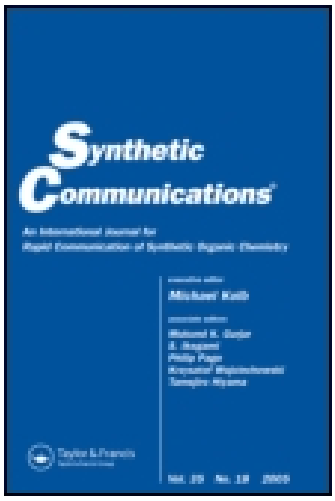

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The Reaction of Hydrazine with α-Cyanocinnamate Esters: A Caveat

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ABSTRACT

α-Cyanocinnamate esters react with hydrazine to give initial products of conjugate addition that then undergo a fragmentation to give the azine of the carbonyl precursor to the starting ester, rather than intramolecular aminolysis to give the pyrazolidinone.

Key Words: Addition reactions; Retro reactions; Cleavage; Cyanocinnamates; Hydrazine; Azines.

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INTRODUCTION

Pyrazoles and pyrazolones have become increasingly popular as ligands for metals in model systems for enzyme active sites, where the pyrazole mimics the imidazole side chain of histidine. The synthesis of pyrazole derivatives follows several well established strategies, all of which have been extensively reviewed.[1–5] By far the most common route to these pyrazole derivatives involves the well-established reaction between a 1,3-dicarbonyl compound or its equivalent and hydrazine or a hydrazine derivative. In particular, the reaction between acrylates and hydrazine or β-dicarbonyl compounds and hydrazine gives derivatives of pyrazolone, and this has been a major method for the synthesis of these heterocycles, which are especially useful in the preparation of multidentate ligands.[6] More recently, the reaction between hydrazine and an acetylenic carbonyl compound has been used in the synthesis of pyrazoles lacking a substituent on either nitrogen.[7] To our knowledge, there are no reports of fragmentation of the acrylate derivatives during the synthesis of pyrazolones, although a similar fragmentation to that observed here by us has recently been reported by Cardillo.[8] Herein, we report that the reaction between hydrazine and α-cyanoacrylate esters gives not the expected pyrazolinone, but the azine arising from what may be characterized formally as a retro-Mannich or retro-ene fragmentation of the intermediate β-hydrazinoester.

RESULTS AND DISCUSSION

The α-cyanocinnamate esters used in this study were all prepared straightforwardly using the McElvain[9] or Vogel[10] procedure for the Doebner modification of the Knoevenagel condensation of ethyl cyanoacetate with the corresponding aromatic aldehyde. All the aldehydes used gave a only the *E*-α-cyanocinnamate ester. All three esters prepared gave IR spectra with strong C≡N stretching vibrations.

On treatment with hydrazine in ethanol under reflux, the cyanocinnamate **1a** gave a product whose spectra were not at all in accord with the spectrum expected for the pyrazolidinone. The IR spectrum lacked C=O and C≡N stretching vibrations. The ^{1}H NMR spectrum showed no resonances for the ethyl ester or amide groups, nor any of the resonances expected for the sp^3 hybridized carbon atoms of the pyrazolidinone ring; the ^{13}C NMR spectra contained too few carbon resonances, lacking both the sp^3 resonances of the ring and the C=O and C≡N resonances. Based on these spectroscopic data, we were able to deduce that the major product of this reaction, isolated in well over 80% yield in all cases, was the azine (**5**) of the aldehyde precursor of the

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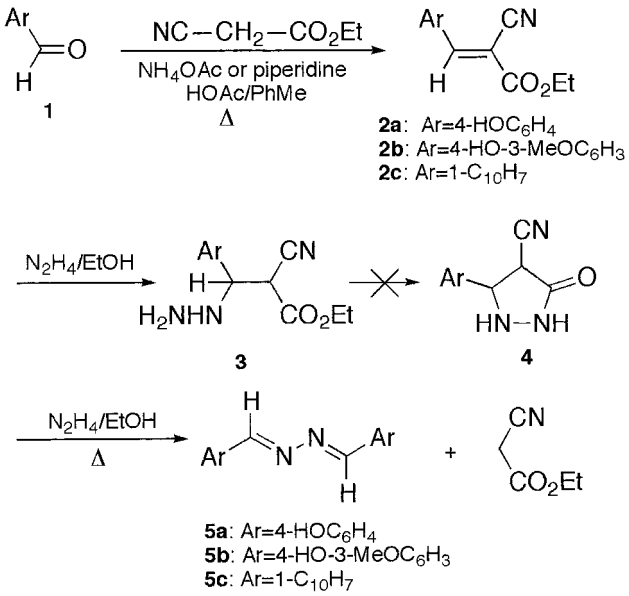
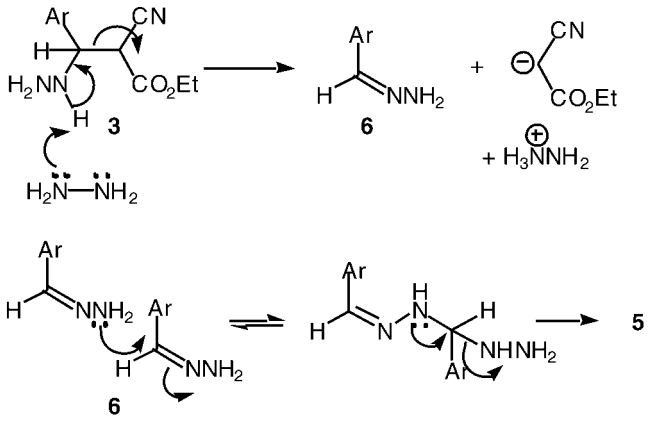


Scheme 1. Reaction between hydrazine and α-cyanocinnamates.

α-cyanocinnamate (Sch. 1). Ether extraction of the mother liquors from the initial crystallization of the azine gave a colorless oil which was identified as ethyl cyanoacetate. All the α-cyanocinnamates studied gave the same result.

The simpler rationalization (Sch. 2) for this reaction is that the initial conjugate addition is followed by a base-promoted retro-Mannich reaction to give the hydrazone and the enolate of ethyl cyanoacetate. Since the pK_a of ethyl cyanoacetate is 11, it is conceivable that the anion of this compound could function as a leaving group under suitable circumstances. Sch. 2 also shows one possible pathway for the hydrazone initially formed (**6**) to be converted to the isolated azine by a disproportionation reaction. (For an extensive discussion of keto-enol tautomerism in active mehtylene compounds see: Ref.[11].)

The second rationalization (scheme 3) is that the β-hydrazinoester formed in the initial step undergoes a retro-ene fragmentation through a six-membered cyclic transition state to give the enol of ethyl cyanoacetate and the hydrazone of the aldehyde. Ethyl cyanoacetate has a pK_a of 11, so the enolate anion of the ethyl cyanoacetate is a much weaker base than the anion of a simple ester or nitrile. More importantly, ethyl cyanoacetate has 0.25% equilibrium enol content in methanol solution.[12] Thus, in contrast to simple esters or nitriles, ethyl cyanoacetate has a relatively low-energy enol, which should make it a

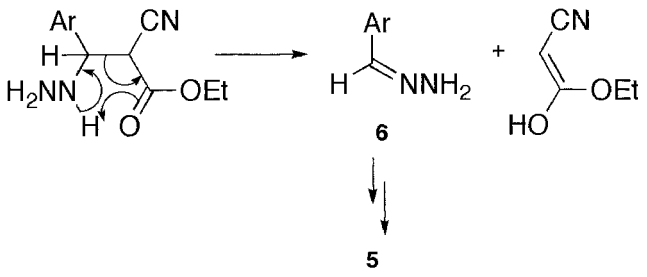


Scheme 2. Base-promoted fragmentation of β-hydrazinoester.

better leaving group during the retro-ene reaction. This would, in turn, facilitate the fragmentation to form the enol.

A third rationalization for the formation of the azine (Sch. 4), is that the β-hydrazinoester **3** reacts with a second mole of the Michael acceptor to give the dimeric species **7**, prior to fragmentation to give the azine.

Each of these mechanisms predicts that ethyl cyanoacetate should be formed in the reactions. It was therefore gratifying to find that ethyl cyanoacetate was isolated from these reaction mixtures in yields commensurate with that of the azine. This also lends support to the hypothesis that it is Michael addition that initiates the reaction, since hydrazinolysis of the ester group would lead to a hydrazide, which is not isolated. Interestingly, **2a** does not react with other nucleophiles which would appear to be equally suitable for Michael addition. To date, we have found that the uncatalyzed reaction



Scheme 3. Retro-ene mechanism for fragmentation

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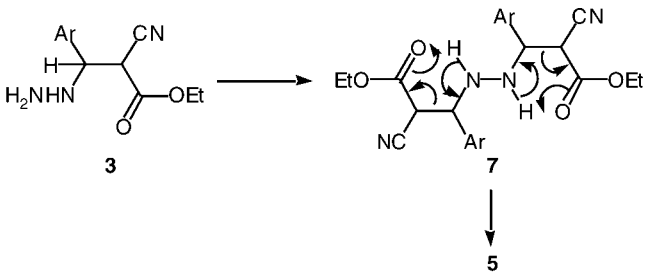

Scheme 4. Fragmentation of diester by ene mechanism.

between **2a** and urea, thiourea, and phenylhydrazine fails to give any product of a nucleophilic addition or substitution. This observation may lend support to the mechanism in Sch. 4, since none of these nucleophiles would be capable of forming the diester **7**.

The fact that we have not been able to obtain definitive proof for the presence of 3 in the reaction suggests that the fragmentation reaction proceeds at least as rapidly as the initial addition. This may support the view that the fragmentation more likely occurs by the retro-ene pathway in Sch. 3, since this reaction is then unimolecular, with the hydrazone formation and the base-promoted elimination reactions both being bimolecular. We do not, however, hold this view without some equivocation.

Regardless of the mechanism of the fragmentation, *these results sound a caveat about conjugate addition reactions of primary amine nucleophiles to Michael acceptors capable of eliminating the anion or the enol of an active methylene compound after the Michael addition.*

EXPERIMENTAL

General

Melting points were measured on a Fisher-Johns hotstage melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded as $CDCl_3$ solutions using a JEOL Eclipse NMR spectrometer operating at 400 MHz; peak positions are reported as δ (ppm) downfield from internal Me_4Si. ^{13}C NMR spectra were recorded as $CDCl_3$ solutions at 100 MHz; peak positions are reported as δ (ppm) relative to the center peak of $CDCl_3$ (77.1 ppm) and peak multiplicities as singlet (s), doublet (d) triplet (t) or quartet (q). Infrared spectra were recorded as KBr pellets using a Nicolet Avatar 360 FTIR spectrophotometer. Thin layer chromatography (TLC) was

carried out on Merck Kieselgel 60F_{254}. Microanalyses were carried out by Galbraith Laboratories, Knoxville, TN.

α-Cyanocinnamate Esters

These esters were prepared by a modification of the method of McElvain and Lyle,[9] or by a modification of the method of Vogel.[10] Ethyl cyanoacetate (1.0 eq), the aromatic aldehyde (1.0 eq), ammonium acetate (0.4 eq) or piperidine (0.16 eq), and acetic acid (1.25 eq) were dissolved in toluene (1 ml/mmol aldehyde), and the resultant solution was stirred under reflux using a Dean-Stark water separator. During the reaction, a solid was gradually formed. When no more water continued to accumulate, the reaction mixture was cooled in ice and the solid deposited was collected by vacuum filtration. The crude solid was recrystallized from methanol to give the pure *E*-cyanocinnamate ester.

Ethyl E-*2-cyano-3-(4-hydroxyphenyl)propenoate (**2a**)* was prepared by this method by heating ethyl cyanoacetate (5.70 g, 50.4 mmol), *p*-hydroxybenzaldehyde (6.11 g, 50.0 mmol), ammonium acetate (1.56 g, 20.2 mmol), and acetic acid (5.40 g mL, 75 mmol) in toluene (50 mL) for 3 hr under reflux. During the reaction, bright yellow crystals of **2a** were deposited. Recrystallization from methanol gave pure **2a** (9.41 g, 87%) as a bright yellow solid, m.p. 175–178°C.

ν_{max} (KBr) 3228, 2234, 1732, 1714, 1587, 1519, 1443, 1292, 1270, 1176, 837, 762 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 8.17 (1H, s, ArCH =), 7.96 (2H, d $J = 8.4$ Hz, $ArH_{C2,C6}$), 6.95 (2H, d $J = 8.4$ Hz, $ArH_{C3,C5}$), 4.37 (2H, q $J = 7.2$ Hz, CH_2CH_3), 1.39 (3H, t $J = 7.2$ Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$) δ 162.7, 162.5, 154.2, 134.0 (2 C), 123.6, 116.4 (2 C), 116.1, 98.6, 62.0, 13.7 ppm.

Anal. Found: C, 66.57; H 5.08; N 6.50. $C_{12}H_{11}NO_3$ req. C, 66.35; H, 5.10; N, 6.45.

Ethyl E-*2-cyano-3-(4-hydroxy-3-methoxyphenyl)-propenoate (**2b**)* was prepared by this method by heating ethyl cyanoacetate (21.29 g, 0.19 mol), vanillin (24.36 g, 0.16 mol), piperidine (3 g, 35 mmol), and acetic acid (13.23 g, 0.221 mol) in toluene (150 mL) for 18 hr under reflux. During the reaction, bright yellow crystals of **2b** were deposited. Recrystallization from methanol gave pure **2b** (34.57 g, 89%) as a bright yellow solid, m.p. 107–109°C.

ν_{max} (KBr) 3375, 3280, 2982, 2229, 1721, 1704, 1577, 1510, 1432, 1275, 1191, 1165, 1096, 1025, 856, 764, 760, 628, 569 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 8.11 (1H, s, ArCH =), 7.83 (1H, d $J = 2.0$–Hz, ArH_{C2}), 7.36 (1H, d $J = 8.2$ Hz, of d, $J = 2.0$ Hz, ArH_{C6}), 6.96 (1H, d $J = 8.2$ Hz, ArH_{C5}), 4.34 (2H, q $J = 7.3$ Hz, OCH_2CH_3), 3.94 (3H, s, OCH_3), 1.37 (3H, t $J = 7.3$ Hz, CH_2CH_3) ppm.

^{13}C NMR ($CDCl_3$) δ 163.3, 155.0, 151.1, 147.0, 128.8, 124.3, 116.5, 115.1, 111.3, 98.9, 62.5, 56.2, 50.8, 14.3 ppm.

Anal. Found: C, 62.89; H 5.30; N 5.64. $C_{13}H_{13}NO_4$ req. C, 63.15; H, 5.30; N, 5.67.

Ethyl E-*2-cyano-3-(1-naphthyl)propenoate (**2c**)* was prepared by this method by heating ethyl cyanoacetate (20.36 g, 0.18 mol), 1-naphthaldehyde (24.98 g, 0.16 mol), piperidine (3 g, 35 mmol), and acetic acid (13.24 g, 0.22 mol) in toluene (150 mL) for 15 hr under reflux. The reaction mixture was evaporated under reduced pressure, and the off-white residue of **2c** was recrystallized from methanol gave pure **2c** (20.5 g, 51%) as a white solid, m.p. 79.5–80°C.

ν_{max} (KBr) 2967, 2925, 2223, 1717, 1602, 1285, 1235, 1082, 781, 759 cm^{-1}.

^{1}H NMR (CD_3COCH_3) δ 9.10 (1H, s, ArCH =), 8.23 (1H, d $J = 7.3$ Hz, ArH_{C2}*), 8.15 (1H, d $J = 8.1$ Hz, ArH_{C4}*), 8.09 (1H, d $J = 8.4$ Hz, ArH_{C5}*), 8.03 (1H, d $J = 8.4$ Hz, ArH_{C8}*), 7.73–7.60 (4H, m, $ArH_{C3,C6,C7}$), 4.4 (2H, q $J = 7.0$ Hz, CH_2CH_3), 1.40 (3H, t $J = 7.0$ Hz, CH_2CH_3) ppm. Assignments of peaks labeled * may be interchanged.

^{13}C NMR (CD_3COCD_3) δ 161.9, 152.6, 133.7, 133.1, 131.5, 129.1, 128.9, 128.0, 127.9, 127.0, 125.4, 123.2, 114.9, 106.9, 62.5, 13.6 ppm.

Anal. Found: C, 76.25; H 5.30; N 5.64. $C_{16}H_{13}NO_2$ req. C, 76.48; H, 5.21; N, 5.57.

Reactions with Hydrazine

A mixture of the cyanocinnamate ester (1.0 eq) and hydrazine (1.1 eq) in ethanol (5 mL/mmol ester) was heated under reflux for 6–10 hr and monitored by TLC (CH_2Cl_2: EtOAc 95 : 5). When TLC analysis showed that the starting ester had been consumed, heating was discontinued and the ethanol was removed by evaporation under reduced pressure. Water (50 mL) was added to the resultant yellow-brown oil, and the mixture was heated to boiling. The solution was cooled in ice and the solid deposited was collected by vacuum filtration, washed with water, and dried. The filtrate was extracted with ether (3 × 50 mL), and the ether extracts were combined, dried, and evaporated to give an oil which was distilled under reduced pressure to give ethyl cyanoacetate.

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p-*Hydroxybenzaldehyde azine* (**5a**, 1.80 g, 90%) was obtained by this method from **2a** (2.17 g, 10.0 mmol) and hydrazine (0.55 g, 11 mmol) in EtOH (50 mL) as a pale yellow solid, m.p. 265–267°C (lit.[12] 268°C). Ethyl cyanoacetate (0.41 g, 36%) was isolated from the filtrate as a colorless liquid, b. 32°C/0.05 mm Hg.

4-Hydroxy-3-methoxybenzaldehyde azine (**5b**, 1.32 g, 88%) was obtained by this method from **2b** (2.47 g, 10.0 mmol) and hydrazine (0.55 g, 11 mmol) in EtOH (50 mL) as a pale yellow solid, m.p. 169–171°C (lit.[12] 174–176). Ethyl cyanoacetate (0.54 g, 48%) was isolated from the filtrate as a colorless liquid, b. 32°C/0.05 mm Hg.

1-Naphthaldehyde azine (**5c**, 1.39 g, 90%) was obtained by this method from **2c** (2.51 g, 10 mmol) and hydrazine (0.55 g, 11 mmol) in EtOH (50 mL) as a pale yellow solid, m.p. 152–153°C (lit.[13] 154–155°C). Ethyl cyanoacetate (0.61 g, 54%) was isolated from the filtrate as a colorless liquid, b. 32°C/0.05 mm Hg.

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