Rapid, High-Yield Oxidation of Hantzsch-Type 1,4-Dihydropyridines with Ceric Ammonium Nitrate[1]

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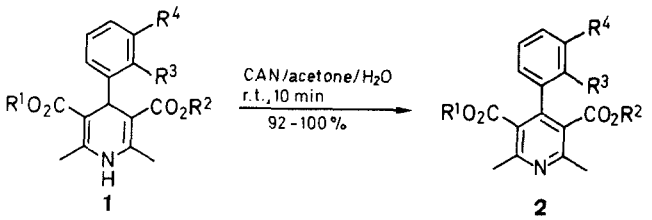
4-Aryl-2,6-dimethyl-1,4-dihydro-3,5-pyridinedicarboxylates, Hantzsch-type 1,4-dihydropyridines, are rapidly oxidized to the corresponding pyridine derivatives in excellent yields using two equivalents of ceric ammonium nitrate.

Calcium entry blockers of the 1,4-dihydropyridine type are rapidly emerging as one of the most important classes of drugs for the treatment of cardiovascular disease.[2] These compounds generally undergo oxidative first pass metabolism in the liver to form the corresponding pyridine derivatives. Further metabolism involves cleavage of the ester groups.[3] Since these metabolites are important as reference standards, a convenient and high-yield method for the oxidation of the dihydropyridines would be of interest, particularly for the synthesis of the respective radiolabeled compounds.

Although a plethora of reagents has been utilized for this oxidation,[4] heating the substrates with nitric acid is the method most often used.[3,5] However, yields are often moderate, especially when the substrate contains a free carboxylic acid group in the 3-position. This may be due to the fact that, as vinylogous carbamic acids, these compounds can undergo decarboxylation when heated.

In the present work, it was found that ceric ammonium nitrate[6] (CAN) rapidly and cleanly oxidizes 1,4-dihydropyridine-3,5-dicarboxylates to the corresponding pyridine derivatives (Scheme **A**) according to the stoichiometry indicated in Scheme **B**. Although CAN slowly attacks many organic solvents (even acetonitrile, which appears to be the solvent of choice for CAN oxidations), a variety of solvents were found acceptable for this application; the most convenient of these being acetone. Adding an aqueous solution of CAN (2.0 equivalents) to an acetone solution of the substrate **1** at ambient temperature or below rapidly gave the pyridines **2** in excellent yield (Table), which appears to be limited only by the purity of the starting material and the efficacy of the isolation procedure.

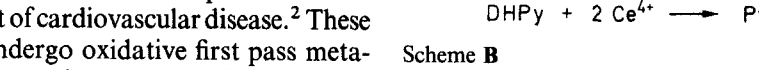


1 2

CAN = ceric ammonium nitrate

1, 2	R^1	R^2	R^3	R^4
a	Me	Me	CF_3	H
b	Me	Me	Cl	H
c	Me	Me	NO_2	H
d	Me	Me	Me	H
e	Me	Me	H	MeO
f	Et	Et	H	H
g	$PrO(CH_2)_2$	$PrO(CH_2)_2$	H	NO_2
h	Me	Et	Cl	H
i	Me	Et	H	NO_2
j	Me	H	H	NO_2
k	Et	H	Cl	H

Scheme **A**



Scheme **B**

Because CAN is relatively expensive, it was of interest to investigate the possibility of utilizing the catalytic CAN oxidation system with sodium bromate as the co-oxidant.[7] Again using aqueous acetone as the solvent in the presence of CAN (0.1 equivalents) and sodium bromate (2.0 equivalents) at room temperature, only traces of the expected pyridine derivatives were observed. This

Table. Pyridines **2a–k** Prepared

Product	Yield[a,b] (%)	mp[c] (°C)	Molecular Formula[d] or Lit. mp (°C)	MS[e] (*m/z*)
2a	~100	97–98	$C_{18}H_{16}NO_4F_3$ (367.3)	368 ($M^+ + 1$), 367 (M^+), 347, 336, 281, 88
2b	98	69–71	$C_{17}H_{16}NO_4Cl$ (333.8)	302 ([M – OCH_3]$^+$), 299 ([M – Cl]$^+ + 1$), 298 ([M – Cl]$^+$), 266, 252, 224, 134, 105
2c	92[f]	104–105	106[9]	
2d	~100	78–79	$C_{18}H_{19}NO_4$ (313.3)	314 ($M^+ + 1$), 313 (M^+), 281, 250, 222, 194, 152
2e	~100	70–71	$C_{18}H_{19}NO_5$ (329.3)	330 ($M^+ + 1$), 329 (M^+), 297, 266, 265, 238, 210
2f	~100	60–61	61–62[3]	
2g	~100	50–51	43–45[3]	
2h	~100	47–48	$C_{15}H_{18}NO_4Cl$ (347.8)	313 ([M – Cl]$^+ + 1$), 312 ([M – Cl]$^+$), 285, 284, 252, 224
2i	~100	59–61	61–62[10]	
2j	94	198–200	201–202[10]	
2k	93	209–211	$C_{17}H_{16}NO_4Cl$ (333.8)	299 ([M – Cl]$^+ + 1$), 298 ([M – Cl]$^+$), 271, 270, 252, 224

[a] Yield of isolated, pure product.
[b] The disappearance of the singlet at $\delta = 5.0$–5.3 in the ^{1}H-NMR spectrum (DHP CH-4) was diagnostic.
[c] Melting points were determined with a Mel-Temp apparatus and are uncorrected.
[d] Satisfactory microanalyses obtained.
[e] Obtained on a Varian MAT 311A instrument.
[f] Isolated by addition of H_2O, concentration, and suction filtration of crystalline product.

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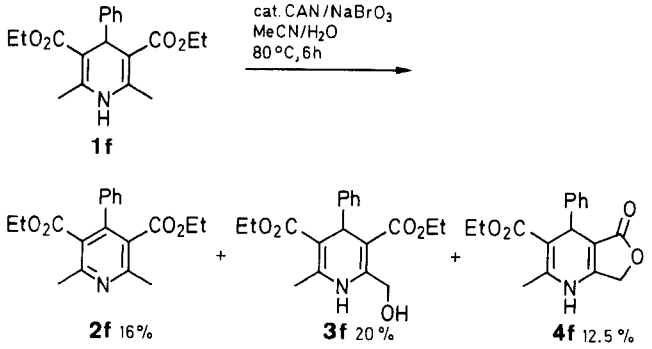
may be explained by the occurrence of a Belousov–Zhabotinskii reaction,[8] in which acetone would be acting as a reducing agent, forming bromoacetone, and thereby consuming the oxidants. Replacing the acetone by acetonitrile and using **1f** as the substrate at 80 °C, only a small amount of the expected **2f** was formed. In this case, the two other products were identified as the hydroxymethyl derivative **3f** and the lactone **4f** (Scheme **C**). The formation of these products can again be rationalized in terms of a Belousov–Zhabotinskii reaction, leading to the formation of the 2-bromomethyl derivative of **1f**, followed by solvolysis to **3f** and partial lactonization to **4f**. No reaction was observed when this experiment was carried out using sodium bromate alone.



Scheme **C**

The known starring materials **1a**,[11] **1b**,[12] **1c** (nifedipine),[13] **1d**[14], **1e**[15], **1f**[11], **1g** (niludipine),[16], **1h**,[17] **1i** (nitrendipine),[18] and **1j**[19] were prepared using variants of the Hantzsch condensation.[20] Compound **1k** (mp 168–169 °C) was obtained by β-elimination of the corresponding 2-cyanoethyl ester under mild alkaline conditions.[21]

Pyridines 2; General Procedure:

To a solution of the dihydropyridine (**1**; 2 mmol) in acetone (15 mL) is added a solution of ceric ammonium nitrate (CAN; 2.19 g, 4 mmol) in H_2O (3.5 mL) fairly rapidly dropwise from a hand-held pipette at r.t. The orange color of the reagent disappears immediately on addition of each drop. After stirring for 10 min, the resulting solution is concentrated to a small volume under reduced pressure. H_2O (20 mL) is added and the mixture is extracted with CH_2Cl_2 (2 × 30 mL). The organic phase is washed with brine (20 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The resulting pyridines are homogeneous by TLC (30% acetone/hexane). Analytical samples can be prepared by recrystallization from pentane at −20 °C; these compounds are appreciably soluble at r.t. in most organic solvents.

Reaction of 1f with CAN/$NaBrO_3$ in aqueous MeCN:

A solution of **1f** (1.32 g, 4 mmol), CAN (220 mg, 0.4 mmol), and $NaBrO_3$ (1.2 g, 8 mmol) in $MeCN/H_2O$ (35 mL, 4:1) is stirred vigorously at 80 °C for 6 h. The cooled mixture is diluted with H_2O (150 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts are washed with brine (50 mL) and dried ($MgSO_4$). The residue obtained after evaporation is chromatographed on silica gel (gradient 1:2 EtOAc/hexane to EtOAc), successively eluting, to give, in addition to **2f** (210 mg) and unreacted **1f** (550 mg), the following compounds:

3f; 270 mg (20%); mp 145–146 °C.

$C_{19}H_{24}NO_5$ (346.4) calc. C 65.87 H 6.98 N 4.04; found 65.93 6.80 3.87

MS (DEI): m/z = 346 (M^+).

IR (KBr): ν = 3385 (OH), 1690 cm^{-1} (CO_2Et).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.22 (t, 3H, J = 3 Hz, $CO_2CH_2C\underline{H}_3$), 2.36 (s, 3H, CH_3), 2.87 (t, 1H, J = 2 Hz, OH), 4.08 (q, 2H, J = 3 Hz, $CO_2C\underline{H}_2CH_3$), 4.77 (d, 2H, J = 2 Hz, CH_2), 4.98 (s, 1H, CH), 7.02 (s, 1H, NH), 7.22 (m, 5H_{arom}).

4f; 150 mg (12.5%); mp 180–182 °C.

$C_{17}H_{17}NO_4$ (299.3) calc. C 68.21 H 5.72 N 4.67; found 67.87 5.82 4.53

MS (DEI): m/z = 299 (M^+).

IR (KBr): ν = 3260 (NH), 1713 (CO), 1699 cm^{-1} (CO_2Et).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.1 (t, 3H, J = 3 Hz, $CO_2CH_2C\underline{H}_3$), 2.37 (s, 3H, CH_3), 4.01 (q, 2H, J = 3 Hz, $CO_2C\underline{H}_2$ CH_3), 4.51 (d, 2H, J = 1 Hz, CH_2), 4.88 (s, 1H, CH), 7.27 (m, 5H_{arom}), 7.73 (s, 1H, NH).

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