1 = Ph, Ar^2 = 4-BrC_6H_4, R = Me (78)	**5d** Ar^1 = Ph, Ar^2 = 4-BrC_6H_4, R = Me (67)
5	**3e** Ar^1 = Ph, Ar^2 = 4-FC_6H_4 (49)	**4e** Ar^1 = Ph, Ar^2 = 4-FC_6H_4, R = Me (100)	**5e** Ar^1 = Ph, Ar^2 = 4-FC_6H_4, R = Me (84)
6		**4f** $Ar^1 = Ar^2$ = Ph, R = All (100)	**5f** $Ar^1 = Ar^2$ = Ph, R = All (78)
7		**4g** $Ar^1 = Ar^2$ = Ph, R = Bn (100)	**5g** $Ar^1 = Ar^2$ = Ph, R = Bn (61)
8	2*R*,3*S*-**3a** $Ar^1 = Ar^2$ = Ph (33)	2*R*,3*S*-**4a** $Ar^1 = Ar^2$ = Ph, R = Me (79)	3*S*,4*S*-**5a** $Ar^1 = Ar^2$ = Ph, R = Me (62)



Scheme 2 Synthesis of hexahydroquinolin-2(1*H*)-one derivatives **8**

(3*S*,4*S*)-**5a** (ee >99.5%) was obtained without racemization (entry 8, Table 2).

The reaction was readily extended to alkyl-substituted enamide substrates. Scheme 2 illustrates, for example, the construction of a hexahydroquinolin-2(1*H*)-one skeleton. Under the identical *p*-toluenesulfonic acid catalyzed conditions, intramolecular cyclization of enamide **7**, which was derived from the cross-coupling reaction between oxiranecarboxamide **1** and 1-iodocyclohexene followed by N-methylation, proceeded very rapidly to furnish fused bicyclic product **8a**. In addition, compound **8b** with carbon–carbon double bond shifted to *exo* position of δ-lactam ring was also isolated. Evidenced by the ^{1}H NMR spectra, compounds **8a** and **8b**, which were separated using silica gel column chromatography, were able to undergo slow interconversions to yield a mixture of **8a** and **8b** in equilibrium in solution. For example, the ^{1}H NMR spectrum of isolated **8a** in $CDCl_3$ exhibited two sets of proton signals corresponding to **8a** and **8b** in a 2:1 ratio.



Scheme 3 Proposed reaction pathways of oxirane-containing tertiary enamides

The formation of 3-hydroxy-3,4-dihydropyridin-2(1*H*)-one derivatives from oxirane-containing enamides is best explained by the regioselective intramolecular enaminic attack of an enamide to the C-3 position of the epoxide oxonium **A**. The resulting iminium intermediate **B** undergoes deprotonation to afford heterocyclic product **5**. In the presence of water, however, iminium intermediate **B** was trapped by a water molecule, yielding an *N*,*O*-ketal intermediate. Ring-chain transformation leads to the formation of product **6** (Scheme 3)

In conclusion, we have provided a new method for the synthesis of 3-hydroxy-3,4-dihydropyridin-2(1*H*)-one derivatives from *p*-toluenesulfonic acid catalyzed intramolecular cyclization of oxirane-containing tertiary enamides.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are experimental procedures and spectroscopic data for compounds **3**–**8**. Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **3**–**8**.

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(12) **Typical Procedure for the Conversion of 4a into Compound 6**

Refluxing a suspension of enamide **4a** (0.4 mmol, 111 mg) in deionized H_2O (12 mL) for 4 h under argon protection gave rise to a homogeneous solution. After addition of brine (30 mL), the mixture was extracted with EtOAc (3 × 20 mL). The organic layer was dried with anhyd Na_2SO_4, filtered, and concentrated under vacuum. The residue was subjected to chromatography using a silica gel (200–300 mesh) column eluting with a mixture of PE and EtOAc (1:1) as mobile phase to give product **6**.

Mp 130–132 °C. IR (KBr): ν = 3307, 1637 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 300 K): δ = 7.23–7.98 (m, 10 H), 6.26 (s, 1 H), 4.38 (dd, *J* = 3.9, 5.2 Hz, 1 H), 3.73–3.85 (m, 2 H), 3.41–3.47 (m, 1 H), 3.29 (d, *J* = 5.6 Hz, 1 H), 2.71 (d, *J* = 2.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 199.5, 172.8, 139.2, 136.8, 133.4, 128.76, 128.7, 128.4, 128.2, 127.3, 73.6, 44.8, 40.7, 25.7. ESI-MS: 298 (52) $[M + 1]^+$, 320 (100) $[M + Na]^+$. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.94; H, 6.59; N, 4.86.

(13) **General Procedure for the Synthesis of Compounds 5 and 8**

To a solution of **4** or **7** (0.4 mmol) in dry MeCN (12 mL) was added PTSA (0.08 mmol, 14 mg) while stirring at 0 °C. The mixture was then kept stirring until the starting material was completely consumed. Water (100 mL) was added, and the mixture was extracted with EtOAc (3 × 50 mL). The organic layer was dried with anhyd $MgSO_4$ and concentrated. The residue was subjected to a silica gel (200–300 mesh) column eluted with a mixture of PE and EtOAc (3:1) to afford pure **5** or **8**.

Selected Data for Compound 5a

Mp 143–145 °C. IR (KBr): ν = 3442, 1668 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 300 K): δ = 7.25–7.40 (m, 10 H), 5.35 (d, *J* = 2.4 Hz, 1 H), 4.38 (dd, *J* = 1.0, 13.7 Hz, 1 H), 3.88 (d, *J* = 1.8 Hz, 1 H), 3.78 (dd, *J* = 2.4, 13.7 Hz, 1 H), 3.04 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 172.9, 141.6, 140.6, 135.0, 128.9, 128.7, 128.66, 128.0, 127.7, 127.3, 113.3, 71.3, 45.8, 32.7. ESI-MS: *m/z* = 280 (26) $[M + 1]^+$, 302 (100) $[M + Na]^+$. Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.25; H, 6.39; N, 4.94.