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Oxidative Cyclization of Sulfamate Esters Using NaOCl – A Metal-Mediated Hoffman-Löffler Freytag Reaction

David N. Zalatan and J. Du Bois*

Department of Chemistry, Stanford University, Stanford, CA 94305-5080

Abstract

Intramolecular C–H amination with sulfamate esters occurs under the action of dinuclear Rh catalysts and iodine(III) oxidants, and has recently emerged as a powerful tool for synthesis. Insights gained through mechanistic studies of this process suggest that other terminal oxidants, including common halogenating agents such as NaOCl, could function to promote the cyclization reaction. Results described in this report demonstrate that the combination of NaOCl and 3 mol% Rh₂(oct)₄ is effective in select cases for converting sulfamate substrates to the corresponding [1,2,3]-oxathiazinane-2,2-dioxide heterocycles. The mechanism for C–H functionalization, however, is distinct from that induced by hypervalent iodine reagents and likely involves the intermediacy of an *N*-centered radical.

Keywords

C–H amination; catalysis; rhodium; bleach; oxathiazinane

Catalytic methods for C–H and π -bond amination have emerged recently as selective and practical tools for fine chemicals synthesis.¹ Starting from any one of a number of amine derivatives (e.g., carbamates, ureas, guanidines, sulfamates, sulfonamides, sulfamides), intramolecular C–H insertion is effected under the action of a dinuclear Rh(II) catalyst and a diacyloxyiodobenzene oxidant (Figure 1). Experimental and theoretical studies suggest that this process occurs through an iodoimine (RN=I⁺Ph), which is intercepted by the Rh complex to generate a transient metallo-nitrene intermediate.^{2,3} The reactive nitrenoid is capable of oxidizing C–H bonds and does so through a concerted asynchronous insertion step. Consideration of this mechanism as well as reports describing the application of chlora- and bromamine-T (TsN(Na)X) as “nitrene” equivalents have led us to examine alternative oxidants in place of PhI(O₂CR)₂.^{4,5,6,7} These studies ask whether a surrogate species of the iodoimine can be generated *in situ* under conditions compatible with the dirhodium complex. The discovery of substitute oxidants for the C–H amination process has important practical consequences as well as the potential to bring with it the identification of new catalyst systems.

The reported reactivity of haloamine-T salts with metal catalysts for C–H and π -bond functionalization led us to examine initially reactions of **1** with common halogenating agents (Figure 2).⁶ The admixture of NaOCl and NaBr (i.e., NaOBr) under biphasic alkaline conditions (CH₂Cl₂, aqueous Na₂HPO₄) affords *N*-bromosulfamate **2**.⁸ Although this material is not formed cleanly and attempts to isolate **2** were not made, the combination of these reagents and 3 mol% Rh₂(oct)₄ results in an efficient cyclization event to furnish the corresponding [1,2,3]-oxathiazinane-2,2-dioxide **7** (eq 1).^{9,10} While other brominating agents such as *N*-bromosuccinimide and Br₂ can be used in place of NaOCl/NaBr, none give results that are comparable to our optimized protocol.^{11,12}

(1)

Following these exploratory investigations, analysis of the reaction scope began to expose striking differences between this process and that employing $\text{PhI}(\text{OAc})_2$ as the terminal oxidant (Table 1).¹³ Both electron-rich and electron-deficient 3-arylpropylsulfamate derivatives are consumed completely under the NaOCl/NaBr conditions to give the respective heterocycles (entry 1). The decreased yield of the *p*-methoxyphenyl substrate is likely the result of over-oxidation of the oxathiazinane and does not stem from an inherent inefficiency in the cyclization reaction. Oxidation of 3-heteroaryl-substituted sulfamates affords surprisingly disparate results, with the pyrazole adduct proving to be one of the top performing substrates (entry 2). By contrast, the indole-based sulfamate gives only trace product, returning mostly starting material instead (entry 3). The same substrate, when treated with a Rh-tetracarboxylate catalyst and $\text{PhI}(\text{OAc})_2$ affords >75% yield of the oxathiazinane product.^{13a} Other disparities between the NaOCl/NaBr protocol and that employing $\text{PhI}(\text{OAc})_2$ are noted in reactions of isoamylsulfamate and 2-phenethylcarbamate (entries 4 and 5). Neither of these substrates form product under the former set of conditions; both cyclize efficiently, however, when treated with a Rh-tetracarboxylate catalyst and $\text{PhI}(\text{OAc})_2$.^{13a,14}

The inability to oxidize the 3° C–H bond in isoamylsulfamate provided the first indication that the NaOCl/NaBr reaction was, in all likelihood, not proceeding through an intermediate Rh-nitrene. Our previous work to develop amination chemistry has established that substrates possessing 3° centers are among the very best for intramolecular Rh-catalyzed insertion.^{2b,c} In light of the result from entry 4 (Table 1), we speculated that a stepwise mechanism involving the formation of a *N*-centered radical might be operative under the NaOCl/NaBr conditions. While such supposition does not account for all of the observed performance trends (i.e., the inability to effect cyclization of the indole substrate), it is consistent with a reaction process that favors benzylic over 3° C–H oxidation. Accordingly, we wondered if metal salts or complexes other than $\text{Rh}_2(\text{oct})_4$ could catalyze oxathiazinane formation.

Attempts to oxidize sulfamate **1** using different metal catalysts delivered surprising results (Figure 3). While none of the complexes tested performed more effectively than $\text{Rh}_2(\text{oct})_4$, all gave discernible amounts of product. Subsequent studies further demonstrated that ambient light could promote modest conversion of **1** to oxathiazinane **7**. The photochemically-driven process could be further improved by the addition of 0.5 equiv. of ZnCl_2 (100% conversion). These data provide circumstantial evidence for a reaction mechanism that parallels the classic Hoffman-Löffler-Freytag (HFL) and proceeds through a reactive amidyl species.¹⁵

Two additional experiments were performed to give weight to our mechanistic hypothesis. Oxidation of the optically enriched, 3° benzylic substrate **8** would be expected to give product of reduced enantiopurity for a process involving the intermediate formation of a carbon-centered radical (Figure 4). When subjected to the reaction conditions, sulfamate **8** afforded a modest yield of racemic oxathiazinane **9** in addition to 3° alcohol **10**. The alcohol product does not cyclize under the reaction conditions; its formation is likely the result of hydrolysis of the corresponding 3° bromide. The same starting material **8** has been oxidized with catalytic $\text{Rh}_2(\text{oct})_4$ and $\text{PhI}(\text{OAc})_2$, conditions that result in the stereospecific formation of the heterocycle. As a final control experiment, *N,N*-dimethylsulfamate **11** was treated with

$\text{Rh}_2(\text{oct})_4$ and NaOCl/NaBr . This substrate, without the ability to form an *N*-halogenated species, is entirely unreactive towards the oxidizing mixture.

Collectively, these data have led us to postulate a stepwise mechanism for sulfamate oxidation with NaOCl/NaBr (Figure 6). The process is reminiscent of the HFL reaction, requiring *N*-halogenation as a first step.¹⁵ Metal- or light-promoted decomposition of this intermediate results in the generation an *N*-centered radical **14**, which is capable of abstracting a benzylic C–H bond. Benzylic halogenation and subsequent intramolecular $\text{S}_{\text{N}}2$ displacement afford the oxathiazinane product. Although we have never isolated a benzylic bromide species, the formation of such an intermediate is inferred from isolation of **10**.¹⁶

We have developed an operationally simple procedure for C–H amination using NaOCl as the terminal oxidant. This process is mechanistically distinct from analogous reactions that employ hypervalent iodine reagents, and likely occurs through amidyl-directed C–H halogenation.¹⁷ Although limited in scope when compared to other C–H amination methods, the application of this chemistry in select, large-scale processes may have considerable value. These findings also raise questions as to the operative mechanism in catalytic systems that utilize haloamine-T reagents and have been suggested to take place through nitrenoid pathways.

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8. Tentative structural assignment of **2** is based on ^1H NMR analysis of the reaction mixture.
9. The rather modest isolated yield of this material is likely due to product over-oxidation. Analysis of the ^1H NMR spectrum of the unpurified reaction mixture is quite clean, however. We assume that product(s) of over-oxidation are removed in the aqueous work-up.
10. We have found that $\text{Rh}_2(\alpha,\alpha,\alpha',\alpha'\text{-tetramethyl-1,3-benzenedipropionate})_2$ (also known as $\text{Rh}_2(\text{esp})_2$, see: Espino CG, Fiori KW, Kim M, Du Bois J. *J Am Chem Soc* 2004;126:15378. [PubMed: 15563154] gives comparable results to that of $\text{Rh}_2(\text{oct})_4$.
11. The overall efficiency of the reaction is reduced when NaBr is excluded.
12. **Optimized reaction protocol:** To a biphasic solution of 2.5 mL of CH_2Cl_2 and 2.5 mL of saturated Na_2HPO_4 (pH ~9) was added sequentially sulfamate (0.25 mmol), $\text{Rh}_2(\text{oct})_4$ (6 mg, 7.5 μmol , 0.03 equiv), and NaBr (77 mg, 0.75 mmol, 3.0 equiv). The reaction flask was wrapped in aluminum foil prior to the dropwise addition of 1.6 M aqueous NaOCl (Acros, 470 μL , 0.75 mmol, 3.0 equiv). The biphasic mixture was stirred for 2 h, following which time the reaction was quenched by the addition of 1.0 mL of 1.0 M aqueous NaHSO_4 . The contents were transferred to a separatory funnel with 10 mL of CH_2Cl_2 and 5 mL of H_2O . The organic layer was collected and the aqueous layer was extracted with 1×10 mL of CH_2Cl_2 . The combined organic fractions were dried over Na_2SO_4 and concentrated under reduced pressure to a yellow oil. Purification of this material by chromatography on silica gel (hexanes/EtOAc) afforded the desired oxathiazinane product.
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16. Consistent with the proposed mechanism, when *N*-methyl-3-phenylpropylsulfamate is subjected to the reaction conditions, an oxidized product is formed. This material has been tentatively assigned as *N*-methyl-3-bromo-3-phenylsulfamate
17. In general, reactions of iodoimine derivatives with certain metal catalysts (e.g., complexes of Mn, Fe, Ru, Cu) afford amine derivatives through an apparent C–H abstraction/radical rebound-type mechanism. For examples, see reference 1 and (a) Mahy J-P, Bedy G, Battioni P, Mansuy D. *Tetrahedron Lett* 1988;29:1927. (b) Mahy J-P, Bedy G, Battioni P, Mansuy D. *New J Chem* 1989;13:651.

Figure 1.
Finding new oxidants for sulfamate ester cyclization.

Figure 2.

A proposed catalytic cycle that mirrors the reaction with hypervalent iodine oxidants.

catalyst	% conversion	catalyst	% conversion
none	trace	RhCl ₃	20
FeCl ₂	30	MnCl ₂	20
CuCl ₂	30	Mn(salen)Cl	65
ZnCl ₂	trace	ambient hν	50

Figure 3.
Oxidation reaction promoted by different metal catalysts.

Figure 4.
Optical purity of the starting material is not preserved.

Figure 5.

No observed reaction of *N,N*-dimethylsulfamate ester.

Figure 6.

Proposed catalytic cycle for NaOCl-based oxidation proceeds through amidyl intermediate **14**.

Table 1

Sulfamate ester oxidation with NaOCl.

Entry	Substrate
1

Entry

Substrate

2

3

Entry	Substrate
4

Entry

Substrate

5

^aReaction performed with 3 mol% Rh₂(oct)₄, NaOCl, NaBr in CH₂Cl₂/aqueous Na₂HPO₄; yields are based on isolated material.

^bProduct over-oxidation is responsible for reduced yield.

^cYield is estimated based on analysis of the unpurified ¹H NMR spectrum.