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The Hantzsch Ester Production in a Water-based Biphasic Medium, Using Infrared Irradiation as the Activating Source

Raquel Gómez-Pliego,[1,3] Roberto Osnaya,[1,2] Isai Zamora,[1] Benjamín Velasco-Bejarano,[1] Gabriel Arroyo,[1] Eduardo Ramírez-San Juan,[2] José Trujillo,[3] Francisco Delgado,[2] René Miranda[1]*

[1] Departamento de Ciencias Químicas, Facultad de Estudios Superiores Cuautitlán, Campo 1, Universidad Nacional Autónoma de México, Av. 1ro de Mayo s/n, Cuautitlán Izcalli, Estado de México, C. P. 54740. *e-mail: mirruv@yahoo.com.mx

[2] Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Prolongación Carpio y Plan de Ayala, C. P. 11340 México, D. F.

[3] Sección de Estudios de Posgrado e Investigación, Escuela Superior de Medicina, Instituto Politécnico Nacional, Plan de San Luis y Díaz Mirón s/n Col. Santo Tomás, México, D.F., C. P. 11340.

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Abstract. The reaction of a wide number of benzaldehydes (**1a-n**) with ethyl (**2a**) or methyl (**2b)** acetoacetate and aqueous ammonia (**3**) has been carried out in the absence of an organic solvent, and using for the first time infrared irradiation as the heating mode. Thus, under the green chemistry protocole, the corresponding *mono*-1,4-dihydropyridines (**4a-j**) and *bis*-1,4-dihydropyridines (**4k-n**) were obtained in good yields and short reaction times.

Key words: Hantzsch synthesis, benzaldehydes, 1,4-dihydropyridines, infrared irradiation, green chemistry.

Resumen: En este trabajo se presentan y discuten los resultados obtenidos de la reacción entre varios banzaldehídos (**1a-n**) con acetoacetato de etilo (**2a)** o metilo (**2b**) e hidróxido de amonio (**3**); lo anterior mediante el protocolo de la química verde: ausencia de disolvente orgánico y empleando irradiación infrarroja como fuente de activación. De esta manera se obtuvieron las correspondientes *mono*-1,4-dihidropiridinas (**4a-j**) y *bis*-1,4-dihidropiridinas (**4k-n**) con buenos rendimientos y en tiempos cortos de reacción.

Palabras clave: Síntesis de Hantzsch, benzaldehídos, 1,4-dihidropiridinas, radiación infrarroja, química verde.

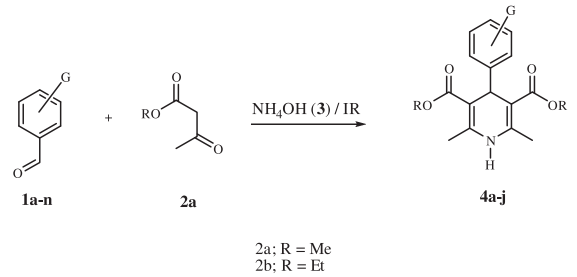
Introduction

One of the objectives of Green Chemistry is to carry out reactions using conditions which are not detrimental to the environment [1]. Under this protocole an ideal synthesis is that in which a target molecule is produced quantitatively in one step, from available and inexpensive starting compounds, in an environmentally acceptable process [2].

The typical procedure leading to 1,4-dihydropyridines (1,4-DHPs) is the Hantzsch reaction. It is a one-pot condensation of β-dicarbonylic compounds with aldehydes and ammonia, using ethanol as the solvent under reflux [3].

It is worth mentioning, that many 1,4-DHPs possess important pharmacological properties. For example, some of them have been employed as anti-hypertensive agents and calcium channel blockers [4a]; some others are used as multidrug reversal agents in tumor cells [4b] or have activity against the epimastigotes of some strains of *Trypanosome cruzi* [4c]. Recently, various fulleropyrrolidines bearing the DHP system were synthesized, showing an inhibitory effect of the HIV-protease [4d].

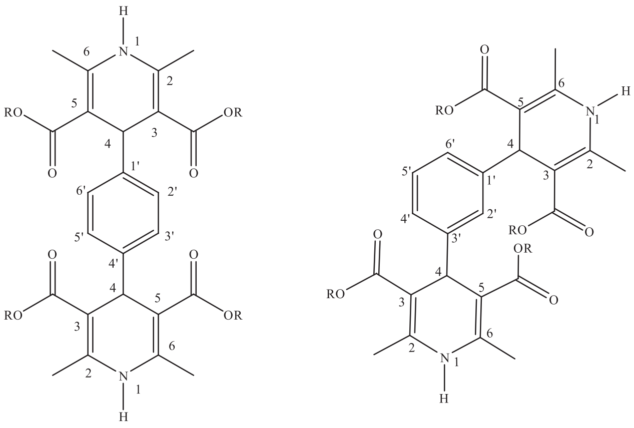
Consequently, a large number of modified methods to produce 1,4-DHPs under improved conditions have been reported [5]. However, many of them suffer from drawbacks such as unsatisfactory yields, or require high temperatures and long reaction times. All these facts clearly demonstrate the importance of developing new, efficient and versatile procedures for the preparation of this class of compounds. Following the main subject of our research group, namely, the revision of fundamental synthetic reactions under the green chemistry protocole, now we look into the Hantzsch ester synthesis under nonconventional reaction conditions [6]. Thus, in this paper we report the preparation of a set of ten *mono*-1,4 DHPs **4a-j** (Scheme 1) in addition to four *bis*-1,4-DHPs **4k-n** (Scheme 2) under non ethanolic conditions, using for the first time for this class of molecules, infrared irradiation as the activating source.



Scheme 1

Results and Discussion

Table 1 summarizes the reaction conditions employed in this protocole to obtain **4a-n**. As it can be seen **4a-n** were obtained with good yields (70–97%) in short reaction times (0.7–2.5 h). In general, the reactions showed no further progress after the times indicated, as evidenced by thin layer chromatography. These results shown that infrared irradiation can be used as an efficient promoter for the production of Hantzsch esters. In addition, this methodology represents a new alternative to



4k; R = Et
4m; R = Me

4l; R = Et
4n; R = Me

Scheme 2

Table 1. Yields and reaction times in the Hantzsch ester synthesis in a water-based biphasic medium under IR radiation.

Product	**G**	R	Time (h)	**Yield** (%)[a]
4a	H	Et	2.5	72
4b	*p*-CH_3	Et	2.3	83
4c	*p*-OH	Et	2.5	81
4d	*p*-CH_3O	Et	2.0	70
4e	*m*-CH_3O	Et	2.0	77
4f	*p*-N$(Me)_2$	Et	2.2	90
4g	*p*-CN	Et	1.5	83
4h	*p*-NO_2	Et	2.2	88
4i	*o*-Cl	Et	2.0	86
4j	*p*-F	Et	2.5	86
4k	*p*-DHP-4-yl [b, c,]	Et	0.8	97 [d]
4l	*m*-DHP-4-yl [b, c]	Et	1.7	95 [d]
4m	*p*-DHP-4-yl [b, c]	Me	0.7	92 [d]
4n	*m*-DHP-4-yl [b, c]	Me	1.5	90 [d]

[a] After purification by crystallization. [b] These products are insoluble in common organic solvents, however partially soluble in DMSO. [c] DHP-4-yl = 3,5-dicarbalcoxy-2,6-dimethyl-1,4-dihydropyridin-4-yl. [d] Yields after intensive washing of the product with hot ethanol

Table 2. Main ion fragments observed by EIMS for compounds **4a-n**.

DHP	Fragments
4a-l	$M^{+\bullet}$, $[M-29]^+$, $[M-45]^+$, $[M-73]^+$, *m/z* 252 (100)*
4m-n	$M^{+\bullet}$, $[M-15]^+$, $[M-31]^+$, $[M-59]^+$, *m/z* 224 (100) $[DHP\text{-}4\text{-}yl]^+$
	***4k** and **4l**: $[DHP\text{-}4\text{-}yl]^+$

the synthesis of 1,4-DHPs. It is worth noticing that this work is a contribution to the Green Chemistry protocole since the method is environmentally safe, mainly because the use of water as the medium.

For the structural characterization of the target heterocycles, we first analyzed their electron impact mass spectra (EIMS), looking for the analogies expected in their fragmentation patterns as a consequence of their structural similarity (Table 2) [4d], Thus, two sets of peaks were of particular interest, those corresponding to the molecular ions, and the base peaks arising from the loss of the substituent at the C-4 position, which leads to the formation of stable pyridinium cations ($[DHP\text{-}4\text{-}yl]^+$). The structures of the *mono*-products were further confirmed by their corresponding ^1H and ^{13}C NMR data, which was found to be in agreement with the literature [8]. In addition, since the spectral data of the *bis*-DHPs (Scheme 2) is sparse, these molecules were fully characterized by ^1H and ^{13}C NMR, EIMS, and high resolution mass spectrometry (HRMS); the corresponding information is described in the experimental section.

It is also worth noting that after an intensive search in the literature, we found sparse information about compounds containing two Hantzsch ester units [9-14]. In other words, attention so far has been mainly paid to the synthesis and biological activity of monofunctional 1,4-DHPs derivatives, while the respective *bis*-Hantzsch (Scheme 2) have been scarcely investigated.

It is also important to mention that recent studies in our laboratory [15] demonstrated that these *bis*-dihydropyridines (**4k-n**) have potent hypotensor effect *in vivo*, this in addition to protection against pentylenetetrazole-induced seizure (90 mg/Kg) and maximum electroshock (50 mA). Complementarily, the determination of the acute low toxicity, provided DL_{50} values higher than 1000 mg/kg.

Conclusions

A novel procedure for the synthesis of 1,4-dihydropyridines via condensation of benzaldehydes with ethyl or methyl acetoacetate and aqueous ammonia was developed, involving the use of infrared irradiation as the activating mode a water-based biphasic medium. The reaction conditions were simpler and the corresponding yields were good; it is also worth noting, that this is a contribution to the green chemistry protocol since this new method is environmentally benign.

Experimental

General. The reactions were monitored by tlc (*n*-hexane/EtOAc, 7:3) performed on pre-coated (0.25 mm) Merck silica-gel 60-F_{254} aluminum sheets; the visualization was done using a 365 nm UV lamp. Melting points, uncorrected, were determined on a Fisher-Johns apparatus. The EIMS and HRMS measurements were determined using JEOL (JMS-SX102-

A and JMS-AX505-HA) mass spectrometers. EIMS was performed with a source temperature of 230 °C, ionization energy of 70 eV, and an ionization trap current of 100 μA. Polyethylene glycols 400, 800 and 1000 were used as internal mass reference in the HRMS studies. The range of mass measurements was set so as to include the two standard peaks that encompassed the sample peak of interest. The mass resolution and scan speed used were 10 000 (10% valley) and 120 s/decade, respectively. The accurate mass was calculated as the mean value of the values measured in 5–10 scans, obtained from the mass centroids of the M$^{+\cdot}$ ion and other peaks. Theoretical elemental compositions were calculated within a mass window of ± 10 ppm from the measured accurate mass using the program installed in the data system, and the elemental composition with a mass that best fitted the measured value and that made chemical sense was assigned to the ion. NMR experiments were determinate in a Varian Mercury-300 spectrometer at 300 MHz and 75 MHz for hydrogen and carbon respectively, the solvents were CDCl$_3$ or DMSO-*d*$_6$, and TMS was employed as internal reference. The infrared radiation was generated by a Phillips IR lamp (375 W/220 V) as indicated in a recent publication [6d].

General procedure for the preparation of *mono*-DHPs 4a-j

A mixture of corresponding benzaldehyde (10 mmol), ammonia (28% W in water, 10.78 mmol) and ethyl acetoacetate (20 mmol) was placed in a round-bottomed flask (25 mL) equipped with a condenser, and treated with infrared irradiation [6d], monitoring the reaction by tlc. After cooling at room temperature, the solid product was recristallyzed from ethanol, affording products **4a-j**; the target compounds were characterized by their physical and spectral data. Compounds **4a-j** have been previously described, consequently their melting points were compared with the literature data: **4a**, mp 157-158 °C (lit.[16a] 156; lit.[16b] 156-157; lit.[16c] 157-158, lit.[16d-f] 157-159; lit.[16g] 158-159; lit.[16h] 160-162), **4b**, mp 139-140 °C (lit.[17] 140), **4c**, mp 226-227 °C (lit.[16e] 225-229; lit.[18a] 227; lit.[18b] 227-228), **4d**, mp 158-160 °C (lit.[18a-b] 159), **4e**, mp 115-117 °C, **4f**, mp 159-160 °C (lit.[19] 158.5; lit.[5a] 158.5-159.5), **4g**, mp 166-167 °C (lit.[12] 166-168), **4h**, mp 136-137 °C (lit.[17] 136; lit.[20] 129-131), **4i**, mp 131-132 °C (lit.[18b] 132, lit.[21] 122.5-123), **4j**, mp 153-154 °C.

General procedure for the preparation of *bis*-DHPs 4k-n

A mixture of a dialdehyde (10 mmol), ammonia (28% W in water, 21.56 mmol) and ethyl or methyl acetoacetate (40 mmol) were thoroughly mixed in a round-bottomed flask (25 mL), equipped with a condenser, it was also treated with infrared irradiation. The reaction was monitored by tlc, until the corresponding dialdehyde disappeared (0.8-1.7 h). After cooling the solid mixture was washed with hot EtOH (5 × 25 mL), affording **4k** and **4n** as pure compounds in excellent yields (90-97%). Finally, since there is scarce spectroscopic data for the *bis*-Hantzsch esters these products were fully characterized by nuclear magnetic resonance and mass spectrometry.

Diethyl 4-[4-(2,6-dimethyl-3,5-ethoxycarbonyl-1,4-dihydropyridin-4-yl)phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4k**): Following the general procedure for the preparation of *bis*-DHPs, **4k** was obtained (97 %) as a yellowish solid, mp 297-298 °C (decomposition) **4k**, mp (lit.[8] 295-296); ^{1}H NMR (DMSO-*d*$_6$, 300 MHz,) δ 8.82 (2H, br s, N*H*), 7.01 (4H, s, Ar*H*), 4.80 (2H, s, CH), 4.02-3.91 (8H, m, CH$_3$C*H*$_2$O), 2.22 (12H, s, CH$_3$), 1.09 (12H, t, *J* = 7.2 Hz, C*H*$_3$CH$_2$O); ^{13}C NMR (DMSO-*d*$_6$, 75 MHz) δ 167.66 (*C*O$_2$Et), 146.27 (C$_{1',4'}$), 145.97 (C$_{2,6}$), 127.48 (C$_{2',3',5',6'}$), 102.46 (C$_{3,5}$), 59.63 (*C*H$_2$O), 38.91 (*C*H), 18.90 (*C*H$_3$), 14.79 (*C*H$_3$CH$_2$O); EIMS (70 eV) *m/z* (rel. int.): 580 (7.5) M$^{+\cdot}$, 565 (1) [M-Me]$^+$, 535 (10) [M-EtO]$^+$, 252 (100), [DHP-4-yl]$^+$, HRMS: calcd for C$_{32}$H$_{40}$O$_8$N$_2$; found: 580.2792.

Diethyl 4-[3-(2,6-dimethyl-3,5-ethoxycarbonyl-1,4-dihydropyridin-4-yl)phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4l**): Following the general procedure for the preparation of *bis*-DHPs, **4l** was obtained (95 %) as a yellowish solid, mp 186-188 °C; ^{1}H NMR (DMSO-*d*$_6$, 300 MHz,) δ 8.85 (2H, br s, N*H*), 6.8-7.2 (4H, m, Ar*H*), 4.80 (2H, s, CH), 3.97 (8H, q, CH$_3$C*H*$_2$O), 2.22 (12H, s, CH$_3$), 1.17 (12H, t, *J* = 7.2 Hz, C*H*$_3$CH$_2$O); ^{13}C NMR (DMSO-*d*$_6$,75 MHz) δ 167.0 (*C*O$_2$Et), 147.61 (C$_{1',3'}$), 145.37 (C$_{2,6}$), 127.35 (C$_{2'}$), 126.42 (C$_{5'}$), 124.91 (C$_{4'}$), 101.93 (C$_{3,5}$), 58.93 (CH$_3$*C*H$_2$O), 38.64 (*C*H), 18.20 (*C*H$_3$), 14.27 (*C*H$_3$CH$_2$O); EIMS (70 eV) *m/z* (rel. int.): 580 (2) M$^{+\cdot}$, 565 (2) [M-Me]$^+$, 535 (2) [M-EtO]$^+$, 252 (100), [DHP-4-yl]$^+$, HRMS: calcd for C$_{32}$H$_{40}$O$_8$N$_2$; found: 580.2790.

Dimethyl 4-[4-(2,6-dimethyl-3,5-methoxycarbonyl-1,4-dihydropyridin-4-yl)phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4m**): Following the general procedure for the preparation of *bis*-DHPs, **4m** was obtained (92 %) as a yellowish solid, mp > 300 °C (decomposition) **4m**, mp (lit.[9] 301-302); ^{1}H NMR (DMSO-*d*$_6$, 300 MHz): δ 8.85 (2H, br s, N*H*), 6.95 (4H, s, Ar*H*), 4.82 (2H, s, CH), 3.55 (12H, s, C*H*$_3$O), 2.23 (12H, s, CH$_3$); ^{13}C NMR (DMSO-*d*$_6$, 75 MHz): δ 167.47 (*C*O$_2$CH$_3$), 147.39 (C$_{1',4'}$), 145.79 (C$_{2,6}$), 124.62 (C$_{2',3',5',6'}$), 101.58 (C$_{3,5}$), 58.90 (*C*H$_3$O), 36.20 (*C*H), 18.65 (*C*H$_3$); EIMS (70 eV) *m/z* (rel. int.): 524 (10) M$^{+\cdot}$, 509 (6) [M-Me]$^+$, 493 (3) [M-MeO]$^+$, 224 (100), [DHP-4-yl]$^+$, HRMS: calcd for C$_{28}$H$_{32}$N$_2$O$_8$; found: 524.2250.

Dimethyl 4-[3-(2,6-dimethyl-3,5-methoxycarbonyl-1,4-dihydropyridin-4-yl)phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4n**): Following the general procedure for the preparation of *bis*-DHPs, **4n** was obtained (90 %) as a yellowish solid, mp 157-159 °C; ^{1}H NMR (DMSO-*d*$_6$, 300 MHz) δ 8.82 (2H, br s, N*H*), 7.18-6.82 (4H, m, Ar*H*), 4.78 (2H, s, CH), 3.52 (12H, s, C*H*$_3$O), 2.21 (12H, s, CH$_3$); ^{13}C NMR (DMSO-*d*$_6$, 75 MHz): δ 167.5 (*C*O$_2$CH$_3$), 147.4 (C$_{1',3'}$), 145.7 (C$_{2,6}$), 127.7 (C$_{2'}$), 125.9 (C$_{5'}$), 124.6 (C$_{4',6'}$), 101.6 (C$_{3,5}$), 50.6 (CH_3O), 38.2 (CH), 18.2 (CH_3); EIMS (70 eV) *m/z* (rel. int.): 524 (8) $M^{+\bullet}$, 509 (5) $[M-Me]^+$, 493 (3) $[M-MeO]^+$, 224 (100), $[DHP\text{-}4\text{-}yl]^+$, HRMS: calcd for $C_{28}H_{32}N_2O_8$; found: 524.2249.

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