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A Novel Application of the Oxidizing Properties of Pyridinium Chlorochromate : Aromatization of Hantzsch 1,4-Dihydropyridines

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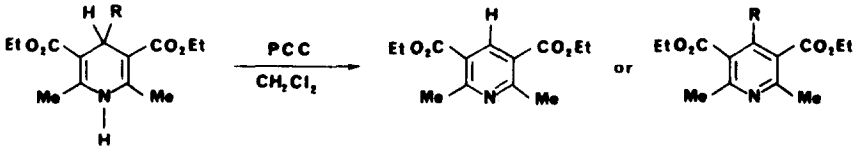
Abstract: diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates can be readily oxidized under neutral conditions using pyridinium chlorochromate adsorbed on a solid support.

It has been reported[1, 2] that clay-supported cupric nitrate ("Claycop"[1, 3]) is a mild reagent to oxidize diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates (Hantzsch 1,4-DHP). Reactions can be carried out in a neutral solvent (chloroforme[1] or dichloromethane[2]) at room temperature. However the method cannot be used in the 4-alkyl series even under sonication.[2] Because of our current interest in oxidation processes,[4, 5] we sought another mild reagent but of wider applicability than "Claycop". As chromium (VI) oxide,[6] in boiling acetic acid, had been sometimes used to oxidize 1,4-DHP, we thought that an oxochromium-amine complex[7] should be tested as such reagents can act under neutral conditions.

Thus we found that pyridinium chlorochromate[8] (PCC) is remarkably efficient in oxidizing 1,4-DHP in dichloromethane. But during preliminary experiments we encountered several difficulties to isolate the final products because of the formation of black gums at the end of the reactions. To obtain superior results we decided to use PCC in conjunction with a solid (alumina, silica gel, or montmorillonite K-10 clay). Such supported systems were readily prepared by adding the solid to a solution of PCC in acetone and by removing the solvent under reduced pressure. The so-obtained orange powders can be dried at 100° C and stored for several weeks (at least) without any decrease of their efficiency. The advantage of using a solid support is that it acts as an in situ absorbent of the reduced chromium tars. Therefore the work-up procedure is easier and consits in a mere filtration.

The only drawback that we noticed is the necessity of using a modest excess (2 equivalents) of oxidant to complete the reactions.[9] However it is largely offset by the excellent yields of isolated products (more than 90 %) and by the simplicity of the method.

Inspection of our results (see Figure and Table 1) reveals that dealkylation (in addition to aromatization) occurs when the 1,4-DHP bears a secondary alkyl group or a benzyl group at the 4-position (pyridine **14** was identified without any ambiguity by the presence of a singlet due to the H^4 proton at 9.4 ppm in the nmr spectra of the crude reaction products). This is a general trend in the oxidation of 1,4-DHP and it is explained by a sequence proceeding by a hydride abstraction in the first step.[10]



1-13 **14** **15-23**

Fig. Oxidation of 1,4-DHP by solid-supported PCC.

Our method, which uses dichloromethane as a solvent, also offers the possibility of optimizing reaction times because syntheses can be monitored by ^1H nmr. Indeed 1,4-DHP and final pyridines are soluble in that solvent, contrary to PCC so that nmr spectra can be recorded in good conditions and without significant broadening of the peaks. Furthermore mean signals do not interfere with the solvent peak (δ $\underline{CH_2Cl_2}$: 5.4 ppm). 1,4-DHP are characterized (see Tables 2 and 3) by an intense singlet around 2.2 ppm due to the protons of the methyl groups in positions 2 and 6 of the ring whereas the corresponding protons in the oxidized products resonate around 2.5 ppm. Therefore quantitative data can be easily obtained by measuring the variations of intensity of those peaks. This way we observed (Table 1) that reaction times are strongly dependent on the nature of the substituent at the 4-position in the starting heterocycles. 4-Alkyl derivatives are readily oxidized while aromatization of 4-(hetero)aryl derivatives requires several hours. However we noticed that reaction times can be shortened by reducing the particle size of the support (methods B-D, G) or by heating the reaction mixture (methods F, G). In our hands sonication[11] did not give impressive results (method E) but we wish to emphasized that final products were always obtained in high yields independently of the nature of the 1,4-DHP and of the method.

To our knowledge aromatization of 1,4-DHP represents the first example of the use of PCC to oxidize heterocycles and further investigations in that field are in progress in our laboratory.

Table 1. Aromatization of Hantzsch 1,4-DHP by solid-supported PCC.[a]

R	1,4-DHP N°	Product N°	Time (method)
H-	1	14	5 min (A)
C_2H_5-	2	15	1 h (A)
C_3H_7-	3	16	4 h (A) 30 min (B) 1 h (C) 30 min (D) 2 h (E)
$(CH_3)_2$-CH-	4	14[b]	30 min (A) 15 min (B) 15 min (C) 15 min (D)
$(C_6H_5)_2$-CH-	5	14[c]	5 min (A)
C_6H_5-CH_2-	6	14[d]	30 min (A)
C_6H_5-	7	17	8 h (A) 5 h (B) 2 h (C) 2 h (D) 6 h (E)
4-(OCH_3)-C_6H_4-	8	18	5 h (A)
4-Cl-C_6H_4-	9	19	15 h (A)
3-(NO_2)-C_6H_4-	10	20	26 h (A)
4-(NO_2)-C_6H_4-	11	21	17 h (A)
2-Furyl-	12	22	24 h (A)
2-Thienyl-	13	23	26 h (A) 9 h (B) 5 h (C) 6 h (D) 8 h (F) 2 h (G)

a: final products are isolated in yields exceeding 90%; b: presence of 2-propanol and acetone in the reaction mixture; c: presence of benzophenone in the reaction mixture; d: presence of benzyl alcohol and benzaldehyde in the reaction mixture.

EXPERIMENTAL

Preparation of solid-supported PCC

The solid support (200 g) was added to a solution of PCC (45 g; 190 mmols) in acetone (200 ml). The solvent was evaporated under reduced pressure and the resulting solid was dried at 100°C for two hours.

Oxidation procedures

Method A. The 1,4-DHP (10 mmols) was rapidly added to a stirred suspension of neutral alumina (50-200 μ)-supported PCC (36 g corresponding to 30 mmols of PCC) in dichloromethane. After the period quoted in Table 1, the solid was eliminated by filtration and the solution was concentrated under reduced pressure to yield the crude final product.

Method B. Same procedure as method A but with neutral alumina 10-40 μ.

Method C. Same procedure as method A but with silica gel 10-40 μ.

Method D. Same procedure as method A but with montmorillonite K-10 clay (2 μ).

Method E. A suspension of 1,4-DHP (10 mmols) and neutral alumina (50-200 μ)-supported PCC (36 g) was sonicated (VC 375 Ultrasonic Processor; Sonics and Materials, Inc.) for the period quoted in the Table. The work-up procedure was the same as in method A.

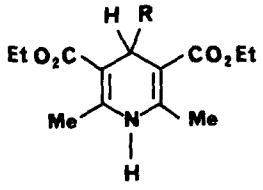
Method F. Same procedure as method A but in refluxing dichloromethane.

Method G. Same procedure as method A but with neutral alumina 10-40 μ and in refluxing dichloromethane.

1,4-DHP were prepared by a standard procedure[12] or by a novel method[5] that will be published elsewhere.

All compounds are described in the literature (**1**,[13] **2**,[14] **3**,[15] **4**,[14] **5**,[16] **6**,[17] **7**,[18] **8**,[19] **9**,[20] **10**,[20] **11**,[21] **12**,[18] **13**,[22] **14**,[14] **15**,[14] **16**,[15] **17**,[23] **18**,[19] **19**,[24] **20**,[25] **21**,[25] **22**,[26] and **23**[27]) and were fully characterized by their spectral data (^{1}H nmr: Varian EM-360 L; I.R.: Perkin-Elmer 577; M.S.: Varian Mat 311A) and m.p. (uncorrected, hot-stage microscope).

Table 2. nmr Data ($CDCl_3$ - δ in ppm) of Diethyl 1,4-Dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates 1 - 13.



1 - 13

N°	R	δ R	δ C⁴-H
1	H-	3.2(s)	3.2(s)
2	C_2H_5-	1.2-0.8(5H)[a]	4.1[a]
3	C_3H_7-	1.2-0.8(7H)[a]	4.1[a]
4	$(CH_3)_2$-CH-	1.3(1H)[a]; 0.8(d-6H)	4.1[a]
5	$(C_6H_5)_2$-CH-	7.5-7.0(c-10H); 3.8(1H)[a]	4.9(d)
6	C_6H_5-CH_2-	7.4-6.9(c-5H); 2.6(d-2H)	4.1[a]
7	C_6H_5-	7.3-7.0(c-5H)	5.0(s)
8	4-(OCH_3)-C_6H_4-	7.3(d-2H); 6.7(d-2H); 3.7(s-3H)	5.0(s)
9	4-Cl-C_6H_4-	7.2(s-4H)	4.9(s)
10	3-(NO_2)-C_6H_4-	8.0-7.2 (c-4H)	5.0(s)
11	4-(NO_2)-C_6H_4-	8.2(d-2H); 7.5(d-2H)	5.1(s)
12	2-Furyl-	7.1(s);6.1(c-1H); 5.85(c-1H)	5.1(s)
13	2-Thienyl-	7.1-6.4(c-3H)	5.1(s)

δ $C\underline{H}_3$-: 2.2(s); δ -CO_2-$C_2\underline{H}_5$: 4.0(q-4H); 1.1(t-6H) ppm; δ $N\underline{H}$: variable

[a]: overlapped by other signals.

Table 3. nmr Data ($CDCl_3$ - δ in ppm) of Diethyl 2,6-Dimethyl-3,5-pyridinedicarboxylates 14 - 23.

14 - 23

N°	R	δ R
14	H-	9.4(s-1H)
15	C_2H_5-	2.6(2H)[a]; 1.2(3H)[a]
16	C_3H_7-	2.6(2H)[a]; 1.6-0.8(5H)[a]
17	C_6H_5-	7.1(s-5H)
18	4-(OCH_3)-C_6H_4-	7.2(d-2H); 6.9(d-2H); 3.3(s-3H)
19	4-Cl-C_6H_4-	7.1(c-4H)
20	3-(NO_2)-C_6H_4-	8.2(c-2H); 7.5(c-2H)
21	4-(NO_2)-C_6H_4-	8.2(d-2H); 7.4(d-2H)
22	2-Furyl-	7.5(c-1H); 6.6-6.3(c-2H)
23	2-Thienyl-	7.3-6.7(c-3H)

δ CH_3-: 2.5 (s-6H); δ-$CO_2C_2H_5$: 4.3(q-4H); 1.2(t-6H) ppm
[a]: overlapped by other signals.

REFERENCES

1. Balogh, M.; Hermecz, I.; Meszaros, Z.; Laszlo, P. Helv. Chim. Acta **1984**, 67, 2270.
2. Maquestiau, A.; Mayence, A.; Vanden Eynde, J.-J. Tetrahedron Lett. **1991**, 32, 3839.
3. Laszlo, P.; Cornelis, A. Aldrichimica Acta **1988**, 21, 97.
4. Maquestiau, A.; Berte, L.; Mayence, A.; Vanden Eynde, J.-J. Synth. Commun. submitted.
5. Mayence, A. Novel Syntheses of Heterocycles Assisted by Pyridinium Salts University of Mons-Hainaut **1991**.
6. Sausins, A.; Duburs, G. Heterocycles **1988**, 27, 291.
7. Luzzio, F.A.; Guziec, F.S., Jr. Org. Prep. Proc. Int. **1988**, 20, 533.
8. Piancatelli, G.; Scettri, A.; D'Auria, M. Synthesis **1982**, 245.
9. Cheng, Y.-S.; Liu, W.-L.; Chen, S.-H. Synthesis **1980**, 223.
10. Loev, B.; Snader, K.M. J. Org. Chem. **1965**, 30, 1914.
11. Adams, L.L.; Luzzio, F.A. J. Org. Chem. **1989**, 54, 5387.
12. Norcross, B.E.; Clement, G.; Weinstein, M. J. Chem. Educt. **1969**, 46, 694.
13. Hantzsch, A. Ann. **1882**, 215, 1.

14. Engelman, F. Ann. **1885**, 231, 37.
15. Jaeckle, A. Ann. **1888**, 246, 32.
16. Materne, C. Ger. Offen. DE 3021958 AI, Chem. Abstr. **1982**, 96, 122639.
17. Jeanrenaud, A. Ber., **1888**, 21, 1783.
18. Schiff, R.; Puliti, J. Ber. **1883**, 16, 1607.
19. Emmert, D.; Diefenbach, E.; Eck, R. Ber. **1927**, 60, 2220.
20. von Walther, W.; Raetze, R. J. Prakt. Chem. **1902**, 65, 287.
21. Lepetit, R. Ber. **1887**, 20, 1338.
22. Loev, B.; Goodman, M.; Kenneth, M.; Tedeschi, R.; Macko, E. J. Med. Chem. **1974**, 17, 956.
23. Skraup, S. Ann. **1919**, 419, 58.
24. Hinkel, L.E.; Madel, W.R. J. Chem. Soc. **1929**, 750.
25. Cook, A.H.; Heilborn, J.M., Steger, L. J. Chem. Soc. **1943**, 413.
26. Heiber, F. Ber. **1892**, 25, 2405.
27. Grischkewitsch-Trochimowski, G.; Mazurewitsch, M. Chem. Zentr. **1912**, 6, 1562.