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Facile, Efficient, and Catalyst-Free Electrophilic Aminoalkoxylation of Olefins: Scope and Application

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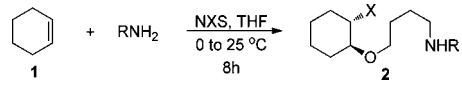
Abstract: A new one-pot electrophilic aminoalkoxylation reaction using olefin, cyclic ether, amine, and *N*-bromosuccinimide has been developed. The olefinic substrates and the cyclic ether partners can be flexibly varied to produce a range of amino ether derivatives. This novel protocol has been applied in the facile and efficient synthesis of biologically active morpholine compounds.

The limited supply of natural resources and the impact on environmental pollution have been problems for the pharmaceutical industry for decades. To address these problems, many research endeavors to develop green and sustainable manufacturing processes have been carried out.[1] One of the recent focuses is on multicomponent reactions (MCRs), which allow the quick assembly of several simple components into complex structures in one pot. MCRs require very careful design, and the usefulness of the reactions is demonstrated by their numerous applications.[2] Among MCRs, electrophilic MCRs have been less reported, partly because of the common incompatibility of electrophiles with the other components. Herein we describe a facile, efficient, and catalyst-free one-pot electrophilic aminoalkoxylation of olefins and its application in morpholine synthesis.

On the basis of electrophilic cascades,[3] we reasoned that a cyclic ether could act as the nucleophile in the opening of bromonium cation ring **A** to yield intermediate **B**.[4] The resulting oxonium cation **B** could be captured by an amine and should provide the corresponding aminoether derivative **C**. To test this hypothesis, we examined the reaction cascade using cyclohexene, *N*-bromosuccinimide (NBS), and primary amines in tetrahydrofuran (THF) at room temperature. An alkylamine and arylamine were tested first, and only trace amounts of products were observed (Table 1, entries 1 and 2). To our surprise, a 78% yield of the desired product was obtained when benzenesulfonamide was used (Table 1, entry 3). Poorer yields were observed when more electron-rich sulfonamides were used (Table 1, entries 4, 7, and 8). Finally, the use of electron-deficient *p*-nitrobenzenesulfonamide gave an excellent yield (Table 1, entry 9). There are several features in this novel electrophilic aminoalkoxylation reaction: (1) unlike typical NBS electrophilic reactions,[5] the addition of a Lewis acid in this reaction led to a decrease in reaction yield (Table 1, entries 5 and 6); (2) NBS was found to be superior to other halogen sources (Table 1, entries 12 and 13); (3) the reaction proceeded equally smoothly when 10 equiv of THF in CH_2Cl_2 was used as the cosolvent (Table 1, entry 10);[6] (4) performing the reaction on a 1.0 g scale showed no change in efficiency (Table 1, entry 11); and (5) the yield was not affected when the addition sequence of the components was changed.[7]

Table 1. Electrophilic Aminoalkoxylation of Cyclohexene[a]

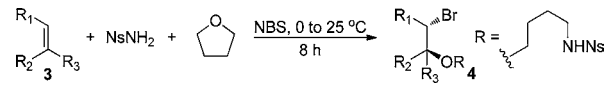


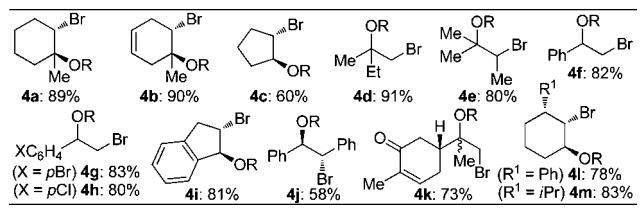
entry	R	X	yield (%)[b]	entry	R	X	yield (%)[b]
1	*i*Pr	Br	trace	8	Ms	Br	60
2	*p*-$NO_2C_6H_4$	Br	trace	9	Ns	Br	94
3	$C_6H_5SO_2$	Br	78	**10**[e]	**Ns**	**Br**	**94**
4	Ts	Br	65	**11**[f]	**Ns**	**Br**	**95**
5[c]	Ts	Br	50	12	Ns	Cl	41
6[d]	Ts	Br	23	13	Ns	I	trace
7	*p*-$MeOC_6H_4SO_2$	Br	60				

[a] Reactions were carried out with cyclohexene (0.6 mmol), RNH_2 (0.5 mmol), and NBS (0.6 mmol) in THF (4.0 mL). [b] Isolated yield. [c] $BF_3 \cdot Et_2O$ (0.2 mmol) was added. [d] $Cu(OTf)_2$ (0.1 mmol) was added. [e] THF (5.0 mmol) in CH_2Cl_2 (2.0 mL) was used instead of pure THF. [f] The reaction was conducted on a 1.0 g scale.

We had suspected that the reaction might proceed through the addition of a preformed aminoalcohol to the bromonium cation ring **A**. In fact, this pathway was ruled out simply by mixing THF, $NsNH_2$, and NBS at 25 °C, which showed no reaction after 24 h.[7] Once the optimum conditions had been identified, various olefins were subjected to investigation. The scope of the aminoalkoxylation is indicated by the 13 examples listed in Table 2. All of the reactions proceeded smoothly with good to excellent yields. In addition, excellent chemoselectivities were observed, as the reaction occurred on the electron-rich olefins (Table 2, **4b** and **4k**). In the cases of trisubstituted cyclic (Table 2, **4a** and **4b**), acyclic (Table 2, entries **4d**, **4e**, and **4k**), and benzylic (Table 2, **4f-i**) olefins, the desired positional selectivities (Markovnikov-type) were achieved. Interestingly, **4l** and **4m** were isolated as the only stereoisomers when the corresponding allylic substituted olefins were used.[7] The X-ray

Table 2. Synthesis of Amino Ethers Using Various Olefins[a]



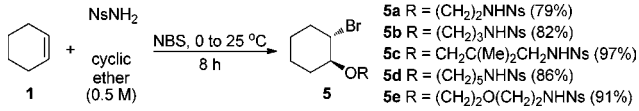


[a] Reactions were carried out with olefin (0.6 mmol), $NsNH_2$ (0.5 mmol), and NBS (0.6 mmol) in THF (4.0 mL). The product yields are isolated yields.

crystallographic structure of **4b** confirmed the regio- and stereoselectivity of the reaction protocol.[7]

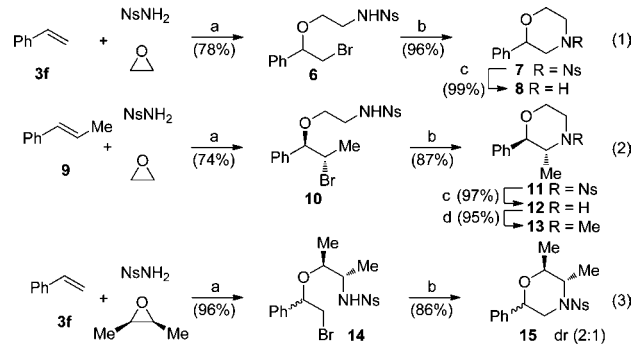
The scope of the aminoalkoxylation disclosed herein appears to be quite broad in regard to not only the olefinic component but also the cyclic ether partner.[7] We carried out the reaction using cyclohexene, $NsNH_2$, and NBS in cyclic ethers having different ring sizes (Table 3). Amino ether **5a** was isolated in 79% yield when ethylene oxide was used. Treatment of the substrates in oxetane gave the desired product **5b** in 82% yield, whereas **5c** was isolated in 97% yield when 3,3-dimethyloxetane was used as the solvent. In addition to three- and four-membered-ring cyclic ethers, a six-membered-ring tetrahydropyran was also found to be effective in the reaction, giving **5d** in 86% yield. Interestingly, aza-ether **5e** was isolated (91% yield) when 1,4-dioxane was used in the reaction; aza-ethers are important building blocks in the synthesis of novel aza-crown ethers.[8]

Table 3. Synthesis of Amino Ethers Using Various Cyclic Ethers



To further demonstrate the usefulness of this protocol, we attempted to synthesize substituted morpholines[9] using the novel electrophilic MCR strategy. Thus, a mixture of styrene, ethylene oxide, $NsNH_2$, and NBS in CH_2Cl_2 was stirred at 25 °C for 8 h, affording amino ether **6** in 78% yield. Stirring **6** with K_2CO_3 in MeCN at 25 °C followed by filtration furnished morpholine derivative **7** in 96% yield. Subsequent deprotection of **7** gave the free morpholine **8** quantitatively; **8** is the fundamental unit of many norepinephrine−dopamine releasing agents.[10] In a similar manner, (±)-phenmetrazine (**12**), which is a potent releaser of [^{3}H]norepinephrine (EC_{50} = 50 nM) and [^{3}H]dopamine (EC_{50} = 131 nM),[11] and the anorexigenic drug (±)-phendimetrazine (Bontril) (**13**)[12] were synthesized using β-methylstyrene (**9**) as the starting material. Similarly, the trisubstituted analogue **15** was synthesized using *cis*-2,3-epoxybutane (Scheme 1).

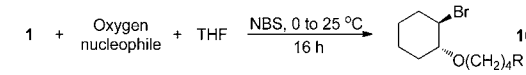
Scheme 1. Synthesis of Substituted Morpholines[a]



[a] Conditions: (a) NBS, CH_2Cl_2, 25 °C, 8 h; (b) K_2CO_3, MeCN, 25 °C, 6 h; (c) LiOH, n-C_3H_7SH, MeCN, 25 °C, 2 h; (d) HCHO, HCO_2H, reflux, 8 h.

We also examined the use of other brominating sources, including bromine, $PyHBr_3$, nBu_4NBr_3, 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO), and $Et_2SBr\cdot SbCl_5Br$,[3f] none of which were found to be as effective as NBS.[7] Interestingly, a 21% yield of the phenoxy adduct **16a** (Table 4, entry 1) and a 40% yield of the desired product **2** (Table 1, X = Br, R = Ns) were obtained when TBCO was used; this led us to investigate the use of phenol partners, and the preliminary results are listed in Table 4. In the case using phenol, 2,4,6-tribromophenol was initially formed and subsequently reacted with intermediate **B** to yield **16a**.[7] In addition to phenols, carboxylic acids were found to be effective in the reaction (Table 4, entries 7 and 8).[13]

Table 4. Electrophilic Alkoxyetherification of Cyclohexene[a]



entry	oxygen nucleophile	product (R)	yield (%)
1[b]	none	**16a** (2,4,6-tribromophenoxy)	56
2[c]	phenol	**16a** (2,4,6-tribromophenoxy)	42
3	2,4,6-tribromophenol	**16a** (2,4,6-tribromophenoxy)	42
4[d]	4-nitrophenol	**16b** (2,6,-dibromo-4-nitrophenoxy)	85
5[d]	2-nitrophenol	**16c** (4,6-dibromo-2-nitrophenoxy)	45
6[d]	4-*t*Bu-phenol	no desired product	–
7	AcOH	**16d** (AcO)	48
8	BzOH	**16e** (BzO)	33

[a] Reactions were carried out with cyclohexene **1** (0.6 mmol), oxygen nucleophile (0.5 mmol), and NBS (0.6 mmol) in THF (4.0 mL). The product yields are isolated yields. [b] TBCO (0.6 mmol) was used instead of NBS. [c] Using 4.5 equiv of NBS. [d] Using 3.5 equiv of NBS.

In summary, we have developed a general, efficient, regio- and stereoselective, and atom-economical electrophilic aminoalkoxylation using olefin, cyclic ether, amine, and NBS. The reaction is catalyst-free and readily scalable, and the experimental setup is extremely convenient. The olefin and cyclic ether partners can be flexibly varied to produce different kinds of amino ether derivatives. Also, the introduction of nitrogen functionality without the use of intrinsically hazardous organic azide would be of great interest to the manufacturing sector.[1] The synthetic utility of this novel MCR has been illustrated with the efficient synthesis of a substituted morpholine core **8**, (±)-phenmetrazine (**12**), (±)-phendimetrazine (**13**), and analogue **15**. Other oxygen nucleophiles, including phenols and carboxylic acids, were found to be viable nucleophilic alternatives in the reaction. Further investigations of other applications, including the use of other nucleophilic partners, as well as the study of the asymmetric version[14] are underway.

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Supporting Information Available: Experimental procedures, spectral data for reaction products, complete ref 9, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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