

# Ammonium Niobium Oxalate (ANO)

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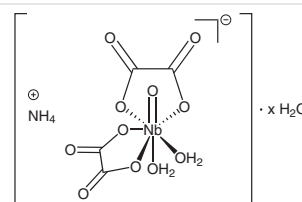
Niobium is a metal, the majority of reserves of which are found in Brazil.<sup>1</sup> Ammonium niobium oxalate (ANO, Figure 1) is a white powder, odorless, stable, nonexplosive, easy to handle, water-soluble, and with low toxicity. ANO has the molecular formula of  $\text{NH}_4[\text{NbO}(\text{C}_2\text{O}_4)_2(\text{H}_2\text{O})_2] \cdot x\text{H}_2\text{O}$ , where the niobium atom is coordinated by two groups of bidentate oxalates linked to two water molecules and an oxygen atom, forming a pentagonal bipyramid with a double bond,  $\text{Nb}=\text{O}$ . The ammonium group is surrounded by seven oxygen atoms, belonging to the oxalate group and the niobium group in an irregular arrangement. ANO is widely used as a starting material for the preparation of oxides, mixtures of oxides, or as a support for heterogeneous catalysts in chemical reactions. It is produced by the addition of niobic acid and ammonium oxalate to an aqueous solution of oxalic acid.<sup>2</sup>

In organic synthesis, ANO behaves as a Lewis acid, but its role as a catalyst is still under-represented in the literature, even though it is a readily available and inexpensive compound (ca. USD 750/kg).<sup>3</sup> These features together with its water-solubility render this compound a promising catalyst in Green Chemistry.<sup>4</sup>



**Lorena Fortes** and **Pamella M. Monte** are undergraduate students, and **Anna Paula P. M. da Silva** is a graduate student at Universidade Federal do Rio de Janeiro – UFRJ/Brazil. Their research interests involve the use of several Nb compounds as catalysts in the preparation of heterocycles. José C. Barros and Tiago L. da Silva supervised the students in their projects.

Herein, a highlight of several applications developed for ANO over recent years is presented, and where possible, a comparison with traditional catalysts will be shown. As a new niobium catalyst, it is currently being tested by groups within Brazil against established methodologies as a proof of concept of its usefulness. However, the very mild reaction conditions indicate ANO has the potential to enter the chemist's Lewis acid toolbox and reach a global audience.



**Figure 1** Niobium ammonium oxalate (ANO) structure

**Table 1** Applications of Ammonium Niobium Oxalate (ANO)

<p>(A) Bis(indolyl)methanes (BIMs) are important compounds due to their biological and pharmacological properties, such as antibacterial, anti-inflammatory, and antibiotic activity. ANO was applied as a catalyst to prepare BIMs following Green Chemistry principles. Initially, the reaction conditions were optimized using indole and benzaldehyde in water. The best result was obtained with 5 mol% of catalyst at 50 °C under conventional heating for 2 h (97% yield). This reaction was also performed under ultrasonic irradiation in glycerol using the same amount of catalyst at a final temperature of 110 °C for 3 min (99% conversion of indole). The recycling of the catalyst was studied in both reactions. Using water as the solvent, the catalyst could be reused up to 5 times without loss of activity and the reaction yield remained the same. However, using glycerol as the solvent, the catalyst was inactive after the first use.<sup>5a</sup> Starting from unactivated 5-bromo-1<i>H</i>-indole and 4-methylbenzaldehyde, the respective BIM was obtained in better yield than when using catalysts such as sulfonic acid functionalized ionic liquid,<sup>5b</sup> ferrous oxalate,<sup>5c</sup> PdCl<sub>2</sub>(MeCN)<sub>2</sub>,<sup>5d</sup> or tetramethyl guanidinium chlorosulfonate.<sup>5e</sup></p>	
<p>(B) 2-Substituted benzothiazoles are present in various bioactive molecules and 1,4-benzoxazine-containing compounds have pharmacological and biological activities. ANO was used as a catalyst to develop a new methodology to obtain 2-substituted benzothiazoles and 3-substituted 1,4-benzoxazine-2-ones from <math>\alpha</math>-phenylglyoxylic acid (PGA) using PEG-400 as solvent. At first, the study focused on optimizing the reaction conditions in the formation of 2-arylbenzothiazoles under conventional heating. The best result was obtained in the reaction between PGA and 2-aminothiophenol using 10 mol% of ANO and PEG-400 as solvent at 100 °C for 2 h (85% yield). This methodology has been applied to different <math>\alpha</math>-arylglyoxylic acids and 2-aminophenols to produce 3-substituted 2<i>H</i>-benzo[<i>b</i>][1,4]benzoxazine-2-ones. In general, the yields obtained were good (the majority over 70%). These reactions were performed under ultrasonic irradiation as well and the yields were satisfactory after a few minutes of reaction (over 85% yield).<sup>6a</sup> For the methyl-substituted benzoxazine highlighted in the scheme, ANO was superior to reported catalysts such as TFA<sup>6b,c</sup> or Oxone.<sup>6d</sup></p>	
<p>(C) 3-Arylquinoxalin-2(1<i>H</i>)-ones are biologically active molecules with great importance in a pharmaceutical context, being structures present in relevant precursors to antidiabetics, anticancer therapeutics, antidepressants, and spasmolytic molecules such as caroverine (Tinnex®). Current approaches to the target structure are based on the use of harsh conditions, flammable volatile organic compounds (VOC), or chlorinated solvents. A new method was developed based on the reaction of <math>\alpha</math>-phenylglyoxylic (PGA) and <i>ortho</i>-phenylenediamine, with ANO as catalyst (5 mol%) in PEG-400 under sonication in an open flask for 10 min, and the corresponding 3-phenylquinoxalin-2(1<i>H</i>)-one was obtained in 96% yield. Several <math>\alpha</math>-ketoacids were then tested with success. However, the use of substituted <i>ortho</i>-phenylenediamine gives rise to a mixture of regioisomers that can be quantified by <sup>1</sup>H-<sup>15</sup>N HMBC NMR spectroscopy. The mechanism is based on initial imine formation, niobium-catalyzed carboxyl activation, and subsequent nucleophilic attack of the second nitrogen of the diamine to furnish the 3-arylquinoxalin-2(1<i>H</i>)-one. To demonstrate the robustness of this new method, a gram-scale preparation (5 mmol) of the pharmaceutically relevant 3-phenylquinoxalin-2(1<i>H</i>)-one was demonstrated in 87% yield.<sup>7</sup> Ultrasound is considered as a green energy source, resulting in reduced energy consumption in some cases by 85%.<sup>7b</sup> ANO is the only catalyst demonstrated for preparation of the three substituted 3-arylquinoxalin-2(1<i>H</i>)-one shown. Notably for 3-(2-bromophenyl)-2(1<i>H</i>)-quinoxalinone, the conventional method of electrochemical cross-coupling with the aryldiazonium salt resulted in 0% yield.<sup>7c</sup></p>	
<p>(D) Biodiesel is a biodegradable fuel that is considered a viable substitute for petroleum-derived diesel itself. It can be obtained through the transesterification of vegetable oil (triacylglycerol) with an alcohol in the presence of a catalyst. ANO was used as the catalyst for biodiesel production under reflux or using ultrasound. Conversion of about 90% was observed for ethyl biodiesel from soya bean oil using ANO as the catalyst in a refluxing system, varying the mass ratio (20% and 100% molar ratio catalyst/oil), temperature (25 °C and 75 °C) in ethanol for 24 h. For the ultrasonic conditions, the best result used soya bean oil for 4 h, at 42 kHz in ethanol at 60 °C, achieving a conversion of about 43%.<sup>8</sup></p>	

<p>(E) Amide hydrolysis is a significant reaction in industrial and biochemical processes, due to its applications in peptide and protein modifications. In a preliminary screening, ANO was applied in the hydrolysis of acetamide under reflux in moderate yield (45%) after 20 h. However, the best results of the study were obtained using the heterogeneous catalyst niobium oxide.<sup>9</sup></p>	
<p>(F) Enantiomerically enriched alcohols have an important role in the synthesis of different chiral biologically active compounds present in pharmaceuticals and food products. Enzymatic kinetic resolution (KR) is the most used method to obtain chiral secondary alcohols using lipases as biocatalysts. Unfortunately, KR shows a maximum conversion of 50%. To overcome this drawback and attain quantitative conversion, a racemization agent is employed in a dynamic kinetic resolution process (DKR). Different niobium catalysts, including ANO, were used as racemization agents in the DKR of secondary alcohols. A solution of racemic 1-phenylethanol was reacted with CALB lipase and vinyl acetate in hexane for 4 h. The kinetic resolution showed an isolated yield of 43% of (R)-1-phenylethyl acetate and 41% of (S)-1-phenylethanol. Subsequently, the racemization of (S)-1-phenylethanol was performed using a niobium salt in toluene at 60 °C. Four niobium compounds were tested, including ANO, and the enantiomeric excess (ee) of which reaction was measured after 3 h and 24 h. Unfortunately, the racemization results using ANO were quite disappointing: 94% and 76% of ee after 3 h and 24 h, while the best racemization results were found with niobium phosphate, with complete racemization resulting after 24 h. Starting from racemic 1-phenylethanol, using niobium phosphate as catalyst and CAL-B, vinyl acetate in toluene at 60 °C, (R)-1-phenylethyl acetate was obtained with 92% conversion and 85% ee.<sup>10</sup></p>	

## Conflict of Interest

The authors declare no conflict of interest.

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