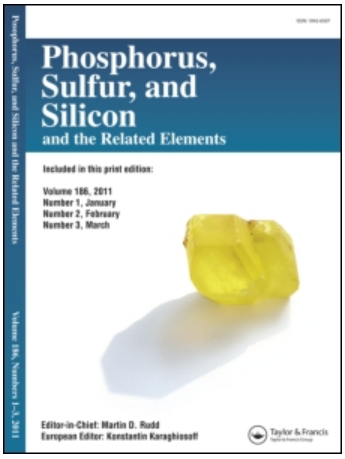

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CARO'S ACID SUPPORTED ON SILICA GEL. PART 7: A VERSATILE REAGENT FOR THE AROMATIZATION OF HANTZSCH 1,4-DIHYROPYRIDINES UNDER NON-AQUEOUS CONDITION AND MICROWAVE IRRADIATION

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Efficient oxidation of 1,4-dihydropyridines with Caro's acid on silica gel is achieved under nonaqueous conditions and in a domestic microwave oven. The reactions under microwave irradiation were shorter in duration and higher in yields than the reactions in conventional method, confirming the potentiality of microwave heating in aromatization of Hantzsch 1,4-dihydropyridines.

Keywords: Caro's acid; dihydropyridines; oxidation; silica gel

Amlodipine besylate, nifedipine, and related dihydropyridines are Ca^{2+} channel blockers, and are rapidly emerging as one of the most important classes of drugs for the treatment of cardiovascular diseases including hypertention. In the human body it has been observed that these compounds undergo oxidation to form pyridine derivatives. These oxidized compounds are largely devoid of the pharmacological activity of the parent compounds. Additionally, dihydropyridines are often produced in a synthetic sequence which have to be oxidized to pyridines.[1]

The oxidation of dihydropyridines is an old reaction in general organic chemistry. Even in recent years, several groups have reported new methods for aromatization, including oxidations with ferric or cupric nitrates on a solid support,[2] ceric ammonium nitrate,[3] clay supported cupric nitrate accompained by ultrasound-promotion,[4] pyridinium chlorochromate,[5] tert-butylhydroproxide,[1] potassium permanganate,[6]

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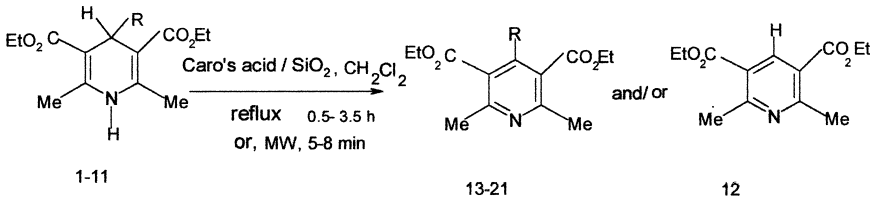
ultrasound-promoted oxidation with cupric nitrate,[7] photochemical oxidation,[8] $FeCl_3 \cdot 6H_2O/AcOH\text{-}H_2O$,[9] $[NO^+ \cdot CROWN \cdot H(NO_3)_2^-]$,[10] nicotinium dichromate (NDC),[11] barium manganate,[12] and tetrakis pyridine cobalt (II) dichromate (TPCD).[13] There also has been reported a general method using nitric acid.[14] Recently, Ohsawa et al. reported the use of NO gas as a clean and efficient oxidant for this purpose.[15] However, many of the reported methods still suffer from some drawbacks, such as requiring severe conditions, needing excess of the reagents or tedious work-up procedures. Most of the reported reagents produce by-products which are difficult to remove from the desired products. Another major drawback to the older procedures is their use of reagents which are either highly toxic or present serious disposal problems (or both). For example, we know that the NO gas is corrosive and highly toxic and must be used under argon atmosphere and an effective hood with caution. Therefore, we decided to choose a new reagent to overcome the above limitationes; it was also important to us to have a clean and easy work-up. The heterogeneous reagent systems have many advantages such as simple experimental procedure, mild reaction conditions, and minimal chemical wastes as compared to the liquid phase counterparts. During the last decade, microwave methodology,[16–20] and solventless[21,22] experiments have been carried out in organic synthesis. They offer shorter reaction times, increased yields, clean, efficient, economical procedures, safe work-up, and are environmentally friendly. In the present investigation, we report a simple, cost-effective, and convenient method for the efficient conversion of 1,4-dihydropyridines to their corresponding pyridine derivatives under both heterogenous and solvent free microwave conditions (Scheme 1).



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SCHEME 1

RESULTS

Different kinds of dihydropyridines were subjected to oxidation reaction with Caro's acid on silica gel in CH_2Cl_2 to give the corresponding

TABLE I Oxidation of 1,4-Dihydropyridines to the Corresponding Pyridine Derivatives with Caro's Acid/SiO_2[a]

Entry	R	Product	Time (min)	Yield (%)[b]	m.p (°C)	Lit. m.p. (°C)[23]
1	H	12	30	92	68–69	69–70
2	$(CH_3)_2CH$—	12	150	84	68–69	69–70
3	C_3H_7—	12,13	140	43+57[c]	oil	oil
4	C_2H_5—	12,14	100	39+61[c]	oil	oil
5	C_6H_5—	15	120	80	61–62	62–63
6	4-$CH_3C_6H_4$—	16	110	85	oil	oil
7	$C_6H_5CH_2$—	12,17	167	50+50[c]	oil	oil
8	2-ClC_6H_4—	12,18	200	40+60[c]	60–61	62
9	4-ClC_6H_4—	19	160	82	65–66	65–67
10	2-$NO_2C_6H_4$—	20	150	78	74–75	75
11	3-$NO_2C_6H_4$—	21	180	20	62–63	61–63

[a]Reactions were performed in CH_2Cl_2at reflux temperature using 1:3 molar ratio of substrate to oxidation reagent.
[b]Isolated yields.
[c]Alkylated and dealkylated products.

pyridine derivatives in good yields (Table I). These reactions were also conducted under microwave irradiation which gave the same products in comparatively higher yields (Table II).

A comparison of yields obtained by both methods and duration of the reactions is shown in Table III. In both conditions the molar

TABLE II Oxidation of 1,4-Dihydropyridines to the Corresponding Pyridine Derivatives with Caro's Acid/SiO_2 Under Microwave Irradiation[a]

Entry	R	Product	Time (min)	Yield (%)[b]	m.p (°C)	Lit. m.p. (°C)[23]
1	H	12	5	98	68–69	69–70
2	C_6H_5–	13	6	85	61–62	62–63
3	4-$CH_3C_6H_4$–	14	7	98	oil	oil
4	$(CH_3)_2CH$–	12	6	86	68–69	69–70
5	C_3H_7–	12,15	6	30+70[c]	oil	oil
6	2-ClC_6H_4–	16	7	80	60–61	62
7	C_2H_5–	12,17	7	36+64[c]	oil	oil
8	2-$NO_2C_6H_4$–	18	8	90	74–75	75
9	3-$NO_2C_6H_4$–	19	8	20	62–63	61–63
10	4-ClC_6H_4–	20	6	85	65–66	65–67
11	$C_6H_5CH_2$–	12	6	95	oil	oil

[a]Reactions were conducted under microwave irradiation at 900 w power using 1:3 molar ratio of substrate to caro's acid on silica gel.
[b]Yields refer to isolated products.
[c]Alkylated and dealkylated products.

TABLE III Comparison of Reaction Times and Yields in Oxidation of 1,4-Dihydropyridines Using Microwave and Conventional Heating

1,4-Dihydropyridine	Oxidized products 7–12 R	Time (min) conventional	Time (min) microwave	Yield (%) conventional	Yield (%) microwave
1	H	30	5	92	98
2	4-$CH_3C_6H_4$—	110	7	85	98
3	2-ClC_6H_4—	200	7	60	80
4	2-$NO_2C_6H_4$	150	8	78	90
5	C_6H_5—	120	6	85	92
6	$(CH_3)_2CH$—	150	6	84	86

ratio of reagent to substrate was 3:1. This method exhibit several preferred qualities for oxidation of such substrates, for example easier work-up, good yields, and simpler exprimental manipulations and pure products.

DISCUSSION

In both conditions it was observed that the oxidation of 1,4-diyhdropyridines bearing an isopropyl substituent at the 4-position gave only dealkylated pyridine derivatives. This is in agreement with the observation made by others employing different oxidative conditions.[1] But for 1,4-dihydropyridines with R = propyl, ethyl, benzyl and 2-chlorophenyl (entry 3, 4, 7, 8 Table I) and R = C_2H_5, C_3H_7 (entry 5, 7 Table II) both alkylated and dealkylated products have been obtained.

Comparison of the two conditions shows that microwave irradiation does not modify the nature of the oxidized products but rates are significantly enhanced and for R = $C_6H_5CH_2$— only the dealkylated product was produced (Table II). Reactions are generally complete within a few minutes (5–8 min) whereas hours (0.5–3.5 h) are required under conventional conditions. Our results demonstrated that oxidation of 1,4-dihydropyridines with Caro's acid on silica gel conducted under microwave irradiation gave better yields than conventional reflux heating (Table III).

In conclusion we have developed an extremely simple, convenient, and efficient protocol of conversion of 1,4-dihydropyridines to the pyridine derivatives with Caro's acid on silica gel employing both nonaqueous conditions and solvent free under microwave irradiation. The microwave reaction system was practical, efficient, and

safe, giving higher yields and shorter reaction time than the conventional method, reinforcing the use of microwave technology for organic reactions.

EXPERIMENTAL

The melting points were determined on an Electro thermal 9100 melting point apparatus. IR spectra were determined on a SP-1100, P-UV-COM instrument. The ^{1}H-NMR spectra were recorded on a EM 360 A (60 MHz) spectrometer using $CDCl_3$ as solvent and TMS as internal reference, 1,4-dihydropyridines were prepared according to the reported method.[24]

Typical Procedure

1) Conventional: aromatization of diethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates (1); a mixture of diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1 mmol, 0.253 g) in CH_2Cl_2 (10 Cm^3) and Caro's acid/SiO_2 (3 mmol, 1.8 g) was stirred and refluxed for 0.5 h. The progress of the reaction was monitored by TLC. After completion of the reaction the mixture was filtered and the filtrate dried with Na_2SO_4. Concentration of the filtrate after removal of Na_2SO_4 under reduced pressure yielded the pyridine derivative **12** a crystalline pale yellow solid, 0.233 g (92%). m.p. 68–69°C (Lit.[23] m.p. 69–70°C). ^{1}H-NMR ($CDCl_3$ / TMS): 1.2 (t, 6H). 3.0 (s, 6H), 4.36 (q, 4H), 8.69 (s, 1H) (Lit [23]).
2) Microwave: mixture of diethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates (1 mmol, 0.253 g) and Caro's acid/SiO_2 (3 mmol, 1.8 g) was irradiated in a domestic microwave oven for 5 min at 900W. The mixture was cooled to room temperature and extracted with dichloromethan (10 Cm^3), dried with magnesium sulfate, and evaporated to give **12** a crystalline pale yellow solid, 0.248 g (98%).

Preparation of Caro's Acid

To ice cooled 98% sulfuric acid (4.7 g) is added in small portion potassium persulfate (4.5 g) with stirring; to this is added crushed ice (13 g) and water (4 g) while the temperature is kept below 15°C. Silica gel (5 g, TLC grade, kieselgel 60 G, particle size 15 μm) is added in portions to the mixture and stirred for 4 h in an ice-water bath. The mixture is then filtered under suction and the residue dried in a desiccator to give a white free flowing powder.[25]

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