

Scope and Mechanistic Studies of
Electrophilic Alkoxyetherification

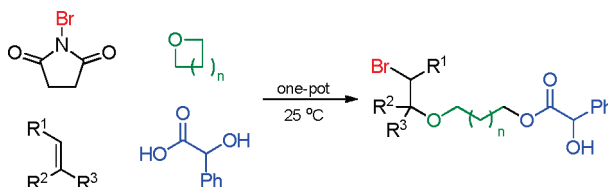
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Received October 13, 2011

ABSTRACT

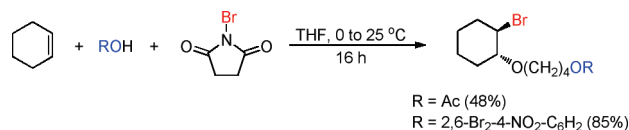


A one-pot electrophilic alkoxyetherification using an olefin, a cyclic ether, a carboxylic acid, and *N*-bromosuccinimide has been developed. The oxygen nucleophiles, the olefinic substrates, and the cyclic ether partners can be varied to produce a wide range of alkoxyether derivatives.

Multicomponent reactions (MCRs) are important and useful synthetic methods that offer an opportunity for building complex molecules in a convergent and atom-economic manner.¹ A major focus of MCR is on the development of new reactions,² and many endeavors to develop green and sustainable processes have been carried out.³ However, electrophilic MCRs have been less reported, partly because of the common incompatibility of electrophiles with the other components.⁴

In the course of our effort on the development of electrophilic bromine initiated MCR, recently we reported a novel electrophilic cascade using an olefin, a cyclic ether, a sulfonamide, and NBS. During that study, we also disclosed that instead of a sulfonamide, an oxygen nucleophile, which contained an acidic proton, could also participate in this cascade (Scheme 1).⁵

Scheme 1. Bromonium Ion Promoted Electrophilic Cascades



Further investigation using acetic acid as the nucleophilic partner showed that the reaction was highly dependent on the concentration, in which a higher reaction yield (86%) of the desired product was obtained under a diluted (0.04 M) condition (Table 1, entry 3). The reaction was readily scalable without loss of efficiency (Table 1, entry 4).⁶

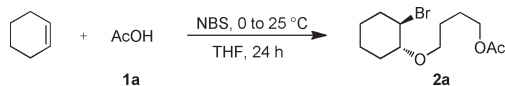
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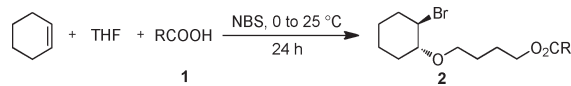
Table 1. Alkoxyetherification of Cyclohexene Using Acetic Acid

entry ^a	concentration (M)	isolated yield (%)
1	0.13	48
2	0.06	58
3	0.04	86
4 ^b	0.04	85

^a Reactions were carried out with cyclohexene (0.6 mmol), NBS (0.6 mmol), and AcOH (0.5 mmol) in THF at 25 °C for 24 h. ^b Reaction was conducted on a 1.0 g scale.

Other carboxylic acids were also subjected to investigation. In general, the reaction varied with the acidity of the carboxylic acid partner (Table 2). Comparing to benzoic acid (**1b**) (entry 1, $pK_a = 4.20$), less acidic partners including 3-methylbenzoic acid (**1c**) (entry 2, $pK_a = 4.24$), 4-methylbenzoic acid (**1d**) (entry 3, $pK_a = 4.34$), and 4-methoxybenzoic acid (**1e**) (entry 4, $pK_a = 4.47$) gave lower yields. Moderate yields were obtained when relatively more acidic partners were used, such as 4-chlorobenzoic acid (**1f**) (entry 5, $pK_a = 3.99$) and 4-nitrobenzoic acid (**1g**) (entry 6, $pK_a = 3.44$).⁷ In particular, high yield (78%) of the desired product was obtained using pentafluorobenzoic acid (**1h**) (Table 1, entry 7).

Interestingly, when using hydroxyl carboxylic acids including glycolic acid (**1k**) (entry 10, $pK_a = 3.83$), (*R*)-(-)-mandelic acid (**1l**) (entry 11, $pK_a = 3.41$), and salicylic acid (**1n**) (entry 13, $pK_a = 2.98$),⁸ and 3,5-dibromosalicylic acid (**1o**) (entry 14), high reaction yields of the carboxylate-adducts were obtained.^{7,9} It is noteworthy that in these acids, although both the hydroxyl and the carboxylic acid groups could potentially participate in the reaction, the less nucleophilic carboxylic group preferred to attack (*vide infra*). Masking the hydroxyl group of **1l** as a methyl ether (i.e., acid **1m**), however, led to a lower reaction yield

Table 2. Alkoxyetherification of Cyclohexene Using Various Oxygen Nucleophiles^a

entry	RCOOH	pK_a	yield (%)
1	C ₆ H ₅ COOH 1b	4.20	22
2	3-Me-C ₆ H ₄ COOH 1c	4.24	19
3	4-Me-C ₆ H ₄ COOH 1d	4.34	21
4	4-MeO-C ₆ H ₄ COOH 1e	4.47	8
5	4-Cl-C ₆ H ₄ COOH 1f	3.99	51
6	4-NO ₂ -C ₆ H ₄ COOH 1g	3.44	50
7	C ₆ F ₅ COOH 1h	—	78
8	C ₆ H ₅ CH ₂ COOH 1i	4.31	34
9	(1-naphthyl)-CH ₂ COOH 1j	—	36
10		3.83	74
11		3.41	87
12		—	60
13 ^b		2.98	88
14		—	88

^a Reactions were carried out with cyclohexene (0.6 mmol), NBS (0.6 mmol), and oxygen nucleophile **1** (0.5 mmol) in THF (0.04 M) at 25 °C for 24 h. The product yields are isolated yields. ^b 1.8 mmol NBS was used, and the corresponding 3,5-dibromosalicylic adduct was obtained.

(Table 2, entry 12).^{10,11} The products were confirmed not only by NMR but also by the hydrolysis of **2l**.¹²

Next, various olefinic substrates were examined using (*R*)-(-)-mandelic acid (**1l**) and 3,5-dibromosalicylic acid (**1o**) as the nucleophilic partners. In many cases, the desired alkoxyethers **3** were obtained with good yields. In addition, excellent chemoselectivities and positional selectivities were observed, wherein the reaction occurred on the more electron-rich olefin (Table 3, entry 2), and the Markovnikov-type products were isolated (Table 3, entries 1–8).¹⁰ Furthermore, high stereoselectivity was also obtained, where the cascade resulted

(6) We have briefly investigated using less THF, i.e., using THF as a stoichiometric reagent instead of a solvent. However, the results were not satisfactory. For details, see the Supporting Information.

(7) For references of the pK_a values, see: (a) Brown, H. C. et al. In Braude, E. A.; Nachod, F. C. *Determination of Organic Structures by Physical Methods*; Academic Press: New York, 1955. (b) Dippy, J. F. J.; Hughes, S. R. C.; Rozanski, A. J. *Chem. Soc.* **1959**, 2492. (c) Bjerrum, J. et al. *Stability Constants*; Chemical Society: London, 1958.

(8) When using salicylic acid (**1n**), the corresponding 3,5-dibromosalicylic adduct was obtained as the sole product. Identical result was observed when using 3,5-diromosalicylic acid (**1o**) as the nucleophilic partner.

(9) **Representative procedure:** To a solution of olefin (0.6 mmol) and oxygen nucleophile (0.5 mmol) in dry THF (6 mL) in the dark was added *N*-bromosuccinimide (107 mg, 0.6 mmol) in four portions at 1-h intervals at 25 °C. After stirring for 24 h at 25 °C, the reaction was quenched with saturated Na₂S₂O₃ (10 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography to yield the corresponding product.

(10) For the reactions that used acids **1l** and **1m** (Table 2, entries 11 and 12; Table 3, entries 1 and 2; Table 4), the products existed as diastereoisomeric mixtures.

(11) The carboxylic acids with neighboring hydroxyl groups (acids **1k**, **1l**, **1n**, and **1o**) returned high reaction yields; for acid **1l**, removing (Table 2, entry 11 vs 8) or masking (Table 2, entry 11 vs 12) the hydroxyl group gave a lower yield. The hydroxyl group seemed could enhance the acidity of the carboxylic acid, potentially through an intramolecular hydrogen bonding (Table 2, entry 1 vs 13; 8 vs 11).

(12) The details appear in the Supporting Information.

Table 3. Alkoxyetherification of Various Olefins

entry ^a	substrate	product	RCOOH, yield (%) ^c
1			1i , 54 1o , 51
2			1i , 89 1o , 84
3 ^b			1i , 78 1o , 67
4 ^b			1i , 45 1o , 44
5			1o , 52
6			1o , 91
7			1o , 96
8			1o , 89
9			1o , 84
10			1o , 85
11			1o , 60

^a Reactions were carried out with olefin (0.6 mmol), NBS (0.6 mmol), and oxygen nucleophiles (0.5 mmol) in THF (0.04 M) at 25 °C for 24 h. ^b 1.0 mmol of olefin was used. ^c Isolated yield.

in the formation of only *trans*-addition products (Table 3, entries 5 and 9–11).

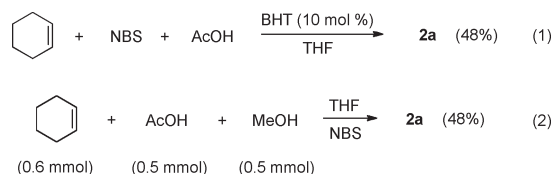
Other than examining the olefinic substrates, a variety of cyclic ethers, including oxetane, 3,3-dimethyloxetane, tetrahydropyran, and 1,4-dioxane, were also subjected to investigation. Cyclohexene, NBS, and (*R*)-mandelic acid (**1i**) were used as the counter partners, and moderate to good reaction yields of the corresponding alkoxyethers were observed (Table 4).¹⁰

Toward the understanding of the mechanism, we believed that the carboxylic acid partner played a crucial role in activating NBS; an additional NBS activator was not necessary in this alkoxyetherification, and the reaction

Table 4. Alkoxyetherification of Cyclohexene Using Various Cyclic Ethers^a

entry	cyclic ether	product	yield (%)
1			70
2			29
3			33
4			57

^a Reactions were carried out with cyclohexene (0.6 mmol), NBS (0.6 mmol), and (*R*)-mandelic acid (**1i**) (0.5 mmol) in cyclic ether (0.04 M) at 25 °C for 24 h. The product yields are isolated yields.

Scheme 2. Probing the Reaction Mechanism

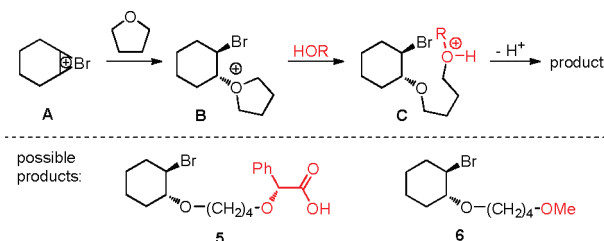
yield was highly dependent on the acidity of the nucleophilic partner.¹³

In fact, we have carried out two experiments in order to further illuminate the mechanistic picture. First, 10 mol % of radical scavenger 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to the cascade reaction involving cyclohexene, NBS, acetic acid, and THF (Scheme 2, eq 1). After 24 h, 48% of the desired product was obtained, which was identical to the reaction without the addition of BHT. Second, a competition experiment, which involved equal molar amounts of methanol and acetic acid as the nucleophiles in the cyclohexene–THF–NBS cascade, was also performed (Scheme 2, eq 2). After 24 h, a 48% of the acetic acid-adduct was obtained, while no methanol-associated product was detected.

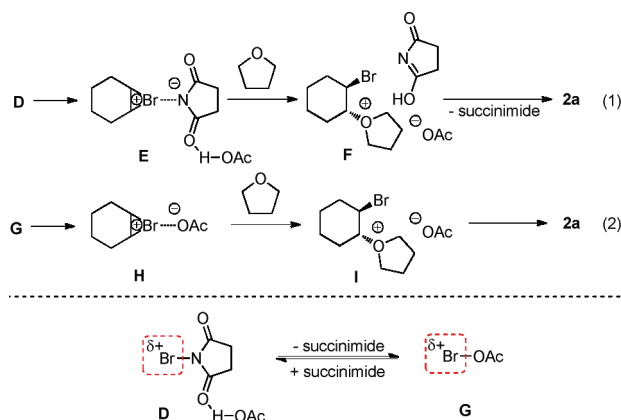
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Scheme 3. A Plausible Mechanistic Pathway



Scheme 4. Proposed Mechanism of the Electrophilic Bromoalkoxyetherification Reaction



Since this MCR seemed not to be a radical-type reaction, based on the cationic proposal,¹⁴ the mechanistic pathway should ensue: (1) nucleophilic attack of bromonium intermediate **A** by a cyclic ether (e.g., THF) to form **B**; (2) oxonium intermediate **B** is captured by an oxygen nucleophile to give **C**; (3) deprotonation of **C** yields the desired product (Scheme 3). This proposal should follow the nucleophilicity, in which comparing to a carboxylic acid group, the more nucleophilic hydroxyl group should be more reactive and should attack **B** to form **C**, i.e., in the cascade (e.g., Table 2, entry 11) and the competition

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experiment (Scheme 2, eq 2), and alcohol-adducts **5** and **6** should be obtained as the major products, respectively.

However, since only the carboxylic acid-associated products were obtained (Tables 2–4), this type of reaction may not follow the proposal presented in Scheme 3. A possible explanation is that instead of a carboxylic acid group, a carboxylate anion, which is more nucleophilic than a hydroxyl group, may be involved in capturing intermediate **B**.¹⁵

In accordance to our previous mechanistic proposal,^{13b} the carboxylic acid nucleophile might act as a Brønsted acid to activate NBS (Scheme 4, species **D**). After the formation of bromonium intermediate with an olefin (e.g., cyclohexene) (**D** → **E**) and the cyclic ether nucleophilic attack (**E** → **F**), the counter succinimide anion might deprotonate the acid and give the carboxylate-oxonium pair **F**. Subsequent capturing of the oxonium ion by the acetate could furnish the desired product **2a** (Scheme 4, eq 1). On the other hand, a Br exchange between the acid and NBS might exist, which would result in the active electrophilic brominating source AcOBr (Scheme 4, species **G**).^{16,17} Through a **G** → **H** → **I** sequence, the target molecule **2a** could also be obtained (Scheme 4, eq 2).

In summary, we have developed a general and efficient electrophilic alkoxyetherification that uses an olefin, NBS, a carboxylic acid, and a cyclic ether. This MCR is catalyst-free, readily scalable, and highly practical using inexpensive and commercially available reagents. Furthermore, good regio- and stereoselectivity are also observed in this MCR.

Acknowledgment. We are thankful for financial support from National University of Singapore (Grant No. 143-000-428-112). We also thank Prof. Scott E. Denmark (University of Illinois) for his valuable advice on this project.

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

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