ORGANIC LETTERS

2002
Vol. 4, No. 22
3955−3957

Oxidative Aromatization of 1,3,5-Trisubstituted Pyrazolines and Hantzsch 1,4-Dihydropyridines by Pd/C in Acetic Acid

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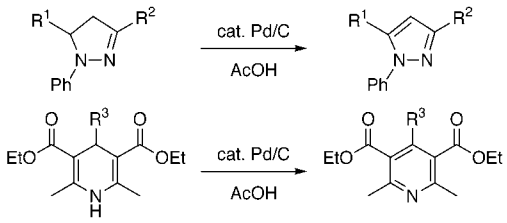
Received August 29, 2002

ABSTRACT



1,3,5-Trisubstituted pyrazolines and Hantzsch 1,4-dihydropyridines were converted to the corresponding pyrazoles and pyridines effectively by the treatment of a catalytic amount of Pd/C in acetic acid.

Five- and six-membered heterocyclic compounds are important constituents that often exist in biologically active natural products and synthetic compounds of medicinal interest.[1] Among them, 1,3,5-trisubstituted pyrazolines can be easily prepared from phenylhydrazine and chalcone derivatives; on the other hand, dihydropyridines are also synthesized by the reaction of aldehydes, β-ketoesters, and ammonia (Hantzsch reaction). Therefore, oxidative aromatization of such dihydro compounds, namely, pyrazolines and dihydropyridines, with some oxidizing reagents should provide an efficient method for the preparation of pyrazole and pyridine derivatives. Actually, pyrazolines have been oxidized to the corresponding pyrazoles by several reagents such as lead tetraacetate,[2] manganese dioxide,[3] mercury oxide,[4] potassium permanganate,[5,6] and silver nitrate.[7] Recently, Singh reported the conversion of 1,3,5-trisubstituted pyrazolines to pyrazoles using iodobenzene diacetate.[8]

Here we report an extremely facile and environmentally friendly method for the preparation of pyrazoles and pyridines by the oxidation of pyrazolines and Hantzsch dihydropyridines, respectively.

We first examined the reaction of 1,3,5-trisubstituted pyrazolines using a Pd/C catalyst. During the course of the screening of a variety of reaction conditions such as solvent, reaction temperature, and the amount of the catalyst, we found that the use of acetic acid as a solvent was essential for the efficient conversion of 1,3,5-trisubstituted pyrazolines to pyrazoles. That is, treatment of 1,3,5-triphenylpyrazoline (**1**) with 20 wt % 10% Pd/C in acetic acid at 80 °C for 6.5 h afforded the 1,3,5-triphenylpyrazole (**7**) in 86% yield.[9] The reactions in CH_3CN and ethanol, which were effective

(1) (a) Gilchrist, T. L. *Heterocyclic Chemistry*, 3rd ed.; Addison-Wesley Longman, Ltd.: England, 1998. (b) Lednicer, D. *Strategies for Organic Drugs Synthesis and Design*; Wiley & Sons: New York, 1998; Chapters 8 and 9.

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(8) Singh, S. P.; Kumar, D.; Prakash, O.; Kapoor, R. P. *Synth. Commun.* **1997**, *27*, 2683−2689.

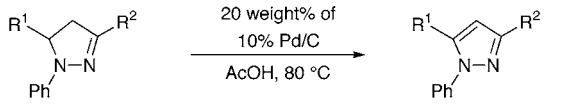
(9) Use of propionic acid as a solvent instead of acetic acid exhibited almost the same results (78% yield).

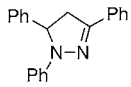
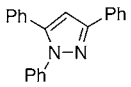
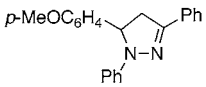
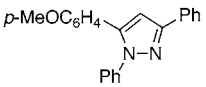
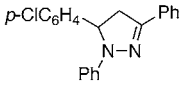
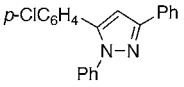
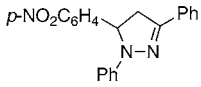
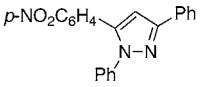
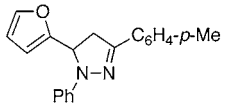
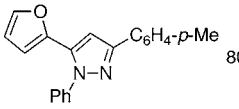
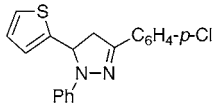
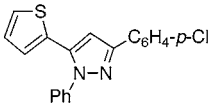
10.1021/ol0268135 CCC: $22.00
Published on Web 10/03/2002

solvents for the oxidation of some allylic and benzylic alcohols by a Pd/C−ethylene system,[10] produced the corresponding pyrazoles only in low yield (1−33% yield). It should be noted that the use of a 1:5 mixture of acetic acid/CH_3CN in the reaction of **1** afforded the product in 81% yield (18 h). Table 1 exemplifies the conversion of 1,3,5-trisubstituted pyrazolines (**1**−**6**) to pyrazoles (**7**−**12**). The pyrazolines possessing a variety of substituents at the 5-position were treated with 20 wt % 10% Pd/C at 80 °C for 5.5−19 h to produce the corresponding pyrazoles in high yield (77–86% yield). We found that when the reactions were run under aerobic conditions (in the presence of air), slow conversion was observed even in the absence of Pd/C. Furthermore, when the oxygen was blown into the reaction mixture, the reaction proceeded efficiently even without Pd/C (Table 2). It took less time to consume starting pyrazolines (1.3−2 h), though the yields of pyrazoles were not so high (45−78%) compared with those of Pd/C-catalyzed reactions. This is due to the formation of *N*-oxides of pyrazolines and pyrazoles, which was confirmed by HPLC-MS spectra (*m*/*z* 314 and 312 for entry 1 in Table 2).[11]

Then, we applied a Pd/C−acetic acid system to the oxidation of Hantzsch 1,4-dihydropyridines to pyridines. This process has also been conventionally done using an excess of oxidizing reagents such as HNO_3,[12] DDQ,[13] $NaNO_2$,[14] $(NH_4)_2Ce(NO_3)_6$,[15] $Cu(NO_3)_2$,[16] and $Bi(NO_3)_5{\cdot}5H_2O$.[17] We found in this process that the Pd/C−acetic acid system also

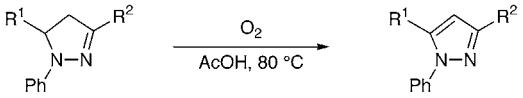
Table 1. Conversionof 1,3,5-Trisubstituted Pyrazoline to Pyrazole Catalyzed by Pd/C[a]

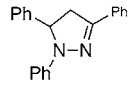
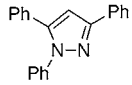
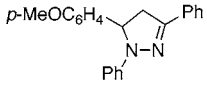
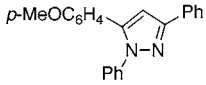
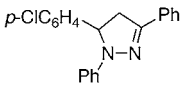
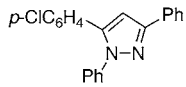
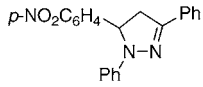
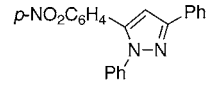
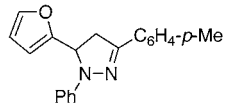
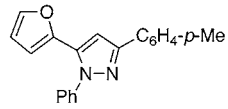
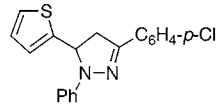
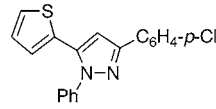


entry	substrate	time/h	product	yield/%[b]
1	 **1**	6.5	 **7**	86
2	 **2**	5.5	 **8**	85
3	 **3**	6.5	 **9**	84
4	 **4**	7.5	 **10**	77
5	 **5**	11	 **11**	80
6	 **6**	19	 **12**	84

[a] All reactions were carried out in a gram scale. [b] Isolated yield.

Table 2. Conversionof 1,3,5-Trisubstituted Pyrazoline to Pyrazole without Pd/C[a]



entry	substrate	time/h	product	yield/%[b]
1		1.3		70
2		1.5		54
3		1.5		62
4		1.5		45
5		2.0		53
6		1.5		78

[a] All reactions were carried out in a gram scale. [b] Isolated yield.

(10) (a) Hayashi, M.; Yamada, K.; Arikita, O. *Tetrahedron Lett*. **1999**, *40*, 1171−1174. (b) Hayashi, M.; Yamada, K.; Arikita, O. *Tetrahedron* **1999**, *55*, 8331−8340. (c) Hayashi, M.; Yamada, K.; Nakayama, S. *Synthesis* **1999**, 1869−1871. (d) Hayashi, M.; Yamada, K.; Nakayama, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1501−1503. (e) Hayashi, M.; Yamada, K.; Nakayama, S.; Hayashi, H.; Yamazaki, S. *Green Chem.* **2000**, 257−260. (f) Hayashi, M.; Kawabata, H. *J. Synth. Org. Chem. Jpn*. **2002**, *60*, 137−144.

(11) Trace amounts of *N*-oxides of pyrazoline and pyrazole were observed even in the reactions under aerobic conditions.

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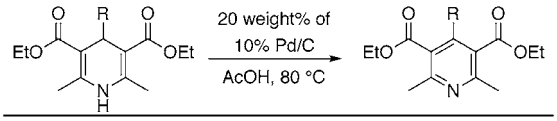
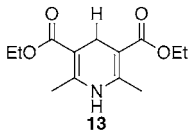
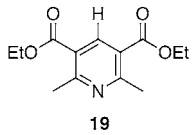
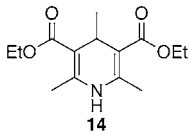
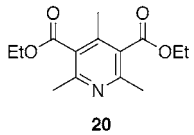
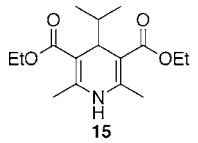
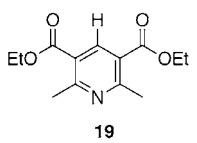
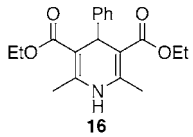
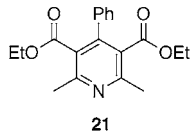
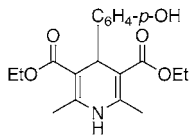
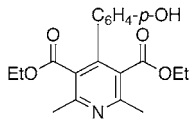
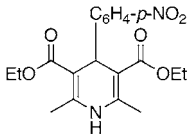
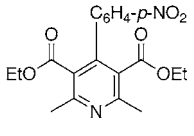
Table 3. Conversion of 1,4-Dihydropyridines to Pyridines Catalyzed by Pd/C[a]



entry	substrate	time/h	product	yield/%[a]
1	 **13**	3.5	 **19**	84
2	 **14**	5.0	 **20**	91
3	 **15**	3.5	 **19**	98
4	 **16**	2.0	 **21**	97
5	 **17**	4.5	 **22**	96
6	 **18**	8.5	 **23**	91

[a] Isolated yield.

exhibited high performance. Treatment of diethyl 4-phenyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**16**) with 20 wt % 10% Pd/C in acetic acid at 80 °C for 2 h afforded the pyridine derivative **21** in 97% yield (99% yield at 50 °C for 15 h). In this case also, the use of CH_3CN and ethanol as a solvent was ineffective (11% yield at 80 °C for 24 h). The Hantzsch 1,4-dihydropyridines possessing a variety of substituents such as H, Me, *i*-Pr, Ph, *p*-OH−C_6H_4, and *p*-NO_2−C_6H_4 at the 4-position (**13**−**18**) were oxidized to the corresponding pyridine derivatives (**19**−**23**) in high yield (Table 3). It should be mentioned the reaction of the 1,4-dihydropyridine **15** bearing an isopropyl group at the 4-position afforded the dealkylated pyridine **19** in 98% yield.

The above-mentioned oxidative aromatization step is also important for the synthesis of pyrazole and pyridine derivatives, because the introduction of substituents such as alkyl groups into the inherent heteroaromatic compounds destroys the aromaticity and reoxidation would be required.

In conclusion, we have disclosed an extremely facile and environmentally benign oxidative aromatization process to convert 1,3,5-trisubstituted pyrazolines and 1,4-dihydropyridines to the corresponding pyrazoles and pyridines by the use of a catalytic amount of Pd/C in acetic acid.[18] We are aware that the present Pd/C-catalyzed oxidative aromatizations in acetic acid do not include the simple dehydrogenation step. When the reaction was done under an ethylene atmosphere, ethylene was not hydrogenated to ethane, which was in contrast with the dehydrogenation of allylic alcohols[10e] and 1,2,3,4-tetrahydroisoquinoline in CH_3CN.[19] A study of the detailed reaction mechanism, including the role of acetic acid, is now in progress in our laboratory.

Acknowledgment. This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0268135

(18) Typical procedure is as follows (entry 1 in Table 1). A 200 mL flask was charged with 1,3,5-triphenylpyrazoline (**1**) 1.02 g (3.42 mmol), acetic acid (15 mL), and 200 mg (20 wt %) of 10% Pd/C. The mixture was warmed to 80 °C and stirred for 6.5 h at this temperature. After confirmation of the consumption by TLC analysis, Pd/C was filtered off using Celite. The filtrate was then poured into saturated $NaHCO_3$ and extracted with ethyl acetate (40 mL × 3). After usual workup, the obtained residue was column chromatographed on silica gel to afford 1,3,5-triphenylpyrazole (**7**) 0.87 g (86%) as a pale yellow solid. Mp 141–142 °C (lit.[8] 138–139 °C).

(19) Reaction of 1,2,3,4-tetrahydroisoquinoline with 50 wt % 10% Pd/C in CH_3CN under an ethylene atomsphere (80 °C, 48 h) gave isoquinoline in 79% yield. In this reaction, ethylene was hydrogenated to ethane, which was confirmed by GLC analysis.