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# AROMATIZATION OF HANTZSCH 1,4-DIHYDROPYRIDINES WITH MAGTRIEVE™

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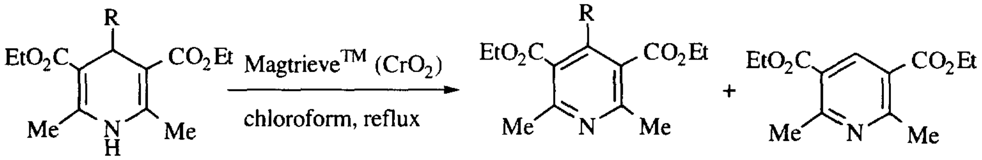
**ABSTRACT**: Hantzsch 1,4-dihydropyridines (1,4-DHPs) can be aromatized to pyridines by refluxing in chloroform with Magtrieve™ in high yields.

Aromatization of Hantzsch 1,4-dihydropyridines (Hantzsch 1,4-DHPs) has attracted considerable attention due to the fact that 1,4-DHPs based antihypertensive drugs ($Ca^{2+}$ channel blockers) are oxidatively converted to pyridine derivatives by the action of cytochrome P-450 in the liver.[1] Also, some Hantzsch 1,4-DHPs act as NADH mimics that can reduce the carbonyl groups.[2] During this reduction process, 1,4-DHPs are oxidized to pyridines. Furthermore, the oxidation of Hantzsch 1,4-DHPs provides an easy access to pyridine derivatives.

Oxidation of 1,4-DHPs has been achieved using various oxidants.[3] However, some methods suffer from low chemical yields,[4] strong oxidative conditions,[3a-b,h] cumbersome workup[3j-k] or side-product formation.[3j] Therefore, it is still necessary to find a milder and high-yielding oxidant for the Hantzsch 1,4-DHPs.

Recently, Magtrieve™, a magnetically retrievable and environmentally safe oxidant ($CrO_2$) has been shown to oxidize alcohols in high yields.[5] This report prompted us to examine its potential as an oxidant for the Hantzsch 1,4-DHPs. We now report that Magtrieve™ can indeed serve as a mild oxidant for the aromatization of the Hantzsch 1,4-DHPs in high yields (>90%).[6]

As shown in Table, the oxidation of **1a** was completed within 2 h in chloroform or toluene. However, the oxidation was slower in lower-boiling dichloromethane solvent. Afterward, we used chloroform solvent, except for **1d** which was slightly soluble in chloroform. The oxidation was very clean, as evidenced by the absence of any side products in TLC. Compared to other methods, the workup procedure was very simple; decanting followed by the concentration of the solution gave the pyridine product in high yield. This crude product was pure based on proton NMR analysis and could be further purified by crystallization or column chromatography. As previously observed by other research groups,[3c-d] 1,4-DHPs **1e** and **1h** bearing a benzyl group or an isopropyl group at the 4-position underwent simultaneous dealkylation to give **3**.



**1a-i** **2a-i** **3**

In summary, we have found that Magtrieve™ can serve as a mild and clean oxidant for the aromatization of Hantzsch 1,4-dihydropyridines to pyridines in high yields, giving an additional benefit of easy workup.

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Table. Aromatization of Hantzsch 1,4-Dihydropyridines with Magtrieve™

| 1,4-DHPs | R | Solvent | Oxidant[a] | Time | Pyridines[b] | Yield %[c] | mp (°C) | Lit. mp (°C) |
|---|---|---|---|---|---|---|---|---|
| **1a** | $C_6H_5$ | $CHCl_3$ | 1.51 g | 2 h | **2a** | 97 | 60-61 | 61-62[1a] |
| **1a** | $C_6H_5$ | $CH_2Cl_2$ | 1.68 g | 3 h | **2a** | 96 | | |
| **1a** | $C_6H_5$ | toluene | 1.51 g | 2 h | **2a** | 95 | | |
| **1b** | $3\text{-}NO_2C_6H_4$ | $CHCl_3$ | 2.02 g | 3 h | **2b** | 97 | 61-62 | 61-63[3g] |
| **1c** | $2\text{-}ClC_6H_4$ | $CHCl_3$ | 1.68 g | 2 h | **2c** | 96 | 61-62 | 62[7] |
| **1d** | $4\text{-}HOC_6H_4$ | acetone | 2.18 g | 6 h | **2d** | 97 | 168-169 | 171[3k] |
| **1e** | $C_6H_4CH_2$ | $CHCl_3$ | 1.68 g | 2 h | **3** | 98 | 72-73 | 70-71[3k] |
| **1f** | $C_6H_4CH{=}CH_2$ | $CHCl_3$ | 1.68 g | 2 h | **2f** | 93 | 162-163 | 162-163[3k] |
| **1g** | $CH_3$ | $CHCl_3$ | 1.68 g | 2 h | **2g** | 94 | oil | oil[3g] |
| **1h** | $(CH_3)_2CH$ | $CHCl_3$ | 1.68 g | 2 h | **3** | 98 | 72-73 | 70-71[3k] |
| **1i** | $CH_3CH_2CH_2$ | $CHCl_3$ | 1.68 g | 2 h | **2i** | 95 | oil | oil[3g] |

a: the amount of Magtrieve™ (available from Aldrich) used per 1.0 mmol of 1,4-DHPs. b: all products are known compounds and were characterized by their mps and NMR spectra. c: yield refers to the isolated pure product.

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## References and Notes

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2. Meyers, A. I.; Brown, J. D. *J. Am. Chem. Soc.* **1987**, *109*, 3155.
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4. For example, it has been reported that the oxidation of **1f** using bismuth nitrate pentahydrate[3j] and $RuCl_3/O_2$[3k] gave pyridine **2f** in 50% and 20% yields, respectively.
5. Lee, R. A.; Donald, D. S. *Tetrahedron Lett.* **1997**, *38*, 3857.
6. In a typical experiment, a solution of Hantzsch 1,4-DHP (**1a**, 330 mg, 1 mmol) in chloroform (15 ml) was treated with Magtrieve™ (1.51 g) and the mixture was stirred at reflux. The progress of the reaction was monitored by thin layer chromatography (for **1a**, $R_f$ = 0.20; for **2a**, $R_f$ = 0.36 in hexanes/EtOAc = 5/1). After 2 h, the reaction was found to be complete. Workup was carried out, as suggested in the literature[5]; magnet was placed on one side of the flask and the solution was decanted. The solvent was removed using a rotary evaporator under reduced pressure and the resulting crude product was crystallized to give 320 mg (97% yield) of **2a** as a pale yellow solid, mp 60-61 °C (Lit.[1a] mp 61-62 °C). Recovered Magtrieve™ can be reconverted to the active form by heating in air at 300-350 °C for 1-2 hrs.[5]
7. *Beilstein* E II **22**, 127.