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### SYNTHETIC COMMUNICATIONS, 22(21), 3101-3108 (1992)

## AZINE SYNTHESIS VIA NITROGEN-NITROGEN BOND FORMATION

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Abstract: Imine anions, generated by reaction of nitriles with organometallic reagents, are dimerized to form symmetrical azines through the use of CuI and t-butyl peroxybenzoate.

Azines are typically prepared through carbon-nitrogen bond formation, by the action of hydrazine on carbonyl compounds.<sup>1</sup> We wish to report a conceptually different azine synthesis resulting from the dimerization of imine anions which proceeds via nitrogen-nitrogen bond formation, and thus avoids the use of highly toxic hydrazine.<sup>2</sup> Azines are produced in good yield from imine anions (prepared by the addition of an organolithium or Grignard reagent to a nitrile) upon treatment with Cu(I) salts and any of a variety of oxidants. Preliminary studies<sup>3</sup> of several reagent systems suggested use of copper(I) iodide and t-butyl peroxybenzoate to be the most convenient and effective. Although this combination of reagents has been used to oxidize a wide range of substrates,<sup>4</sup> it has never been employed in the oxidative dimerization of imines to give azines. Other oxidative

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A variety of azines may be prepared by this method, as indicated in Tables 1 and 26. While crude yields were generally quite high, significant loss was frequently observed during purification.<sup>7</sup> The best yields were usually obtained when aromatic nitriles were employed (compare specifically products 3ac and 3ag in Table 1 with products 3eh and 3fh, respectively, in Table 2, or in general, all entries listed in Table 1 with the those listed in Table 2). Use of organolithium reagents tended to produce higher azine yields than were obtained using Grignard reagents (compare products 3aa, 3ea and 3ga with products 3ad, 3ed and 3gd, respectively--products 3ab and 3af represent an Additionally, while imine anion formation exception to this trend). was usually complete within 30 min. when nitriles were reacted with organolithiums, reactions with Grignard reagents often required several hours. The azines listed in Tables 1 and 2 have all been reported previously, with the exception of o-chloroacetophenone azine (3da), for which satisfactory clemental analysis was obtained.<sup>8</sup>

	Crude	Purificd	m.p./b.p.	Exact Mass <sup>c</sup>
Product <sup>a</sup>	Yield <sup>b</sup>	Yield <sup>b</sup>	(Lit.)	Calc. (Found)
3aa	100	61 <sup>d</sup>	119-121 (121) <sup>9</sup>	
3ab	100	46 <sup>e</sup>	oil (32-4) <sup>10</sup>	
3ac	79	64 <sup>d</sup>	79-80.5 (79) <sup>11</sup>	
3ad	54	28 <sup>d</sup>	116-19 (121) <sup>9</sup>	
3ae	94	57e,f	oil (40-1) <sup>12</sup>	293.2018(293.2027)
3af	100	82 <sup>f</sup>	oil (32-4) <sup>10</sup>	321.2331(321.2330)
3ag	96	44d	64-5 (66-7) <sup>13</sup>	
3ah	50	42 <sup>d</sup>	162-163.5 (164) <sup>10</sup>	
3ba	100	46 <sup>d</sup>	133-4 (137-8) <sup>13</sup>	
3ca	81	49 <sup>d</sup>	144-7 (153-4)13	
3da	95	55 <sup>e</sup>	92-94	305.0612(305.0607)

Table 1: Preparation of Azines 3 from Aromatic Nitriles

a) The first letter of the product designation refers to the nitrile precursor; the second letter refers to the organometallic reagent.
b) Ísolated yields

- c) Calculated for  $M^+$  ion obtained by EI, or for M + 1 ion, obtained by CI.
- d) Purified by recrystallization
- e) Purified by column chromatography (SiO<sub>2</sub>)
- f) Purified by kugelrohr distillation

	Crude	Purified	m.p./b.p.	Exact Mass <sup>c</sup>
Product <sup>a</sup>	Yield <sup>b</sup>	Yicld <sup>b</sup>	(Lit.)	Calc. (Found)
3ea	87	71 <sup>f</sup>	(213-6/760mm) <sup>16</sup>	197.2018(197.2018)
3ed	25		(213-6/760mm) <sup>16</sup>	
3eg	38	27 <sup>e</sup>	(122/18mm) <sup>17</sup>	224.2252(224.2256)
3eh	86	30 <sup>d</sup>	81-82 (79) <sup>11</sup>	
3fg	45	16 <sup>f</sup>	(99/45mm) <sup>18</sup>	169.1705(169.1700)
3fh	100	33 <sup>d</sup>	62-4 (66-7) <sup>13</sup>	
3ga	68	49 <sup>e</sup>	(92/29mm) <sup>18</sup>	168.1626(168.1631)
3 g d	16		(92/29mm) <sup>18</sup>	

Table 2: Preparation of Azines 3 from Aliphatic Nitriles

a) The first letter of the product designation refers to the nitrile precursor; the second letter refers to the organometallic reagent.

- b) Isolated yields
- c) Calculated for  $M^+$  ion obtained by EI, or for M + 1 ion, obtained by CI.
- d) Purified by recrystallization
- e) Purified by column chromatography (SiO<sub>2</sub>)
- f) Purified by, kugelrohr distillation

Although three stereoisomers are possible for some of the azines reported above, in all cases except one  $(3ga/3gd)^{14}$  only one stereoisomer was observed (as determined by 400 MHz NMR and capillary GC). Literature precedent<sup>15</sup> suggests this to be the (E,E)

isomer, which was confirmed in one case (3ca) by an X-ray crystal structure determination.

In summary, we have demonstrated that the t-butyl peroxybenzoate/CuI reagent system effects the oxidative dimerization of imine anions, resulting in the formation of azines in good yield. Azine synthesis via N-N bond formation may find utility in the synthesis of azines and related compounds which cannot be prepared by more traditional methods. Further applications of this reaction are currently under investigation.

Typical Procedure: A solution of EtMgBr (8.8 mmol) in ethyl ether (10 mL) was cooled in an ice bath under a nitrogen atmosphere. Benzonitrile (1.13 g, 10.9 mmol) in ether (10 mL), was added dropwise over 10 min. The solution was heated at reflux for 2 hrs, then CuI (2.05 g, 10.8 mmol) was added, followed by an additional 30 min of The reaction mixture was then cooled in an ice bath heating at reflux. while t-butyl peroxybenzoate (2.12 g, 10.9 mmol) in THF (10 mL), was added over a period of 10 min. The reaction mixture was heated at reflux for 5 hrs, then cooled to room temperature and filtered. The precipitate was/washed with ether (50 mL), and the combined filtrates were washed with water (2 x 50 mL). The organic phase was then dried (MgSO<sub>4</sub>), and the solvent removed under reduced pressure. The crude product was recrystallized (EtOH) to give .63 g (43.5%) of propiophenone azine, m.p. 64-65° (Lit.<sup>13</sup> 66-67°). <sup>1</sup>H NMR(CDCl<sub>3</sub>): 8.0-7.8 (m, 4H), 7.5-7.3 (m, 6H), 2.89 (q, J = 7.7, 4H), 1.13 (t, J = 7.7, 6H);  ${}^{13}$ C NMR(CDCl<sub>3</sub>): 162.8, 137.3, 129.4, 128.4, 126.8, 21.9, 11.4.

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6) Azines were characterized by NMR and capillary GC, by which they were readily distinguished from the corresponding ketones and imines. In many instances the products were compared with (and found to be identical to) authentic samples prepared by reaction of ketones with hydrazine.

7) Purification procedures were not optimized. As the crude products were typically greater than 80% pure (by GC), we believe further work would improve the yields of purified products.

8) Analysis calculated for C<sub>16</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>: C, 62.97; H, 4.62; N, 9.18.
Found: C, 62.76; H, 4.64; N, 9.08. <sup>1</sup>H NMR(CDCl<sub>3</sub>): 7.5-7.45 (m, 2H),
7.43-7.40 (m, 2H), 7.35-7.30 (m, 4H), 2.26 (s, 6H); <sup>13</sup>C NMR(CDCl<sub>3</sub>): 158.2,
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