A GREEN AND EFFICIENT METHOD FOR THE SYNTHESIS OF HOMODIMERIC (B-DICARBONYL) ARYLMETHANES AND DIHYDROPYRIDINE FROM DIMEDONE IN WATER

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ABSTRACT

A direct method has been developed for the synthesis of the dihydropyridine ring system by means of Michael reaction. The reaction of dimedone with 1.0 equiv. of amines in water provides intermediate product, which allowed dihydropyridine derivatives by intramolecular cyclization in various yields. Of particular interest is the use of the water as solvent of reaction and in absence of catalyst. Also these operating conditions protect the environment and economic points of view.

Keywords aqueous synthesis; bioactivity; dihydropyridine; dimedone; green method; selective conditions.

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1. INTRODUCTION
Homodimeric (β-dicarbonyl) arylmethane derivatives have attracted considerable attention since they exhibit potent bioactivity, like anti-inflammatory, antibiotic and anti-oxidant principle [1-3]. Several syntheses have been developed for the preparation of these homodimeric compounds. These routes usually involved condensation of aldehydes with electron-rich carbon nucleophiles (enols, etheroaromatics) [4-6].

The molecule dimedone 1, known for a long time, has been scarcely used in the synthesis of heterocyclic structures [7-13]. According to the literature, the homodimer 3 of dimedone has been obtained in various organic solvents like acetic acid and in the presence of toxic and not toxic catalysts such as cyanuric chloride and triethylamine.

In this work, we have obtained selectively, the homodimer 3 of dimedone along with the xanthene structure 4 by a green method as we have discover that in aqueous solution, no catalysis is required and products are isolated by filtration avoiding the use of any organic solvent (Scheme 1). Under these clean operating conditions, we have improved yields and master their reaction times compared to those cited in the literature [14]. Our interest in this type of structure is mainly based on its functional groups likely to give new heterocyclic structures. In particular, the action of primary amines on 3 forms a structure dihydropyridine (DHP) which exhibit an interesting functionalization.

![Scheme 1](image)

\[ R = \text{CH}_2, \text{C}_6\text{H}_5, \text{C}_6\text{H}_4\text{NO}_2, \text{C}_6\text{H}_4\text{CO}_2\text{CH}_3 \]

2. RESULTS AND DISCUSSION
When two equivalents of dimedone 1 (5,5-Dimethyl-1,3-cyclohexanediene) and one equivalent of aldehyde 2 are dissolved in dichloromethane under magnetic stirring, at room temperature or heated under reflux, only the structure 4 was obtained. The same result is obtained in a 50:50 mixture of CH2Cl2 / H2O. On the other hand, the use of H2O as a solvent drives the reaction selectively to 3 or 4 depending on the temperature and time. Thus, heating
at 100°C, promotes the formation of the structure 4. At room temperature, we obtained selectively 3 and 4, depending on the reaction time.

**Table 1**: Conditions of formation and physical data of 3 and 4 in water at 25 °C.

| Compounds | R          | Time (h) | Yield (%) | mp (°C)   |
|-----------|------------|----------|-----------|-----------|
| 3a        | CH₃        | 3        | 55        | 129-131   |
| 3b        | C₆H₅       | 2.30     | 83        | 188-190   |
| 3c        | C₆H₄CH₃   | //.      | 61        | 131-133   |
| 3d        | C₆H₄NO₂   | //.      | 78        | 192-194   |
| 3e        | C₆H₄F     | //.      | 86        | 165-167   |
| 3f        | C₆H₄CO₂CH₃| //.      | 89        | 197-199   |
| 3g        | C₆H₄OH    | //.      | 75        | 209-211   |
| 4a        | CH₃        | 5        | 67        | 184-186   |
| 4b        | C₆H₅      | 4.30     | 88        | 196-198   |
| 4c        | C₆H₄CH₃   | //.      | 74        | 219-221   |
| 4d        | C₆H₄NO₂   | //.      | 96        | 231-233   |
| 4e        | C₆H₄F     | //.      | 93        | 213-215   |
| 4f        | C₆H₄CO₂CH₃| //.      | 97        | 229-231   |
| 4g        | C₆H₄OH    | //.      | 81        | 241-243   |

The formation of 3 and 4, can be explained by the condensation of the enolic form of the dimedone on aldehyde, according to the reaction of Knoevenagel, followed by an addition on a second molecule of dimedone, according to the reaction of Michael (Scheme 1).

In CH₂Cl₂ or CH₂Cl₂/ H₂O at 50%, the interactions OH---O=C, present in 3, are weak and lead in each case to structure 4. On the other hand in H₂O, the hydrogen bonds OH---O=C are accentuated and consolidated by the polarity of H₂O. These interactions support the formation of 3. But energy brought, in the course of the reaction time under the effect of agitation, is favorable to the rupture of the hydrogen bonds, to transform 3 into 4, by an intramolecular ceto-enolic condensation.

Since our objective is to obtain new heterocyclic molecules, as the dihydropyridine 5, potentially active in various fields of applications [15-17]. As a first step, we valued structure
3 in the synthesis of new heterocyclic molecules, standard dihydropyridine, by subjecting it to the action of two monoamines (Scheme 2).

\[ \text{Scheme 2} \]

Under clean operating conditions i.e. H\(_2\)O at 100 °C, we easily isolated the structure dihydropyridine 5, according to the reaction of Hantzsch [18].

All compounds 5 were characterized by the various spectroscopic methods. Their physical properties are summarized in table 2.

**Table 2**: Conditions of formation and physical data of 5 at 100 °C.

| Compounds | R | R\(_1\) | Time (h) | Yield (%) | mp (°C) |
|-----------|---|--------|----------|-----------|---------|
| 5a        | C\(_6\)H\(_4\)-F | CH\(_3\) | 5        | 45        | 215-217 |
| 5b        | // | C\(_6\)H\(_5\) | 4        | 63        | 231-233 |
| 5c        | C\(_6\)H\(_4\)-CO\(_2\)CH\(_3\) | CH\(_3\) | 6        | 51        | 223-225 |
| 5d        | // | C\(_6\)H\(_5\) | 3        | 67        | 239-241 |

The amine's basicity allows, in a first step, the breaking of the hydrogen bond OH\(--\)O=\(\)C by electronic interaction N\(--\)H, according to the acid-base properties of Lewis. In a second step, the primary amine reacts with the carbonyl present in 3 to form the corresponding imine. Finally, the equilibrium enol-ketone and imine-enamine present in the reactional intermediary, leads, by interaction ketone-enamine to a heterocyclization of the structure dihydropyridine 5.

**3. EXPERIMENTAL**

All chemicals were obtained from Aldrich. Melting points were taken on a Thomas Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained with a Bruker AC 300 at 300 MHz (\(^1\)H) or 75 MHz (\(^13\)C). The chemical shifts are reported in ppm.
(δ-scale) relative to internal TMS and coupling constants are reported in Hertz (Hz). The impact ionization mass spectra were recorded on a Nermag R10-10C at 70 eV.

**General procedure for synthesis of 3 and 4**

In 20 ml water, a dimedone 1 (2.10^-2 mol) was reacted with aldehydes 2 (a to g) (10^-2 mol). The mixture was stirred at room temperature 2 hours or refluxed for 4 h under magnetic stirring. We obtained selectively, after filtration and dry vacuum the corresponding compound 3 (a to g) or 4 (a to g).

**General procedure for synthesis of 5**

Homodimer compound 3 (10^-2 mol) in 20 ml of water, reacted with monoamines (10^-2 mol). The mixture was refluxed for 4 h at 100 °C, under magnetic stirring. After filtration and dry vacuum, we obtained the corresponding compounds 5 (a to d).

2,2’-(ethane-1,1-diyl)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) 3a

Yield: 55%; 1H NMR (300MHz, CDCl3): δ (ppm) 1.07 (s, 6H, 2CH3), 1.12 (s, 6H, 2CH3), 1.29 (d, J=6.1 Hz, 3H, CH3), 2.13-2.18 (m, 8H, 4CH2), 4.89 (d, J=6.1Hz, 1H, CH), 10.98 (s, 1H, OH); 13C NMR ( 75 MHz, CDCl3): δ (ppm) 21 (CH3), 25 (2CH3), 28 (2CH3), 30 (2Cq), 31 (CH), 43(2CH2), 45(2CH2), 113(2Cq), 161(2 =C-OH), 187(2C=O). E.I. (70 eV), m/z (%) : M+ = 306 (14)

2,2’-(phenylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) 3b

Yield: 83%; 1H NMR (300MHz, CDCl3): δ (ppm) 1.04 (s, 6H, 2CH3), 1.11 (s, 6H, 2CH3), 2.31-2.39 (m, 8H, 4CH2), 5.39 (s, 1H, CH), 7.03-7.15 (m, 5H, CHarom), 11.81 (s, 1H, OH); 13C NMR ( 75 MHz, CDCl3): δ (ppm) 28 (2CH3), 32 (2CH3), 33 (2Cq), 34 (CH), 48(2CH2), 51(2CH2), 116(2Cq), 161(2 =C-OH), 188(2C=O). E.I. (70 eV), m/z (%) : M+ = 368 (40), 229 (100)

2,2’-(p-tolylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) 3c

Yield: 61%; 1H NMR (300MHz, CDCl3): δ (ppm) 1.07 (s, 6H, 2CH3), 1.20 (s, 6H, 2CH3), 2.27 (s, 3H, CH3), 2.37-2.41 (m, 8H, 4CH2), 5.48 (s, 1H, CH), 6.97-7.04 (m, 4H, CHarom), 11.87 (s, 1H, OH); 13C NMR ( 75 MHz, CDCl3): δ (ppm) 26 (CH3arom), 27 (2CH3), 29 (2CH3), 30 (2Cq), 31 (CH), 44(2CH2), 45(2CH2), 112(2Cq), 127-128-134-156(6Charom), 161(2 =C-OH), 191(2C=O). E.I. (70 eV), m/z (%) : M+ = 382 (33), 243 (59).
2,2'-(4-nitrophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) 3d
Yield: 78%; 1H NMR (300MHz, CDCl3): δ (ppm): 1.12 (s, 6H, 2CH3), 1.25 (s, 6H, 2CH3), 2.35-2.49 (m, 8H, 4CH2), 5.54 (s, 1H, CH), 7.19-8.01 (m, 4H, CH_arom), 11.87 (s, 1H, OH); 
13C NMR (75 MHz, CDCl3): δ (ppm) 28 (2CH3), 32 (2CH3), 34 (2Cq), 35 (CH), 49(2CH2), 52(2CH2), 116(2Cq), 123-129-141-157(6C_arom), 164(2 =C-OH), 189(2=C=O). E.I. (70 eV), m/z (%): M^+ + = 413 (27), 275(65).

2,2'-(4-fluorophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) 3e
Yield: 86%; 1H NMR (300MHz, CDCl3): δ (ppm): 1.01 (s, 6H, 2CH3), 1.22 (s, 6H, 2CH3), 2.40-2.43 (m, 8H, 4CH2), 5.48 (s, 1H, CH), 6.92-7.03 (m, 4H, CH_arom), 11.88 (s, 1H, OH); 
13C NMR (75 MHz, CDCl3): δ (ppm) 27 (2CH3), 30 (2CH3), 31 (2Cq), 32 (CH), 46(2CH2), 47(2CH2), 115(2Cq), 117-128-133-159(6C_arom), 162(2 =C-OH), 189(2=C=O). C.I. (NH3) : MH^+ + = 387 (23%), 244(5%).

Methyl- 4-(bis(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)methyl)benzoate 3f
Yield: 89%; 1H NMR (300MHz, CDCl3): δ (ppm): 1.10 (s, 6H, 2CH3), 1.23 (s, 6H, 2CH3), 2.34-2.45 (m, 8H, 4CH2), 3.88(s, 3H, O-CH3), 5.53 (s, 1H, CH), 7.16-7.94 (m, 4H, CH_arom), 11.84 (s, 1H, OH); 
13C NMR (75 MHz, CDCl3): δ (ppm) 19 (CH3), 22 (2CH3), 25 (2CH3), 31 (2Cq), 32 (CH), 46(2CH2), 49(O-CH3), 53(2CH2), 118(2Cq), 129-130-131-159(6C_arom), 165(2 =C-OH), 167(Cq), 192(2C=O). E.I. (70 eV), m/z (%): M^+ + = 436 (15), 298 (64).

2,2'-(4-hydroxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) 3g
Yield: 75%; 1H NMR (300MHz, CDCl3): δ (ppm): 1.08 (s, 6H, 2CH3), 1.19 (s, 6H, 2CH3), 2.34-2.41 (m, 8H, 4CH2), 5.47 (s, 1H, CH), 6.20(s, 1H, OH), 7.01-7.11 (m, 4H, CH_arom), 11.85 (s, 1H, OH); 
13C NMR (75 MHz, CDCl3): δ (ppm) 19 (CH3), 22 (2CH3), 25 (2CH3), 31 (2Cq), 32 (CH), 47(2CH2), 50(2CH2), 117(2Cq), 119-129-136-157(6C_arom), 163(2 =C-OH), 191(2C=O). E.I. (70 eV), m/z (%): M^+ + = 384 (23), 246 (57).

3,3,6,6,9-pentamethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione 4a
Yield: 67%; 1H NMR (300MHz, CDCl3): δ (ppm): 1.04 (s, 6H, 2CH3), 1.09 (s, 6H, 2CH3), 1.24 (d, J=6.1 Hz, 3H, CH3), 2.01-2.13 (m, 8H, 4CH2), 4.57 (d, J=6.1 Hz, 1H, CH); 
13C NMR (75 MHz, CDCl3): δ (ppm) 19 (CH3), 22 (2CH3), 25 (2CH3), 28 (2Cq), 30 (CH), 41(2CH2), 43(2CH2), 111(2Cq), 157(2 =C-O), 183(2C=O). E.I. (70 eV), m/z (%): M^+ + = 288 (33), 166.
(37).

3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione 4b

Yield: 88%; $^1$H NMR (300MHz, CDCl$_3$): δ (ppm) : 1.01 (s, 6H, 2CH$_3$), 1.09 (s, 6H, 2CH$_3$), 2.21-2.31 (m, 8H, 4CH$_2$), 4.59 (s, 1H, CH), 7.01-7.24 (m, 5H, CH$_{arom}$); $^{13}$C NMR ( 75 MHz, CDCl$_3$): δ (ppm) 25 (2CH$_3$), 30 (2CH$_3$), 32 (2Cq), 34 (CH), 45(2CH$_2$), 49(2CH$_2$), 123-125-127-154(6C$_{arom}$), 114(2Cq), 159(2 =C-O), 184(2C=O). E.I. (70 eV), m/z (%) : M$^{+}$ = 350 (45), 228 (7).

3,3,6,6-tetramethyl-9-(p-tolyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione 4c

Yield: 74%; $^1$H NMR (300MHz, CDCl$_3$): δ (ppm) : 1.03 (s, 6H, 2CH$_3$), 1.11 (s, 6H, 2CH$_3$), 2.15-2.27 (m, 8H, 4CH$_2$), 2.47 (s, 3H, CH$_3$), 4.72 (s, 1H, CH), 6.86-7.24 (m, 4H, CH$_{arom}$); $^{13}$C NMR ( 75 MHz, CDCl$_3$): δ (ppm) 24 (CH$_3$$_{arom}$), 26 (2CH$_3$), 28 (2CH$_3$), 30 (2Cq), 31 (CH), 41(2CH$_2$), 43(2CH$_2$), 110(2Cq), 125-126-131-152(6C$_{arom}$), 160(2 =C-O), 189(2C=O). E.I. (70 eV), m/z (%) : M$^{+}$ = 364 (38), 242 (51).

3,3,6,6-tetramethyl-9-(4-nitrophenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione 4d

Yield: 96%; $^1$H NMR (300MHz, CDCl$_3$): δ (ppm) : 1.02 (s, 6H, 2CH$_3$), 1.15 (s, 6H, 2CH$_3$), 2.15-2.46 (m, 8H, 4CH$_2$), 4.74 (s, 1H, CH), 7.39-8.06 (m, 4H, CH$_{arom}$); $^{13}$C NMR ( 75 MHz, CDCl$_3$): δ (ppm) 26 (2CH$_3$), 30 (2CH$_3$), 33 (2Cq), 35 (CH), 47(2CH$_2$), 51(2CH$_2$), 114(2Cq), 121-127-140-155(6C$_{arom}$), 162(2 =C-O), 185(2C=O). E.I. (70 eV), m/z (%) : M$^{+}$ = 395 (39), 273(65).

9-(4-fluorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione 4e

Yield: 93%; $^1$H NMR (300MHz, CDCl$_3$): δ (ppm) : 1.01 (s, 6H, 2CH$_3$), 1.14 (s, 6H, 2CH$_3$), 2.31-2.42 (m, 8H, 4CH$_2$), 4.69 (s, 1H, CH), 6.91-7.04 (m, 4H, CH$_{arom}$); $^{13}$C NMR ( 75 MHz, CDCl$_3$): δ (ppm) 25 (2CH$_3$), 28 (2CH$_3$), 31 (2Cq), 33 (CH), 45(2CH$_2$), 49(2CH$_2$), 113(2Cq), 117-125-131-157(6C$_{arom}$), 160(2 =C-O), 187(2C=O). E.I. (70 eV), m/z (%) : M$^{+}$ = 368 (32), 246 (43).

Methyl-4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)benzoate 4f
Yield: 97%; $^1$H NMR (300MHz, CDCl$_3$): δ (ppm): 1.02 (s, 6H, 2CH$_3$), 1.13 (s, 6H, 2CH$_3$), 2.33-2.46 (m, 8H, 4CH$_2$), 3.86(s, 3H, O-CH$_3$), 4.71 (s, 1H, CH), 7.14-7.93 (m, 4H, CH$_{arom}$); $^{13}$C NMR (75 MHz, CDCl$_3$): δ (ppm) 27 (2CH$_3$), 32 (2CH$_3$), 34 (2Cq), 35 (CH), 48(2CH$_2$), 49(O-CH$_3$), 53(2CH$_2$), 118(2Cq), 129-130-131-159(6C$_{arom}$), 163(2 =C-O), 167(Cq), 192(2C=O). E.I. (70 eV), m/z (%) : M$^{+}$ = 348 (15).

9-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione 4g
Yield: 81%; $^1$H NMR (300MHz, CDCl$_3$): δ (ppm): 1.01 (s, 6H, 2CH$_3$), 1.11 (s, 6H, 2CH$_3$), 2.31-2.39 (m, 8H, 4CH$_2$), 4.57 (s, 1H, CH), 6.20(s, 1H, OH), 6.69-7.08 (m, 4H, CH$_{arom}$); $^{13}$C NMR (75 MHz, CDCl$_3$): δ (ppm) 26 (2CH$_3$), 31 (2CH$_3$), 32 (2Cq), 33 (CH), 47(2CH$_2$), 50(2CH$_2$), 117(2Cq), 119-129-136-157(6C$_{arom}$), 163(2 =C-O), 191(2C=O). E.I. (70 eV), m/z (%) : M$^{+}$ = 366 (32), 244(43).

9-(4-fluorophenyl)-3,3,6,6,10-pentamethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione 5a
Yield: 45%; $^1$H NMR (300MHz, CDCl$_3$): δ (ppm): 0.98 (s, 6H, 2CH$_3$), 1.07 (s, 6H, 2CH$_3$), 2.15-2.33 (m, 8H, 4CH$_2$), 2.95(s, 3H, N-CH$_3$), 5.07 (s, 1H, CH), 6.91-7.02 (m, 4H, CH$_{arom}$); $^{13}$C NMR (75 MHz, CDCl$_3$): δ (ppm) 26 (2CH$_3$), 31 (2CH$_3$), 32 (2Cq), 33 (CH), 44(2CH$_2$), 47(2CH$_2$), 112(2Cq), 116-129-134-158(6C$_{arom}$), 161(2 =C-N), 191(2C=O). C.I. (NH$_3$) : MH$^{+}$ = 382 (41%), 244(43%).

9-(4-fluorophenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H, 5H)-dione 5b
Yield: 63%; $^1$H NMR (300MHz, CDCl$_3$): δ (ppm): 0.97 (s, 6H, 2CH$_3$), 1.08 (s, 6H, 2CH$_3$), 2.17-2.36 (m, 8H, 4CH$_2$), 5.06 (s, 1H, CH), 6.77-7.41 (m, 9H, CH$_{arom}$); $^{13}$C NMR (75 MHz, CDCl$_3$): δ (ppm) 27 (2CH$_3$), 32 (2CH$_3$), 31 (2Cq), 33 (CH), 46(2CH$_2$), 49(2CH$_2$), 113(2Cq), 115-117-118-124-128-133-134-156(12C$_{arom}$), 163(2 =C-N), 192(2C=O). C.I. (NH$_3$) : MH$^{+}$ = 444 (37%), 231(29%).

Methyl-4-(3,3,6,6,10-pentamethyl-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridin-9-yl)benzoate 5c
Yield: 51%; $^1$H NMR (300MHz, CDCl$_3$): δ (ppm): 0.99 (s, 6H, 2CH$_3$), 1.12 (s, 6H, 2CH$_3$),
2.31-2.39 (m, 8H, 4CH₂), 3.01 (s, 3H, N-CH₃), 3.83 (s, 3H, O-CH₃), 5.12 (s, 1H, CH), 7.09-7.88 (m, 4H, CH₉ arom); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 25 (2CH₃), 33 (2CH₃), 34 (2Cq), 36 (CH), 39 (N-CH₃), 46 (O-CH₃), 48 (2CH₂), 55 (2CH₂), 114 (2Cq), 126-129-131-159 (6C arom), 165 (2 =C-N), 167 (Cq), 193 (2=C=O). E.I. (70 eV), m/z (%): M⁺ = 390 (43), 244 (39).

Methyl-4-(3,3,6,6-tetramethyl-1,8-dioxo-10-phenyl-1,2,3,4,5,6,7,8,9,10-decahydroacridin-9-yl) benzoate 5d

Yield: 67%; ¹H NMR (300MHz, CDCl₃): δ (ppm): 1.09 (s, 6H, 2CH₃), 1.21 (s, 6H, 2CH₃), 2.33-2.41 (m, 8H, 4CH₂), 3.87 (s, 3H, O-CH₃), 5.11 (s, 1H, CH), 6.89-7.91 (m, 9H, CH₉ arom); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 26 (2CH₃), 31 (2CH₃), 35 (2Cq), 37 (CH), 47 (O-CH₃), 49 (2CH₂), 56 (2CH₂), 114 (2Cq), 116-119-123-128-130-132-134-159 (12C arom), 162 (2 =C-N), 168 (Cq), 194 (2=C=O). E.I. (70 eV), m/z (%): M⁺ = 466 (49), 308 (76).

4. CONCLUSION

In this work, we achieved the synthesis of a new type of dihydropyridinemolecules under clean operating conditions: H₂O as a solvent, no-catalysts and a simply work-up by filtration. The selectivity formation of structures 3 and 4, obtained with good yields, is determined to be conditioned by the reaction time.

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