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D. Boles Bryan, Ralph F. Hall, Kenneth G. Holden  
 William F. Huffman, John G. Gleason\*

Research & Development Division  
 Smith Kline & French Laboratories  
 Philadelphia, Pennsylvania 19101

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### Decarboxylative 1-Aza-1'-oxa [3,3]Sigmatropic Rearrangements of Enolizable or Enolized *N*-Aryl-*N,O*-diacylhydroxylamines to *o*-(*N*-Acylamino)aryl Ketones, Esters, and Amides: a New Synthetic Method for Ortho Alkylation

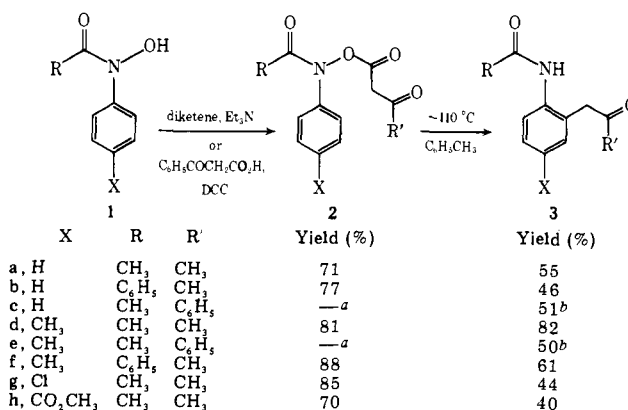
Sir:

The introduction of allyl substituents into the ortho position of phenols by the Claisen rearrangement of allyl aryl ethers is a long-known and effective synthetic process.<sup>1</sup> Although the scope of the more recently discovered amino-Claisen rearrangement for the synthesis of ortho allyl anilines is at present less well defined,<sup>2</sup> the high temperatures or acid catalysts usually employed for this reaction would appear to impose certain limitations on its utility, and indeed a number of side reactions have already been encountered.<sup>3</sup> The ortho alkylation of anilines may also be accomplished through [2,3]sigmatropic rearrangements of *N*-aryl azasulfonium ylides albeit with a subsequent reduction to remove the sulfur function from the side chain.<sup>4</sup> We wish to report a new regiospecific synthesis of anilides having carbonyl-functionalized alkyl groups in the ortho position by means of 1-aza-1'-oxa [3,3]sigmatropic rearrangements<sup>5</sup> of enolizable or enolized *N*-aryl-*N,O*-diacylhydroxylamines.

Although a number of reactions which appear to involve rearrangements of this type has been reported in the literature,<sup>6,7</sup> apart from the acid-catalyzed isomerization of *O*-aryl ketoximes to *o*-hydroxyphenylketimines or benzofurans,<sup>6c</sup> the synthetic applications of this 1'-aza analogue of the Claisen rearrangement have been restricted. One factor which has no doubt impeded the exploitation of this inherently exothermic transformation<sup>8</sup> is the instability of the requisite *N,O*-divinyl- and *N*-aryl-*O*-vinylhydroxylamines. Accordingly we choose to model our initial approach after the Carroll reaction,<sup>9</sup> a variant of the Claisen rearrangement in which the vinyl ether grouping is generated simply by enolization of an allyl acetate.

*N*-Aryl-*N*-hydroxylamines (**1**), readily available by partial

Scheme I



<sup>a</sup> Yield not determined at this stage. <sup>b</sup> Overall yield from **1**.

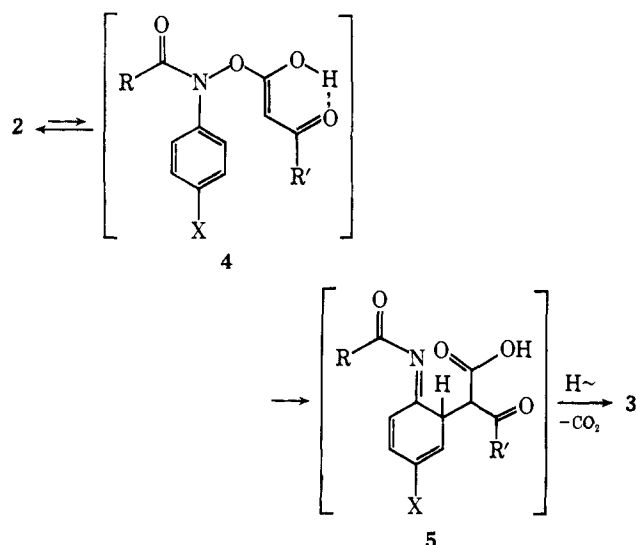
reduction of nitroarenes to *N*-arylhydroxylamines<sup>10,11</sup> and selective *N*-acylation,<sup>11,12</sup> are transformed into *O*-acetoacetyl derivatives (**2**) by reaction with diketene in the presence of a catalytic amount of triethylamine (1.1 equiv of diketene, 1:1 chloroform-ether, 0 °C, overnight). The two phenyl substituted intermediates (**2c** and **2e**) were obtained in a complementary manner by the dicyclohexylcarbodiimide (DCC)-induced condensation of benzoylacetate with the appropriate *N*-hydroxy amides. Since these compounds proved, with two exceptions, to be liquids and rather unstable, they were for the most part purified only by extraction (5–10% sodium bicarbonate) to remove any unreacted *N*-hydroxyamide and characterized chiefly by infrared and NMR spectral data.<sup>13</sup>

When heated in toluene at reflux temperature (~110 °C for 30–90 min), the  $\beta$ -keto esters undergo decarboxylation and give rise to *o*-(*N*-acylamino)aryl ketones (**3**) as major products in 40–82% yield after purification by chromatography on silica gel.<sup>13b,14</sup> Two of the products were identified as the known 2'-acetylacetanilide (**3**, X = H; R = R' = CH<sub>3</sub>; mp 134–136 °C)<sup>15a</sup> and 2'-acetylbenzanilide (**3**, X = H; R = C<sub>6</sub>H<sub>5</sub>; R' = CH<sub>3</sub>; mp 115–117 °C)<sup>15b</sup> by the correspondence of melting points and spectral data. The structural assignments for the others are based upon the similarity of the spectra and analogy.

According to the analogy with the Carroll reaction,<sup>9</sup> one plausible mechanism for this reaction consists of a [3,3]sigmatropic rearrangement of the ketene hemiacetal tautomer **4**, prototropic rearomatization, and decarboxylation of the resulting  $\beta$ -keto acid intermediate. Although the apparent absence of appreciable amounts of the para isomer of **3**<sup>16</sup> would seem inconsistent with a dissociative mechanism involving free radicals or ions, the possibility of radical or ion pair pathways cannot be discounted. It is pertinent to note that these reactions occur at much lower temperature (~110 °C as opposed to  $\geq$  150 °C) than is required to isomerize *N*-aryl-*N,O*-diacylhydroxylamines to *o*-acyloxyanilides<sup>17</sup> and that there are indications that the ortho alkylation step precedes decarboxylation (see below).

Hydrolysis of four of the *o*-(*N*-acylamino)aryl ketones (**3a**, **3c**, **3d**, and **3g**) with 10% hydrochloric acid in 95% ethanol for 15 min at reflux afforded the corresponding substituted indoles in 79–91% yield, a reaction which provides both additional support for the structures proposed and a practical application for the 1'-aza Claisen rearrangement. In this connection it is noteworthy that the uncyclized ketones (**3**) produced in this ortho alkylation reaction (**2**  $\rightarrow$  **3**) may be isolated and, in principle, utilized for other purposes, in contrast to the spontaneous cyclization which occurs in the Fischer<sup>18</sup> and Gassman<sup>4b,d</sup> indole syntheses. The only alternative synthesis of *o*-(*N*-acylamino)aryl ketones (**3**) of which we are aware

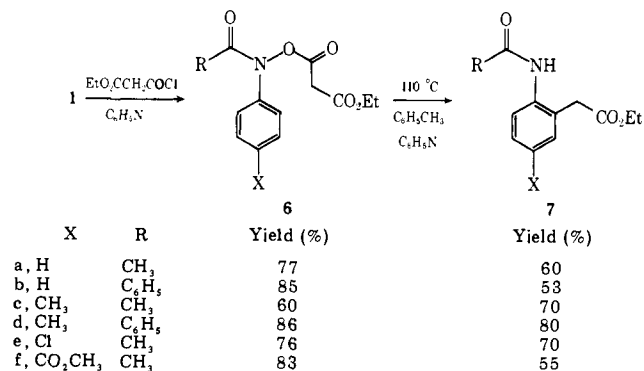
Scheme II



involves a photochemical rearrangement and hydrolysis of quinoline *N*-oxides.<sup>15,19</sup>

The following two variations upon this 1'-aza Claisen rearrangement serve to illustrate further the synthetic utility of the reaction. Mixed malonates (**6**)<sup>13b</sup> are readily prepared in 60–86% yield by acylation of the *N*-aryl-*N*-hydroxyamides with ethylmalonyl chloride<sup>20</sup> (1 equiv of pyridine, methylene chloride, 25 °C, 30 min). Thermolysis of these esters in toluene containing approximately 1 equiv of pyridine at reflux (1–7 h) gave rise to 55–80% yields of the *o*-(*N*-acylamino)aryl acetates **7**,<sup>13b</sup> two of which have been previously reported in the literature.<sup>21–23</sup> In this case, it proved possible to detect the formation of an intermediate by TLC analysis during the reaction which could be isolated in 11% yield and identified as the monoethylmalonic acid corresponding to **7d**. This finding indicates that decarboxylation occurs subsequent to the ortho alkylation step.

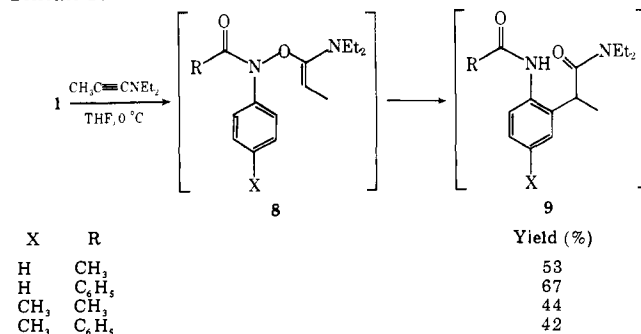
Scheme III



A modification of the Claisen rearrangement involves the addition of allylic alcohols to ynamines and subsequent [3,3]sigmatropic rearrangement of the resulting allyloxy enamines to  $\gamma,\delta$ -unsaturated amides.<sup>24</sup> We find that *N*-aryl-*N*-hydroxyamides react spontaneously with the ynamine, *N,N*-diethyl-1-amino-1-propyne, at 0 °C to form *o*-(*N*-acylamino)aryl propionamides **9** in yields ranging from 42 to 67%,<sup>13b</sup> presumably by way of adduct **8**. A minor side product consistently encountered in these reactions is the simple anilide (18–34%) arising from deoxygenation of the starting *N*-hydroxyamide.

Although the product yields in these 1'-aza-Claisen rearrangements are moderate (40–70% in most cases), the mild

Scheme IV



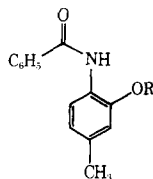
conditions and the ready availability of a variety of substrates suggest that the reaction will provide a useful method for the introduction of functionalized alkyl groups onto aromatic rings.

**Acknowledgment.** We wish to thank the National Science Foundation for financial assistance.

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- i (R = COCH<sub>2</sub>CO<sub>2</sub>Et, 50%)  
 ii (R = H, 35%)

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Robert M. Coates,\* Ikram Md. Said<sup>25</sup>

Department of Chemistry, University of Illinois  
 Urbana, Illinois 61801

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### The Copper-Cadmium *N*-Methyltetraphenylporphyrin Electrophilic Substitution Reaction: Evidence for a Cis Attack

Sir:

The kinetics of the substitution of one metal ion in solution for another coordinated to a porphyrin molecule usually follow a rate law first order in replacing ion and first order in metalloporphyrin, with no evidence for rate retardation by the departing ion.<sup>1</sup> One common interpretation is that the activated complex has the form [M-P-M\*], with the entering and leaving metal ions on opposite sides of the porphyrin plane. Such activated complex geometries in solutions are also suggested by solid state crystal structures of several dimetallic mononuclear porphyrins.<sup>2</sup> We report a kinetic study of copper replacing cadmium from the Cd(II) *N*-methyltetraphenylporphyrin (Cd-N-MeTPP<sup>+</sup>) complex. The *N*-methyl group prohibits the copper from occupying a position on the distal side of the porphyrin plane from the cadmium ion.<sup>3</sup>

The kinetics were run at 25 °C in DMF at an ionic strength of 0.36 using (Et)<sub>4</sub>NBF<sub>4</sub>. Using the mole ratio method, cadmium forms only a 1:1 complex with the *N*-methylporphyrin,<sup>4</sup> even at concentrations of cadmium/porphyrin of 30:1. The Cu(BF<sub>4</sub>)<sub>2</sub>/Cd-N-MeTPP<sup>+</sup> reaction, followed spectrophotometrically, went clearly to Cu-N-MeTPP<sup>+</sup>. Isosbestic points were found at 597, 575, and 435 nm, and no evidence for the demethylation<sup>5</sup> of Cu-N-MeTPP<sup>+</sup> into Cu-TPP was observed during the course of the reaction. Under pseudo-first-order conditions with at least a 20-fold excess of copper to porphyrin, the reaction was first order in porphyrin. As shown in Figure 1, the reaction was also first order in copper, and independent of added cadmium. The second-order rate constant was 25.7 ± 2.2 M<sup>-1</sup> min<sup>-1</sup>.

The lack of rate inhibition by added cadmium tends to rule out a mechanism whereby cadmium first dissociates before copper incorporation. Since the *N*-methyl group sterically blocks one face of the porphyrin toward metal ion coordination, the simplest interpretation is that cadmium and copper are on

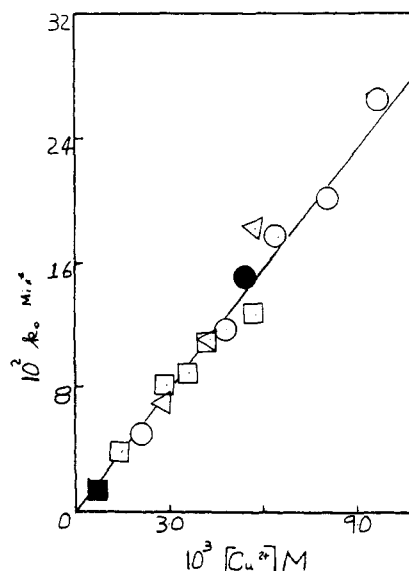
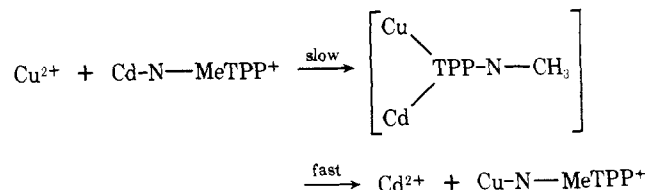


Figure 1. Plot of the observed rate constant  $k_{\text{obsd}}$  vs.  $[\text{Cu}^{2+}]_0$  for the  $\text{Cu}^{2+}/\text{Cd-N-MeTPP}^+$  reaction at 25 °C in DMF at an ionic strength of 0.36 [(Et)<sub>4</sub>NBF<sub>4</sub>]. The  $\text{Cd}(\text{BF}_4)_2$  concentrations are:  $\blacksquare$  =  $7.2 \times 10^{-4}$  M,  $\circ$  =  $14.8 \times 10^{-4}$  M,  $\square$  =  $35.1 \times 10^{-4}$  M,  $\bullet$  =  $50 \times 10^{-4}$  M,  $\triangle$  =  $1.76 \times 10^{-2}$  M.

the same side of the porphyrin plane during the substitution process.



The observations on *N*-methylporphyrins imply that either or both cis and trans geometries may occur during electrophilic substitution reactions of metalloporphyrins themselves.

Preliminary work indicates that, consistent with their basicities, the Cu/Cd-TPP reaction is orders of magnitude faster than that of Cu/Cd-N-MeTPP<sup>+</sup>. In addition, the former reaction is also faster than the Cu/H<sub>2</sub>-TPP process, where *N*-H bond breaking may be the rate limiting step.

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Charlie Stinson, Peter Hambright\*

Chemistry Department, Howard University  
 Washington, D.C. 20059

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