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Scope and Mechanistic Studies of Electrophilic Alkoxyetherification

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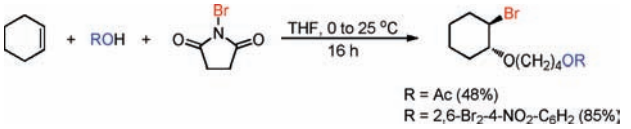
ABSTRACT

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]

(1) For selected reviews, see: (a) Ugi, I.; Domling, A.; Horl, W. *Endeavour* **1994**, *18*, 115–122. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (c) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005. (d) Domling, A. *Chem. Rev.* **2005**, *106*, 17–89. (e) Dömling, A. *Chem. Rev.* **2005**, *106*, 17–89. (f) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486. (g) Sunderhaus, J. D.; Martin, S. F. *Chem.—Eur. J.* **2009**, *15*, 1300–1308.

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(3) (a) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411–420. (b) Rosamilia, A. E.; Scott, J. L.; Strauss, C. R. *Org. Lett.* **2005**, *7*, 1525–1528. (c) Rosamilia, A. E.; Strauss, C. R.; Scott, J. L. *Pure Appl. Chem.* **2007**, *79*, 1869–1877. (d) Shi, D. Q.; Ni, S. N.; Yang, F.; Ji, S. J. *J. Heterocycl. Chem.* **2008**, *45*, 1275–1280. (e) Andriushchenko, A. Y.; Desenko, S. M.; Chernenko, V. N.; Chebanov, V. A. *J. Heterocycl. Chem.* **2011**, *48*, 365–367.

(4) For selected electrophilic MCRs, see: (a) Serguchev, Y. A.; PonomarenkoM. V.; Lourie, L. F.; Chernega, A. N. *J. Fluorine Chem.* **2003**, *123*, 207–215. (b) Nair, V.; Menon, R. S.; Beneesh, P. B.; Sreekumar, V.; Bindu, S. *Org. Lett.* **2004**, *6*, 767–769. (c) Nair, V.; Beneesh, P. B.; Sreekumar, V.; Bindu, S.; Menon, R. S.; Deepthi, A. *Tetrahedron Lett.* **2005**, *46*, 201–203. (d) Yeung, Y. Y.; Gao, X. R.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 9644–9645. (e) Church, T. L.; Byrne, C. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2007**, *129*, 8156–8162. (f) Hajra, S.; Bar, S.; Sinha, D.; Maji, B. *J. Org. Chem.* **2008**, *73*, 4320–4322. (g) Abe, T.; Takeda, H.; Miwa, Y.; Yamada, K.; Yanada, R.; Ishikura, M. *Helv. Chim. Acta* **2010**, *93*, 233–241. (h) Braddock, D. C.; Millan, D. S.; Perez-Fuertes, Y.; Pouwer, R. H.; Sheppard, R. N.; Solanki, S.; White, A. J. P. *J. Org. Chem.* **2009**, *74*, 1835–1841. (i) Bonney, K. J.; Braddock, D. C.; White, A. J. P.; Yaqoob, M. *J. Org. Chem.* **2011**, *76*, 97–104. (j) Snyder, S. A.; Treitler, D. S.; Bruchks, A. P.; Sattler, W. *J. Am. Chem. Soc.* **2011**, *133*, 15898–15901.

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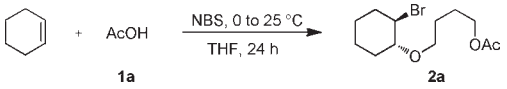
Table 1. Alkoxyetherification of Cyclohexene Using Acetic Acid



1a 2a

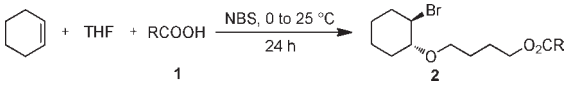
entry[a]	concentration (M)	isolated yield (%)
1	0.13	48
2	0.06	58
3	0.04	86
4[b]	0.04	85

[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.

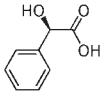
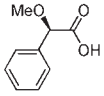
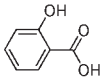
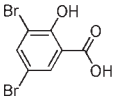
Other carboxylic acids were also subjected to investigation. In general, the reaction varied with the acidity of the carboxylic acid partner (Table 2). Comparing to benzoic acid (**1b**) (entry 1, pK_a = 4.20), less acidic partners including 3-methylbenzoic acid (**1c**) (entry 2, pK_a = 4.24), 4-methylbenzoic 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 salicyclic acid (**1n**) (entry 13, pK_a = 2.98),[8] and 3,5-dibromosalicyclic 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 (*vida 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]



1 2

entry	RCOOH		pKa	yield (%)
1	C_6H_5COOH	**1b**	4.20	22
2	3-Me-C_6H_4COOH	**1c**	4.24	19
3	4-Me-C_6H_4COOH	**1d**	4.34	21
4	4-MeO-C_6H_4COOH	**1e**	4.47	8
5	4-Cl-C_6H_4COOH	**1f**	3.99	51
6	4-NO_2-C_6H_4COOH	**1g**	3.44	50
7	C_6F_5COOH	**1h**	--	78
8	$C_6H_5CH_2COOH$	**1i**	4.31	34
9	(1-naphthyl)-CH_2COOH	**1j**	--	36
10		**1k**	3.83	74
11		**1l**	3.41	87
12		**1m**	-	60
13[b]		**1n**	2.98	88
14		**1o**	--	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-dibromosalicyclic 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-dibromosalicyclic 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 salicyclic acid (**1n**), the corresponding 3,5-dibromosalicyclic adduct was obtained as the sole product. Identical result was observed when using 3,5-diromosalicyclic acid (**1o**) as the nucleophlic partner.

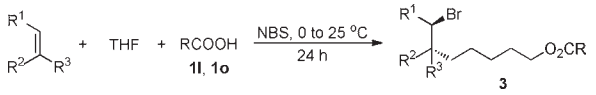
(9) **Representative procedure:** To a solution of olefin (0.6 mmol) and oxygen nucleophile (0.5 mmol) in dry THF (6 mL) in the dark was added *N*-bromosuccinimide (107 mg, 0.6 mmol) in four portions at 1-h intervals at 25 °C. After stirring for 24 h at 25 °C, the reaction was quenched with saturated $Na_2S_2O_3$ (10 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.

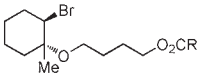
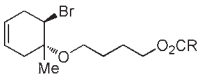
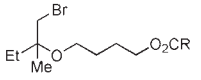
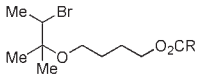
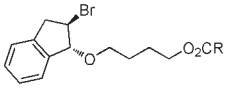
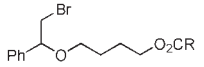
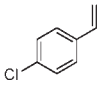
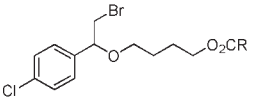
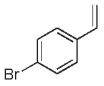
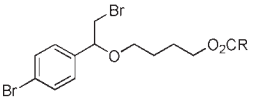
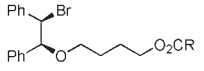
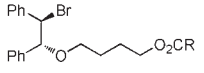
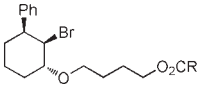
(10) For the reactions that used acids **1l** and **1m** (Table 2, entries 11 and 12; Table 3, entries 1 and 2; Table 4), the products existed as diastereoisomeric mixtures.

(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		 **3a**	**1l**, 54 **1o**, 51
2		 **3b**	**1l**, 89 **1o**, 84
3[b]		 **3c**	**1l**, 78 **1o**, 67
4[b]		 **3d**	**1l**, 45 **1o**, 44
5		 **3e**	**1o**, 52
6		 **3f**	**1o**, 91
7		 **3g**	**1o**, 96
8		 **3h**	**1o**, 89
9		 **3i**	**1o**, 84
10		 **3j**	**1o**, 85
11		 **3k**	**1o**, 60

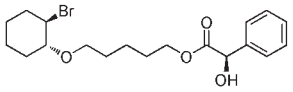
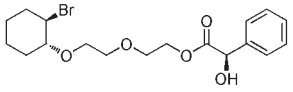
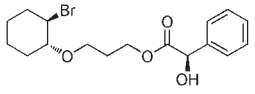
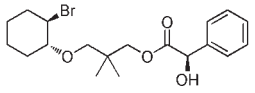
[a] Reactions were carried out with olefin (0.6 mmol), NBS (0.6 mmol), and oxygen nucleophiles (0.5 mmol) in THF (0.04 M) at 25 °C for 24 h. [b] 1.0 mmol of olefin was used. [c] Isolated yield.

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 (**1l**) were used as the counter partners, and moderate to good reaction yields of the corresponding alkoxyethers were observed (Table 4).[10]

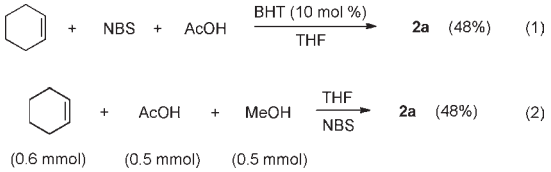
Toward the understanding of the mechanism, we believed that the carboxylic acid partner played a crucial role in activating NBS; an additional NBS activator was not necessary in this alkoxyetherification, and the reaction

Table 4. Alkoxyetherification of Cyclohexene Using Various Cyclic Ethers[a]

entry	cyclic ether	product		yield (%)
1			**4a**	70
2			**4b**	29
3			**4c**	33
4			**4d**	57

[a] Reactions were carried out with cyclohexene (0.6 mmol), NBS (0.6 mmol), and (*R*)-mandelic acid (**1l**) (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



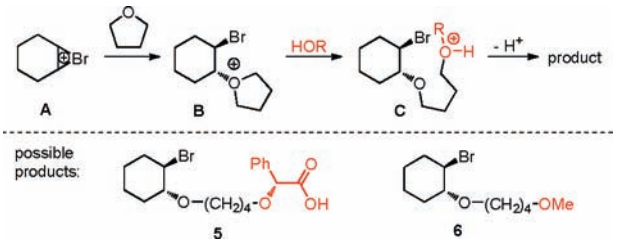
yield was highly dependent on the acidity of the nucleophilic partner.[13]

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.

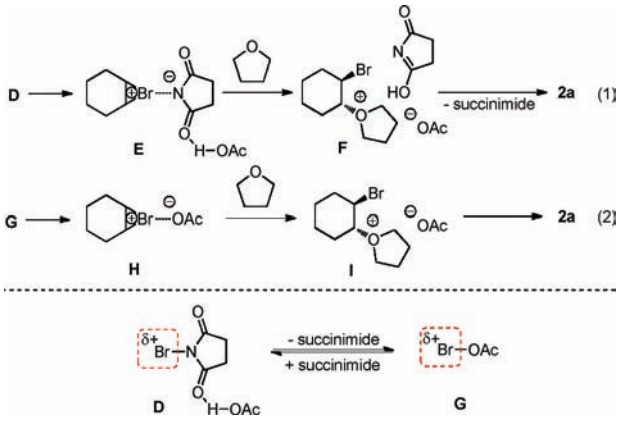
(13) Similar observation appeared in related studies; for reference, see: (a) Zhou, L.; Zhou, J.; Tan, C. K.; Chen, J.; Yeung, Y.-Y. *Org. Lett.* **2011**, *13*, 2448–2451. (b) Zhou, L.; Chen, J.; Zhou, J.; Yeung, Y.-Y. *Org. Lett.* **2011**, *13*, 5804–5807.

(14) (a) DeLaMare, P. B. D.; Bolton, R. *Electrophilic Additions to Unsaturated Systems*, 2nd ed.; Elsevier: New York, 1982; pp 136−197. (b) Ruasse, M.-F. *Adv. Phys. Org. Chem.* **1993**, *28*, 207. (c) Schmid, G. H.; Garrat, D. G. In *The Chemistry of Double Bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, 1977; Suppl. A, Part 2, p 725.

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 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 steroselectivity are also observed in this MCR.

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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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