JOC*Note*

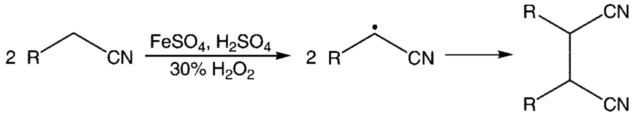
Reactions in Water: Alkyl Nitrile Coupling Reactions Using Fenton's Reagent

Christopher L. Keller,[†] James D. Dalessandro,[†]
Richard P. Hotz,*[,†] and Allan R. Pinhas*[,‡]

Department of Chemistry, College of Mount St. Joseph, Cincinnati, Ohio 45233-1670, and Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221-0172

richard_hotz@mail.msj.edu; allan.pinhas@uc.edu

Received December 18, 2007

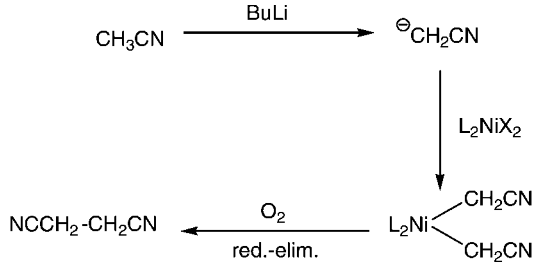


The coupling reaction of water-soluble alkyl nitriles using Fenton's reagent (Fe(II) and H_2O_2) is described. The best metal for the reaction is iron(II), and the greatest yields are obtained when the concentration of the metal is kept low. Hydrogen-atom abstraction is selective, preferentially producing the radical α to the nitrile. In order to increase the production of dinitrile, in situ reduction of iron(III) to iron(II), using a variety of reducing agents, was investigated.

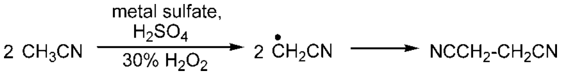
For the past several years, we have been interested in carbon−carbon bond formation by oxidative coupling of stabilized anions[1] and anion equivalents.[2] The coupling of anions α to nitriles using transition-metal dihalide complexes has been previously reported.[3] As shown in Scheme 1, nickel halides containing diphosphine ligands were treated with cyanomethanide anion, generated by reaction of acetonitrile with butyllithium, to produce bis(cyanomethanide)phosphine complexes. When these nickel(II) complexes were exposed to oxygen, reductive elimination produced succinonitrile as the only organic product. Among the drawbacks to this method are the need for an inert atmosphere and the cold reaction conditions (−78 °C).

Due to our desire to form new carbon−carbon bonds under "green reaction conditions", a water-compatible method for coupling nitriles at the α-position was desired. This would allow the reaction to be run at or near room temperature and the use of costly solvents could be avoided. Thus, we became interested in the use of Fenton chemistry.

SCHEME 1



SCHEME 2



For this reaction, it does not matter if a free radical or an iron−oxo complex is formed. What matters is that the Fenton chemistry generates a radical[4,5] or radical-equivalent[6] that can remove a hydrogen atom from the alkyl chain of the alkyl nitrile, and then two of these "alkyl radicals" can couple. This type of coupling reaction was first mentioned about 50 years ago,[7] but unfortunately, the yields were low and the regiochemistry was not investigated in detail.

In this paper, we discuss the coupling of acetonitrile and other water-soluble alkyl nitriles.[8] We have improved the reaction yield, and in addition, we have investigated the regiochemistry of the coupling reaction. This regiochemistry not only is important from a synthetic perspective, but it tells us about the energetics of hydrogen-atom removal from various positions on the alkyl chain. We wanted to determine whether hydrogen-atom abstraction from an alkyl nitrile is statistical or selective, with preferential removal of a hydrogen atom from the α-carbon of the nitrile producing a resonance-stabilized carbon radical. In situ reduction of iron(III) to iron(II), using a variety of reducing agents, will also be discussed.

Variations in Metal. The ability of several transition metal ions to do "Fenton-type" chemistry with acetonitrile was examined (Scheme 2). In these experiments, the metal ion was the limiting reagent. Metal ions with two readily available common oxidation states were examined, and the best yields were obtained using iron(II). Manganese(II) and cobalt(II) complexes each failed to produce more than a trace amount of succinonitrile. Copper(II) and nickel(II), which are metals with a less common higher oxidation state, were also unsuccessful in producing succinonitrile.[9,10]

[†] College of Mount St. Joseph.

[‡] University of Cincinnati.

(1) Belletire, J. L.; Spletzer, E. G.; Pinhas, A. R. *Tetrahedron Lett.* **1984**, *25*, 5969.

(2) (a) LaDuca, M. J. T.; Simunic, J. L.; Hershberger, J. W.; Pinhas, A. R. *Inorg. Chim. Acta* **1994**, *222*, 165. (b) Pinhas, A. R.; Hershberger, J. W. *Organometallics* **1990**, *9*, 2840.

(3) Alburquerque, P. R.; Pinhas, A. R.; Krause Bauer, J. A. *Inorg. Chim. Acta* **2000**, *298*, 239.

(4) Walling, C. *Acc. Chem. Res.* **1998**, *31*, 155.

(5) (a) See, for example: MacFaul, P. A.; Wayner, D. D. M.; Ingold, K. U. *Acc. Chem. Res.* **1998**, *31*, 159. (b) Goldstein, S.; Meyerstein, D. *Acc. Chem. Res.* **1999**, *32*, 547.

(6) See, for example: Sawyer, D. T.; Sobkowiak, A.; Matsushita, T. *Acc. Chem. Res.* **1996**, *29*, 409.

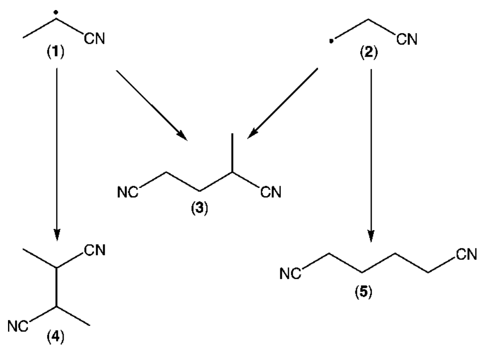
(7) (a) Coffman, D. D.; Jenner, E. L.; Lipscomb, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 2864. (b) Also see: Walling, C.; El-Taliawi, G.; M, *J. Am. Chem. Soc.* **1973**, *95*, 844.

(8) Attempted radical-coupling reactions of phenylacetonitrile were unsuccessful due to its insolubility in water.

(9) Metal sulfates are used in the reaction because use of metal halides will result in the generation of the corresponding halogen gas. The reaction mixture must be kept acidic to prevent occurrence of nucleophilic attack at the nitrile carbon.

10.1021/jo7026905 CCC: $40.75

SCHEME 3



Variations in Concentration. The best yields were obtained when the iron(II) concentration was kept low. The reported percent yields are based on the two iron(II) ions required per alkyl dinitrile formed. With a constant amount of iron(II) sulfate, using a large volume of acetonitrile and water (25 mL of each), a 70% yield of succinonitrile was obtained. Using either 5 mL of acetonitrile and 5 mL of water, or using 1 mL of acetonitrile and 10 mL water, the yield was only 10–20%.

Selectivity of Hydrogen Abstraction. Since the cyanomethyl radical is the only radical that can be obtained from acetonitrile, succinonitrile is the only dinitrile product. However, propionitrile can form two radicals: a resonance-stabilized secondary radical (**1**) formed by abstraction of an α-hydrogen atom or a primary radical (**2**) by abstraction of a *β*-hydrogen atom. The products formed by all possible combinations of these two radicals are illustrated in Scheme 3.

Stereoisomers of 2,3-dimethylsuccinonitrile (**4**) (*d,l*-pair and a meso compound) are formed by the coupling of two molecules of the secondary radical (**1**), while two primary radicals (**2**) combine to form adiponitrile (**5**). Cross-coupling of these two radicals produces 2-methylglutamonitrile (**3**). The observed ratio for dinitrile isomers **3**:**4**:**5** is 50:45:5. After correcting for the number of abstractable hydrogens at each position, it was determined that the resonance-stabilized secondary radical (**1**) and the primary radical (**2**) form in a 3.5:1 ratio rather than the statistical ratio of 2:3.

Isobutyronitrile also can form two radicals: a resonance-stabilized tertiary radical (**6**) formed by abstraction of an α-hydrogen atom or a primary radical (**7**) by abstraction of a *β*-hydrogen atom. The products formed by all possible combinations of these two radicals are illustrated in Scheme 4.

Stereoisomers of 2,5-dimethyladiponitrile (**10**) (*d,l*-pair and a meso compound) are formed by the coupling of two molecules of the primary radical (**7**), while two tertiary radicals (**6**) combine to form 2,2,3,3-tetramethysuccinonitrile (**9**). Cross-coupling of these two radicals produces 2,2,4-trimethylglutamonitrile (**8**). The observed ratio for dinitrile isomers **8**:**9**:**10** is 26:29:45. After correcting for the number of abstractable hydrogens at each position, it was determined that the resonance-stabilized tertiary radical (**6**) and the primary radical (**7**) form in a 4.3:1 ratio rather than the statistical ratio of 1:6.

SCHEME 4

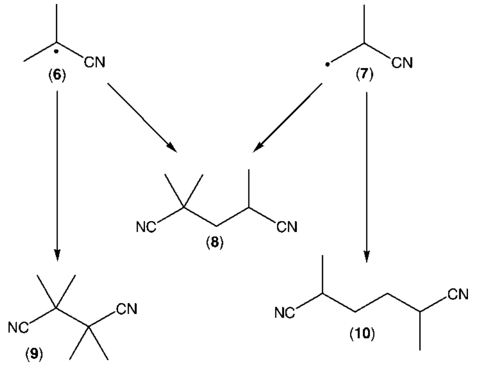


TABLE 1. Attempts at Reducing the Iron(III) Byproduct Back to Iron(II)

Fe(III) reducing agent	*T* (°C)	time (hr)	succinonitrile (mmol)
none	25	3	1.75
Mn(II)	25	3	2.38
Mn(II)	40	0.5	2.00
Cu(II)	25	3	0.75
Ni(II)	25	3	0.75
H_2S	25	1	8.00
Fe(0)	25	1	9.00
Fe(0)	25	3	7.62
Fe(0)	44	1	8.00
Fe(0)	80	1	4.50

SCHEME 5

$$2\ \mathrm{Fe(III)} + \mathrm{Fe(0)} \longrightarrow 3\ \mathrm{Fe(II)}$$

Attempts at Catalysis. Although there is literature precedent for using Fenton's reagent to prepare succinonitrile, in those studies, a stoichiometric amount of iron(II) was added slowly to a H_2O_2—acetonitrile mixture, and an 18% yield was obtained. Since the cyanomethyl radical is easily reduced to the cyanomethyl anion by iron(II), with a stoichiometric amount of iron, the lower yield is not surprising. To improve the yield, the concentration of iron(II) should be kept low. Thus, for the large-scale preparation of succinonitrile via Fenton's reagent, the reaction should be catalytic in iron(II), keeping its concentration as low as possible.

The ideal catalyst has no abstractable hydrogens and is capable of reducing iron(III) to iron(II) without also reducing the nitrile radical to the anion. These requirements greatly limit the number of possible reducing agents. Table 1 summarizes the reactions done in the presence of a reducing agent.

A second transition-metal ion was added as a potential reducing agent; however, only the use of manganese(II) resulted in an improved yield. When either copper(II) or nickel(II) was used, a notable decrease in yield was observed. An increased yield was obtained with hydrogen sulfide, but the coproduction of elemental sulfur made succinonitrile isolation difficult.

Iron(0) is an attractive candidate as a reducing agent because iron(II) is the only product of the oxidation–reduction reaction (Scheme 5).

Although the use of iron(0) creates a heterogeneous reaction which leads to greater variability in the product yield, the increased production of succinonitrile indicates iron(0) has an effect on the coupling reaction by reducing iron(III) to iron(II).

The observed trend is that with longer time and higher temperatures, the lower the yield. A possible explanation is that as the reaction proceeds, the concentration of iron(II) increases and the yield approaches an upper limit. In addition, at higher reaction temperatures, reduction of the radical to the anion becomes more competitive with the radical coupling. We also observed that at extended reaction times, intractable materials,

---

(10) The insolubility of copper(I) salts in water precluded their use in this reaction: Cotton, F. A.; Wilkinson, G.; Murillo, C. A.; Bochmann, M. *Advanced Inorganic Chemistry*, 6th ed.; Wiley-Interscience: New York, 1999.

which mostly likely arose from further reaction of the dinitrile, were formed.

Conclusion

The radical α to the nitrile is formed preferentially. The greatest yields are obtained using a low concentration of iron(II) to generate the radical. Initial studies indicate that it is possible to make the reaction catalytic in iron(II); however, lower yields are observed with longer reaction times and elevated temperatures.

Experimental Section

All materials are commercially available and were used as received. Usually, no precautions were made to remove air from the reagents or solvents. In those reactions in which reagents and solvents were degassed, the experimental results were the same.

General Procedure. In an Erlenmeyer flask, 5.0 mmol metal sulfate (1.4 g of $FeSO_4 \cdot 7H_2O$; 0.67 g of $MnSO_4$; 1.4 g of $CoSO_4 \cdot 7H_2O$; 1.2 g of $CuSO_4 \cdot 5H_2O$; or 1.3 g of $NiSO_4 \cdot 6H_2O$), 25 mL of acetonitrile, 25 mL of H_2O, and 1.0 mL of concd H_2SO_4 were combined. Five milliliters (~44 mmol) of 30% aq H_2O_2 was then added slowly over 15–20 min. After the mixture was stirred at rt for the specified amount of time, 12 g of NaCl was added, the reaction mixture was extracted with 2 × 50 mL of CH_2Cl_2, extracts were dried over Na_2SO_4, and the solvent was removed by rotary evaporation. The residual material was analyzed by GC−mass spectrometry.

For the catalysis studies, 5–10 mmol of reducing agent was added prior to the addition of 30% aq H_2O_2. The variations in reaction time and temperature are summarized in Table 1.

General Procedure (Selectivity Studies). A 1.4 g (5.0 mmol) portion of $FeSO_4 \cdot 7H_2O$, 1.0 mL of nitrile [acetonitrile (0.79 g, 19 mmol), propionitrile (0.77 g, 14 mmol), or isobutyronitrile (0.76 g, 11 mmol)], and 1 drop of concd H_2SO_4 were dissolved in 10 mL of H_2O. After the mixture was cooled in an ice bath, 2.0 mL (~17 mmol) of 30% aq H_2O_2 was added slowly over 10 min. After the mixture was stirred at rt for 2 h, 3 g of NaCl was added, the reaction mixture was extracted with 2 × 25 mL of CH_2Cl_2, extracts were dried over Na_2SO_4, and the solvent was removed by rotary evaporation. The residual material was analyzed by GC−mass spectrometry.

Acknowledgment. We thank BP Chemicals, the University Research Council of the University of Cincinnati, and the College of Mount St. Joseph for financial support of this research. C.L.K. thanks the NSF-REU program for a summer fellowship.

JO7026905