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# Synthesis of Acetophenone Azine

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#### SYNTHESIS OF ACETOPHENONE AZINE

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Abstract: Conditions for preparing acetophenone azine via the oxidative dimerization of acetophenone imine anion are investigated.

We wish to report the results of our investigation into the use of various oxidants and copper salts to effect the oxidative dimerization of N-lithioacetophenone imine to yield acetophenone azine. This method of preparing acetophenone azine, a compound which possesses a broad spectrum of microbiocidal activity,<sup>1</sup> and in particular, anthelmintic activity,<sup>2</sup> avoids the use of highly toxic hydrazine, which is normally employed in the synthesis of this compound.<sup>3</sup>

In a typical procedure, N-lithioacetophenone imine was generated by addition of benzonitrile to 1.1 equivalents of methyllithium in ether, and the solution heated at reflux for 30 minutes. A copper salt was then added, followed by a further 30 minutes of

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heating at reflux. Finally, an oxidant was added and the solution once again heated at reflux (2-24 hrs). Filtration of the reaction mixture and washing the filtrate with water afforded an organic layer which was analyzed for acetophenone azine by capillary GC. Major contaminants were acetophenone and acetophenone imine. In several instances acetophenone azine was isolated from the ether solution and purified by recrystallization from ethanol.

Table 1 summarizes the effectiveness with which various oxidants and copper salts achieved this transformation. Use of salts other than copper  $(MgBr_2, Zn(OTs)_2)$  gave only trace amounts of acetophenone azine. Entries 1-4 illustrate that peroxides do not produce a significant amount of (1) in the absence of copper salts, nor do copper salts accomplish the transformation without the aid of oxidants. When oxygen is used as the oxidant, however, moderate yields of the azine can be obtained, even in the absence of copper salts (entry 5)<sup>4</sup>. Of the several oxidants investigated, (entries 6-10) t-butyl peroxybenzoate (2) gave consistently high yields in addition to being convenient to use, and thus became our reagent of choice in further reactions.

Neither use of tetrahydrofuran instead of diethyl ether (compare entries 8 & 11), nor CuBr instead of CuI (compare entries 8 & 12) had a significant effect on the yield. Use of a catalytic amount of CuI (entry 13) resulted in significantly lower yields. Finally, cupric salts were found to be essentially ineffective in this reaction (entry 14).

We next conducted a brief investigation of the effect of reagent stoichiometry on the product yield, which is summarized in Table 2. If

Entry	PhCN + MeLi -	$CuX/[O]$ $Ph \longrightarrow Ph 1$	
		Et <sub>2</sub> O CH <sub>3</sub> CH <sub>3</sub>	
	Copper Salt <sup>a</sup>	Oxidant <sup>a</sup>	% of Products (by GC) <sup>b</sup>
1	CuI	None	0
2	CuBr <sub>2</sub>	None	0
3	None	(CH <sub>3</sub> ) <sub>3</sub> SiOOSi(CH <sub>3</sub> ) <sub>3</sub>	1.0
4	None	PhC(O)OOC(CH <sub>3</sub> ) <sub>3</sub> (2)	3.4
5	None	O <sub>2</sub> c	58.6
6	Cul	(CH <sub>3</sub> ) <sub>3</sub> SiOOSi(CH <sub>3</sub> ) <sub>3</sub>	37.7
7	CuI	(CH <sub>3</sub> ) <sub>3</sub> COOC(CH <sub>3</sub> ) <sub>3</sub>	3.5
8	Cul	(2)	88.6
9	Cul	O <sub>2</sub> c	83.9
10	Cul	PhC(O)OOC(O)Ph <sup>d</sup>	69.9
11	CuI	( <b>2</b> ) <sup>d</sup>	82.0
12	CuBr	(2)	83.3
13	CuI <sup>e</sup>	(2)	16.1
14	CuBr <sub>2</sub>	(2)	8.5

### Table 1

a) 1 equivalent unless otherwise noted

- b) Yields have not been optimized.
- c) Bubbled through the reaction mixture for 30 min. at room temp.

\_\_\_\_\_

- d) Reaction conducted in tetrahydrofuran
- e) Catalytic amount (5%) of CuI used





we compare entries 1 and 4 in which the lithioimine:peroxide ratio is held constant but the lithioimine:copper iodide ratio is varied, we see essentially no change in the yield. Similarly, entries 2 and 3 can be compared, with the same observation. Conversely, by comparing entries 1 and 2 with entries 3 and 4, respectively, one can see that keeping the copper iodide:lithioimine ratio constant and increasing the peroxide:lithioimine ratio from 1:2 to 1:1 results in a modest increase in the yield of acetophenone azine. Presumably, however, a peroxide:lithioimine ratio of 1:2 should be sufficient to carry out the reaction, assuming the peroxide to be a two-electron oxidant.<sup>5</sup>

Finally, although three stereoisomers of acetophenone azine are theoretically possible, only one was observed (400 MHz NMR, capillary GC), which we believe is the (E,E) isomer shown in Table 1, based on literature precedent. $^{6,7}$ 

In summary, acetophenone azine can be prepared in good yield by the reaction of acetophenone imine anion with t-butyl peroxybenzoate in the presence of copper iodide. Although the t-butyl peroxybenzoate/copper salt system has been used for the oxidation of a variety of substrates,<sup>8</sup> to the best of our knowledge it has never been employed in the oxidative dimerization of imine anions to give azines.<sup>9</sup> Further applications of this reaction are currently under study.

Acetophenone \_azine: m.p. 119-121° (Lit.<sup>3</sup> 121°); <sup>1</sup>H NMR(CDCl<sub>3</sub>): 8.0-7.8(m, 4H), 7.5-7.3 (m, 6H), 2.32 (s, 6H); <sup>13</sup>C NMR(CDCl<sub>3</sub>): 157.6, 138.4, 129.5, 128.2, 126.5, 15.0; IR(thin film): 1602, 1441, 1360, 759, 689.

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