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Generation of Ketenes from Acid Chlorides Using NaH/Crown Ether Shuttle-Deprotonation for Use in Asymmetric Catalysis

Andrew E. Taggi, Harald Wack, Ahmed M. Hafez, Stefan France, and Thomas Lectka*

Department of Chemistry, Johns Hopkins University, 3400 North Charles Street, Baltimore, Maryland 21218

lectka@jhunix.hcf.jhu.edu

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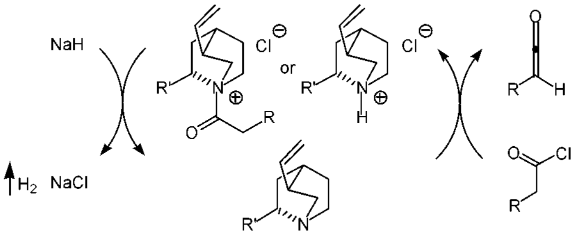
ABSTRACT



We describe methodology for the in situ generation of reactive monosubstituted ketenes from acid chlorides through a shuttle deprotonation process using NaH as an inexpensive stoichiometric base and a crown ether cocatalyst. We have successfully applied this new procedure to the catalytic, asymmetric synthesis of β-lactams and α-haloesters.

Reactive monosubstituted ketenes are most often accessed in situ from acid chlorides through trialkylamine-promoted dehydrohalogenation reactions, although for many purposes this procedure may not be ideal.[1] Recently, we have demonstrated that homogeneous as well as heterogeneous bases (proton sponge,[2] potassium carbonate,[3] or the resin-bound phosphazine base BEMP[4]) can effectively promote the formation of reactive ketenes (or their synthetic equivalents) from the corresponding acid chlorides without interfering in subsequent reactions. Cinchona alkaloid derivatives and other tertiary amines (including benzoylquinine, BQ, **2a**) can serve not only as catalysts but also as "shuttle" bases promoting the initial dehydrohalogenation step.[2] We wish to highlight herein a new procedure that employs inexpensive and low molecular weight sodium hydride as a stoichiometric base to generate ketenes in situ (Scheme 1). To illustrate the utility of this new ketene synthesis we applied it to two

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[1] (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223−3235. (b) Lynch, J. E.; Riseman, S. M.; Laswell, W. L.; Tschaen, D. M.; Volante, R. P.; Smith, G. B.; Shinkai, I. *J. Org. Chem.* **1989**, *54*, 3792−3796.

[2] Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832.

[3] Hafez, A. M.; Taggi, A. E.; Wack, H.; Esterbrook. J.; Lectka, T. *Org. Lett.* **2001**, *3*, 2049−2051.

[4] (a) Hafez, A. M.; Taggi, A. E.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 10853−10859. (b) Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J., III.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531−1532. (c) Hafez, A. M.; Taggi, A. E.; Wack, H.; Drury, W. J., III.; Lectka, T. *Org. Lett.* **2000**, *2*, 3963−3965.

[5] The popular conception that β-lactams are exclusively antibiotics has been altered by the extensive development of serine protease inhibitors; for representative references see the following. Thrombin: (a) Cutrona, K. J.; Sanderson, P. E. J. *Tetrahedron Lett.* **1996**, *37*, 5045−5048. Cholesterol absorption: (b) Alcaide, B.; Almendros, P.; Salgado, N. R.; Martínez-Alcázar, M. P.; Hernández-Cano, F. *Eur. J. Org. Chem.* **2001**, 2001−2009. Human leukocyte elastase: (c) Wilmouth, R. C.; Kassamally, S.; Westwood, N. J.; Sheppard, R. J.; Claridge, T. D. W.; Aplin, R. T.; Wright, P. A.; Pritchard, G. J.; Schofield, C. J. *Biochemistry* **1999**, *38*, 7989−7998. (d) Firestone, R. A.; Barker, P. L.; Pisano, J. M.; Ashe, B. M.; Dahlgren, M. E. *Tetrahedron*, **1990**, *46*, 2255−2262. Prostate specific antigen: (e) Adlington, R. M.; Baldwin, J. E.; Becker, G. W.; Chen, B.; Cheng, L.; Cooper, S. L.; Hermann, R. B.; Howe, T. J.; McCoull, W.; McNulty, A. M.; Neubauer, B. L.; Prichard, G. J. *J. Med. Chem.* **2001**, *44*, 1491−1508.

[6] α-Halo carbonyl compounds have been found to have beneficial biological properties, such as anti-convulsant activity: Choi, D.; Stables, J. P.; Kohn, H. *Bioorg. Med. Chem.* **1996**, *12*, 2105−2114.

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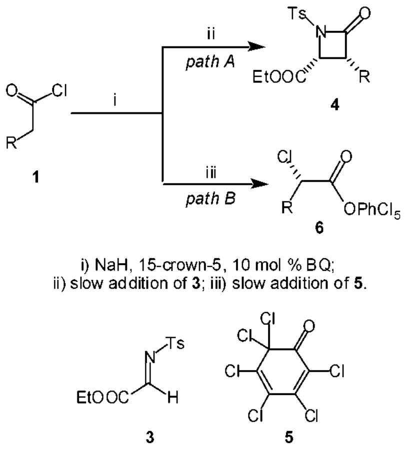
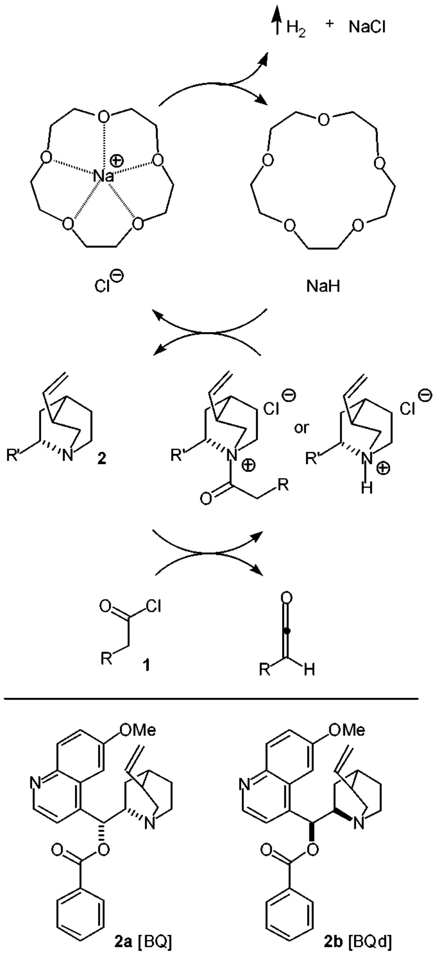
Scheme 1. Ketenes Generated with NaH and Their Subsequent Reaction with Electrophiles **3** or **5**



i) NaH, 15-crown-5, 10 mol % BQ;
ii) slow addition of **3**; iii) slow addition of **5**.

Scheme 2. Catalytic Shuttle Deprotonation of Acid Chlorides to Generate Ketenes Using Cinchona Alkaloid Derivatives



different types of catalytic, asymmetric reactions recently developed in our labs: the enantioselective synthesis of β-lactams,[2] and enantioselective tandem α-chlorination/esterification.[4b] The resulting procedure proves to be a general, convenient, and cost-effective way to prepare ketenes for asymmetric catalysis on a millimole scale, yielding a variety of optically enriched products, such as β-lactam-based serine protease inhibitors[5] and α-halogenated esters (Scheme 1).[6]

NaH is usually employed as a dispersion in mineral oil, the precise titer of which is often difficult to determine. Therefore, we chose powdered NaH (95% purity), which allows for greater accuracy in measurement. We added 10 mol % 15-crown-5 as a phase transfer cocatalyst to help solubilize the NaH.[7] Initially, we found that a mixture of NaH and 15-crown-5 alone in toluene at -78 °C forms ketene very slowly, resulting in an extremely low yield of products. However, the inclusion of 10 mol % BQ catalyst from the outset increased the product yield dramatically and presumably the rate of ketene formation as well.[8] We found this result consistent with our previous reports in which BQ acts as a "proton shuttle".[2,3] Although monosubstituted ketenes are difficult to isolate and their existence is best implied through trapping, diphenylketene is stable and easy to characterize. Treatment of diphenylacetyl chloride with NaH/15-crown-5/10 mol % BQ leads smoothly to ketene formation as evidenced by the yellow color of the reaction mixture and the characteristic IR stretch at 2100 cm^{-1}. Perhaps surprisingly, the excess of acid chloride had little effect on the activity of the nucleophilic catalyst BQ. Furthermore, we found that excess NaH did not epimerize the products to any appreciable extent under the reaction conditions. A working hypothesis for the mechanism is presented in Scheme 2. A catalytic "shuttle" base, such as BQ, effects dehydrohalogenation of an acid chloride to the corresponding ketene. The acid chloride either forms an acylammonium salt with BQ and is deprotonated by NaH or the BQ deprotonates the acid chloride (possibly as its ammonium salt) and then shuttles the proton to the NaH, thus regenerating BQ for another catalytic cycle.

We first chose to illustrate the utility of the new process in the catalytic, enantioselective β-lactam synthesis. We began with commercially available hydrocinnamoyl chloride **1a**, which was stirred with 15-crown-5 and 10 mol % BQ in toluene at -78 °C for 7 h. A solution of α-imino ester **3** in toluene was then added by syringe pump over 1 h, and the reaction was slowly warmed to room temperature. A standard workup was followed by column chromatography on silica to afford the *cis*-(3*R*,4*R*)-β-lactam **4a** in 60% yield (6:1 diastereomeric ratio [dr], 99% ee).[9] Recrystallization of **4a** from diethyl ether/hexanes increased the dr to 49:1. It should be noted that compound **4a** represents a prototype very similar in structure to known inhibitors of human leukocyte elastase (HLE).[5d] We discovered that using 2.2 equiv of acid chloride doubled the yield, while only decreasing the dr

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(7) In the case of β-lactams, the use of more polar solvents such as propionitrile and THF was found to decrease the diastereoselectivity greatly, possibly as a result of solubilized salts.

(8) When the BQ was added after the ketene formation step, the yield of β-lactam was drastically decreased, implying that the amount of ketene formed was also diminished.

(9) The opposite enantiomer of the β-lactam can be obtained using benzoylquinidine (**2b**) with similar selectivities and yields.

Table 1. Changes in Selectivity and Yield of **4a** by Varying Equivalents of **1**

entry	equiv of **1a**	% yield of **4a**[a]	dr (*cis*/*trans*)[b]
1	1.1	33	7/1
2	2.2	60	6/1
3	3.3	65	3/1

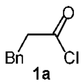
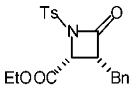
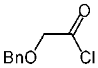
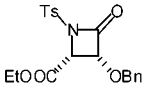
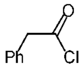
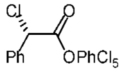
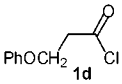
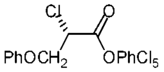
[a] Yield after column chromatography. [b] *cis*/*trans* ratio determined via ^{1}H NMR of the crude residue.

slightly (Table 1, entries 1 and 2). Adding a third equivalent of acid chloride only increased the yield slightly (65%) but decreased the dr drastically (3:1, entry 3). As an example of a ketene containing an α-heteroatom, benzyloxyacetyl chloride was also examined, yielding **4b** in 65% yield (99% ee, 25:1 dr).

To explore the scope of this methodology further, we applied it to the catalytic, enantioselective synthesis of α-chloroesters (**6**) using additional ketene candidates. Aliphatic as well as aromatic ketenes were used in conjunction with perchlororthoquinone **5**. Solvent studies suggested the use of THF instead of toluene in this reaction. Despite poor diastereoselectivity for the β-lactam synthesis when using THF as the solvent, we found that the α-chlorination reaction proceeds in high selectivity and yield in THF.[10]

In a typical α-halogenation reaction, the corresponding acid chloride was added to a magnetically stirred suspension of NaH/15-crown-5 and BQ in THF. The hexachloroquinone solution was then added slowly over 3 h, and the reaction was allowed to warm to room temperature overnight. Aqueous workup followed by column chromatography on silica afforded analytically pure α-chlorinated products in generally good yield and high selectivity (Table 2). It should be noted that the β-lactam and α-chlorination reactions had different optimal procedures. We believe that this is largely due to the varying reactivities of the ketenes as well as the electrophiles, which in turn depends on their respective substituents.[11]

Table 2. Reactions of Acid Chlorides **1** with Imino Ester **3** or Chlorinating Agent **5**

entry[a]	acid chloride	product	% yield[b]	dr[c]	% ee[d]
1	 **1a**	 **4a**	60	6/1	99
2	 **1b**	 **4b**	65	25/1	99
3	 **1c**	 **6a**	63	--	95
4	 **1d**	 **6b**	61	--	92

[a] The use of benzoylquinidine (**2b**) yielded the opposite enantiomer in all cases with similar yield and selectivity. [b] Isolated yield after column chromatography. [c] *cis*/*trans* ratio determined via ^{1}H NMR of the crude residue. [d] Determined by chiral HPLC.

Although the yield and selectivity of these reactions are comparable with our previously developed methods, we have greatly improved the economical aspect of the ketene preparation. Not only was this new methodology applied to the 1.3 mmol scale synthesis of optically pure β-lactams and α-chloroesters,[12] the use of NaH rendered our reaction 11 times less expensive than proton sponge and over *850 times* less expensive than BEMP (Table 3). By utilizing NaH as our dehydrohalogenation reagent, we have furthermore simplified purification of the reaction, with NaCl and H_2 as benign byproducts.[13]

Table 3. Economical Aspect of Various Bases Used in the in Situ Generation of Ketenes

entry	base	equiv[a]	mass (g)[b]	cost ($)[c]	ratio
1	NaH	2.0	0.19	0.11	1
2	proton sponge	1.1	0.94	1.20	11
3	BEMP	1.2	2.4	95.00	863

[a] Equivalents of base needed according to the appropriate procedure. [b] Mass of base needed to produce 1 g of **4a**. [c] Cost based on the least expensive cost per gram from the 2000−2001 Aldrich catalog.

In summary, we have developed a cost-effective, catalytic asymmetric synthesis of β-lactams and α-chloroesters that is amenable to larger scale reactions by using NaH to generate ketenes. Additionally, we have improved on our previously published methods by greatly reducing the cost of the base, by easing the purification, and by eliminating byproducts. Having successfully used aryl, alkyl, and oxo ketenes, we believe that this methodology will be applicable to various other substituted ketenes. Work is currently underway to produce sizable quantities of a number of optically enriched β-lactams and α-halogenated products to be screened for pharmaceutically useful applications.

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Supporting Information Available: General experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The more polar THF works in conjunction with the 15-crown-5 to help solubilize the NaH.

(11) See Supporting Information for details.

(12) These reactions were run at 10 times the scale attainable with our previous α-halogenation reaction methods.

(13) Anastas P. T.; Warner. J. C. *Green Chemistry: Theory and Practice;* Oxford University Press: New York 1998.