Heteroatom Chemistry
Volume 6, Number 5, 1995

New Method for the Synthesis of 3(2H)-Pyridazinones and Their Alkene Precursors: Solvent-Free Reactions under Microwave Irradiation

Sandrine Jolivet, Françoise Texier-Boullet,* and Jack Hamelin

Groupe de Physicochimie Structurale 3 associé au CNRS, Université de Rennes I, Campus de Beaulieu, 35042 Rennes—France

Patrick Jacquault

Prolabo, 54 rue Roger Salengro, 94126 Fontenay-sous-bois—France

Received 2 December 1994; revised 17 January 1995

ABSTRACT

Several 3(2H)-pyridazinones **4** *were prepared from monophenylhydrazones of 1,2 dicarbonyl compounds* **1** *and various active methylene compounds* **2** *within 1–15 minutes, without solvent, under microwave irradiation, in the presence of carefully adjusted amounts of piperidine or solid potassium t-butoxide. The intermediate alkenes* **3** *were successfully prepared in several cases.* © *1995 John Wiley & Sons, Inc.*

INTRODUCTION

Pyridazinone derivatives [1] exhibit pharmacological activities, such as hypotensive, antibacterial, antiinflammatory, and antitumor properties. This is the basis for their great economical and biological interest [2–5]. Recently, Patel et al. reported the synthesis of 3(2H)-pyridazinones by the action of the triethylphosphonoacetate carbanion on the monophenylhydrazones of several 1,2 dicarbonyl compounds [6].

Organic reactions carried out in dry media have been widely used [7]. Microwave irradiation applied to organic synthesis has been reviewed recently [8,9]. The coupling of the two techniques, the use of "dry media" and microwave irradiation has attracted much attention [10] and is one of the main areas of research in our laboratory [11–14]. As part of our program to develop the synthesis of heterocyclic compounds under these conditions, we describe here a preparation of 3(2H)-pyridazinones without use of a solvent by using a mild, simple technique.

RESULTS AND DISCUSSION

The 3(2H)-pyridazinones can be obtained by condensation of monophenylhydrazones of α-dicarbonyl compounds **1** with active methylene compounds **2**, as shown in Scheme 1.

We first studied the model reaction of the monophenylhydrazone of glyoxal **1a** with methyl cyanoacetate **2a** under various conditions (Scheme 2).

Either the heterogeneous system KF/Al_2O_3 [15–17] or montmorillonite K10 [18] are suitable supporting agents for the preparation of pyridazinone **4a**, but the yield of the product is not satisfactory because of the irreversible adsorption of the final product on the inorganic supports after irradiation. For instance, the reaction of 5 mmol of **1a** with **2a** over KF/Al_2O_3 (1.5 g/3 g) (5 minutes at 600 W in a domestic microwave oven), led to **4a** (47% yield estimated by ^1H NMR), and over clay K10 in a fo-

*To whom correspondence should be addressed.

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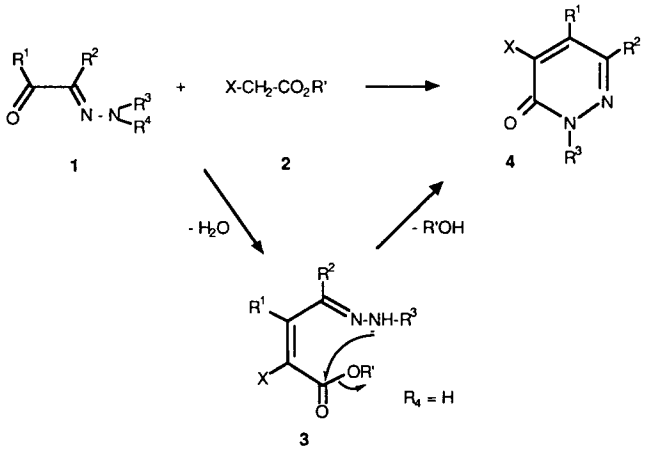


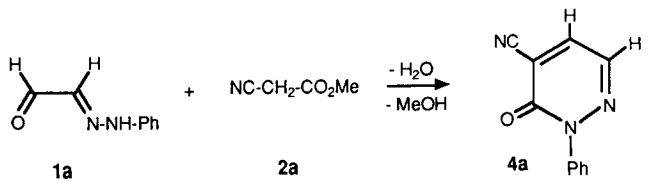
SCHEME 1

cused oven [19] during 3 minutes at 75 W, the yield was 75% (^{1}H NMR).

We reported recently the Knoevenagel condensation of active methylene compounds with carbonyl derivatives by use of catalytic amounts of piperidine in a domestic microwave oven [20]. The first step of pyridazinone synthesis is the postulated formation of the intermediate alkene **3**, resulting from the addition of monophenylhydrazones of 1,2 dicarbonyl compounds **1** with active methylene compounds **2**.

Therefore, we studied the catalytic effect of piperidine on the reaction of **1a** with **2a**. The conditions had to be carefully adjusted, including consideration of the mass of piperidine, shape of vessel, reaction time, and microwave power. The best result was obtained after 5 minutes at low power (30 W) in a focused microwave oven [19] (72% of pure **4a** after flash column chromatography). When the same reaction mixture was heated in an oil bath previously set at 90°C (temperature measured for the microwave irradiation experiment in the computer-monitored Prolabo system) over the same time period, the result was analogous. Thus, in this case, we can exclude a specific microwave effect; nevertheless, microwave heating was more convenient.

The method using piperidine was less expensive, fast, and simple; the final products were obtained by washing the reaction mixture with CH_2Cl_2 and chromatography on an alumina column. It



SCHEME 2

could be generalized to include various active methylene compounds (X = CO_2Me, CO_2Et; R′ = Me, Et) for the preparation of pyridazinones **4a–c**. It was not necessary in all cases to irradiate the reaction mixture (Table 1: runs 3 and 4). In the same way, methylglyoxal (R^1 = H, R^2 = Me) gave **4e–g**. It is important to note that only *t*BuOK was able to promote the reaction of the triethyl- or methyldiethylphosphonoacetate anion with the monophenylhydrazone of glyoxal, methylglyoxal, or 2,3-butanedione (Table 1: runs 5, 6, 9, and 10).

Remark: When pyridazinone **4b** (X = CO_2Me) was synthesized under microwave irradiation, decarboxylation after hydrolysis was observed and resulted in the formation of **4d** (73% isolated yield) after 15 minutes at 120 W in the presence of piperidine (75%, 0.25 mL). So, **4d** which had already been obtained from the triethylphosphonoacetate anion **2d′** could be formed directly from dimethyl malonate by a more simple and inexpensive method. In the same way, **4f** gave **4g** after 9 minutes at 120 W in a Maxidigest MX350 oven (60% isolated yield).

The intermediate alkene **3** was obtained either at low microwave power in the focused oven (Table 2: runs 1 and 2) or at room temperature according to the cases listed in Table 2: runs 3–6. Compounds **3** could be obtained after a very detailed study of experimental conditions (focused microwaves, low power, short reaction time). We have verified that alkene **3** is quantitatively transformed to pyridazinone **4** after alcohol elimination by microwave irradiation at 750 W during 15 minutes.

CONCLUSIONS

We believe that the protocol using piperidine without solvent under focused microwave irradiation at low power affords a clean, efficient, and selective method for the preparation of either pyridazinones **4** or their hydrazonoalkene precursors **3**. The previous procedures did not allow us to isolate the intermediate **3** [6] or did not lead to pyridazinones **4** [28].

EXPERIMENTAL

General

Unless otherwise specified, the starting materials were commercially available.

Montmorillonite clay K10 was purchased from Fluka company.

Melting points were taken with a Kofler hot-stage apparatus and are uncorrected.

IR spectra were recorded using a Perkin-Elmer 157G spectrometer, and mass spectra were taken with a VARIAN MAT 311 instrument.

The NMR spectra were obtained on BRUKER

WP 80CW or BRUKER AC 300P instruments (^{1}H NMR at 80 MHz and 300 MHz, ^{13}C NMR at 75.47 MHz).

All the reactions are run in a focused microwave oven Maxidigest MX 350 Prolabo [19].

Monohydrazones of glyoxal or methylglyoxal were readily prepared by standard methods [21–23].

Preparation of the Monophenylhydrazone of 2,3-Butanedione

2,3-Butanedione (50 mmol; 4.3 g) and phenylhydrazine (50 mmol; 5.4 g) were dispersed separately on molecular sieves (10 g) by thorough mixing. (The reagents must be completely adsorbed on the solid support.) The adsorbed compounds were then mixed together and allowed to stand at room temperature for 5 minutes. The monohydrazone was extracted by washing with dichloromethane and the solvent evaporated under reduced pressure. The crude product was used without further purification. (Yield: 86%; Mp 135°C [24]).

Preparation of 3(2H)-Pyridazinones **4** *or Functionalized Alkenes* **3**

Monohydrazones **1** and active methylene compound **2** (5 mmol) were mixed together at room temperature without solvent. The mixture was then adsorbed on the appropriate inorganic solid (alumina, alumina-potassium fluoride, montmorillonite clay K10) or mixed with potassium *t*-butylate or piperidine in amounts given in Table 1 for **4** and Table 2 for **3**.

The reaction mixture was submitted to focused microwaves in a 1.5 cm diameter open vessel or allowed to stand at room temperature. After addition of CH_2Cl_2 and filtration over celite when a solid catalyst was used, then washing or crystallizing with an appropriate solvent or purification by column chromatography on alumina gave the isolated pure product.

2-Phenyl-4-cyano-3-pyridazinone **4a**. 72% yield, 5 minutes at 30 W, piperidine 0.15 mL; pale brown crystals; mp 135°C from chromatography on alumina (CH_2Cl_2:AcOEt = 95:5). IR (Nujol): 2230, 1650 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$) δ: 7.39–7.58 (m, 5H, C_6H_5); 7.64 (d, 1H, HC=N, ^3J = 4Hz); 7.97 (d, 1H, HC=C–CN, ^3J = 4Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 113.2/116.2 (dd/dd, C–CN/CN, $^2J_{CH}$ = 6.67/5.78 Hz, $^3J_{CH}$ = 6.67/5.78 Hz); 129.15–140.5 (m, C_6H_5); 135.5 (dd, HC=C–CN, $^1J_{CH}$ = 171.1 Hz, $^2J_{CH}$ = 8.6 Hz); 137.3 (dd, HC=N, $^1J_{CH}$ = 192.7 Hz, $^2J_{CH}$ = 2.8 Hz); 156.3 (d, C=O, $^3J_{CH}$ = 7.54 Hz). Exact MS calcd 197.0589, found 197.0592. Anal. calcd for $C_{11}H_7N_3O$: C, 67.00; H, 3.58; N, 21.30. Found: C, 66.49; H, 3.57; N, 20.75.

2-Phenyl-4-methoxy-3-pyridazinone **4b**. 88% yield, 5 minutes at 20°C, piperidine 0.15 mL; pale brown crystals; mp 106°C from washing with ether. IR (Nujol): 1700, 1650 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$) δ: 3.87 (s, 3H, O–CH_3); 7.35–7.62 (m, 5H, C_6H_5); 7.75 (d, 1H, HC=N, ^3J = 4.01 Hz); 7.95 (d, 1H, HC=C–CO_2Me, ^3J = 4.01 Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 52.9 (q, CO_2CH_3, $^1J_{CH}$ = 147.9 Hz); 125.4–141.3 (m, C_6H_5); 130.96 (dd, CO_2Me–C=CH, $^2J_{CH}$ = 4.61 Hz, $^3J_{CH}$ = 1.98 Hz); 133.3 (dd, HC=C–CO_2Me, $^1J_{CH}$ = 166.8 Hz, $^2J_{CH}$ = 8.3 Hz); 135.7 (dd, HC=N, $^1J_{CH}$ = 190.3 Hz, $^2J_{CH}$ = 2.4 Hz); 156.9 (d, C=O, $^3J_{CH}$ = 8 Hz); 163.9 (dq aspect quint., CO_2CH_3, $^3J_{CH}$ = 4.3 Hz). Exact MS calcd 230.0691, found 230.0699. Anal. calcd for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.41; H, 4.44; N, 12.18.

2-Phenyl-4-ethoxy-3-pyridazinone **4c**. 89% yield, 4 hours at 20°C, piperidine 0.15 mL; pale brown crystals; mp 66–67°C from washing with ether. ^{1}H

TABLE 1 Preparation of 3(2H)-Pyridazinones **4a–h**: R^3 = Ph, R^4 = H

Run	4	X	R'	R^1	R^2	Catalyst: %:mL ou g	Reaction Time	Microwave Power or T[a]	Yield %[b]
1	**a**	CN	Me	H	H	piperidine: 30:0.15 mL	5 min	30 W	72(89)
2	**a**	CN	Et	H	H	piperidine: 30:0.15 mL	3 min	60 W	75(85)
3	**b**	CO_2Me	Me	H	H	piperidine: 30:0.15 mL	5 min	20°C	88(91)
4	**c**	CO_2Et	Et	H	H	piperidine: 30:0.15 mL	4 h	20°C	89(93)
5	**d**	H[c]	Me	H	H	*t* BuOK: 100:0.56 g	3 min	150 W	76(81)
6	**d**	H[d]	Et	H	H	*t* BuOK: 100:0.56 g	4 min	150 W	74(80)
7	**e**	CN	Me	H	Me	piperidine: 30:0.15 mL	5 min	75 W	68(89)
8	**f**	CO_2Me	Me	H	Me	piperidine: 30:0.15 mL	20 min	30 W	58(73)
9	**g**	H[d]	Et	H	Me	*t* BuOK: 100:0.56 g	3 min	150 W	75(91)
10	**h**	H[d]	Et	Me	Me	*t* BuOK: 100:0.56 g	5 min	150 W	51(70)

[a]Focused microwave oven MX350 Prolabo.
[b]Isolated pure product (numbers in brackets give yields estimated by ^{1}H NMR of crude product).
[c]Prepared from methyl diethylphosphonoacetate **2d**.
[d]Prepared from triethylphosphonoacetate **2d'**.

TABLE 2 Preparation of Some Functionalized Alkenes **3**

Run	3	X	R′	R^1	R^2	R^3	R^4	Catalyst: %:mL ou g	Reaction Time	Microwave Power or T	Yield %[a]
1	**a**	CN	Me	H	H	Ph	H	piperidine: 2:0.01 mL	1 min	75 W	100
2	**a′**	CN	Et	H	H	Ph	H	piperidine: 20:0.1 mL	1 min	45 W	83
3	**d**	H[b]	Me	H	H	Ph	H	*t* BuOK: 100:0.56 g	15 min	20°C	75
4	**d′**	H[c]	Et	H	H	Ph	H	*t* BuOK: 100:0.56 g	15 min	20°C	84
5	**e**	CN	Me	H	Me	Ph	H	piperidine: 30:0.15 mL	4 h	20°C	89
6	**i**	CN	Me	H	H	Me	Me	piperidine: 20:0.1 mL	15 min	20°C	96

[a]Isolated pure product.
[b]Prepared from methyl diethylphosphonoacetate **2d**.
[c]Prepared from triethylphosphonoacetate **2d′**.

NMR (300 MHz, $CDCl_3$) δ: 1.37 (t, 3H, $CO_2CH_2\underline{C}H_3$); 4.39 (q, 2H, $CO_2\underline{C}H_2CH_3$); 7.35–7.60 (m, 5H, $\underline{C}_6H_5$); 7.72 (d, 1H, $H\underline{C}$=N, ^3J = 4.02 Hz); 7.94 (d, 1H, $\underline{H}C$=C–CO_2Et, ^3J = 4.02 Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 14.1 (t, $CO_2\underline{C}H_2CH_3$, $^1J_{CH}$ = 127.5 Hz, $^2J_{CH}$ = 2.53 Hz); 62.1 (q, $\underline{C}O_2CH_2CH_3$, $^1J_{CH}$ = 148.4 Hz, $^2J_{CH}$ = 4.47 Hz); 125.4–141.3 (m, C_6H_5); 131.4 (dd, EtO_2C–$\underline{C}$=CH, $^2J_{CH}$ = 6.5 Hz, $^3J_{CH}$ = 1.8 Hz); 132.9 (dd, $H\underline{C}$=C–CO_2Et, $^1J_{CH}$ = 168.9 Hz, $^2J_{CH}$ = 8 Hz); 135.8 (dd, $H\underline{C}$=N, $^1J_{CH}$ = 190.9 Hz, $^2J_{CH}$ = 2.4 Hz); 156.9 (d, C=O, $^3J_{CH}$ = 7.9 Hz); 163.4 (m, $\underline{C}O_2$Et). Exact MS calcd 244.0847, found 244.0839. Anal. calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 64.00; H, 5.04; N, 11.49.

2-Phenyl-3-pyridazinone **4d**. 74% yield (4 minutes starting from **2d′**) or 76% yield (3 minutes starting from **2d**) at 150 W, *t*BuOK 0.56 g; pale brown crystals; mp 108°C from chromatography on alumina (CH_2Cl_2:AcOEt = 95:5) [6]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.00 (dd, 1H, $\underline{H}C$–CO, ^3J = 9.5 Hz, ^4J = 1.6 Hz); 7.17 (dd, 1H, $\underline{H}C$=CH, ^{3}**J** = 9.5 Hz, ^3J = 3.8 Hz); 7.35–7.62 (m, 5H, C_6H_5); 7.85 (dd, 1H, $\underline{H}C$=N, ^3J = 3.8 Hz, ^4J = 1.6 Hz) [25]. ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 125.4–141.5 (m, C_6H_5); 131.3/131.2 (m, =$H\underline{C}$–C=O/$H\underline{C}$=CH=N, $^1J_{CH}$ = 167.9 Hz, $^2J_{CH}$ = 8 Hz); 136.8 (ddd, $H\underline{C}$=N, $^1J_{CH}$ = 179.3 Hz, $^2J_{CH}$ = 5.5 Hz, $^3J_{CH}$ = 3.1 Hz); 160.14 (dd, C=O, $^3J_{CH}$ = 8.06 Hz) [26]. Exact MS calcd 172.0637, found 172.0635.

2-Phenyl-4-cyano-6-methyl-3-pyridazinone **4e**. 68% yield, 5 minutes at 75 W, piperidine 0.15 mL; pale brown crystals; mp 174 °C from chromatography on alumina (CH_2Cl_2:petroleum ether = 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.44 (s, 3H, CH_3); 7.4–7.6 (m, 5H, C_6H_5 et CH). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 20.74 (qd, CH_3, $^1J_{CH}$ = 129.65 Hz, $^3J_{CH}$ = 1.66 Hz); 113.17 (dd, $\underline{C}$–CN, $^2J_{CH}$ = 6.85 Hz); 116.54 (dd, CN, $^3J_{CH}$ = 1.94 Hz); 125.02/128.94–140.67 (m, C_6H_5); 138.96 (dq, NC–C=CH, $^1J_{CH}$ = 169.1 Hz, $^3J_{CH}$ = 3.7 Hz); 143.97 (qd, H_3C–$\underline{C}$=N, $^2J_{CH(CH_3)}$ = 6.7 Hz, $^2J_{CH(NC-C=CH)}$ = 1.7 Hz); 155.57 (d, C=O, $^3J_{CH}$ = 7.77 Hz). Exact MS calcd 211.07456, found 211.07454. Anal. calcd for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.06; H, 4.31; N, 19.63.

2-Phenyl-4-methoxy-6-methyl-3-pyridazinone **4f**. 58% yield, 20 minutes at 30 W, piperidine 0.15 mL; pale brown crystals; mp 91°C from washing with ether/methanol. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.42 (s, 3H, CH_3); 3.94 (s, 3H, CO_2CH_3); 7.38–7.59 (m, 5H, C_6H_5); 7.70 (s, 1H, CH). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 20.83 (qd, $H_3\underline{C}$–C=N, $^1J_{CH}$ = 128.9 Hz, $^3J_{CH}$ = 1.63 Hz); 53.03 (q, $\underline{C}O_2CH_3$, $^1J_{CH}$ = 148.2 Hz); 125.34–128.73/141.43 (m, $\underline{C}_6H_5$); 130.95 (d, MeO_2C–$\underline{C}$=CH, $^2J_{CH}$ = 1.99 Hz); 135.28 (dq, MeO_2C–C=$\underline{C}$H, $^1J_{CH}$ = 166.3 Hz, $^3J_{CH}$ = 3.6 Hz); 144.05 (qd, H_3C–$\underline{C}$=N, $^2J_{CH(MeO2C-C=CH)}$ = 6.8 Hz, $^2J_{CH(H3C-C=N)}$ = 2 Hz); 156.29 (d, C=O, $^3J_{CH}$ = 7.6 Hz); 164.18 (m, $\underline{C}O_2CH_3$, $^3J_{CH}$ = 3.9 Hz). Exact MS calcd 244.08479, found 244.08481. Anal. calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.44; H, 5.00; N, 11.39.

2-Phenyl-6-methyl-3-pyridazinone **4g**. 75% yield, 3 minutes at 150 W, *t*BuOK 0.56 g; pale brown crystals; mp 77°C from chromatography on alumina (CH_2Cl_2:AcOEt = 4:1) [6]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.32 (s, 3H, CH_3); 6.92 (d, 1H, $H\underline{C}$=CH, ^3J = 9.5 Hz); 7.08 (d, 1H, HC=C$\underline{H}$, ^3J = 9.5 Hz); 7.32–7.60 (m, 5H, C_6H_5). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 20.77 (qd, $\underline{C}H_3$–C=N, $^1J_{CH}$ = 128.6 Hz, $^3J_{CH}$ = 1.2 Hz); 125.4–141.61 (m, C_6H_5); 130.95 (dd, $H\underline{C}$–C=O, $^1J_{CH}$ = 170.7 Hz, $^2J_{CH}$ = 0.8 Hz); 133.34 (dq, $H\underline{C}$=$\underline{C}$H, $^1J_{CH}$ = 166.2 Hz, $^3J_{CH}$ = 3.4 Hz); 144.9 (m, $H\underline{C}$=N); 159.3 (dd, C=O, $^2J_{CH}$ = 1.6 Hz, $^3J_{CH}$ = 9 Hz) [26]. Exact MS calcd 186.0793, found 185.0701 (M^{+}-H).

2-Phenyl-5,6-dimethyl-3-pyridazinone **4h**. 51% yield, 5 minutes at 150 W, *t*BuOK 0.56 g; pale brown crystals; mp 112°C from chromatography on alumina (CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.16 (s, 3H, $\underline{C}H_3$–C–C–H); 2.28 (s, 3H, N–CH_3); 6.76 (s, 1H, CH); 7.3–7.6 (m, 5H, C_6H_5). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 18.8 (qd, $H_3\underline{C}$–C=N, $^1J_{CH}$ = 128.4 Hz, $^2J_{CH}$ = 5.51 Hz); 19.22 (q, $H_3\underline{C}$–C=CH, $^1J_{CH}$ = 128.2 Hz); 125.4–128.68/141.49 (m, C_6H_5); 128.60

(d, HC=C–CH_3, $^1J_{CH}$ = 172.8 Hz); 143.25 (m, H_3C–C=CH, $^2J_{CH}$ = 3.1 Hz); 145.71 (m, H_3C–C=N, $^2J_{CH}$ = 3.5 Hz); 160.03 (d, C=O, $^2J_{CH}$ = 1.2 Hz). Exact MS calcd 200.0949, found 200.0936. Anal. calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.58; H, 6.22; N, 13.45.

Methyl 2-Cyano-4-phenylhydrazino but-2-enoate **3a**. 100% yield, 1 minute at 75 W, piperidine 0.01 mL; orange crystals; mp 186°C. IR (Nujol): 2220 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + trifl.ac.) δ: 3.9 (s, 3H, CO_2CH_3); 7.00–7.5 (m, 6H, NH–C_6H_5); 7.77 (dd, HC=C–CN, ^3J = 9.6 Hz); 8.15 (dd, HC–C=N, ^3J = 9.6 Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$)* δ: 53.1 (q, CO_2CH_3); 101.2 (d, CN); 115.165 (dtd, *m*–C); 115.222 (H–C=C–CN); 123.89 (dtt, *p*–C); 129.54 (ddd, *o*–C); 132.44 (dd, H–C=N); 143.9 (tt, C quaternary of C_6H_5); 152.75 (dd, H–C=C–CN); 163.8 (q, CO_2CH_3). Exact MS calcd 229.0851, found 229.0842. Anal. calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.83; N, 18.33. Found: C, 62.67; H, 4.83; N, 18.35.

Ethyl 2-Cyano-4-phenatylhydrazino but-2-enoate **3a'**. 83% yield, 1 minute 45 W, piperidine 0.1 mL; orange crystals; mp 179°C after recrystallizing with EtOH. IR (Nujol): 2200 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + trifl.ac.) δ: 1.35 (t, 3H, $CO_2CH_2CH_3$); 4.35 (q, 2H, $CO_2CH_2CH_3$); 7.00–7.5 (m, 6H, NH–C_6H_5); 7.77 (dd, HC=C–CN, ^3J = 9.6 Hz); 8.15 (dd, HC–C=N, ^3J = 9.6 Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$)* δ: 14.22 (qt, $CO_2CH_2CH_3$); 62.25 (tq, $CO_2CH_2CH_3$); 101.11 (d, CN); 114.453 (dtd, *m*–C); 114.978 (H–C=C–CN); 123.58 (dtt, *p*–C); 129.58 (ddd, *o*-C); 132.19 (dd, H–C=N); 141.84 (tt, C quaternary of C_6H_5); 152.41 (dd, H–C=C–CN); 162.57 (q, $CO_2CH_2CH_3$). Exact MS calcd 243.1007, found 243.0981. Anal. calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.36; H, 5.27; N, 17.35.

Methyl 4-phenylhydrazino but-2-enoate **3d**. 75% yield, 15 minutes at 20°C, *t*BuOK 0.56 g; green brown crystals; mp 152°C from chromatography on alumina (CH_2Cl_2:petroleum ether = 9:1). ^1H NMR (300 MHz, $CDCl_3$) δ: 3.77 (s, 3H, CO_2CH_3);5.97 (d, 1H, H–C–CO_2CH_3); 6.90–7.53 (m, 7H, HC–CH, C_6H_5); 8.07 (s broad, 1H, NH). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 51.7 (q, CO_2CH_3, $^1J_{CH}$ = 146.8 Hz); 113.2–143.2 (m, C_6H_5); 129.4 (dd, H–C–CO_2CH_3, $^1J_{CH}$ = 159.01 Hz, $^2J_{CH}$ = 8.6 Hz); 135.5 (dq, H_3CO_2C–C=CH, $^1J_{CH}$ = 150.9 Hz); 141.7 (dd, H–C=N, $^1J_{CH}$ = 159.8 Hz, $^2J_{CH}$ = 7.5 Hz); 167.3 (quint., CO_2CH_3). Exact MS calcd 204.08987, found 204.09105. Anal. calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.62; H, 5.79; N, 13.81.

Ethyl 4-phenylhydrazino but-2-enoate **3d'**. 84% yield, 15 minutes at 20°C, *t*BuOK 0.56 g; pale brown crystals; mp 112°C from chromatography on alumina (CH_2Cl_2:petroleum ether = 9:1). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.29 (t, 3H, $CO_2CH_2CH_3$); 4.2 (q, 2H, $CO_2CH_2CH_3$); 5.92 (d, 1H, H–C–$CO_2CH_2CH_3$); 6.87–7.5 (m, 7H, HC–CH, C_6H_5); 8.38 (s broad, 1H, NH). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 14.26 (qt, $CO_2CH_2CH_3$, $^1J_{CH}$ = 126.98 Hz, $^2J_{CH}$ = 2.48 Hz); 60.5 (tq, $CO_2CH_2CH_3$, $^1J_{CH}$ = 142.22 Hz, $^2J_{CH}$ = 4.4 Hz); 113.2–143.3 (m, C_6H_5); 125.35 (dd, H–C–CO_2Et, $^1J_{CH}$ = 151.3 Hz, $^2J_{CH}$ = 7.8 Hz); 135.6 (dq, CO_2Et-C=C–H, $^1J_{CH}$ = 160.4 Hz, $^2J_{CH}$ = 4.1 Hz); 141.8 (dd, H–C=N, $^1J_{CH}$ = 152.8 Hz, $^2J_{CH}$ = 7.8 Hz); 167.1 (q, $CO_2CH_2CH_3$). Exact MS calcd 218.1055, found 218.1044. Anal. calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.46; N, 12.87. Found: C, 65.89; H, 6.60; N, 12.92.

Methyl 2-cyano 4-methyl 4-phenylhydrazino but-2-enoate **3e**. 89% yield, 4 hours at 20°C, piperidine 0.15 mL; orange crystals; mp 196°C after washing with ether/ethanol. IR (Nujol):2220 cm^{-1}. ^1H NMR (300 MHz, $(CD_3)_2SO$) δ: 1.82 (s, 3H, CH_3); 3.35 (s, 3H, CO_2CH_3); 6.5–7.02 (m, 5H, C_6H_5); 7.35 (s, 1H, H–C=C); 10.2 (s broad, 1H, NH). ^{13}C NMR (75.47 MHz, $(CD_3)_2SO$) δ: 14.46 (qd, N=C–CH_3, $^1J_{CH}$ = 128.4 Hz, $^3J_{CH}$ = 3.97 Hz); 53.85 (q, CO_2CH_3, $^1J_{CH}$ = 147.96 Hz); 96.43 (s, CN); 115.8 (dtd, *m*-C, $^1J_{CH}$ = 160.01 Hz); 117.5 (d, NC–C=C–H, $^2J_{CH}$ = 13.33 Hz); 123.53 (dtt, *p*-C, $^1J_{CH}$ = 159.40 Hz); 130.1 (ddd, *o*-C, $^1J_{CH}$ = 161.3 Hz, $^2J_{CH}$ = 8.2 Hz); 137.57 (qd, C=N, $^2J_{CH}$ = 6.8 Hz); 144.26 (tt, C quaternary of C_6H_5); 155.33 (dq, H–C–C–CH_3, $^1J_{CH}$ = 159.2 Hz, $^3J_{CH}$ = 3.4 Hz); 164.48 (m, CO_2CH_3). Exacts MS calcd 243.10077, found 243.10225. Anal. calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 63.73; H, 5.37; N, 17.07.

Methyl 2-cyano 4-dimethyl but-2-enoate **3i**. 96% yield, 15 minutes at 20°C, piperidine 0.1 mL; pale brown crystals; mp 72°C after washing with ether. IR (Nujol): 2200 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.29 (s broad, 6H, $N(CH_3)_2$); 3.83 (s, 3H, CO_2CH_3); 7.06 (d, 1H, HC=C–CN); 7.94 (d, 1H, HC=N). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 52.5 (q, CO_2CH_3, $^1J_{CH}$ = 147.64 Hz); 95.6 (s, CN); 115.8 (d, NC–C–CO_2Me, $^2J_{CH}$ = 12.68 Hz); 124.2 (dd, H–C=N, $^1J_{CH}$ = 161.4 Hz, $^2J_{CH}$ = 8.5 Hz); 154.2 (dd, NC–C=CH, $^1J_{CH}$ = 164.8 Hz, $^2J_{CH}$= 0.96 Hz); 163.95 (quint., CO_2CH_3, $^3J_{CH}$ = 4.1 Hz). Remark: At the recording temperature of the spectrum, the two carbons of $N(CH_3)_2$ appear as a broad signal [27]. Exact MS calcd 181.085, found 181.086. Anal.calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 52.79; H, 6.31; N, 23.30.

ACKNOWLEDGMENT

We thank "Conseil Régional de Bretagne" for a fellowship to one of us (SJ).

*__3a__ is not very soluble in $CDCl_3$.
*__3b__ is not very soluble in $CDCl_3$.

REFERENCES

[1] M. Tisler, B. Stanovnik, *Advances in Heterocyclic Chemistry* in A.R. Katritzky, A. J. Boulton (eds): Academic Press, New York, vol. 9, pp. 220–270 (1968) and vol. 24 (1979).

[2] P. Coudert, C. Rubat, J. Couquelet, J. Fialip, P. Bastide, *Eur J. Med. Chem., 24*, 1989, 551–555.

[3] C. Rubat, P. Coudert, P. Tronche, J. Bastide, P. Bastide, A. M. Privat, *Chem. Pharm. Bull., 37 (10)*, 1989, 2832–2835.

[4] H. Okushima, A. Narimatsu, M. Kobayashi, R. Furuya, K. Tsuda, Y. Kitada, *J. Med. Chem., 30*, 1987, 1157–1161.

[5] S. Kamiya, M. Anzai, T. Nakashima, S. Sueyoshi, M. Tanno, *Chem. Pharm. Bull., 25*, 1977, 504.

[6] H. V. Patel, K. A. Vyas, S. P. Pandey, F. Tavares, P. S. Fernandes, *Synthetic Comm., 21*, 1991, 1021–1026; *21*, 1991, 1935–1940.

[7] P. Laszlo, *Acc. Chem. Res., 19*, 1986, 121 and references cited therein.

[8] R. A. Abramovitch, *Org. Prep. Proc. Int., 23 (6)*, 1991, 685–711.

[9] D. N. P. Mingos, D. R. Baghurst, *Chem. Soc. Rev. 20*, 1991,1–47.

[10] G. Bram, A. Loupy, D. Villemin, Ellis Horwood and Prentice-Hall; *Solid Supports and Catalysts in Organic Synthesis*, in K. Smith (ed), Ellis Horwood and Prentice-Hall, Englewood Cliffs, NJ, p. 302 (1983) and references cited therein.

[11] R. Latouche, F. Texier-Boullet, J. Hamelin, *Tetrahedron Lett., 32*, 1991, 1179–1182; *Bull. Soc. Chim. Fr., 130*, 1993, 535.

[12] J. F. Pilard, B. Klein, F. Texier-Boullet, J. Hamelin, *Synlett*, 1992, 219.

[13] B. Rechsteiner, F. Texier-Boullet, J. Hamelin, *Tetrahedron Lett., 34*, 1993, 5071.

[14] B. Touaux, B. Klein, F. Texier-Boullet, J. Hamelin, *J. Chem. Res. (S)*, 1994, 116.

[15] J. Yamawaki, T. Kawate, T. Ando, T. Hanafusa, *Bull. Soc. Chem. Jpn., 56*, 1983, 1985.

[16] D. Villemin, *J. Chem. Soc., Chem. Comm.*, 1983, 1092.

[17] F. Texier-Boullet, D. Villemin, M. Ricard, H. Moison, A. Foucaud, *Tetrahedron, 43*, 1987, 537.

[18] P. Laszlo, *La Recherche, 219*, 1990, 314.

[19] R. Commarmot, R. Didenot, J. F. Gardais, Rhône-Poulenc/Prolabo Patent No. 84/03496. October 27th 1986. Apparatus commercialized by Prolabo under the name Maxidigest MX 350.

[20] S. Abdallah-El Ayoubi, F. Texier-Boullet, J. Hamelin, *Synthesis*, 1994, 258.

[21] M. Begtrup, J. Holm, *J. Chem. Soc., Perkin Trans. I*, 1981, 503–513.

[22] M. Begtrup, H. P. Nytoft, *J. Chem. Soc., Perkin Trans. I*, 1985, 81–86.

[23] Th. Severin, H. Poehlman, *Chem. Ber.*, 1977, 491–499.

[24] C. H. Yoder, S. Kennedy, F. Snavely, *J. Org. Chem., 43*, 1978, 1077–1079

[25] H. Mc Nab, *J. Chem. Soc., Perkin Trans. I*, 1982, 1845–1853.

[26] H. Mc Nab, *J. Chem. Soc., Perkin Trans. I*, 1983, 1203–1207.

[27] H. Mc Nab, *J. Chem. Res.*, 1979, 121.

[28] D. Carrasco, F. Bartullin, *Rev. R. Acad. Cianc. Exactas, Fis. Nat. Madrid, 62*, 1968, 485.