Bicarbonate Salts as Cost-Effective Bases for the Synthesis of Ketenes and Their Synthetic Equivalents Applied to the Asymmetric Synthesis of β-Lactams.

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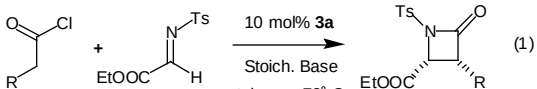
Abstract: We report the use of bicarbonate salts as viable alternatives to more expensive bases for the *in situ* generation of ketenes and their synthetic equivalents. We have successfully applied this to the catalytic, asymmetric synthesis of β-lactams.

Key words: β-lactam, bicarbonate salts, asymmetric catalysis, cinchona alkaloids

A long-standing problem in ketene chemistry has been to utilize the reactive character of pure monosubstituted ketenes for synthetic purposes without having to go through laborious procedures for their synthesis.[1] To date, reactive monosubstituted ketenes are most commonly made *in situ* from acid chlorides through trialkylamine-promoted dehydrohalogenation reactions.[2] For many purposes, this procedure works very well, but in other cases, the trialkylamine can effect undesired side reactions.[3] Along those lines, we have sought alternative ways to make solutions of ketenes or their synthetic equivalents *in situ.* Previous work has shown that homogeneous bases (proton sponge,[4] the phosphazine base BEMP) as well as heterogeneous bases (potassium carbonate,[5] sodium hydride[6] or the resin-bound variant of BEMP[7]) promote the formation of reactive ketenes from the corresponding acid chlorides effectively. However, each of these variants, while suited for particular purposes, does not provide a universal solution to the problem of clean ketene generation.

The major drawback with the homogeneous bases lies with cost. While proton sponge is moderately priced, BEMP is very expensive.[6] To improve cost, we developed procedures using sodium hydride and potassium carbonate. Both are inexpensive bases, however each has important disadvantages. Sodium hydride is extremely hygroscopic and proper precautions must be taken for its use. With potassium carbonate, a specialized dual reaction vessel is necessary to separate the ketene formation and ketene utilization steps.[4] Among other reasons, potassium carbonate has a tendency to racemize or epimerize products, and thus it must be separated out before subsequent chemistry can be accomplished. Recently, we made the somewhat surprising observation that bicarbonate salts can effectively act as stoichiometric bases to produce ketenes or their synthetic equivalents *in situ* for use in the catalytic, asymmetric synthesis of β-lactams (eq 1).[8] The procedure, which we report herein, involves the cinchona alkaloid derivative benzoylquinine (**3a**) and is operationally very simple, cost-effective and has been demonstrated in the synthesis of a variety of β-lactam products.



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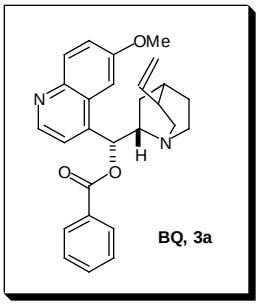
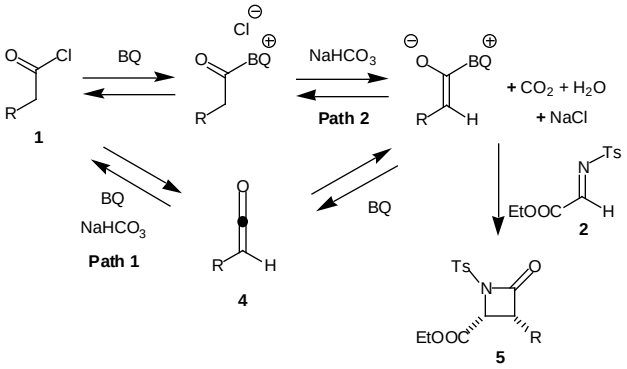


At the outset, the crucial consideration for us was the expected stoichiometric reaction of $NaHCO_3$, for example, with the HCl produced from acid chloride dehydrohalogenation. This reaction should produce NaCl, and more importantly, carbonic acid, which is unstable to dissociation to CO_2 and water (Scheme 1). Water is expected to be deleterious to the reaction--however, if it is effectively sequestered by employing $NaHCO_3$ as a drying agent then we would eliminate this concern. This is indeed what we found in practice by using an excess of $NaHCO_3$ (>15 equivalents). In theory, the mechanism could proceed through one of two pathways: 1) formation of the zwitterionic enolate from attack by BQ on free ketene **4** or, 2) enolate formation from the deprotonation of the acyl ammonium salt.

Scheme 1. Mechanism of β-Lactam Formation with Sodium Bicarbonate



In order to indicate the potential reaction pathway, we designed an experiment to determine the temperature threshold of the bicarbonate reaction. Due to thermal instability of mono-

substituted ketenes they are normally generated in situ at low temperatures. In our previous work with NaH and K_2CO_3, we found that cooling our reaction flasks to –78˚C allowed for the ketene formation. For most ketenes, reactions performed above –10˚C under our published conditions, do not give significant amounts of desired products.[3] Also, extended ketene formation times are often necessary at these lower temperatures. Surprisingly, when phenylacetyl chloride is employed with sodium bicarbonate, β-lactam **5a** is formed in 58% yield with a 3:1 cis:trans ratio and 55 % ee at room temperature. Since phenylketene is not stable at room temperature, we can conclude that significant quantities of free ketene must not be present in solution, and therefore at this time pathway 2 is the more likely mechanism.

In order to determine the optimal reaction conditions, we began to look at other bicarbonate salts. We screened the other available alkali metal bicarbonates and compared their activity (Table 1). These reactions were performed with a catalytic amount of a crown ether to sequester the metal cations and enhance solubility. While the salts gave comparable yields, enantioselectivity and diastereoselectivity were seriously lowered with the potassium (6:1 dr, 72 %ee) and cesium salts (4:1 dr, 65 %ee) as compared to the sodium (12:1 dr, 92 %ee).

Table 1. Effects of Alkali Metal Cation on β-Lactam Formation

entry	bicarbonate	yield (%)[a]	ee[b]	dr[c]
1	$NaHCO_3$	58	92	12/1
2	$KHCO_3$	58	72	6/1
3	$CsHCO_3$	50	65	4/1

[a]Isolated yield after column chromatography. [b]Enantioselectivity determined by chiral HPLC. [c]*cis/trans* ratio determined via ^{1}H NMR of the crude residue

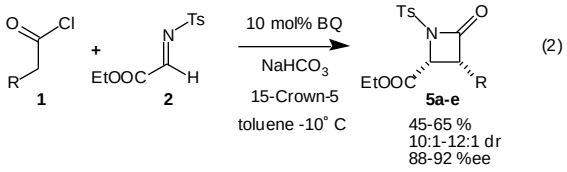
We also examined the effects of the solvent on the formation of β-lactam product (Table 2). We looked at aprotic solvents ranging in polarity and solubility, each with the sodium bicarbonate salt. Generally, toluene was found to be the best solvent for this reaction. Although THF was fairly comparable in terms of yield, a considerable drop in diastereoselectivity was observed with its use. Surprisingly, with more polar solvents like DMSO and CH_3CN, we were only able to obtain trace amounts of the β-lactam.

Table 2. Solvent Effects on β-Lactam Formation

entry	solvent	yield (%)[a]	ee[b]	dr[c]
1	toluene	58	92	12/1
2	THF	50	70	8/1
3	CH_2Cl_2	26	65	5/1
4	CH_3CN	15	--	1/1
5[d]	DMSO	trace	--	--

[a]Isolated yield after column chromatography. [b]Enantioselectivity determined by chiral HPLC. [c]*cis/trans* ratio determined via ^{1}H NMR of the crude residue. [d]Reaction performed at room temp.

With the optimal cation and solvent for the reaction determined, we screened a number of acid chlorides in the reaction with phenylacetyl chloride, N-tosyl imino ester, 10 mol% BQ, 15 equiv. of $NaHCO_3$, and 10 mol% 15-crown-5 at –10˚C over 5 hours and successfully synthesized a variety of β-lactams (eq 2, Table 3).



(2)

Table 3: β-lactam Synthesis using Sodium Bicarbonate

entry	acid chloride	product	yield (%)[a]	ee[b]	dr[c]
1	**1a**	**5a**	58	92	12/1
2	**1b**	**5b**	40	89	10/1
3	**1c**	**5c**	52	88	11/1
4	**1d**	**5d**	47	88	10/1

[a]Isolated yield after column chromatography. [b]Enantioselectivity determined by chiral HPLC. [c]*cis/trans* ratio determined via ^{1}H NMR of the crude residue

We were successfully able to obtain β-lactam products from aryl acid chlorides like phenylacetyl chloride in 58 % yield with 12:1 dr and 92 %ee (entry 1). Furthermore, oxo acid chlorides are highly compatible with this methodology. Phenoxyacetyl chloride **1b** gave the corresponding β-lactam **5b** in 89 %ee with 10:1 dr (entry 2). Benzyloxyacetyl chloride **1c** gave β-lactam **5c** with 11:1 dr and 88 %ee (entry 3).

While the conditions worked for most acid chlorides, they did not seem to work well for less acidic ones like phenoxypropionyl chloride. To remedy this issue, we further cooled the reaction to –40˚C and obtained the β-lactam **5d** in 47 % yield with 10:1 dr and 88 %ee (entry 4).

In summary, we have developed a cost-effective, catalytic asymmetric synthesis of β-lactams using sodium bicarbonate to generate ketenes and their synthetic equivalents without the need for specialized equipment or anhydrous conditions. Furthermore, we improved on our previously published methods by simplifying the synthetic procedure. The bicarbonate salts were found to be cheaper and easier to use than other bases we have tried as suitable alternatives. This method is amenable to aryl, alkyl and oxo acid chlorides and we are confident that this methodology will be applicable to other substituted acid chlorides.

General procedure for β-lactams using Sodium Bicarbonate. To a vigorously stirring solution of $NaHCO_3$ (350 mg, 4.01 mmol), BQ (6 mg, 0.0129 mmol), and 15-crown-5 (3 mg, 0.0129 mmol) in toluene (6 ml) at –40˚C, phenylacetyl chloride **1** (20 mg, 0.129 mmol) in toluene (1 mL) at -78°C is added dropwise followed by α-imino ester **2** (33 mg, 0.129 mmol) in toluene (2 ml). The reaction was allowed to stir for 5 h as it slowly warmed to room temperature. The reaction mixture was washed with 1M HCl, extracted 3x with CH_2Cl_2. The organics were combined and dried with $MgSO_4$. The solvent was removed under reduced pressure and the crude mixture was subjected to column chromatography (15% EtOAc/hexanes) on a plug of silica gel to yield **5a** (58% yield, 28 mg).

All analytical data were consistent with previously published results.[8]

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