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Synthesis of 2-Imidazolones and 2-Iminoimidazoles

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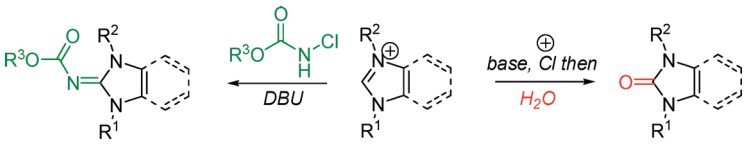
ABSTRACT



Convenient methods for the direct conversion of imidazolium salts to the corresponding 2-imidazolone or 2-imino imidazole derivatives have been developed. Treatment of the salt with commercial bleach leads to effective oxidation at C2 and the formation of the corresponding imidazolone. Alternatively, treatment of the salt with an *N*-chloro amide affords the corresponding protected 2-amino derivative in good yield.

A large number of natural products, most notably those of the *Leucetta* (e.g., **1**–**3**)[1−3] and the oroidin families of alkaloids (e.g., **4** and **5**),[4] have been identified that contain either a 2-aminoimidazole or a 2-imidazolone moiety.[5,6] In the context of our approaches to these molecules,[7] we have generally adopted a strategy that involves the functionalization of pre-existing imidazoles, with the late-stage introduction of the 2-amino group, rather than the *de novo* construction of the heterocycle.[7]

Typically, the C2-amine is introduced via the azide, which in turn is incorporated via lithiation at C2, followed by reaction with TsN_3 or $TrisN_3$,[8,9] whereas the corresponding carbonyl moiety can be introduced by oxidation of the organometallic with a peroxide such as $(TMSO)_2$[10] or $(PhCO_2)_2$.[11] This type of strategy has worked very well in a number of different settings both for us[12] and for other investigators,[13] including en route to modestly complex natural products (Figure 1).

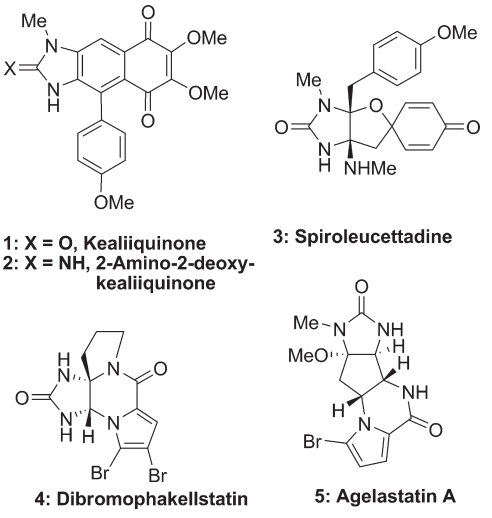


Figure 1. 2-Imidazolone natural product.

Recently, however, in the context of total syntheses of kealiiquinone (**1**)[1,11] and the 2-amino congener **2**,[2] we found that this metalation−electrophile quench approach failed (Scheme 1).[14] Specifically, the advanced intermediate

(1) Akee, R.; Carroll, T. R.; Yoshida, W. Y.; Scheuer, P. J.; Stout, T. J.; Clardy, J. *J. Org. Chem.* **1990**, *55*, 1944–1946.
(2) Fu, X.; Barnes, J. R.; Do, T.; Schmitz, F. J. *J. Nat. Prod* **1997**, *60*, 497–498.
(3) Ralifo, P.; Crews, P. *J. Org. Chem.* **2004**, *69*, 9025–9029.
(4) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Ribes, O.; Pusset, J.; Leroy, S.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1305–1306.
(5) Koswatta, P. B.; Lovely, C. J. *Nat. Prod. Rep.* **2011**, *28*, 511–528.
(6) Forte, B.; Malgesini, B.; Piutti, C.; Quartieri, F.; Scolaro, A.; Papeo, G. *Mar. Drugs* **2009**, *7*, 705–753.
(7) He, Y.; Du, H.; Sivappa, R.; Lovely, C. J. *Synlett* **2006**, 965–992.
(8) Lindel, T.; Hochguertel, M. *J. Org. Chem.* **2000**, *65*, 2806–2809.
(9) Kawasaki, I.; Taguchi, N.; Yoneda, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1996**, *43*, 1375–1379.
(10) Lipshutz, B. H.; Huff, B.; Hagen, W. *Tetrahedron Lett.* **1988**, *29*, 3411–3414.
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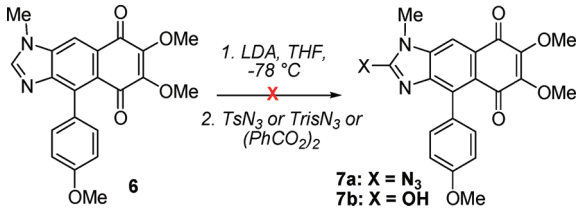
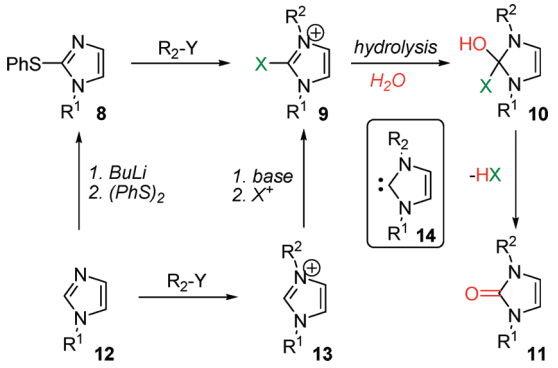
Scheme 1. Attempted C2-Functionalization of an Advanced Kealiiquinone Intermediate



6 was in hand, and we had anticipated that C2-lithiation and then trapping with $(TMSO)_2$ or TsN_3 would provide kealiiquinone (**1**) or 2-amino-2-deoxykealiiquinone (**2**) (after reduction), respectively.

This failure to complete these syntheses was immensely disappointing given that it occurred at such a late stage of the sequence. Accordingly, we set out to identify potential solutions to the problem of introducing the C2 substituent onto these and related substrates.

Scheme 2. Addition–Elimination Pathways to Imidazolones



As a result of this roadblock, we sought to develop a method for the **direct** functionalization at the C2-position that avoided metalation with strong (and potentially nucleophilic) bases. The Ohta group has been a significant contributor to the development of methods for the elaboration of simple imidazoles in the context of the total synthesis of several *Leucetta* alkaloids.[15] They have demonstrated that 2-thio-substituted imidazoles **8** can be converted into imidazolones **11** via hydrolysis of the corresponding imidazolium salt **9** (X = SPh) presumably via **10** (Scheme 2).[16] While this chemistry appears to work quite well, it does require the prefunctionalization of the imidazole by C2-metalation and treatment with $(PhS)_2$ (**12**→**8**, Scheme 2). This requirement adds a step and there are issues associated with odor. In our own setting, application of this chemistry was not considered attractive given the apparent sensitivity of **6** to metalation or the prospect of introducing the thio moiety at the outset of the sequence. From a mechanistic perspective, the Ohta chemistry can be viewed as proceeding via the amidinium species **9**, where the thiophenyl moiety serves as a leaving group. Addition of water, loss of the thiophenyl group and deprotonation of the hydroxyl moiety then provides the imidazolone. We speculated that perhaps this process could be generalized, such that as long as there was an appropriate leaving group at C2 and that an imidazolium salt was employed, the hydrolysis reaction should proceed in a mechanistically similar fashion. Furthermore, there was no reason to suppose that the order of the reactions could not be interchanged such that the imidazolium salt **13** could be prepared first and then advantage could be taken of the relative ease of C2-deprotonation to form the carbene.[17] Subsequent reaction of the carbene **14** with a suitable electrophile to provide the amidinium species **9**, followed by hydrolysis would lead to the formation of the imidazolone, that is, **12**→**13**→**9**→**11**, in a one pot process from **13** (Scheme 2).[16] Herein, we describe the development of an approach using a halonium source to activate the C2 position and subsequent basic hydrolysis.

Given that our initial application of this chemistry would be directed toward the total synthesis of kealiiquinone (**1**), we examined benzimidazole derivatives as substrates. After some preliminary scouting experiments on two imidazolium salts **15a** and **15b**[18] with bases (NaH,[19] NaOH, Na_2CO_3, and K_2CO_3) and NCS, we settled on using either aqueous NaOH, NCS or Na_2CO_3, NCS in THF, from the four conditions examined (Table 1). Occasionally, with the stronger base we observed some hydrolysis (entries 3–5, Table 2) of the imidazolium salt and other unidentified side product formation rather than oxidation. This method was extended to include simple imidazoles in addition to benzimidazoles. The reaction is effective at producing the imidazolones in yields between 36 and 86%, and various combinations of nitrogen substituents are tolerated, including Bn, MOM, SEM and PMB (Table 2, Method A or B)). These yields are similar to

(12) (a) Mukherjee, S.; Sivappa, R.; Yousufuddin, M.; Lovely, C. J. *Org. Lett.* **2010**, *12*, 4940–4943. (b) Koswatta, P.; Lovely, C. J. *Chem. Commun.* **2010**, *46*, 2148–2150. (c) Mukherjee, S.; Sivappa, R.; Yousufuddin, M.; Lovely, C. J. *Synlett* **2010**, 817–821. (d) Koswatta, P.; Lovely, C. J. *Tetrahedron Lett.* **2010**, *51*, 164–166. (e) Bhandari, M. K.; Sivappa, R.; Lovely, C. J. *Org. Lett.* **2009**, *11*, 1535–1538. (f) Koswatta, P. B.; Sivappa, R.; Dias, H. V. R.; Lovely, C. J. *Synthesis* **2009**, 2970–2982. (g) Koswatta, P. B.; Lovely, C. J. *Tetrahedron Lett.* **2009**, *50*, 4998–5000. (h) Koswatta, P. B.; Sivappa, R.; Dias, H. V. R.; Lovely, C. J. *Org. Lett.* **2008**, *10*, 5055–5058.

(13) Jacobi, N.; Lindel, T. *Eur. J. Org. Chem.* **2010**, 5415–5425.

(14) Lima, H. M.; Sivappa, R.; Yousuffudin, M.; Lovely, C. J. 2011, unpublished results.

(15) (a) Ohta, S.; Tsuno, N.; Nakamura, S.; Taguchi, N.; Yamashita, M.; Kawasaki, I.; Fujieda, M. *Heterocycles* **2000**, *53*, 1939–1955. (b) Kawasaki, I.; Sakaguchi, N.; Khadeer, A.; Yamashita, M.; Ohta, S. *Tetrahedron* **2006**, *62*, 10182–10192. (c) Nakamura, S.; Kawasaki, I.; Kunimura, M.; Matsui, M.; Noma, Y.; Yamashita, M.; Ohta, S. J. *Chem. Soc., Perkin Trans. 1* **2002**, 1061–1066.

(16) Nakamura, S.; Tsuno, N.; Yamashita, M.; Kawasaki, I.; Ohta, S.; Ohishi, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 429–436.

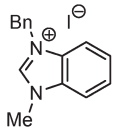
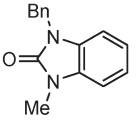
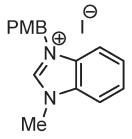
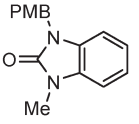
(17) (a) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726. (b) Ennis, E.; Handy, S. T. *Curr. Org. Synth.* **2007**, *4*, 381–389.

(18) These two substrates were chosen initially as they represented models for advanced intermediates in total syntheses projects underway in our lab.

(19) In this case, the reaction was performed through the sequential addition of NaH followed by stirring, the addition of NCS followed by stirring and then the addition of water.

those reported by Ohta and co-workers via the 2-thiobenzimidazole derivatives.[16]

Table 1. Preliminary Base Screen

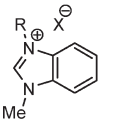
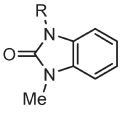
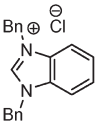
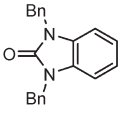
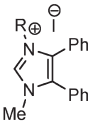
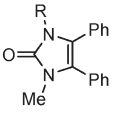
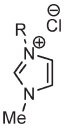
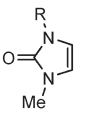
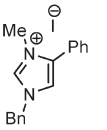
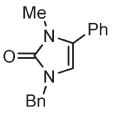
entry	substrate	conditions	product/yield (%)
			
	15a		**16a**
1		NaH, THF then NCS	69
2		2 M NaOH, NCS, THF	84
3		1 M Na_2CO_3, NCS, THF	68
4		1 M K_2CO_3, NCS, THF	62
			
	15b		**16b**
5		NaH, THF then NCS	53
6		2 M NaOH, NCS, THF	83
7		1 M Na_2CO_3, NCS, THF	66
8		1 M K_2CO_3, NCS, THF	62

While these procedures worked reasonably well, it occurred to us that the same transformation might be accomplished through the addition of household bleach (NaOCl), which could serve as both the base and as the source of a chloronium ion. Accordingly, we were delighted to observe that treatment of the substrates in Table 2 (Method C) with bleach at 0 °C resulted in the smooth conversion into the corresponding imidazolones in excellent yield and purity. In some cases, we found that yields were improved and chlorination side reactions were minimized by the reduction of the amount of bleach and addition of NaOH (Method D).

From the substrates depicted in Table 2, it can be observed that most of the imidazolones are relatively simple, and in reality for our purposes we needed this chemistry to be successful on more elaborate substrates. In the context of our kealiiquinone endeavors, imidazolium salt **17**[14] containing a lactone moiety was available, and thus we subjected it to the oxidation chemistry. Gratifyingly, this substrate underwent oxidation to provide the corresponding imidazolone in good yield upon treatment with bleach (Scheme 3).

At this stage, we do not know whether this reaction proceeds mechanistically via carbene **14** as depicted in Scheme 2 or whether the alternative mechanism outlined in Scheme 4 is more likely. Related observations of nucleophilic substitution of 2-haloimidazolium salts have been reported in the literature.[20,21] While these observations do not prove that the 2-chloroimidazolium salt is

Table 2. Substrate Screen[a]

entry	conditions	yield (%)	substrate	product
				
1	B	84	R = Bn; X = I	R = Bn
	C	85	**15a**	**16a**
2	B	83	R = PMB, X = I	R = PMB
	C	81	**15b**	**16b**
3	A	46	R = MOM, X = Cl	R = MOM
	B	81	**15c**	**16c**
4	A	49	R = SEM, X =Cl	R = SEM
	C	79	**15d**	**16d**
				
5	A	50	**15e**	**16e**
	C	88		
6	B	86	R = Bn	R = Bn
	D	79	**15f**	**16f**
7	B	72	R = Me	R = Me
	D	71	**15g**	**16g**
				
8	B	37	R = Bn	R = Bn
	D	39	**15h**	**16h**
9	B	48	R = SEM	R = SEM
	D	36	**15i**	**15i**
				
10	B	52	**15j**	**16j**
	D	67		

[a] Condition A = 1 M Na_2CO_3, NCS, THF; Condition B = 2 M NaOH, NCS, Condition C = 10 equiv, NaOCl, THF, rt; Condition D = 1 equiv, NaOCl, NaOH, THF, rt.

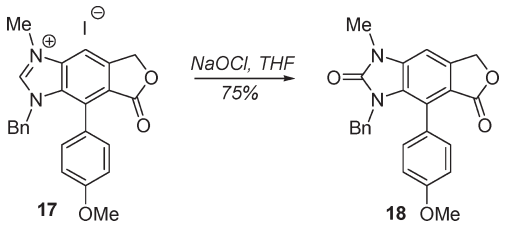
formed in the course of the oxidation, they demonstrate that it is a competent intermediate in this chemistry. In the latter case, hydroxide adds to the imidazolium salt **15** to form **19**.[22] *O*-Chlorination and then base-induced elimination of HCl from **20** results in the formation of the carbonyl

(20) Wamhoff, H.; Kleimann, W.; Kunz, G.; Theis, C. H. *Angew. Chem.* **1981**, *93*, 601–602.

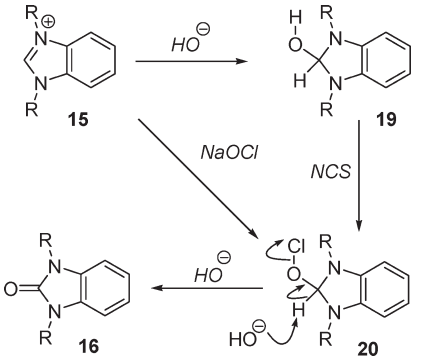
(21) Kitamura, M.; Yano, M.; Tashiro, N.; Miyagawa, S.; Sando, M.; Okauchi, T. *Eur. J. Org. Chem.* **2011**, 458–462.

(22) Medvedeva, M. M.; Pozharskii, A. F. *Khim. Get. Soed.* **1982**, 1086–1088.

Scheme 3. C2-Oxidation of an Advanced Kealiiquinone Intermediate



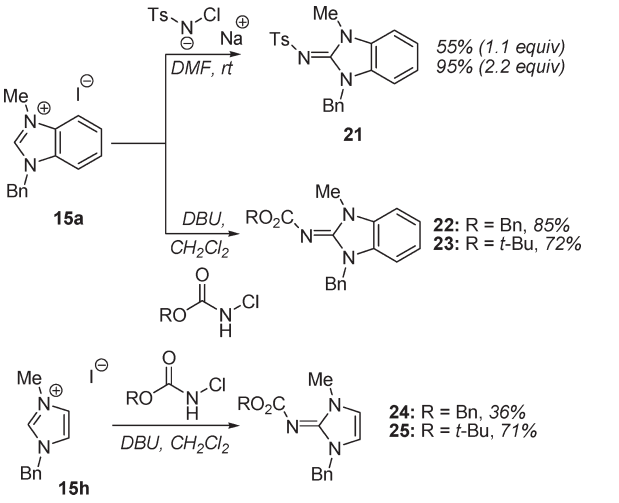
Scheme 4. Possible Mechanistic Pathways for Imidazolium Salt Oxidation



moiety. Alternatively, with hypochlorite ion (either produced in situ or added directly), this may give species **20** directly, which upon base-induced elimination provides the corresponding imidazolone.

While the mechanistic details of this reaction remain unclear pending further investigation, we reasoned that other reagents that contain a nucleophilic site and an appropriately positioned leaving group may also participate in this chemistry. Specifically, it was hypothesized that *N*-chloro amides would permit the direct introduction of an amino moiety. We were delighted to observe that upon treatment of imidazolium salt **15a** with chloramine-T the imino imidazole **21** was formed in 55% yield (Scheme 5). Increasing the equivalents of chloramine-T to 2.2 improved the yield of **21** to 95%. While this result was encouraging,

Scheme 5. Introduction of a 2-Imino Moiety



the tosyl group is not always easy to remove and thus we briefly examined other *N*-chloroamides (prepared in situ from the corresponding carbamates by treatment with *t*-BuOCl).[23] Both the benzimidazole **15a** and simple imidazole derivative **15h** undergo amination with both the benzyl and *t*-butyl chlorocarbamate providing the corresponding imino derivative in good yields (Scheme 5).[24,25]

In summary, we have discovered a convenient procedure for the direct conversion of imidazolium salts to imidazolones by treatment with NCS/aqueous base or hypochlorite. A range of substrates participate in this chemistry, including benzimidazole, simple imidazole derivatives and more elaborate benzimidazole derivatives. Similarly, the use of *N*-chloro amides allows the incorporation of a 2-amino substituent. This process occurs at room temperature or below and avoids the use of strong bases and transition metal catalysts. Current investigations are directed toward determining the mechanistic details, extending the scope of this chemistry and applying it in the total synthesis of various alkaloids.

Acknowledgment. This work was supported by the Robert A. Welch Foundation (Y-1362) and the NIH (GM065503). The NSF (CHE-0234811, CHE-0840509) is thanked for partial funding of the purchases of the NMR spectrometers used in this work.

Supporting Information Available. Detailed experimental procedures, characterization data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(23) Tsuruoka, R.; Nagamachi, T.; Murakami, Y.; Komatsu, M.; Minakata, S. *J. Org. Chem.* **2009**, *74*, 1691–1697.

(24) Ohta has demonstrated that 2-thio imidazolium salts undergo substitution with carbamate anions to provide the corresponding 2-iminoimidazole, see: Kawasaki, I.; H., N.; Yanagitani, S.; Kakuno, A.; Yamashita, M.; Ohta, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3095–3099.

(25) For a recent review of direct methods for the C2-amination of azoles, see: Zhang, M. *Synthesis* **2011**, 10.1055/s-0030-1260231.