

## Catalytic Oxidation of Hydrazo Derivatives Promoted by a $\text{TiCl}_3/\text{HBr}$ System

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Development of efficient processes for preparation of azo derivatives is very important as these compounds are commonly used as organic dyes,<sup>1</sup> indicators,<sup>2</sup> radical reaction initiators,<sup>3</sup> and therapeutic agents.<sup>4</sup> In addition, azo compounds have potential for use in electronic<sup>5</sup> and drug delivery applications.<sup>6</sup>

Presently known synthetic strategies to obtain these materials include a very broad range of stoichiometric processes such as electrophilic reactions of diazonium salts,<sup>7a</sup> coupling of primary arylamines with aromatic nitroso<sup>7b</sup> and nitro<sup>7c</sup> compounds, Wallach rearrangements of azoxy derivatives,<sup>7d</sup> rearrangements of aryl triazenes,<sup>7e</sup> and reduction of azoxy and nitro aromatics.<sup>7f</sup>

Additional important methods for obtaining azo derivatives involve hydrazine oxidation. Most of these methods are based on stoichiometric processes and require use of  $\text{Pb}(\text{CH}_3\text{CO}_2)_4$ ,<sup>8a</sup>  $\text{HgO}$ ,<sup>8b,c</sup>  $(\text{NH}_4)_2\text{S}_2\text{O}_8$ ,<sup>8d</sup> *N*-bromosuccinimide in pyridine,<sup>8e,f</sup> tetrabutylammonium cerium(IV) nitrate<sup>8g</sup> and arylsulfonyl peroxide reagents,<sup>8h</sup>  $\text{NaNO}_2$  in acetic anhydride,<sup>8i</sup> and  $\text{NaNO}_2/\text{NaHSO}_4$  on silica support.<sup>8j</sup>

There are only a few known examples of catalytic oxidation of hydrazo compounds to the corresponding azo derivatives. Utilizing oxygen or  $\text{H}_2\text{O}_2$  as oxidants,  $\text{NH}_4\text{VO}_3$ ,<sup>9a</sup>  $\text{CuCl}_2$ ,<sup>9b</sup> and  $\text{Co}(\text{II})$  complexes<sup>9c,d</sup> were reported to catalyze this transformation. Also,  $\text{FeSO}_4$  was shown to function as hydrazo oxidation catalyst when a mixture of  $\text{KClO}_3/\text{H}_2\text{SO}_4$  was used as an oxidant.<sup>9e</sup>

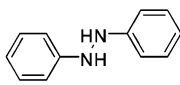
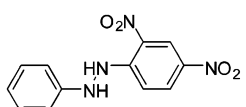
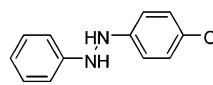
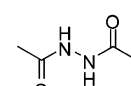
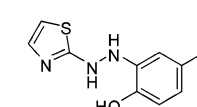
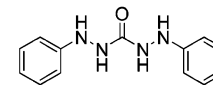
Here we report the discovery of a novel catalytic system, with a conceptually new mechanism of action, capable of highly efficient and selective oxidation of hydrazo compounds into the corresponding azo derivatives. This new process is compatible with a range of substituents, including aryl, methoxyaryl, nitroaryl, and acetyl, on the hydrazo functional group.

In the present study, a series of hydrazo compounds (entries 1–6, Table 1) were treated with  $\text{H}_2\text{O}_2$  and a catalyst mixture comprising  $\text{TiCl}_3$  and  $\text{HBr}$  (Figure 1). The reported reactions proceeded under ambient conditions with fast kinetics and are compatible with a series of solvents, including alcohols and DMSO. For all evaluated hydrazo starting materials, high yields of the corresponding azo products were observed within a short period of time after completion of the  $\text{H}_2\text{O}_2$  addition. Furthermore, versatility and selectivity of the  $\text{TiCl}_3/\text{HBr}$  system was compared to the known  $\text{NH}_4\text{VO}_3$  catalyst, used for  $\text{H}_2\text{O}_2$ -based oxidation of hydrazo compounds. Therefore, in a comparative investigation, previously investigated substrates (entries 1–6, Table 1) were treated with  $\text{H}_2\text{O}_2$ , using  $\text{NH}_4\text{VO}_3$  as a catalyst.<sup>9a</sup>

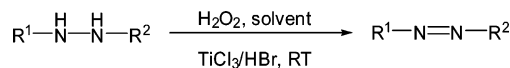
Attempts to perform the reaction using a catalyst composed of  $\text{TiCl}_3$  and  $\text{HCl}$  (instead of  $\text{HBr}$ ) were not successful, and no oxidation products were observed.

The  $\text{TiCl}_3/\text{HBr}$  system is likely to function via two separate and distinctive catalytic cycles, which are linked by radical species (Figure 2). The first cycle involves a single-electron redox transformation between  $\text{Ti}^{3+}$  and  $\text{Ti}^{4+}$  complexes. This reaction is initiated by the well-described process in which  $\text{TiCl}_3$  reacts with

**Table 1.** Hydrogen Peroxide Based Oxidation of Various Hydrazines Using  $\text{TiCl}_3/\text{HBr}$  Catalyst and, For Comparison,  $\text{NH}_4\text{VO}_3$  Catalyst (Isolated Yields of the Corresponding Azo Products Are Presented)

Entry	Substrate	$\text{TiCl}_3/\text{HBr}$ Yields(%) <sup>a</sup>	$\text{NH}_4\text{VO}_3$ Yields (%) <sup>b</sup>
1		95	96
2		88	47
3		95	82
4		90	24
5		88	16
6		85	38

<sup>a</sup> Experimental conditions:  $\text{TiCl}_3$  solution (15% in  $\text{HCl}$  aqueous solution, 0.2–0.25 mol %);  $\text{HBr}$  solution (33% in acetic acid solution, 1.0–1.5 mol %);  $\text{H}_2\text{O}_2$  solution (30% in water, ~1.5 mol %). <sup>b</sup> Experimental conditions:  $\text{NH}_4\text{VO}_3$  solution (1.0% in 1.0 M  $\text{HCl}$  solution, 0.4 mol %);  $\text{H}_2\text{O}_2$  solution (30% in water, ~1.5 mol %).

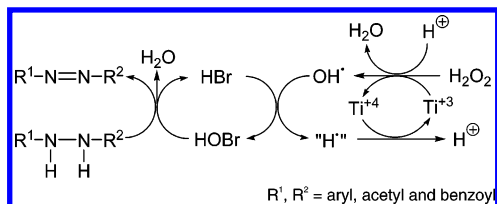


**Figure 1.** General procedure for the catalytic oxidation of hydrazo compounds to the corresponding azo derivatives. Catalyst:  $\text{TiCl}_3/\text{HBr}$ .

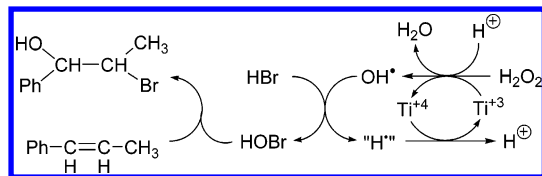
$\text{H}_2\text{O}_2$  under acidic conditions, generating hydroxyl radicals, water, and the  $\text{Ti}^{4+}$  species.<sup>10</sup>

Under investigated reaction conditions, we propose that the formed hydroxyl radicals oxidize  $\text{HBr}$  into the corresponding hypobromous acid. Subsequently, formed  $\text{HOBr}$  is reduced back to the  $\text{HBr}$  and water by the hydrazo substrate, concurrently producing the desired azo derivative and thus closing the  $\text{HBr}-\text{HOBr}$  catalytic cycle (Figure 2).

Although formation of the hydroxyl radical is well-documented, the formation of the hydrogen radical species could not be easily proven, due to very high reactivity and short lifetime. Yet, strong



**Figure 2.** Proposed mechanism for the catalytic oxidation of the hydrazo compounds using  $H_2O_2$  and  $TiCl_3/HBr$  catalyst.



**Figure 3.** Proposed mechanism of olefin hydrobromination process, based on  $HBr$ ,  $H_2O_2$ , and  $TiCl_3$  catalyst.

support for the suggested mechanism was provided by the work of Nenadovic and co-workers who have shown that, in ethanol,  $Ti^{4+}$  could be effectively reduced by hydrogen radicals to  $Ti^{3+}$  complexes with a rate of  $5.95 \times 10^7 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ .<sup>11</sup>

The mechanistic studies of the discovered process were begun with the evaluation of the  $HBr-HOBr$  cycle, starting with validation of the hypobromous acid formation. On the basis of the olefin hydrobromination reaction reported by Saint and others,<sup>12</sup> we used *trans*-methylstyrene as a  $HOBr$ -trapping substrate (Figure 3). The reaction was performed with catalytic and stoichiometric amounts (as compared to *trans*-methylstyrene starting material) of  $HBr$  reagent. In each case, a corresponding amount of hydrobromination product was observed, clearly indicating the formation of  $HOBr$  species in our process.

We have performed stoichiometric oxidations of hydrazo starting materials (entries 1–3, Table 1) by using an in situ generated hypobromous acid from *N*-bromoacetamide and  $HOCl$ .<sup>13a</sup> These oxidation reactions produced the same yields of the azo products as our catalytic process, providing a strong support to our claim that  $HOBr$  is indeed the oxidant of the hydrazo compound in the reaction. It should be mentioned that no azo products were detected when we attempted to react stoichiometric amounts of hydrazo derivatives with  $HOCl$  or directly with  $H_2O_2$ .

Additional studies included evaluation of other metal-containing compounds as potential cocatalysts in our system. Specifically,  $VO(acac)_2$ <sup>13</sup> and  $CuI$ ,<sup>14</sup> both capable of single-electron redox transformation, were used instead of  $TiCl_3$ ; however, no hydrazo oxidation was observed with these compounds.

In summary, a novel method for preparing azo compounds via catalytic oxidation of corresponding hydrazo precursors has been discovered. This oxidation process was highly efficient and selective and represents a valuable addition to the chemistry of azo

compounds. Further investigations to expand the scope of this reaction are currently under active investigation in our laboratories.

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**Supporting Information Available:** Synthetic procedures and characterization of compounds **2** and **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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