A Novel Protocol for Selective Construction of Morpholin-2-one and Morpholin-3-one Heterocycles from Aminoethanol with Divinyl Fumarate

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Received 24 November 2007

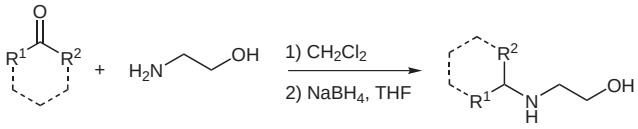
Abstract: A simple and efficient method for selective construction of morphlin-2-one and morphlin-3-one heterocyclic derivatives has been developed from N-substituted aminoethanols and divinyl fumarate. The selectivity of this catalyst-free reaction was easily controlled by different solvents.

Key words: aminoethanol, divinyl fumarate, catalyst-free, selectivity, morpholinone

The morpholinone skeleton is receiving widespread attention due to its potential biological applications.[1] It has also been fully investigated as an effctive template for asymmetric reactions[2,3] and identified as calpain and thrombin inhibitors.[4] Morpholin-3-one was generally obtained from aminoethanol and chloroacetyl chloride or aqueous glyoxylicacid,[3,5] while morpholin-2-one was prepared from aminoethanol and bromoacetate.[6] These reactions required anhydrous conditions or strong bases as catalysts. Dahlgren and co-workers[7] reported the synthesis of morpholinone from malic acid. However, such approach was a multistep process and required highly toxic catalysts. Therefore, manipulation of the morpholinone skeleton through mild and simple methods remained a great challenge. The reactions employing multiple-bond substrates have proven to be very efficient for the straightforward construction of numerous heterocycles.[8] We report herein a simple and efficient method for the selective construction of both morphlin-2-one and morphlin-3-one heterocycles from N-substituted aminoethanols and divinyl fumarate under catalyst-free conditions.

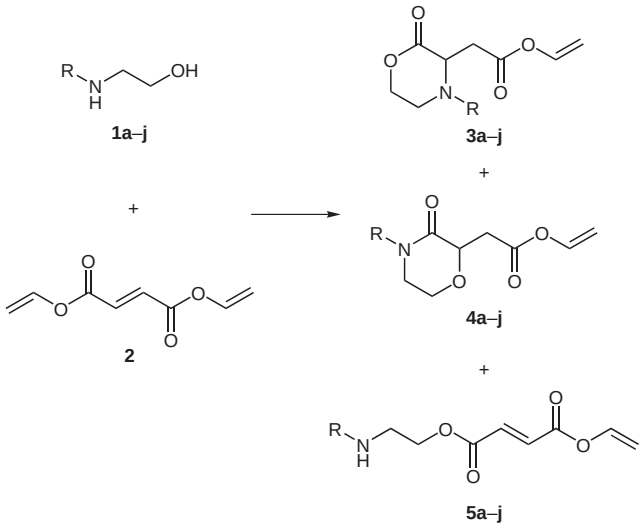
The starting N-substituted aminoethanol derivatives were easily accessible from commercially available aldehydes or ketones with aminoethanol by a two-step reaction according to a previously reported procedure (Scheme 1).[9] Aldehydes or ketones were treated with aminoethanol in dichloromethane to give the imines. Without further purification, the product was reduced with $NaBH_4$ in THF, giving the aminoethanol derivatives in yields ranging from 75% to 87%.

Two experiments were conducted to test the reactivities of ethanolamine derivatives. We firstly examined the reaction of *N*-benzylethanolamine with divinyl succinate in toluene at 50 °C for 40 hours without any catalyst or addi-



R^1= Ph, 4-$MeOC_6H_4$, 4-$Me_2N_6H_4$, Me
R^2 = H, Ph, Me
R^1–R^2 = $(CH_2)_5$

Scheme 1 *Reagents and conditions*: 1) CH_2Cl_2, 4 Å MS; 2) THF, $NaBH_4$.



Scheme 2 Reaction of N-substituted aminoethanol **1** with divinyl fumarate **2** at 50 °C

tive. The substituted nitrogen acylation product was obtained. However, when diethyl fumarate was added to the toluene solution of *N*-benzylethanolamine under the same conditions, the substituted nitrogen added to the double bond of diethyl fumarate through the Michael addition pathway.[10] These results demonstrated that the nitrogen of aminoethanol derivatives underwent acylation reaction with vinyl esters, but Michael addition with fumarate.

Then divinyl fumarate was used as substrate to react with *N*-benzylethanolamine under the same conditions (Scheme 2). As expected, the reaction generated two cyclic products,[11] containing morpholin-2-one (**3a**) as the main product (83%) and morpholin-3-one (**4a**) as the minor product (6%). The structures of **3a** and **4a** were confirmed by ^1H NMR, ^{13}C NMR, HRMS, and two-dimensional NMR techniques (HMBC, HMQC).

SYNLETT 2008, No. 5, pp 0679–0682
Advanced online publication: 26.02.2008
DOI: 10.1055/s-2008-1032109; Art ID: W20408ST

Table 1 Reaction of *N*-Benzylethanolamine with Divinyl Fumarate in Different Solvents for 40 Hours[a]

Entry	Solvent	Time (h)	Yields of **3a** (%)	Yield of **4a** (%)
1	cyclohexane	40	30	2
2	IPE	40	67	<1
3	MTBE	40	84	1
4	toluene	40	83	6
5	acetone	40	66	12
6	MeCN	40	56	30
7	pyridine	40	15	70
8	DMF	40	13	40
9	DMSO	40	2	66

[a] Reactions were carried out on 0.05 mol scale of *N*-benzylethanolamine with 1.2 equiv of divinyl fumarate in 5 mL solvent at 50 °C.

Enlightened by the above results, we optimized the reaction conditions using *N*-benzylethanolamine as a model substrate. Some conventional organic solvents with different log *P* values were screened for the reaction of **1a** with **2**. The results are shown in Table 1. In apolar solvents such as cyclohexane, isopropyl ether (IPE), methyl *tert*-butyl ether (MTBE) and toluene, the main product was **3a**. Excellent selectivity was achieved in MTBE and only **3a** was observed (Table 1, entries 1–4). In polar solvents such as acetone, acetonitrile, pyridine, and DMF, a mixture of **3a** and **4a** was obtained (Table 1, entries 5–8). As the solvent polarity increased, the yield of **4a** increased. Especially in DMSO, the reaction could generate 66% yield of **4a**, while only 2% of **3a** was observed (Table 1, entry 9). It was indicated that the cycloproduct could be manipulated by changing the solvent. Thus, TBME and DMSO were chosen as solvents in the following experiments.

Having the optimal conditions in hand, other N-substituted aminoethanols were examined and the results are summarized in Table 2. Reaction of **1a** with **2** in MTBE could generate 84% of morpholin-2-one (**3a**) after 40 hours at 50 °C (Table 2, entry 1). The yield of morpholin-3-one (**4a**) was less than 1%. As can be seen from Table 2, the substituent groups on the benzyl had no obvious influence on the conversion and the reaction selectivity (Table 2, entries 2 and 3). We then examined the reaction of five different aliphatic N-substituted aminoethanols with **2** in MTBE (Table 2, entries 4–8). Sterically hindered aliphatic N-substituted aminoethanols could result in the main product of morpholin-2-one (**3d**–**f**) in high yields, while providing only 4–8% of morpholin-3-one (**4d**–**f**, Table 2, entries 4–6). The reaction of methyl- or ethyl-substituted aminoethanols only resulted in the corresponding morpholin-2-one (**3g**,**h**, Table 2, entries 7 and 8). The reaction of *N*-benzhydryl- or *N*-phenyl-substituted aminoethanol derivatives only generated acyclic products (**5i**,**j**, Table 2, entries 9 and 10).

Table 2 The Reaction of N-Substituted Aminoethanols with Divinyl Fumarate in TBME and DMSO[a]

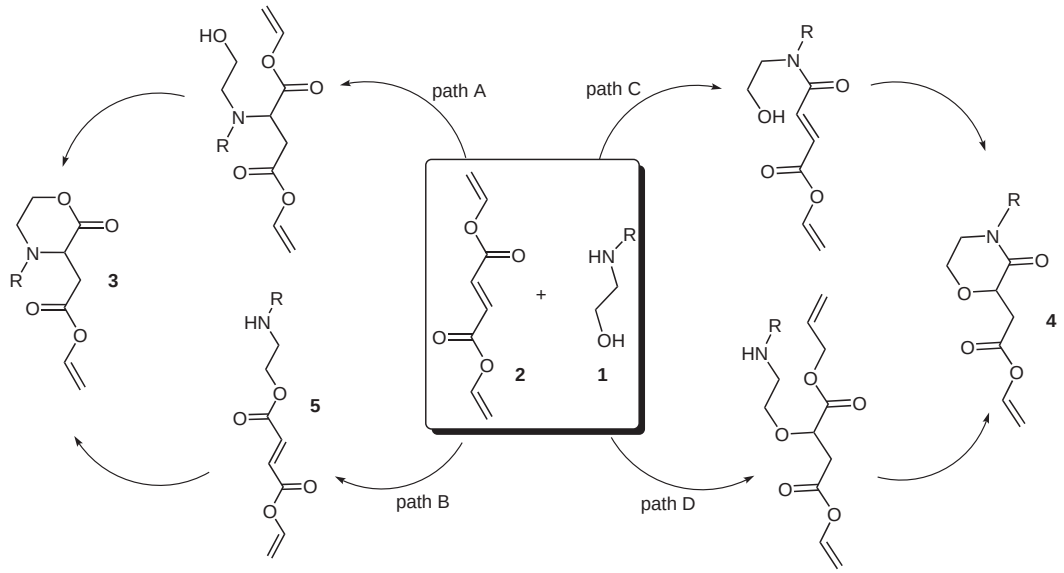
Entry	R		MTBE (yield, %)[b]			DMSO (yield, %)[b]		
			3	**4**	**5**	**3**	**4**	**5**
1	**a**	Bn	84	<1	0	2	66	0
2	**b**	4-$MeOC_6H_4CH_2$	82	<1	0	8	70	0
3	**c**	4-$Me_2NC_6H_4CH_2$	80	<1	0	6	72	0
4	**d**	*c*-Hex	75	5	0	15	68	0
5	**e**	*t*-Bu	77	4	0	17	70	0
6	**f**	*i*-Pr	72	8	0	6	77	0
7	**g**	Et	85	0	0	84	0	0
8	**h**	Me	86	0	0	86	0	0
9[c]	**i**	Ph_2CH	0	0	80	0	0	78
10[c]	**j**	Ph	0	0	82	0	0	80

[a] Reaction conditions: N-substituted aminoethanol (0.05 mol), divinyl fumarate (0.06 mol) in solvent at 50 °C for 40 h.
[b] Isolated yield.
[c] Reacted for 72 h.

Reactions of other structurally diverse aminoethanol derivatives with divinyl fumarate in DMSO were also investigated and the results are shown in Table 2. For methyl, ethyl, phenyl, or benzhydryl N-substituted aminoethanols, the reaction results were similar to that obtained in MTBE (Table 2, entries 7–10). For benzyl-, cyclohexanyl-, *tert*-butyl- and isopropyl-substituted aliphatic aminothanol derivatives, the reactions mainly generated morpholin-3-one (**4a**–**f**, Table 2, entries 1–6). The yields ranged from 66% to 77%. The yields of byproduct morpholin-2-one (**3a**–**f**) were about 6–17%.

In theory, aminoethanol has two reacting groups and both of them may participate in acylation or Michael addition. There are four possible reaction pathways between aminoethanols derivatives and divinyl fumarate **1** (Scheme 3): 1) the substituted nitrogen adds to the double bond of divinyl fumarate, followed by ester formation at the tethered primary alcohol, providing morpholin-2-one derivatives **3** as shown in path A; 2) the O-acylation occurs first, followed by intramolecular Michael addition of the nitrogen atom to the double bond of divinyl fumarate, affording **3** via the intermediates **5** in path B; 3) the N-acylation between aminoethanol derivatives **1** and divinyl fumarate **2** first gives the amide, then the double bond of divinyl fumarate is attacked by the hydroxy group to provide morpholin-3-one derivatives **4** in path C; 4) Michael addition of the hydroxy group followed by intramolecular acylation of the amino moiety provides **4** in path D.

It is well known that acylation of amines is much more sensitive to steric factor than is Michael addition. All of



Scheme 3 Proposed mechanism of cyclization

the substrates in the reaction bore a substitution group on the nitrogen. Thus, acylation between amines and vinyl ester was disfavored and the amines would first take part in the Michael addition. Here, for less bulky aminoethanols (R = Me, Et), amines were more active than alcohols as nucleophiles, and amines preferred to undergo Michael addition in both polar and nonpolar solvents. Thus, the reaction would mainly follow path A, resulting in the formation of **3** as the sole product (Table 2, entries 7 and 8). For other relatively bulky aminoethanols including *N*-alkyl- and benzyl-substituted ones (Table 2, entries 1–6), the reactivity of bulky amine for Michael addition was also more reactive than alcohol as nucleophiles. Consequently, the reaction probably followed path A in nonpolar solvents such as MTBE. Also, it was possible to form **3** via the intermediates **5** in path B, where the alcohol took part in the first reaction. However, the solvent effect had to be considered when the reaction was carried out in DMSO. The polar solvent enhances the nucleophilicity of alcohols much more significantly than that of amines because alcohols are better proton donors in forming hydrogen bonds. Thus, Michael addition of the oxygen atom was favored in polar solvents, leading to products **4**. For the bulky and low-nucleophilicity aminoethanols (Table 2, entries 9 and 10), only O-acylation products were isolated in both nonpolar and polar solvents.

In conclusion, a simple and efficient route for the selective synthesis of morpholine-2-one and morpholine-3-one heterocycles has been developed from N-substituted aminoethanols. The modulation for the synthesis of morpholin-2-one and morpholin-3-one heterocycles was easily achieved by just changing solvents. Furthermore, the resolution of racemic morpholinone by enzyme action is under investigation in our lab.

Acknowledgment

We gratefully acknowledge financial support from the Zhejiang Provincial Science and Technology Council (Project No. 2006C11197)

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(10) Supplementary information can be obtained from the corresponding author upon request.

(11) **Typical Procedure for the Synthesis of Morpholin-3-one**
Benzylethanolamine (0.75 g, 0.05 mol) was dissolved in MTBE and the divinyl fumarate (1.68 g, 0.1 mol) was added. The reaction mixture stirred at 50 °C and monitored by TLC. Upon completion of the reaction, the combined solvents were removed under reduced pressure to give a yellow oil which was purified by column chromatography (hexane–EtOAc = 3:1) to give the product. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.36 (m, 6 H), 4.89 (dd, 1 H, *J* = 1.50, 12.40 Hz), 4.76 (d, 1 H, *J* = 14.65 Hz), 4.56 (m, overlapped, 2 H), 4.50 (d, 1 H, *J* = 14.65 Hz), 3.99 (m, 1 H), 3.79 (m, overlapped, 1 H), 3.52 (d, 1 H, *J* = 4.25 Hz), 3.12 (m, 2 H), 3.02 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.05, 168.02, 141.34, 136.31, 129.03, 128.51, 128.02, 98.30, 74.38, 63.42, 50.20, 46.08, 37.35 ppm. IR (neat): 1751 (C=O), 1647 (C=C) cm^{-1}. ESI-MS: *m/z* = 275.8 $[M + H]^+$. HRMS: *m/z* calculated for $C_{15}H_{17}NO_4$: 275.1158; found: 275.1154.