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Regioselective Radical Reactions on Anhydrides

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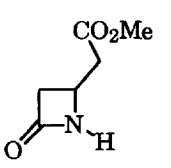
Abstract: *The selective chlorination of anhydrides can be effected by the reaction of sulfuryl chloride and dibenzoyl peroxide. The direct transformation of* **2** *and* **6** *into precursors to β-lactam antibiotics and the kainic acids is described.*

As part of our study of the synthetic potential of hydrogen atom abstraction reactions,[1] we examined radical halogenations involving the reaction of electrophilic radicals with polar substrates. Synthetic objectives of this study are the β-lactam and kainic acid ring systems.



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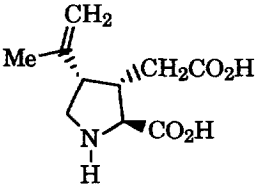

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Selective halogenation followed by substitution by an nitrogen nucleophile was expected to provide the key intermediates. The rationale for the anticipated selectivity in hydrogen atom abstraction came from the works of Tanner,[2] Minisci[3] and Deno[4]. We report herein a useful protocol for the selective chlorination of anhydrides.

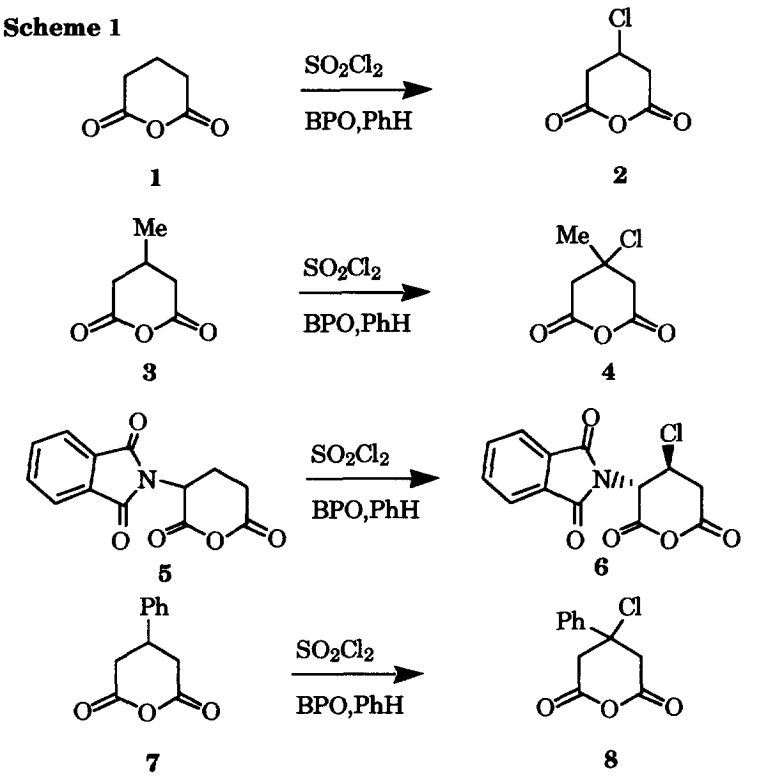
Initially, the radical halogenation using haloamines was examined. Both Minisci and Deno have reported remarkable regioselectivity in the halogenation of carboxylic acids, ammonium salts and alcohols using halodialkylamines.[5] The reaction of anhydride **1** with chlorodiisporopylamine using various reaction conditions did not produce any chlorinated products. Halogenation using N-bromo succinimide was not selective, generating a number of products in roughly equal amounts. Russell and Brown have reported a useful chlorination method which provides good tertiary/primary selectivity towards branched-chain hydrocarbons.[6] The reaction involves radicals generated from the photolysis of sulfuryl chloride in benzene.

Experimentally, this reaction proceeded well using dibenzoyl peroxide (BPO) as an initiator. A representative procedure is as follows: the substrate (10 mmol) and sulfuryl chloride (15 mmol, freshly distilled) and dibenzoyl peroxide (1 mmole) were dissolved in 80 mL of dry benzene. The solution was heated to reflux for 20 hr under argon. After removal of the solvent in vacuo, the crude reaction mixture was analyzed by NMR. The anhydrides were purified by recrystallization.

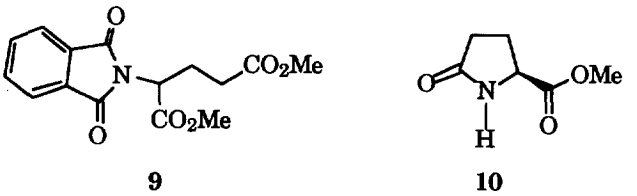
Applying the modified Russell process, we were able to convert anhydrides **1** and **3** into the chlorides **2** and **4**. Products **2** and **4** can readily be separated from the reaction mixture by recrystallization in 65% yield (82% based on recovered starting material) and 72% yield, respectively. Anhydride **6** was obtained from **5** in over 90% yield as evidenced by its proton NMR spectrum. Anhydride **6** was a single stereoisomer as evidenced by proton NMR. The large 11.2 Hz axial-axial coupling constant between the two methine protons indicated that

both the chlorine and phthalimido substituents were in equatorial positions.[7] The chlorination of anhydride **7** produced **8** as the major product along with the product of dehydrohalogenation and starting material in a 6:1:2 ratio in 86% yield. This was the only case in which dehydrohalogenation was observed as a byproduct.

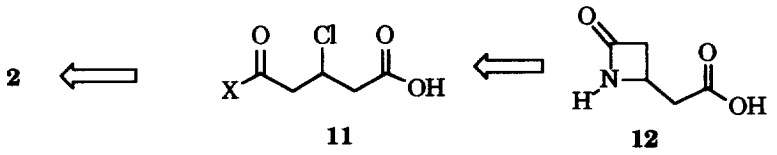
Scheme 1



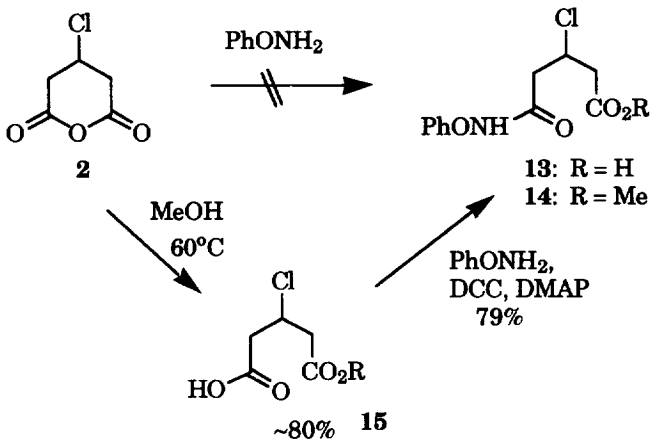
Interestingly, the reaction of **9** or **10** with our standard radical chlorination conditions returned starting material. The case of diester **9** underscores the significance of the anhydride results.



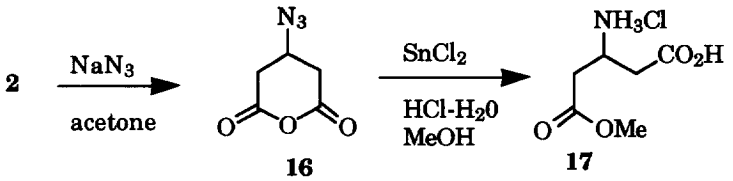
With anhydrides **2** and **6** in hand, we focussed our attention to the application of this reaction to natural products synthesis. Since several β-lactam antibiotics have the general subunit **I**, we evaluated a route based on **2**. Miller and coworkers have reported the clever construction of β-lactams from β-halo hydroxamates.[8,9] We reasoned that the reaction of anhydride **2** with a hydroxylamine followed by cyclization would give β-lactam **12**. The reaction of **2** with O-phenyl hydroxylamine in a number of solvents at temperatures ranging from



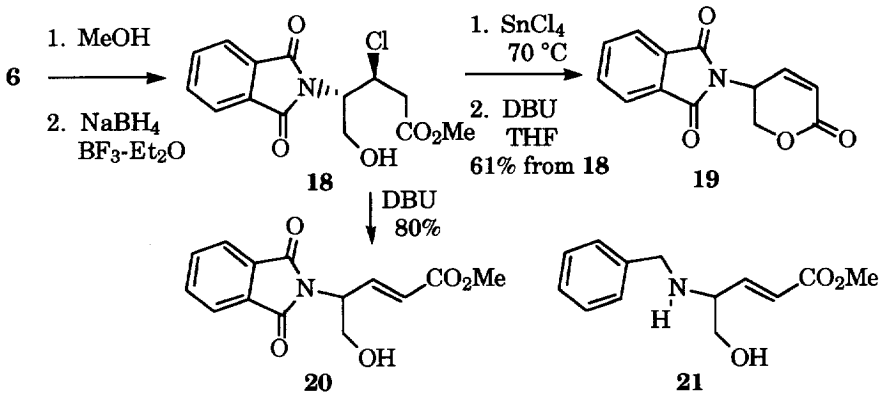
-78 °C to 40 °C failed to produced compound **13**. Fortunately, the solvolysis of **2** in methanol produced monoester **15** which could be converted to **14** by coupling with O-phenyl hydroxylamine and DCC and DMAP.[10] When we subjected hydroxamate **14** to Miller's conditions (NaH, DMF), the major reaction product was the elimination product. This problem had been also encountered by Miller and might have been circumvented if the acid **13** had been available.



An alternative route to β-lactam precursors involves the cyclization of β-amino acids reported by Ohno.[11] To test the feasibility of this process, anhydride **2** was converted into the azido anhydride **16**. The azido anhydride **16** is quite insoluble in organic solvents. Azide **16** could be transformed into **17** by the method of Micetich.[12] Acid **17** provided NMR (^1H, ^{13}C) and an IR spectrum consistent with its assigned structure.



Anhydride **6** provides a direct entry to chloroester **18** and lactone **19** by the sequence shown below. Anhydride **6** was converted into ester **18** in 63% overall yield. In the transformation of **18** into lactone **19** the use of PTSA afforded complex mixtures due to competitive dehydrohalogenation. With 2.5 equivalents of $SnCl_4$ in 1,2-dichloroethane at 70 °C for 2.5 hours, a chloro lactone was produced in 74% yield without significant dehydrohalogenation. Subsequent dehydrohalogenation of the chloro lactone with DBU in THF provided lactone **19** in 82% yield. Short reaction times are critical for optimal yields, since lactone **19** reacts



slowly with base to afford isomeric byproducts. The BOC-amide corresponding to **19** has been used by Ohfune to prepare a conformationally-restricted analog of glutamic acid.[13] Chloroester **18** was readily dehydrohalogenated to produce unsaturated ester **20** in 80% yield. The amine **21** has been employed by Barco in a synthesis of kainic acid.[14]

In summary, our radical-based halogenation using sulfuryl chloride works well on several substrates. Amino acid **17**, lactone **19** and ester **20** represent promising intermediates for the synthesis of heterocyclic natural products.

References

1. Kraus, G. A.; Y. Wu *J. Am. Chem. Soc.*, **1992**, *114*, 8705.
2. Tanner, D. D.; Arhart, R.; Meintzer, C. P. *Tetrahedron* **1985**, *41*, 4261 and references therein.
3. Minisci, F. *Synthesis*, **1973**, 1.
4. Deno, N. C.; Billups, W. E.; Fishbein, R.; Pierson, C.; Whalen, R.; Wyckoff, J. C. *J. Am. Chem. Soc.*, **1971**, *93*, 438.
5. Minisci, F.; Galli, R.; Galli, A.; Bernardi, R. *Tetrahedron Lett.*, **1967**, 2207.
6. Russell, G. A.; Brown, H. C. J. *Am. Chem. Soc.* **1955**, *77*, 4031.
7. Chlorination of glutamic acid in sulfuric acid produced a mixture: Kollonitsch, J.; Rosegay, A.; Doldouras, G. *J. Am. Chem. Soc.*, **1964**, *86*, 1857.
8. Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49.
9. (a) Mattingly, P. G.; Kerwin, Jr., J. F.; Miller, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 3983. (b) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, Jr., J. F. *J. Am. Chem. Soc.* **1980**, *102*, 7026. (c) Morrison, M. A.; Miller, M. J. *J. Org. Chem.* **1983**, *48*, 4421.
10. The transformation of symmetric anhydrides to optically active monoesters have been reported: Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731. Rosen, T.; Watanabe, M.; Heathcock, C. H. *J. Org. Chem.* **1984**, *49*, 3657. Yamamoto, Y.; Yamamoto, K.; Nishioka, T.; Oda, J. *Agric. Biol. Chem.* **1988**, *52*, 3087.
11. Iimori, T.; Takahashi, Y.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 1659.
12. Maiti, S. N.; Singh, M. P.; Micetich, R. G. *Tetrahedron Lett.* **1986**, 1423.
13. Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfune, Y. *J. Org. Chem.*, **1991**, *56*, 4167.
14. Barco, A.; Benetti, S.; Spalluto, G.; Casolari, A.; Pollini, G. P.; Zanirato, V *J. Org. Chem*, **1992**, *57*, 6279.

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