Catalyst-Free One-Pot Synthesis of Ketene Imines under Ultrasound Irradiation

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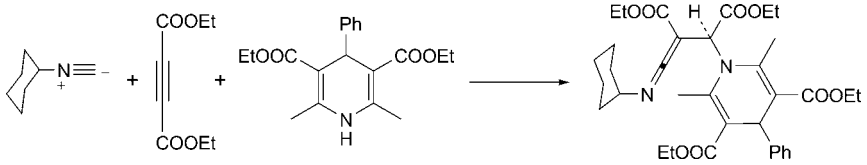
An efficient and simple procedure for the synthesis of ketene imines *via* a one-pot three-component reaction of cyclohexyl isocyanide, diethyl acetylenedicarboxylate, and 1,4-dihydropyridines under ultrasonic irradiation is described. The remarkable advantages are the simplicity of the experimental procedures, high yields, and short reaction times.

Introduction. – Ketene imines are reactive synthetic intermediates, which react readily with a wide range of nucleophiles, electrophiles, or radicals to afford the corresponding N-containing heterocycles [1][2]. They also undergo many pericyclic reactions such as electrocyclic ring closures, and [2+2] and [4+2] cycloaddition reactions [3–5]. Ketene imine derivatives have been prepared *via* various procedures such as imidation of ketene precursors [6], dehydrohalogenation of imidoyl halides under basic conditions [7], treatment of nitriles with a *Brønsted* base, followed by substitution reaction [8], and the reaction of isocyanides, acetylenic esters, and various compounds as proton source [9–13]. As part of our continuing work on the use of ultrasound irradiation in organic reactions [14], we report here a rapid and facile procedure for the synthesis of ketene imines by the ultrasound irradiation-induced reaction of cyclohexyl isocyanide, diethyl acetylenedicarboxylate, and highly substituted 1,4-dihydropyridines (1,4-DHPs).

Results and Discussions. – The ketene imines were synthesized by cyclohexyl isocyanide, diethyl acetylenedicarboxylate, and 4-aryl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates as NH-acids under both established and ultrasonic conditions. For optimizing the experimental conditions, the reaction between cyclohexyl isocyanide, diethyl acetylenedicarboxylate and 1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate was considered as a model reaction. To find the best solvent, several solvents such as THF, CH_2Cl_2, MeCN, EtOH and hexane were employed as media (*Table 1*). The highest yield was achieved with CH_2Cl_2 when the reaction was performed in an established manner, while the formation of the product was more facile and proceeded in shorter time and with high yield under ultrasonic conditions in hexane (*Table 1*, *Entry 5*).

The effect of temperature on the reaction was also studied. We found that the best results were obtained in hexane at 50° (temperature of ultrasonic bath). The ^{1}H- and ^{13}C-NMR spectra of the crude mixture clearly indicated the formation of one

Table 1. *Optimizations of the Reaction Conditions for the One-Pot Synthesis of Ketene Imines*



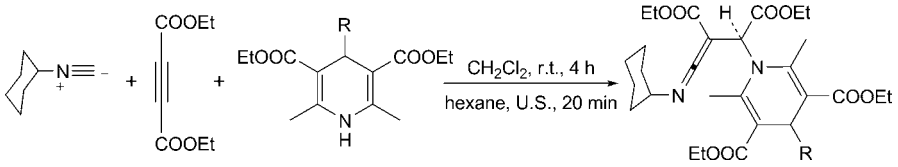
Entry	Solvent	Normal/Sonication[b])	
		Time	Yield[a]) [%]
1	THF	4 h/30 min	75/60
2	CH_2Cl_2	4 h/30 min	85/60
3	MeCN	4 h/30 min	55/30
4	EtOH	4 h/30 min	50/50
5	Hexane	4 h/20 min	80/85

[a]) Yield of the isolated product. [b]) Constant frequency, 60 W.

diastereoisomer of the product. Our attempts to detect the second diastereoisomer in the reaction mixture were not successful.

To further explore the scope and limitations of this reaction, we extended our studies to the reaction of various 1,4-DHPs with cyclohexyl isocyanide and diethyl acetylenedicarboxylate. The results are compiled in *Table 2*. To study the effect of ultrasound irradiation, the reactions were carried out both under normal and ultrasonic irradiation conditions. Ultrasound irradiation was found to accelerate the reactions.

Table 2. *Synthesis of Ketene-Imine Derivatives under Normal and Ultrasonic Conditions*

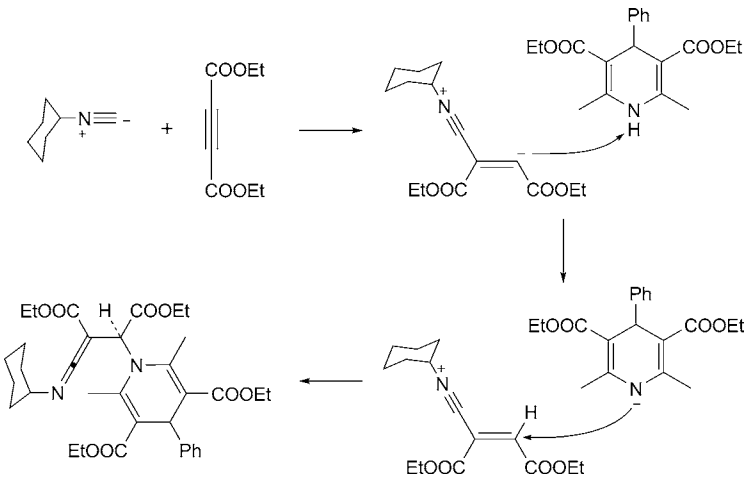


Entry	R	Normal/Sonication[b])[c])	
		Yield[a]) [%]	M.p. [°]
1	Ph	85/90	98–100
2	3-NO_2–C_6H_4	75/82	99–101
3	2-F–C_6H_4	85/82	107–109
4	3-F–C_6H_4	80/85	Oil
5	4-F–C_6H_4	78/83	Oil
6	4-Cl–C_6H_4	80/82	Oil
7	4-MeO–C_6H_4	78/80	116–118
8	4-Me–C_6H_4	81/80	127–129
9	Furan-2-yl	75/85	Oil

[a]) Yield of the isolated product. [b]) Constant frequency, 60 W. [c]) Temp. of ultrasonic bath, 50°.

Although we have not established the mechanism of the reaction experimentally, it is conceivable that the reaction involves the addition of isocyanide to diethyl acetylenedicarboxylate and the subsequent protonation of the adduct by the NH-acid. Then, the positively charged ion might be attacked by the anion of NH-acid to form ketene imine (*Scheme*).

Scheme



In summary, syntheses of substituted ketene imines through coupling of cyclohexyl isocyanide, diethyl acetylenedicarboxylate and various 1,4-DHPs under established and ultrasonic conditions were reported. The mild reaction conditions, high yields, short reaction time, and the stereoselectivity of the products are particularly noteworthy.

Experimental Part

General. Column chromatography: silica gel (*Merck*). 1,4-DHPs were prepared by treatment of alkyl acetoacetate, anh. ammonium carbonate, and aldehydes [15]. The products were characterized by IR, and ^{1}H- and ^{13}C-NMR spectroscopy, and elemental analysis. M.p.: *Büchi* melting point *B-540 B.V.CHI* apparatus. ^{1}H- and ^{13}C-NMR spectra: in (D_6)DMSO; *Bruker Avance 500 MHz* spectrometers (*DRX*). Elemental analysis: *Costech ECS 4010 CHN* analyzer.

General Procedure for the Synthesis of Ketene-Imine Derivatives. Normal Conditions. To a magnetically stirred soln. of diethyl 4-aryl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (1 mmol) and diethyl acetylenedicarboxylate (1 mmol) in dry CH_2Cl_2 (3 ml) was added a soln. of cyclohexyl isocyanide (1 mmol) in dry CH_2Cl_2 (2 ml) dropwise at r.t. over 10 min, and the mixture was stirred at r.t. for 4 h. The solvent was removed under reduced pressure, and diethyl 4-aryl-1-[4-(cyclohexylimino)-1-ethoxy-3-(ethoxycarbonyl)-1-oxobut-3-en-2-yl]-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate was separated by CC (SiO_2; hexane/AcOEt 7:3).

Ultrasonic Irradiation. A soln. of diethyl 4-aryl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (1 mmol), diethyl acetylenedicarboxylate (1 mmol), and cyclohexyl isocyanide (1 mmol) in hexane (6 ml) was sonicated for 20 min in a sonic bath at 60 W (constant frequency) maintained at 50° (temp. of ultrasonic bath). Solvent was evaporated under reduced pressure and diethyl 4-aryl-1-[4-(cyclohex-

ylimino)-1-ethoxy-3-(ethoxycarbonyl)-1-oxobut-3-en-2-yl]-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate was separated as described above.

Selected Data. Diethyl 1-[4-(Cyclohexylimino)-1-ethoxy-3-(ethoxycarbonyl)-1-oxobut-3-en-2-yl]-1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (*Table 2*, *Entry 1*). Yellow solid. M.p. 98–100°. IR: 1695 (2 CO), 1727 (CO), 1747 (CO), 2073 (C=C=N). ^{1}H-NMR: 1.11–1.19 (*m*, 5 H); 1.23–1.36 (3*t*, 12 H); 1.60–1.70 (*m*, 6 H); 2.39 (*s*, 6 H); 4.05 (*s*, 1 H); 4.20–4.35 (3*q*, 8 H); 4.85 (*s*, 1 H); 7.23–7.27 (*m*, 5 H). ^{13}C-NMR: 14.43; 14.52; 17.74; 24.12; 25.83; 32.17; 36.94; 45.90; 60.34; 60.59; 62.10; 64.70; 104.75; 126.78; 128.39; 143.36; 144.40; 146.72; 164.42; 164.77; 173.20; 188.02. Anal. calc. for $C_{34}H_{44}N_2O_8$ (608.72): C 67.09, H 7.29, N 4.60; found: C 67.38, H 7.37, N 4.93.

Diethyl 1-[4-(Cyclohexylimino)-1-ethoxy-3-(ethoxycarbonyl)-1-oxobut-3-en-2-yl]-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate (*Table 2*, *Entry 2*). Yellow solid. M.p. 99–101°. IR: 1692 (2 CO), 1726 (CO), 1746 (CO), 2072 (C=C=N). ^{1}H-NMR: 1.12–1.19 (*m*, 5 H); 1.31–1.37 (3*t*, 12 H); 1.59–1.69 (*m*, 6 H); 2.35 (*s*, 6 H); 4.05 (*s*, 1 H); 4.15–4.30 (3*q*, 8 H); 4.80 (*s*, 1 H); 7.60 (*m*, 2 H); 8.15 (*m*, 2 H). ^{13}C-NMR: 14.95; 15.53; 17.68; 24.12; 25.92; 32.23; 36.07; 43.50; 61.34; 62.50; 64.30; 67.70; 104.07; 121.40; 121.50; 121.75; 135.35; 143.67; 147.76; 149.10; 164.04; 165.25; 168.02; 190.10. Anal. calc. for $C_{34}H_{43}N_3O_{10}$ (653.72): C 62.47, H 6.63, N 6.43; found: C 62.69, H 7.02, N 6.80.

Diethyl 1-[4-(Cyclohexylimino)-1-ethoxy-3-(ethoxycarbonyl)-1-oxobut-3-en-2-yl]-4-(2-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (*Table 2*, *Entry 3*). Yellow solid. M.p. 107–109°. IR: 1697 (2 CO), 1724 (CO), 1748 (CO), 2070 (C=C=N). ^{1}H-NMR: 1.10–116 (*m*, 5 H); 1.25–1.30 (3*t*, 12 H); 1.58–1.75 (*m*, 6 H); 2.37 (*s*, 6 H); 4.10 (*s*, 1 H); 4.25–4.38 (3*q*, 8 H); 4.75 (*s*, 1 H); 7.10 (*m*, 1 H); 7.30 (*m*, 1 H); 7.50 (*m*, 2 H). ^{13}C-NMR: 14.85; 15.22; 17.68; 24.08; 25.92; 33.61; 36.07; 37.10; 60.61; 63.32; 64.12; 66.08; 102.78; 116.22; 125.61; 126.90; 128.15; 131.40; 145.67; 164.12; 165.25; 167.90; 169.10; 189.05. Anal. calc. for $C_{34}H_{43}FN_2O_8$ (643.17): C 65.16, H 6.92, N 4.47; found: C 65.07, H 7.31, N 4.63.

Diethyl 1-[4-(Cyclohexylimino)-1-ethoxy-3-(ethoxycarbonyl)-1-oxobut-3-en-2-yl]-4-(3-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (*Table 2*, *Entry 4*). Yellow oil. IR: 1690 (2 CO), 1727 (CO), 1743 (CO), 2058 (C=C=N). ^{1}H-NMR: 1.11–1.20 (*m*, 5 H); 1.26–1.32 (3*t*, 12 H); 2.34 (*s*, 6 H); 4.20 (*s*, 1 H); 4.28–4.39 (3*q*, 8 H); 4.80 (*s*, 1 H); 6.70 (*m*, 1 H); 7.08 (*m*, 2 H); 7.36 (*m*, 1 H). ^{13}C-NMR: 17.42; 18.70 20.90 23.80; 24.71; 31.72; 36.77; 42.14; 61.34; 62.84; 63.78; 65.62; 102.98; 114.50; 116.61; 126.81; 130.10; 144.26; 145.51; 163.99; 165.82; 168.41; 169.70; 187.10. Anal. calc. for $C_{34}H_{43}FN_2O_8$ (643.17): C 65.16, H 6.92, N 4.47; found: C 65.00, H 7.15, N 4.75.

Diethyl 1-[4-(Cyclohexylimino)-1-ethoxy-3-(ethoxycarbonyl)-1-oxobut-3-en-2-yl]-4-(4-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (*Table 2*, *Entry 5*). Yellow oil, IR: 1697 (2 CO), 1725 (CO), 1740 (CO), 2061 (C=C=N). ^{1}H-NMR: 1.12–1.18 (*m*, 5 H); 1.25–1.35 (3*t*, 12 H); 1.61–1.71 (*m*, 6 H); 2.35 (*s*, 6 H); 4.10 (*s*, 1 H); 4.29–4.40 (3*q*, 8 H) 4.80 (*s*, 1 H); 7.15 (*m*, 2 H); 7.25 (*m*, 2 H). ^{13}C-NMR: 17.13; 18.39; 19.60; 23.79; 25.18; 31.73; 36.95; 43.70; 61.10; 62.28; 63.76; 65.61; 104.24; 116.24; 131.53; 140.02; 145.31; 160.23 163.99; 169.51; 171.35; 191.70. Anal. calc. for $C_{34}H_{43}FN_2O_8$ (643.17): C 65.16, H 6.92, N 4.47; found: C 64.85, H 7.17, N 4.72.

Diethyl 4-(4-Chlorophenyl)-1-[4-(cyclohexylimino)-1-ethoxy-3-(ethoxycarbonyl)-1-oxobut-3-en-2-yl]-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (*Table 2*, *Entry 6*). Brown oil. IR: 1693 (2 CO), 1722 (CO), 1746 (CO), 2068 (C=C=N). ^{1}H-NMR: 1.12–1.19 (*m*, 5 H); 1.30–1.40 (3*t*, 12 H); 1.65–1.75 (*m*, 6 H); 2.40 (*s*, 6 H); 4.14 (*s*, 1 H); 4.15–4.27 (3*q*, 8 H); 4.90 (*s*, 1 H); 7.19 (*m*, 2 H); 7.42 (*m*, 2 H). ^{13}C-NMR: 14.70; 14.90; 18.28; 25.60; 26.17; 34.43; 36.83; 44.05; 62.20; 62.50; 65.83; 66.73; 103.48; 128.52; 131.51; 132.23; 143.10; 146.35; 163.32; 167.89; 169.45; 188.46. Anal. calc. for $C_{34}H_{43}ClN_2O_8$ (643.17): C 63.49, H 6.74, N 4.36; found: C 63.10, H 7.20, N 4.19.

Diethyl 1-[4-(Cyclohexylimino)-1-ethoxy-3-(ethoxycarbonyl)-1-oxobut-3-en-2-yl]-1,4-dihydro-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (*Table 2*, *Entry 7*). Yellow solid. M.p. 116–118°. IR: 1696 (2 CO), 1726 (CO), 1744 (CO), 2062 (C=C=N). ^{1}H-NMR: 1.11–115 (*m*, 5 H); 1.32–1.38 (3*q*, 12 H); 1.59–1.70 (*m*, 6 H); 2.40 (*s*, 6 H); 3.85 (*s*, 3 H); 4.10 (*s*, 1 H); 4.15–4.42 (3*q*, 8 H); 4.90 (*s*, 1 H); 6.81 (*m*, 2 H); 7.23 (*m*, 2 H). ^{13}C-NMR: 15.04; 16.22; 17.36; 25.77; 26.43; 34.72; 36.75; 43.45; 55.80; 61.76; 62.26; 63.20; 66.72; 103.54; 115.39; 130.63; 137.04; 145.34; 158.67; 164.06; 166.91; 169.72; 189.90. Anal. calc. for $C_{35}H_{46}N_2O_9$ (638.75): C 65.81, H 7.26, N 4.39; found: C 66.12, H 7.46, N 4.65.

Diethyl 1-[4-(Cyclohexylimino)-1-ethoxy-3-(ethoxycarbonyl)-1-oxobut-3-en-2-yl]-1,4-dihydro-2,6-dimethyl-4-(4-methylphenyl)pyridine-3,5-dicarboxylate (*Table 2*, *Entry 8*). Yellow solid. M.p. 127–129°.

IR: 1695 (2 CO), 1724 (CO), 1747 (CO), 2072 (C=C=N). ^{1}H-NMR: 1.11 – 1.15 (*m*, 5 H); 1.31 – 1.36 (3*t*, 12 H); 1.48 – 153 (*m*, 6 H); 2.32 (*s*, 3 H); 2.45 (*s*, 6 H); 4.14 (*s*, 1 H); 4.15 – 4.25 (3*q*, 8 H); 4.82 (*s*, 1 H); 7.15 (*m*, 4 H). ^{13}C-NMR: 15.04; 16.14; 17.21; 21.10 25.37; 26.05; 34.74; 36.44; 44.18; 61.09; 62.95; 63.20; 66.71; 104.47; 129.52; 135.10; 143.85; 144.91; 164.06; 166.92; 169.69; 189.14. Anal. calc. for $C_{35}H_{46}N_2O_8$ (622.75): C 67.50, H 7.45, N 4.50; found: C 67.78, H 7.48, N 4.60.

Diethyl 1-[4-(Cyclohexylimino)-1-ethoxy-3-(ethoxycarbonyl)-1-oxobut-3-en-2-yl]-4-(furan-2-yl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (*Table 2*, *Entry 9*). Brown oil, IR: 1698 (2 CO), 1731 (CO), 1745 (CO), 2060 (C=C=N). ^{1}H-NMR: 1.12 – 1.18 (*m*, 5 H); 1.31 – 1.37 (3*t*, 12 H); 1.60 – 1.70 (*m*, 6 H); 2.35 (*s*, 6 H); 4.16 (*s*, 1 H); 4.21 – 4.25 (3*q*, 8 H); 5.12 (*s*, 1 H); 6.10 (*m*, 1 H); 6.27 (*m*, 1 H); 7.68 (*m*, 1 H). ^{13}C-NMR: 15.41; 16.64; 17.32; 25.16; 26.08; 32.18; 33.69; 36.82; 61.65; 62.85; 63.27; 66.10; 103.32; 107.40; 111.65; 142.42; 145.01; 154.28; 164.34; 167.09; 169.71; 189.40. Anal. calc. for $C_{32}H_{42}N_2O_9$ (598.68): C 64.20, H 7.07, N 4.68; found: C 63.90, H 7.29, N 4.79.

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