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One-Pot Synthesis of N-Substituted 4-Aryl-1,4-dihydropyridines Under Solvent-Free Conditions and Microwave Irradiation

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Summary. The three-component condensation of benzaldehyde derivatives, alkyl propiolates, and primary amines catalyzed by silica gel, zeolite HY, montmorillonite K-10, and acidic alumina under microwave irradiation gave N-substituted 4-aryl-1,4-dihydropyridines in short reaction times and high yields. The best results were obtained with silica gel.

Keywords. Cyclocondensation; Microwave irradiation; Solvent-free conditions; 1,4-Dihydropyridines.

Introduction

4-Aryl-1,4-dihydropyridines of the nifedipine type are of interest because of their Ca^{2+} antagonistic and agonistic activities [1]. N-Substituted 1,4-dihydropyridines without substituents in positions 2 and 6 exhibit many pharmaceutical activities and are highly light-sensitive in the solid state. It has been shown that these compounds could be dimerized; the dimers are of interest as novel potential inhibitors of HIV-1 protease and have anticancer activity [2].

There are many methods for the synthesis of N-substituted 1,4-dihydropyridines [3]. For the preparation of 2,6-unsubstituted 1,4-dihydropyridines, propiolates are used instead of β-dicarbonyl compounds. Cyclocondensation of aldehydes, propiolates, and ammonium acetate in refluxing AcOH followed by N-alkylation and cyclocondensation of propiolates, aromatic aldehydes, and primary amines under reflux resulted in N-substituted 1,4-dihydropyridines [4,5]. N-Methyl derivatives were produced by methylation of 1,4-dihydropyridine anions in dimethyl propylene urea (*DMPU*). Meanwhile it has been found that photochemical addition of alkenes to enaminocarbaldehydes leads to tetahydropyridines which undergo dehydration to give N-substituted 1,4-dihydropyridines [6, 7, 8].

A combination of supported reagents and microwave irradiation has been used to carry out a wide range of reactions under solvent-free conditions [9]. In

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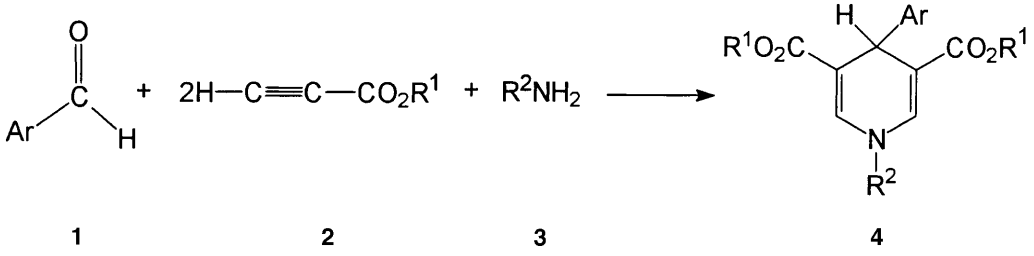
connection with our previous work on solid-state organic synthesis under microwave irradiation [10], we report the three-component condensation of benzaldehyde derivatives, alkyl propiolates, and primary amines on the surface of silica gel, montmorillonite K-10, acidic alumina, and zeolite HY with acidic character under microwave irradiation as a useful method for the synthesis of N-substituted 4-aryl-1,4-dihydropyridines.

Results and Discussion

In order to select the best solid support for this reaction we investigated the condensation of benzaldehyde, ethyl propiolate, and benzylamine on silica gel, montmorillonite K-10, acidic alumina, and zeolite HY under microwave irradiation. Under all conditions, the reaction product was **4e** (62, 44, 41, and 41%). The best yields were obtained with silica gel as the solid support (Table 1). With zeolite HY, yields were lower because the Brønsted acidic sites were partly occupied by the electron pairs of amine nitrogen atoms. It seems that the reaction proceeds on the surface of zeolite HY because the size of channels in zeolite HY is only around 7 Å.



1 2 3 4

Scheme 1

Table 1. Solvent-free synthesis of N-substituted 4-aryl-1,4-dihydropyridines **4a**–**h** under microwave irradiation

	Ar	R^1	R^2	Yield[a]
				%
4a	4-$MeOC_6H_4$	Me	Benzyl	90
4b	4-$MeOC_6H_4$	Et	Benzyl	76
4c	4-$MeOC_6H_4$	Me	Me	90
4d	C_6H_5	Me	Benzyl	90
4e	C_6H_5	Et	Benzyl	62
4f	4-BrC_6H_4	Me	Benzyl	94
4g	4-$MeOC_6H_4$	Et	*n*-Bu	90
4h	4-$MeOC_6H_4$	Et	Cyclohexyl	68

[a] In all experiments the optimized time of irradiation was 4 min; silica gel was used as the solid support

The products were characterized by their IR and ^{1}H NMR spectroscopic data and melting points. In the ^{1}H NMR spectra, the peak at 4.80–5.00 ppm is related to 4-H and is indicative of the reaction products. In the IR spectra, the absence of the carbonyl group and acetylene bands are in accordance with the structure of the reaction products. Microwave irradiation in the absence of solid support under neat conditions resulted in low yields, and the reactants and products adhered to the reaction vessel and led to irreproducible results. The cyclocondensation was also carried out in HOAc without solid support under microwave irradiation, but yield and reproducibility were low and work-up was difficult. In all experiments, the optimized time of irradiation was 4 minutes.

We also tried to synthesize the pyrimidine skeleton *via* a three-component condensation of N,N′-dimethyl urea, methyl propiolate, and benzaldehyde on silica gel under microwave irradiation, but we obtained dimethyl-1-methyl-1,4-dihydro-4-phenylpyridine-3,5-dicarboxylate. Under these conditions, dimethyl urea decomposed to methylamine and methyl isocyanate [11], and the resulting methylamine condensed with methyl propiolate and benzaldehyde to give the above dihydropyridine.

In conclusion, N-substituted 4-aryl-1,4-dihydropyridines are versatile intermediates in the synthesis of pharmacologically active products. Current methods of preparation lead to relatively large amounts of waste; our method is clean and environmentally friendly. The advantages of the method are a) reduction of reaction steps, b) absence of solvents, c) employment of reusable solid catalysts, d) high yields, e) short reaction times and f) easy reaction set-up and work-up.

Experimental

Melting points were measured on an Electrothermal 9100 melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-408 spectrometer in KBr disks. ^{1}H NMR spectra were determined in $CDCl_3$ with *TMS* as internal reference on a Bruker 80 MHz FT-NMR spectrometer. Elemental analysis was performed using a CHN-O Heraeus instrument; the results agreed favourably with the calculated values. Mass spectra were recorded on a GC-MS QP 1100 Shimadzu instrument (70 eV). A domestic microwave oven (Moulinex 2735A) at 2450 MHz (100% power corresponding to 850 W) was used in all experiments.

General procedure

The benzaldehyde derivative (4 mmol), alkyl propiolate (8 mmol), primary amine (4 mmol), and 2 g silica gel were mixed thoroughly in a mortar. Then the reaction mixture was transferred to a beaker and irradiated with microwaves for 4 minutes. The progress of reaction was monitored by TLC. The mixture was extracted with $3 \times 30\,cm^3$ $CHCl_3$, filtered, and the solvent was removed by a rotary evaporator under reduced pressure. Further purification by recrystallization gave the desired pure products **4a**–**h**.

Dimethyl 1-benzyl-1,4-dihydro-4-(4-methoxyphenyl)-pyridine-3,5-dicarboxylate (**4a**; $C_{23}H_{23}NO_5$)

Yield: 90%; m.p.: 120–121°C (petroleum ether:diethyl ether = 2:1; [2d]: 120–122°C); IR (KBr): $\nu = 1705$, $1604\,cm^{-1}$; ^{1}H NMR ($CDCl_3$, δ, 80 MHz): 3.55 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 4.50 (s, 2H, NCH_2), 4.80 (s, 1H, 4-H), 6.60–7.35 (m, 11H, aromatic H, 2,6-H) ppm.

Diethyl 1-benzyl-1,4-dihydro-4-(4-methoxyphenyl)-pyridine-3,5-dicarboxylate (**4b**; $C_{25}H_{27}NO_5$)

Yield: 76%; m.p.: 104–106°C (*n*-hexane: diethyl ether = 2:1; [2d]: 104–106°C); IR (KBr): $\nu = 1705$, 1664, 1605 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 80 MHz): 1.16 (t, $J = 7$ Hz, 6H, CH_2CH_3), 3.75 (s, 3H, OCH_3), 4.06 (q, $J = 7$ Hz, 4H, OCH_2CH_3), 4.57 (s, 2H, NCH_2), 4.85 (s, 1H, 4-H), 6.70–7.35 (m, 11H, aromatic H, 2, 6-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 20 MHz): 37.10, 55.20, 58.15, 60.20, 109.10, 113.30, 127.20, 128.10, 129.30, 136.10, 137.25, 158.40, 167.20 ppm.

Dimethyl 1-methyl-1,4-dihydro-4-(4-methoxyphenyl)-pyridine-3,5-dicarboxylate (**4c**; $C_{17}H_{19}NO_5$)

Yield: 90%; m.p.: 200–202°C (petroleum ether:diethyl ether = 2:1; [2d]: 200–202°C); IR (KBr): $\nu = 1705$, 1608 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 80 MHz): 3.20 (s, 3H, NCH_3), 3.60 (s, 6H, CO_2CH_3), 3.70 (s, 3H, 4-CH_3O-C_6H_4), 4.82 (s, 1H, 4-H), 6.70–7.25 (m, 6H, aromatic H, 2, 6-H) ppm.

Dimethyl 1-benzyl-1,4-dihydro-4-phenylpyridine-3,5-dicarboxylate (**4d**; $C_{22}H_{21}NO_4$)

Yield: 90%; m.p.: 160–162°C (petroleum ether:diethyl ether = 2:1); IR (KBr): $\nu = 1695$, 1660, 1580 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 80 MHz): 3.40 (s, 6H, CO_2CH_3), 4.40 (s, 2H, NCH_2) 4.80 (s, 1H, 4-H), 6.90–7.40 (m, 12H, aromatic H, 2,6-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 20 MHz): 37.00, 51.00, 59.00, 109.10, 125.10, 126.20, 127.50, 129.30, 136.10, 136.50, 138.20, 147.10, 168.20 ppm.

Diethyl 1-benzyl-1,4-dihydro-4-phenylpyridine-3,5-dicarboxylate (**4e**; $C_{24}H_{25}NO_4$)

Yield: 62%; m.p.: 133–135°C (petroleum ether:diethyl ether = 2:1); IR (KBr) $\nu = 1695$, 1580 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 80 MHz): 1.10 (t, 6H, $J = 7.1$ Hz, $2CH_3$), 3.95 (q, 4H, $J = 7.1$ Hz, $2CH_2$) 4.45 (s, 2H, NCH_2) 4.80 (s, 1H, 4-H), 6.90–7.70 (m, 12H, aromatic H, 2,6-H) ppm; MS: $m/z = 391$ $[M]^{\cdot+}$, 362 $[M\text{-}C_2H_5]^+$, 346 $[M\text{-}OC_2H_5]^+$, 314 $[M\text{-}Ph]^+$, 91 $[benzyl]^+$.

Dimethyl 1-benzyl-1,4-dihydro-4-(4-bromophenyl)-pyridine-3,5-dicarboxylate (**4f**; $C_{22}H_{20}BrNO_4$)

Yield: 94%; m.p.: 186–189°C (petroleum ether:diethyl ether = 2:1); IR (KBr): $\nu = 1710$, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 80 MHz) 3.50 (s, 6H, CO_2CH_3), 4.40 (s, 2H, NCH_2), 4.80 (s, 1H, 4-H), 6.90–7.60 (m, 11H, aromatic H, 2, 6-H) ppm; MS: $m/z = 441$ $[M]^{\cdot+}$, 443 $[M+2]^{\cdot+}$, 410 $[M\text{-}OCH_3]^{\cdot+}$, 286 $[M\text{-}C_6H_4Br]^+$, 91 $[benzyl]^+$, 59 $[CO_2CH_3]^+$.

Diethyl 1-butyl-1,4-dihydro-4-(4-methoxyphenyl) pyridine-3,5-dicarboxylate (**4g**; $C_{22}H_{29}NO_5$)

Yield: 90%; m.p.: 117–119°C (petroleum ether: diethyl ether 2:1); IR (KBr): $\nu = 1705$, 1605, 1980 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 80 MHz), 1.10 (t, 3H, $J = 7.1$ Hz, CH_3), 1.20 (t, 6H, $J = 7.1$ Hz, $2CH_3$), 1.40–1.80 (m, 4H, $2CH_2$), 3.50 (t, 2H, $J = 7.1$ Hz, NCH_2), 3.50 (s, 3H, OCH_3), 4.15 (q, 4H, $J = 7.1$ Hz, 2-OCH_2), 4.90 (s, 1H, 4-H), 6.80–7.30 (m, 6H aromatic H, 2,6-H) ppm.

Diethyl 1-cyclohexyl-1,4-dihydro-4-(4-methoxyphenyl) pyridine-3,5-dicarboxylate (**4h**; $C_{24}H_{31}NO_3$)

Yield: 68%; m.p.: 137.6–138.5°C (*n*-hexane:diethyl ether = 2:1); IR (KBr): $\nu = 1700$, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 80 MHz): 1.0 (t, 6H, $J = 7.1$ Hz, $2CH_2CH_3$), 1.20–1.90 (m, 10H, $5CH_2$) 3.10 (m, 1H, N-CH), 3.60 (s, 3H, OCH_3), 3.90 (q, 4H, $J = 7.1$, 2-OCH_2CH_3) 4.70 (s, 1H, 4-H), 6.60–7.15 (m, 6H aromatic, 2,6-H) ppm; MS: $m/z = 413$ $[M]^{\cdot+}$, 384 $[M\text{-}C_2H_5]^+$, 368 $[M\text{-}OC_2H_5]^+$, 340 $[M\text{-}CO_2C_2H_5]^+$, 306 $[M\text{-}C_7H_7O]^+$.

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