

LEWIS ACID-PROMOTED 1,3-DIPOLAR ADDITION REACTIONS OF DIAZOCARBONYL COMPOUNDS.

A GENERAL SYNTHESIS OF OXAZOLES

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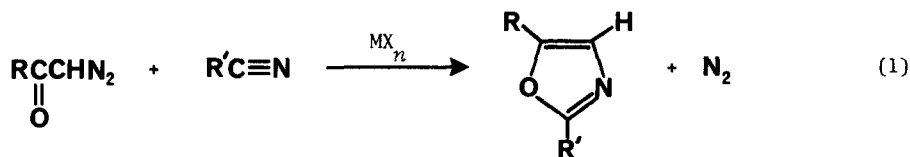
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Diazocarbonyl compounds represent potentially effective precursors for dipolar  $\alpha$ -keto-carbenoid synthons (I).<sup>2</sup> Although subject to the Wolff rearrangement under thermal, photolytic,



and catalytic conditions,<sup>3</sup> such reactive intermediates have been successfully intercepted by unsaturated compounds in the form of 1,3-addition products.<sup>4</sup> However, scavenging of  $\alpha$ -keto-carbenoid intermediates by 1,3-dipolar addition is often inefficient and in nitrile solvents low yields of oxazoles are generally obtained.<sup>4-7</sup> Although recent active efforts to improve the yields from 1,3-dipolar addition of I to nitriles through the use of transition metal catalysts have resulted in marked improvements over the uncatalyzed reactions,<sup>8,9</sup> diazocarbonyl compounds remain generally ineffective reactants for oxazole syntheses.<sup>10</sup>

Surprisingly, the reactions of diazo ketones with unsaturated compounds in the presence of common Lewis acids have not been investigated.<sup>11</sup> Lewis acids hold the potential for activation of diazocarbonyl compounds<sup>12</sup> and, as we now report, can be employed advantageously to effect dipolar addition reactions. We have found that diazocarbonyl compounds react rapidly and efficiently with nitriles in the presence of Lewis acids such as anhydrous aluminum chloride to form oxazoles in high yield (eq 1).



In a typical procedure  $\alpha$ -diazoacetophenone (5.0 mmol) in 5 ml of anhydrous acetonitrile was added by syringe over a 5-min period to 30 ml of an acetonitrile solution containing anhydrous aluminum chloride (10 mmol) at 25°C. The slow addition of the diazo ketone to the acid medium produced an immediate release of nitrogen. Gas evolution terminated within 15 min following the last addition of the diazo ketone and was quantitative (based on eq 1). The reaction solution was subsequently poured into 150 ml of ether. Acid extraction of the ether solution with 150 ml of 3 M aqueous hydrochloric acid was employed to selectively isolate the oxazole from nonbasic products; following addition of excess base to the acidic solution, extraction of the resulting basic solution with ether, and evaporation of the ether under reduced pressure, 2-methyl-5-phenyl oxazole was isolated in 96% yield. Table I presents the yields of oxazoles isolated from the aluminum chloride - promoted dipolar addition reactions of representative diazocarbonyl compounds in a variety of nitrile solvents. For reactions performed in high boiling solvents such as

Table I. Isolated Yields of Oxazoles from Reactions of Diazocarbonyl Compounds with Nitriles in the Presence of Aluminum Chloride<sup>a</sup>

$\text{RCOCHN}_2$	$\text{R}'\text{CN}$	Oxazole, % <sup>b</sup>
$p\text{-CH}_3\text{C}_6\text{H}_4\text{COCHN}_2$	$\text{CH}_3\text{CN}$	94
$\text{C}_6\text{H}_5\text{COCHN}_2$	$\text{CH}_3\text{CN}$	96
$\text{C}_6\text{H}_5\text{COCHN}_2$	$\text{H}_2\text{C}=\text{CHCN}$	63
$\text{C}_6\text{H}_5\text{COCHN}_2$	$\text{NCCH}_2\text{CH}_2\text{CN}$	51 <sup>c</sup>
$\text{C}_6\text{H}_5\text{COCHN}_2$	$(\text{CH}_3)_3\text{CCN}$	71
$\text{C}_6\text{H}_5\text{COCHN}_2$	$\text{C}_6\text{H}_5\text{CN}$	73
$\text{C}_6\text{H}_5\text{COCHN}_2$	$\text{C}_6\text{H}_5\text{CH}_2\text{CN}$	80
$\text{CH}_3(\text{CH}_2)_5\text{COCHN}_2$	$\text{CH}_3\text{CN}$	74
$\text{N}_2\text{CHCO}(\text{CH}_2)_8\text{COCHN}_2$	$\text{CH}_3\text{CN}$	89 <sup>d</sup>

<sup>a</sup>Reactions were performed at 25°C in the nitrile solvent, unless indicated otherwise.

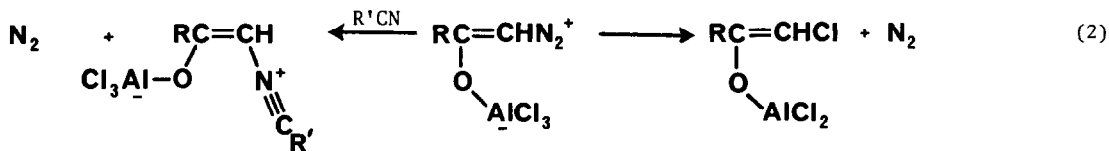
<sup>b</sup>Weight yield of isolated oxazole and not optimized for maximum recovery. <sup>c</sup>Reaction performed with 15-molar equivalents of succinonitrile in methylene chloride. <sup>d</sup>Bis-oxazole.

benzyl nitrile, oxazoles were isolated through a procedure that included base extraction to consume the aluminum chloride and evaporation of the high boiling solvent under reduced pressure.

Optimal yields of oxazoles are obtained when the nitrile is employed as the reaction solvent. Decreased yields of oxazoles generally result from reactions performed with nitriles in solvents such as methylene chloride. For example, aluminum chloride-promoted reactions of  $\alpha$ -diazoacetophenone with 15-molar equivalents of acetonitrile and of succinonitrile in methylene chloride (15 ml) resulted in the formation of the corresponding oxazoles in only 75% and 51% yield, respectively. However, even with this limitation, the Lewis acid - promoted 1,3-dipolar addition process is a general and highly effective method for the synthesis of oxazoles.

The stoichiometric requirement of aluminum chloride for oxazole formation was established by systematic variation of the mole ratio of aluminum chloride to *p*-methyl- $\alpha$ -diazoacetophenone from 0.2 to 2.4 in acetonitrile at 25°C. At  $[AlCl_3]/[ArCOCHN_2] = 0.2$ , the corresponding oxazole was formed in only 5% yield whereas 48% of  $\alpha$ -chloro-*p*-methylacetophenone was obtained and 45% of the diazo ketone was recovered.<sup>13,14</sup> With  $[AlCl_3]/[ArCOCHN_2] = 0.6, 1.0,$  and  $2.4$  the corresponding isolated product yields (given in parentheses) were: oxazole (34%, 56%, and 94%) and  $\alpha$ -chloro ketone (57%, 37%, and 6%). Similar results were obtained in reactions of  $\alpha$ -diazoacetophenone with aluminum chloride in acetonitrile. Thus  $\alpha$ -chlorination of the diazocarbonyl compound effectively competes with oxazole formation when less than 2 molar equivalents of aluminum chloride are employed. At the optimum conditions for the production of oxazoles reported in Table I, less than 6% of the  $\alpha$ -chlorocarbonyl compound was obtained.

Aluminum chloride - promoted reactions of diazocarbonyl compounds in nitrile solvents are remarkably free of competing reactions. Neither products from the Wolff rearrangement<sup>3</sup> nor coupling products<sup>15</sup> are observed. In addition, the absence of pyrazoline and cyclopropane products in reactions with acrylonitrile<sup>9</sup> suggests that  $\alpha$ -ketocarbenoid species are not intermediates in these reactions. The results obtained in this investigation are indicative of a reaction scheme in which the Lewis acid activates the diazocarbonyl compound through association at the carbonyl oxygen.<sup>12</sup> Chloride or nitrile displacement of nitrogen from the intermediate vinyl diazonium ion (eq 2) leads to the observed products. Work is continuing in our laboratories to



determine the scope of Lewis acid-promoted 1,3-dipolar addition reactions and to evaluate the effectiveness of selected Lewis acids in these synthetically useful transformations.

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