

## Novel Palladium Catalyzed Dehydrogenation of $\alpha$ -Hydrazinonitriles to Hydrazonoyl Cyanides Using Cyclopentene. Synthesis of 1*H*-Pyrazole-4-Carboxylate

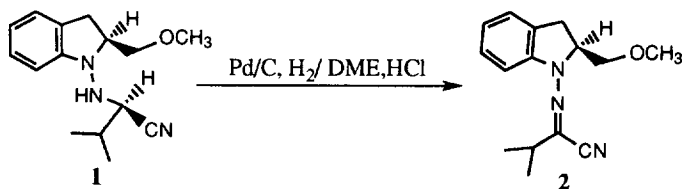
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**Abstract:** Palladium charcoal catalyzed dehydrogenation of  $\alpha$ -hydrazinonitriles has been found to give hydrazonoyl cyanides in the presence of cyclopentene in high yields, which was applied to the synthesis of 1*H*-pyrazole-4-carboxylates. Copyright © 1996 Elsevier Science Ltd

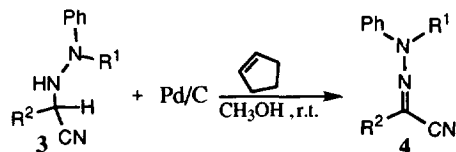
Hydrazones have been extensively utilized as important substrates in heterocyclic synthesis<sup>1</sup> and asymmetric synthesis.<sup>2</sup> Especially, hydrazonoyl halides, aldehyde hydrazones and  $\alpha$ -nitrohydrazones have been used for the generation of nitrile imines, which are well used for 1,3-dipolar cycloadditions.<sup>3</sup> But, there are few reports<sup>4</sup> concerning general syntheses of hydrazonoyl cyanides for the utilization of heterocyclic synthesis.

In this paper, we report a novel palladium<sup>5</sup> charcoal catalyzed dehydrogenation of  $\alpha$ -hydrazinonitriles to hydrazonoyl cyanides in the presence of cyclopentene in high yields. There are many reports concerning stoichiometric<sup>6</sup> or catalytic<sup>5a,7</sup> oxidations of secondary amines to imines but no reports concerning stoichiometric or catalytic oxidation of any kind of hydrazines to hydrazones to our knowledges. During the research for N-N bond cleavage of a chiral  $\alpha$ -hydrazinonitrile **1**<sup>2b,8</sup>, it was unexpectedly found that **1** was dehydrogenated in the presence of Pd/C and H<sub>2</sub> to afford a hydrazonoyl cyanide **2** instead of reductive cleavage of N-N bond.



To examine generality of the present reaction, various  $\alpha$ -hydrazinonitriles **3** were tested as substrates (Table 1).  $\alpha$ -Hydrazinonitriles were prepared from hydrocyanation of aldehyde hydrazones with HCl-NaCN in MeOH-H<sub>2</sub>O at room temperature in 85-90% yields.<sup>9</sup>  $\alpha$ -N,N-Methylphenylhydrazinonitrile **3a** reacted with equimolar amount of commercially available 10% Pd/C in MeOH at room temperature for 3 h to give smoothly a hydrazonoyl cyanide **4a** in 85% yield. But, the stoichiometric use of Pd/C is undesirable from economic and environmental viewpoints. In the case of use of catalytic amount (10 mol %) of Pd/C, most of starting material remained even after 48 h stirring to afford **4a** of trace amounts (below 10%). However, when excess cyclopentene, which is good hydrogen acceptor, was added to the above reaction mixture,

**Table 1. Palladium Catalyzed Oxidation of  $\alpha$ -Hydrazinonitriles to Hydrazonoyl Cyanides Using Cyclopentene.**



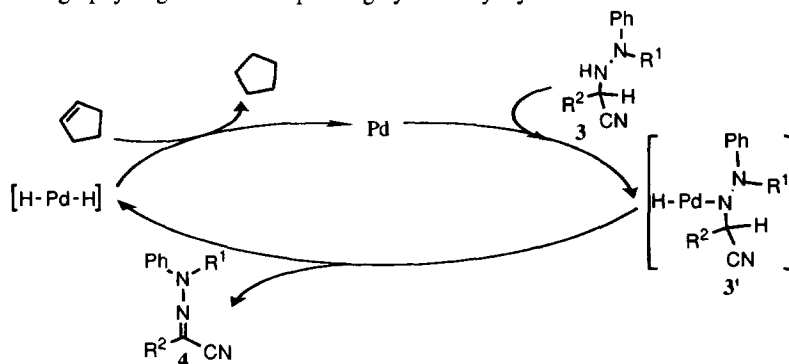
Run	Substrate	R <sup>1</sup>	R <sup>2</sup>	Pd/C*(mol %)	Cyclopentene (eq.)	Time (h)	Product	Yield <sup>b</sup> (%)
1	3a	Me	(CH <sub>3</sub> ) <sub>2</sub> CH	100	-	3	4a	85
2	3a	Me	(CH <sub>3</sub> ) <sub>2</sub> CH	10	-	48	4a	trace
3	3a	Me	(CH <sub>3</sub> ) <sub>2</sub> CH	10	2	3	4a	82
4	3b	Me	CH <sub>3</sub>	100	-	3	4b	83
5	3b	Me	CH <sub>3</sub>	10	2	3	4b	80
6	3c	Me	PhCH <sub>2</sub>	100	-	3	4c	82
7	3c	Me	PhCH <sub>2</sub>	10	2	3	4c	81
8	3d	Me	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	10	2	3	4d	85
9	3e	H	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub>	10	2	10	4e	75
10	3f	H	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	10	2	10	4f	71

a. When Pd(OH)<sub>2</sub> was used, trace amounts of product were obtained.

b. Isolated yield.

surprisingly starting material disappeared completely after 3 h stirring, while cyclohexene had no effect under the same reaction conditions.  $\alpha$ -Substituted **3** (R<sup>2</sup>:Me (**3b**), PhCH<sub>2</sub> (**3c**) and n-Bu (**3d**)) resulted in high yields (80-85%) of **4**.  $\alpha$ -N-Phenylhydrazinonitriles (**3e** and **3f**) were converted into **4** in 75% and 71% respectively without forming any azocompound. Hydrazonoyl cyanides exist as a mixture of *E* and *Z* isomers.<sup>10</sup> Both isomers were observed by <sup>1</sup>H NMR spectroscopy<sup>11</sup> (**4b**, **4e** and **4f**) and a single isomer was observed for others (**4a**, **4c** and **4d**). General experimental procedure is as following:

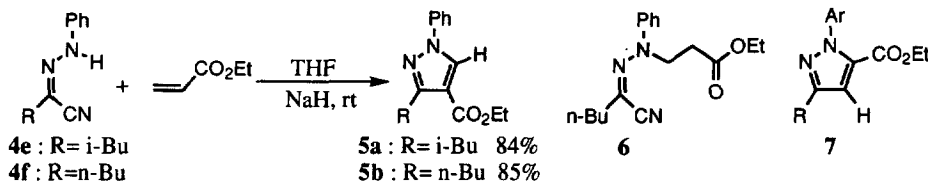
To  $\alpha$ -hydrazinonitrile (1mmol) in MeOH (2 ml) was added 0.1 mmol of commercially available 10 % Pd/C and 2 mmol of cyclopentene at room temperature and stirred for given hours (Table 1). And palladium charcoal was filtered through Celite and the filtrate was condensed under reduced pressure and purified with silicagel chromatography to give the corresponding hydrazonoyl cyanide.<sup>11</sup>



**Figure 1. Oxidative Dehydrogenation of  $\alpha$ -Hydrazinonitriles.**

The present palladium catalyzed dehydrogenation reactions may be rationalized by **Figure 1**.<sup>5</sup> The reaction appears to be initiated by insertion of palladium into the N-H bond of an  $\alpha$ -hydrazinonitrile. Reductive elimination of **3'** gives product **4** and [H-Pd-H], which affords hydrogens to the cyclopentene to reproduce Pd for a catalyst. Similar ruthenium catalyzed activation of C-H bond of the  $\alpha$ -hydrogen of a cyano group has been reported.<sup>12</sup>

$\alpha$ -N-phenylhydrazonoyl cyanide (**4e** and **4f**) turned out to be good substrates for the synthesis of heterocyclic compounds. As one of the applications, N-phenylhydrazonoyl cyanides (**4e** and **4f**) reacted with ethyl acrylate in the presence of NaH to give the corresponding ethyl 3-alkyl-1-phenyl-1H-pyrazole-4-carboxylates (**5a** and **5b**) respectively in high yields (**5a**: 84%, **5b**: 85%)<sup>13</sup>, while formation of 1H-pyrazole-5-carboxylates **7** were not detected. It was reported that 1,3-dipolar cycloaddition from nitrile imine and alkylpropiolate afforded **7** as major product.<sup>14</sup> The cycloadditions may be rationalized by a stepwise path rather than a concerted path<sup>15</sup> which is 1,3-dipolar cycloaddition mechanism of nitrile imines. The reaction appears to involve the conjugate addition of sodium salt of **4e** or **4f** by NaH to ethyl acrylate following by the intramolecular cyclization of the initially formed enolate, accompanying leaving of CN group, and finally following aromatization of pyrazoline to afford thermodynamic stable pyrazoles.<sup>16a</sup> An intermediate **6** of the stepwise reaction was actually isolated in 75% yield and confirmed when the reaction was carried out under mild conditions (reaction temperature: -78 °C-0 °C). The structure of **5** could be characterized by comparison of the chemical shifts (**5a**: 8.33 ppm, **5b**: 8.32 ppm) of proton at the 5 position with those from the similar compounds in <sup>1</sup>H NMR spectrum.<sup>16</sup>



In conclusion, the present reaction provides novel general method for the synthesis of hydrazonoyl cyanide through Pd catalyzed dehydrogenation reaction of  $\alpha$ -hydrazinonitriles in the presence of cyclopentene and thus hydrazonoyl cyanides could be used as the good substrates for the synthesis of 1H-pyrazole-4-carboxylate. Further studies on synthetic application of the present method are in progress.

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  8. The cleavage of N-N bond of hydrazines  $\alpha$ -substituted with alkyl or aryl groups readily occurs by Pd/C system. However, indoline hydrazine **1** containing CN group was oxidized to **2** in 80% yield.
  9. Hydrocyanation reaction of benzaldehyde hydrazone did not occur even under reflux condition.
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  11. **4a**: yellow oil;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  1.24 (6H, dd), 2.83 (1H, m), 3.80 (6H, s), 7.02 (1H, m), 7.28 (4H, m); IR (NaCl) 2191 (CN)  $\text{cm}^{-1}$ ; MS (EI)  $m/z$  201.  
**4b**: mp 49-51  $^\circ\text{C}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  1.96 and 2.29 (3H, 2s, E/Z), 3.47 and 3.81 (3H, 2s, E/Z), 7.04 (1H, m), 7.29 (4H, m); IR (NaCl) 2192 (CN)  $\text{cm}^{-1}$ ; MS (EI)  $m/z$  173.  
**4c**: mp 70-72;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  3.82 (3H, s), 3.83 (2H, s), 7.09 (1H, m), 7.30 (4H, m); IR (NaCl) 2190 (CN)  $\text{cm}^{-1}$ ; MS (EI)  $m/z$  249.  
**4d**: yellow oil;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  0.958 (3H, t), 1.41 (1H, m), 1.65 (1H, m), 2.56 (2H, t), 3.81 (3H, s), 7.04 (1H, m), 7.29 (4H, m); IR (NaCl) 2191 (CN)  $\text{cm}^{-1}$ ; MS (EI)  $m/z$  215.  
**4e**: mp 48-50  $^\circ\text{C}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  0.992 and 1.07 (3H, 2d, E/Z), 2.02 (1H, m), 2.25 and 2.36 (2H, 2d, E/Z), 6.97-7.34 (5H, m), 8.06 and 8.47 (1H, 2s, NH E/Z); IR (NaCl) 2199 (CN)  $\text{cm}^{-1}$ ; MS (EI)  $m/z$  201.  
**4f**: mp 60-62  $^\circ\text{C}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  0.994 and 0.978 (3H, 2t, E/Z), 1.44 (1H, m), 1.65 (1H, m), 2.32 and 2.51 (2H, 2t, E/Z), 6.99-7.34 (5H, m), 7.98 and 8.55 (1H, 2s, NH E/Z); IR (NaCl) 2199 (CN)  $\text{cm}^{-1}$ ; MS (EI)  $m/z$  201.
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  13. General experimental procedure is as following:  
 To a solution of N-phenylhydrazonoyl cyanide **3e** or **3f** (1 mmol) and ethyl acrylate (1.2 mmol) in THF (2ml) was NaH (3 eq) in one portion at room temperature. After 30 min,  $\text{H}_2\text{O}$  was added, and reaction mixture was extracted with  $\text{CH}_2\text{Cl}_2$ , dried over  $\text{MgSO}_4$  and evaporated under reduced pressure. The residue was purified by silica column chromatography to give the corresponding ethyl 3-alkyl-1-phenyl-1H-pyrazole-4-carboxylates.  
**5a**: yellow oil;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  0.957 (6H, d), 1.35 (3H, t), 2.09 (1H, m), 2.82 (2H, d), 4.28 (2H, q), 7.25-7.69 (5H, m), 8.33 (1H, s); IR (NaCl) 1713, 1600, 1547  $\text{cm}^{-1}$ ; MS (EI)  $m/z$  272.  
**5b**: yellow oil;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  0.907 (6H, d), 1.49 (2H, m), 1.69 (2H, m), 2.99 (2H, m), 4.30 (2H, q), 7.29-7.69 (5H, m), 8.32 (1H, s); IR (NaCl) 1716, 1599, 1548  $\text{cm}^{-1}$ ; MS (EI)  $m/z$  272.
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