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Multicomponent Approach in the Synthesis of 2,2,6-Trisubstituted Morpholine Derivatives

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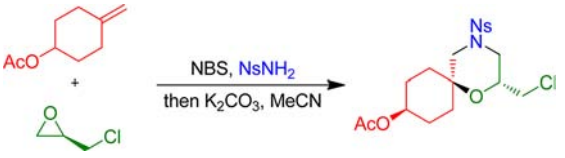
ABSTRACT



An efficient synthesis of 2,2,6-trisubstituted morpholine is described which involves a multicomponent process by simply mixing epichlorohydrin, *N*-bromosuccinimide, nosyl amide, and an olefin. The products contain chloride handles which are suitable for further modification.

The increasing demand for new chemical entities urges synthetic chemists to pursue simple, efficient, selective, high yielding, and environmentally benign reactions.[1] Multicomponent reactions (MCR), which allow the quick assembly of several simple reactants into complex structures in one pot, certainly provide a possible solution for a green and efficient synthesis through a diversity-oriented approach.[2] These one-pot processes are highly efficient to construct the scaffold of natural products and diverse drug-like molecules which make the strategy important in modern organic synthesis and drug discovery research.[3]

Among MCRs, electrophilic MCRs were less reported, partly due to the common incompatibility of electrophiles with other components.[4] Nevertheless, recently, we reported our discovery of electrophilic aminoalkoxylation reactions. This type of reaction was applied to morpholine synthesis.[5] However, a challenging task was encountered during the process development: when a monosubstituted

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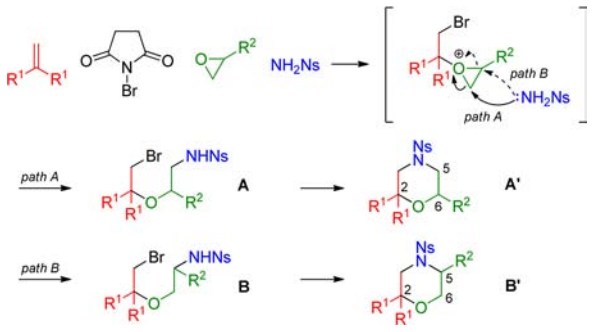
Scheme 1. Aminoalkoxylation Using Monosubstituted Epoxide



epoxide was used, the oxonium intermediate could be opened through the anti-Markovnikov (path A) or the Markovnikov (path B) pathway (Scheme 1).

Product **A**, the anti-Markovnikov product, is a privileged building block for 2- and 6-substituted morpholines. In particular, 2,2,6-trisubstituted morpholine **A′** is an important pharmacophore (Figure 1).[6] Common strategies, such as the cyclization of amino alcohols (derived from amino acids which contain α-nitrogen substituents), can readily achieve 3-substituted morpholine **B′**.[7] In comparison, it is not trivial to achieve **A′** or related compounds, particularly when it is optically active.[8] Herein we report an unexpected finding on the formation of the anti-

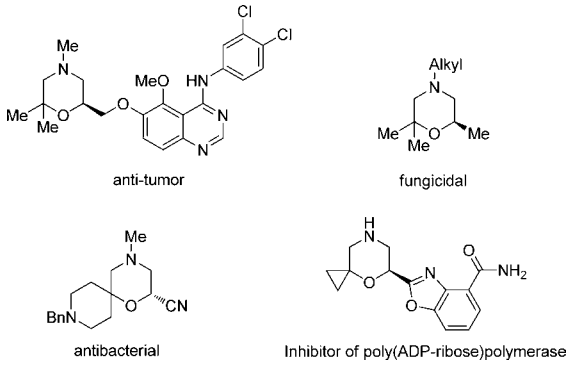


Figure 1. Examples of bioactive morpholines.

Markovnikov product **A** when using epichlorohydrin as the partner in the aminoalkoxylation MCR. Subsequent application to the synthesis of 2,2,6-trisubstituted morpholine **A′** is also described.

We initiated the investigation by studying a number of monosubstituted epoxides using cyclohexene as the model substrate. Propylene oxide gave no regioselectivity regardless of the high reaction yield (Table 1, entry 1). 1,2-Epoxy-3-methylbutane gave a better regioselectivity, presumably due the steric hindrance which suppressed the path B nucleophilic attack (Table 1, entry 2). Other alkoxy/siloxy systems were also examined, and some regioselectivities were observed; up to a 2.5:1 ratio but a relatively low conversion (56% yield) was detected when using the bulky OTBDPS-substituted epoxide (Table 1, entries 3−5). Such steric effect was not significant, which might be attributed to the electron-donating ability of the substituents that favored the Markovnikov-type product **3a**. Interestingly, the electron-deficient epoxides, epibromohydrin and epichlorohydrin, gave good chemical yields and regioselectivity (Table 1, entries 6 and 7). Optimization of the reaction temperature led us to achieve an 8:1 ratio of regioselectivity at −30 °C (Table 1, entry 9). Other halogen sources were investigated. The reaction was sluggish when using *N*-chlorosuccinimide (NCS) (Table 1, entry 11). Although a better regioselectivity was observed when using *N*-iodosuccinimide (NIS), the chemical conversion was only moderate (Table 1, entry 12).

Having identified a suitable system, some 1,1-disubstituted olefins were examined. A number of exocyclic olefins gave the desired products with good regioselectivities and yields (Table 2, entries 1−3).[9] The 4-*O*-substituted cyclohexyl systems including **1e** and **1f** also worked well in the reactions (Table 2, entries 4 and 5). The protected

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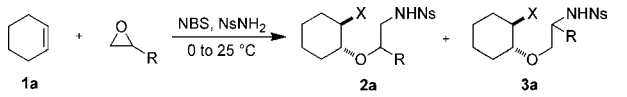
(9) General procedure: To a solution of *N*-bromosuccinimide (43 mg, 0.24 mmol) and nosyl amide (40 mg, 0.2 mmol) in epichlorohydrin (0.4 mL) in dark was added olefin **1** (0.24 mmol) at −30 °C. After stirring for 16 h at this temperature, the reaction was quenched with saturated $Na_2S_2O_3$ (2 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography to yield the corresponding product.

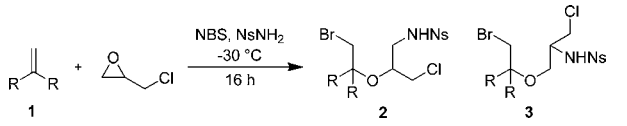
Table 1. Investigation of Various Monosubstituted Epoxides[a]



entry	R	temp (°C)	time (h)	yield (%)[b]	ratio (**2a**/**3a**)[c]
1	Me	25	8	80	1.0:1
2	$CHMe_2$	25	8	77	3.5:1
3	CH_2OBn	25	8	71	2.0:1
4	CH_2OTBS	25	8	64	2.3:1
5	$CH_2OTBDPS$	25	8	56	2.5:1
6	CH_2Br	25	8	84	4.3:1
7	CH_2Cl	25	8	86	4.5:1
8	CH_2Cl	0	8	92	7.1:1
9	*CH_2Cl*	*−30*	*16*	*90*	*8.0:1*
10	CH_2Cl	−40	16	81	8.0:1
11[d]	CH_2Cl	−30	24	trace	NA
12[e]	CH_2Cl	−30	24	30	10:1

[a] Reactions were carried out with cyclohexene (**1a**) (0.24 mmol), $NsNH_2$ (0.2 mmol), and NBS (0.24 mmol) in epoxide (0.4 mL). [b] Isolated yield of the mixture of **2a** and **3a**. [c] Based on NMR analysis of crude product. [d] *N*-Chlorosuccinimide was used. [e] *N*-Iodosuccinimide was used.

Table 2. Aminoalkoxylation of Olefin **1**[a]



entry	substrate		yield (%)[b]	ratio (**2**:**3**)[c]
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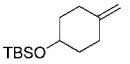
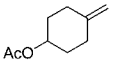
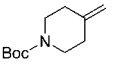
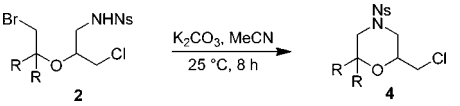
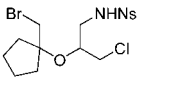
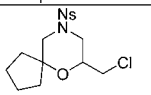
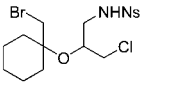
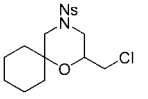
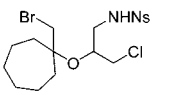
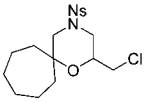
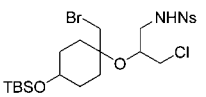
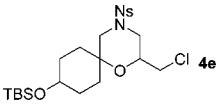
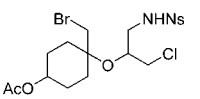
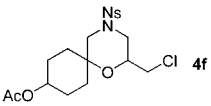
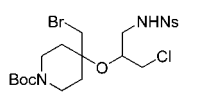
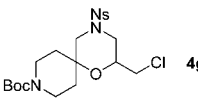
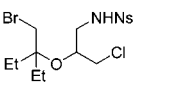
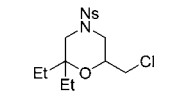
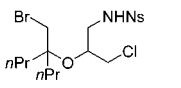
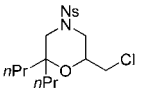
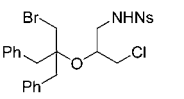
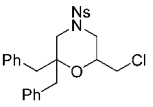
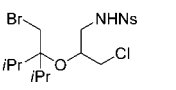
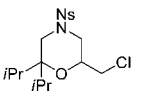
2		**1c**	78	9.3:1
3		**1d**	85	9.4:1
4		**1e**	80	8.6:1
5		**1f**	93	6.5:1
6		**1g**	92	6.0:1
7		**1h**	91	10.6:1
8		**1i**	67	5.8:1
9		**1j**	43	3.1:1
10		**1k**	41	8.0:1

[a] Reactions were carried out with $NsNH_2$ (0.2 mmol), olefin **1** (0.24 mmol), and NBS (0.24 mmol) in epichlorohydrin (0.4 mL) at −30 °C for 16 h. [b] Isolated yield of the mixture of **2** and **3** by column chromatography. [c] Based on NMR analysis of the crude product.

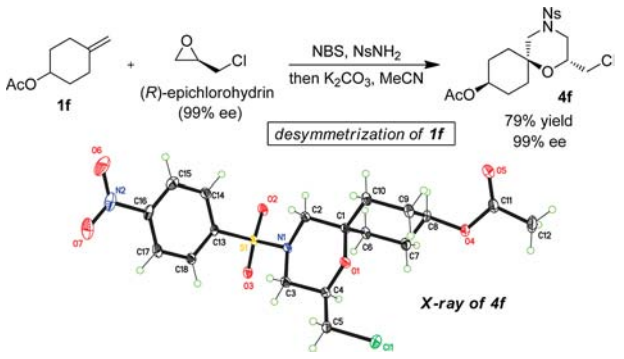
Table 3. Base-Mediated Cyclization of **2**[a]



entry	substrate		product		yield (%)[b]
1		**2b**		**4b**	94
2		**2c**		**4c**	96
3		**2d**		**4d**	94
4		**2e**		**4e**	92
5		**2f**		**4f**	95
6		**2g**		**4g**	94
7		**2h**		**4h**	95
8		**2i**		**4i**	94
9		**2j**		**4j**	92
10		**2k**		**4k**	93

[a] Reactions were carried out with **2** (0.1 mmol) and K_2CO_3 (0.2 mmol) in MeCN (2 mL) at 25 °C. [b] Isolated yield.

Scheme 2. One-Pot Synthesis of **4f**



piperidine substrate **1g** gave the corresponding product in 92% yield with a 6:1 ratio of regioselectivity (Table 2, entry 6). This type of MCR reaction worked equally smooth for aliphatic 1,1-disubstituted olefins, but the reaction rate was somewhat deteriorated when using bulkier substrates (Table 2, entries 7−10). The stereochemical relationship of **2** was established by X-ray crystallographic study of **2d**.[10]

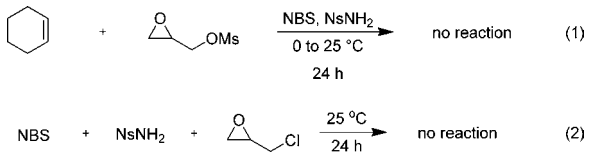
After performing the aminoalkoxylation, we were interested to further manipulate product **2** to achieve the morpholine compounds. In all cases, treatment of **2** with base in MeCN at room temperature gave the corresponding morpholine products exclusively and no chlorine substitution (i.e., the four-membered ring formation) was observed (Table 3). The structures of **4** were further confirmed by an X-ray crystallographic study of **4d**.[10]

In fact, the reaction can be conducted in a one-pot fashion. For instance, after the standard aminoalkoxylation MCR of **1f** under standard conditions, the unused epichlorohydrin was recovered using distillation. The crude mixture was then treated with K_2CO_3 in MeCN to give the desired morpholine **4f** (Scheme 2).

Next, we examined the use of enantiopure (*R*)-epichlorohydrin in the reaction using **1f**, and the desired morpholine **4f** was obtained with equal magnitude of enantiomeric excess (99% ee). The stereochemistry of **4f** was established by an X-ray crystallographic study.[10] It is noteworthy that **4f** was isolated exclusively as a single enantiomer; that is, the meso-substrate **1f**, which contains a 4-substituted unit, was desymmetrized in the reaction (Scheme 2).

For this type of MCR, it was surprising to observe that the electron-deficient epoxide epichlorohydrin gave similar reactivity to the corresponding alkyl or alkoxy/siloxy epoxides (Table 1). We have performed the MCR using an electron-deficient OMs epoxide which returned with no reaction (Scheme 3, eq 1). A preopening of the epoxide in the MCR was proven to be unlikely to happen (Scheme 3, eq 2). We suspect that the chlorine atom may play a role in the reaction; this remains unclear and is subjected to more intensive clarification.

Scheme 3. Mechanistic Investigation of the MCR



In summary, we have developed an efficient electrophilic multicomponent reaction using epichlorohydrin, an olefin, nosyl amide, and *N*-bromosuccinimide, giving the halogenated products with high regioselectivity. 2,2,6-Trisubstituted morpholines were achieved by using this protocol. The morpholines contained methylene chloride handles that can readily be derivatized to yield other functional molecules. When enantiopure epichlorohydrin was used, the corresponding optical pure morpholine was accomplished. Interestingly, it was found that the meso-olefinic substrate **1f** was desymmetrized in the reaction.

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Supporting Information Available. Experimental procedures, CIF files, and additional information. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) The details appear in the Supporting Information.

The authors declare no competing financial interest.