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# Efficient Tautomerization Hydrazone-Azomethine Imine under Microwave Irradiation. Synthesis of [4,3'] and [5,3']Bipyrazoles

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*Abstract:* Microwave irradiation induces the thermal isomerization of pyrazolyl hydrazones to the corresponding azomethine imines which undergo 1,3-dipolar cycloaddition with electron-poor dipolarophiles in a few min with good yields. By classical heating, several dipolarophiles do not react in comparable reaction conditions. Regiochemistry of bipyrazoles obtained from unsymmetrical dipolarophiles has been inferred by spectroscopic experiments. 

The first series of bipyrazoles were synthesized in 1893.[1] Since then many bipyrazolyl derivatives have been reported in the literature.[2] Some of them were shown to be useful compounds as potential antiinflamatory agents,[3] cytotoxic agents,[4] insecticides,[5] herbicides,[6] fungicides,[7] and in the photographic and paint industry.[8]

In most cases, bipyrazolyl derivatives have been synthesized by cyclization reactions.[9] However, 1,3-dipolar cycloadditions are one of the most versatile tools for the construction of five-membered heterocycles,[10] and bipyrazoles have been also prepared through these reactions using diarylnitrilimines[11] or diazocompounds[12] as reagents.

Hydrazones give a thermal 1,2-hydrogen shift to afford azomethine imine intermediates that can undergo a 1,3-dipolar cycloaddition, as it is known since 1978.[13] Recently it has been described that a protonated substrate can intramolecularly assist, if a carbonyl group is present in an adequate position, the hydrazone-azomethine imine isomerization under mild conditions.[14] However, in most cases the intermolecular cycloaddition of thermally generated azomethine imines with very activated dipolarophiles must be performed under reflux in high-boiling solvents (e.g., xylene) with long reaction times (several hours or days).[15] This reduces the synthetic utility of the reaction.

Microwave irradiation in solvent-free conditions has well demonstrated its utility as the energy source in many organic reactions,[16] including 1,3-dipolar cycloadditions.[17] The rapid heating induced by the radiation

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leads to the formation of products under mild reaction conditions with short reaction times, thus, sometimes, increasing the yield.

In this paper we report a new approach for the preparation of bipyrazolyl derivatives by 1,3-dipolar cycloaddition under microwave irradiation. The radiation produces the thermal isomerization of the pyrazolyl hydrazones **1**, **2**, **16** or **17** to the corresponding azomethine imines. These intermediates undergo 1,3-dipolar cycloaddition with double or triple bonded dipolarophiles to afford [4,3'] or [5,3'] bipyrazolyl adducts in 10-45 min with 30-84% yield. The reaction we describe permits, together with the study of the periselectivity, the synthesis of useful compounds such as bipyrazoles in good yields by a useful and clean synthetic methodology.

## RESULTS AND DISCUSSION

4-Pyrazolyl hydrazones **1** or **2** reacted with electron-poor dipolarophiles, such as **3-6**, under microwave irradiation within 10-45 min affording the [4,3']-bipyrazoles **7-13**. Reaction conditions and results are summarized in the Table 1.

**1**, R = H
**2**, R = $NO_2$

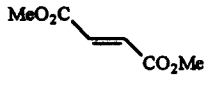
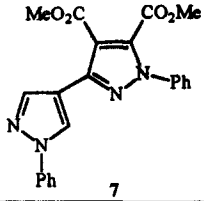
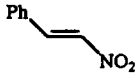
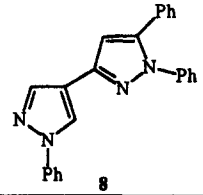
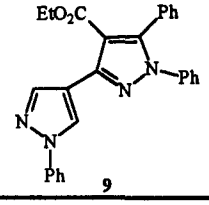
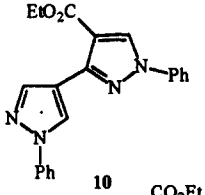
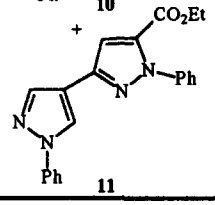
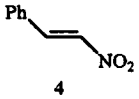
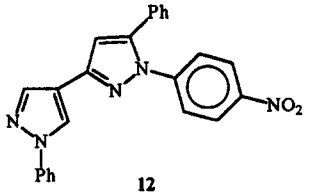
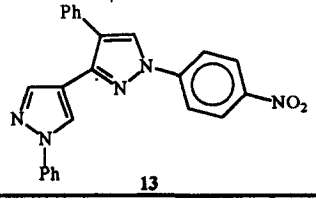
**1'**, R = H
**2'**, R = $NO_2$

Cycloadditions were performed at atmospheric pressure in a focused microwave reactor or into hermetically closed teflon tubes in a domestic oven. In this case internal pressures were not measured. All cycloadditions were optimized to obtain the best yield and until complete consumption of the starting materials. Reaction products showed a high stability under microwave irradiation. Reactions did not show equilibrium between reactants and products and the adduct ratio did not change under microwaves.

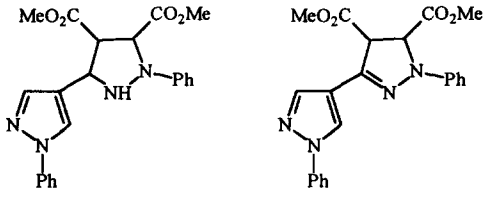
As it is has been reported, hydrazones can react via azomethine imine tautomer with very activated dipolarophiles, such as N-phenylmaleimide.[13a] Intramolecular reactions to non-activated alkenes have also been achieved.[15,18] In both processes reaction times are prolonged and yields are, in most cases, moderate. Acid-catalyzed [$3^+$ + 2] cycloadditions of hydrazones are faster and give better yields.[19] Under microwaves, 1,3-dipolar cycloadditions were dramatically accelerated achieving good yields of the aromatic bipyrazoles in a few minutes. The effect of microwave irradiation is not exclusively a reaction acceleration : the hydrazone **1** and ethyl propiolate **6** did not react by classical heating in an oil bath in comparable reaction conditions (time and temperature). Finally, this simple procedure avoids the use of acid to catalyze the cycloaddition.

Owing to their structure, hydrazones **1** or **2** could also undergo a [4 + 2] cycloaddition reacting as a 1-azadiene to afford pyrazolopyridines. Recently, we have reported Diels-Alder cycloadditions of 4- or 5-vinylpyrazoles under microwave irradiation.[20] However, with **1** and **2** we did not observe this process.

**Table 1.** 1,3-Dipolar Cycloaddition Reaction of 1-Phenylpyrazole-4-carbaldehyde hydrazones **1** or **2**

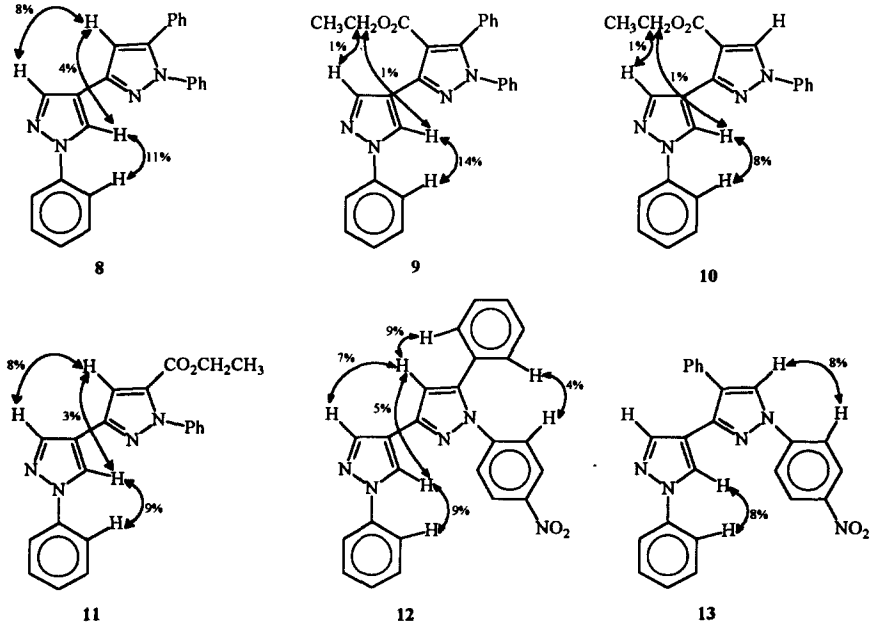
| Hydrazone | Dipolarophile | Reaction conditions | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  **3** | MW, 255 W, 155 °C, 45 min |  **7** | 84 |
| 1 |  **4** | MW, 135 W, 135 °C, 10 min |  **8** | 67 |
| 1 |  **5** | MW, 780 W, 185 °C, 15 min |  **9** | 59 |
| 1 |  **6** | MW, 780 W, 170 °C, 15 min |  **10** +  **11** | 22 + 8 |
| 2 |  **4** | MW, 135 W, 130 °C, 10 min |  **12** +  **13** | 70 + 5 |

In the cycloaddition with dimethyl fumarate shorter reaction times, 15 min, allowed the intermediate products **14** and **15** be isolated. The intermediates **14** and **15** aromatise *in situ* to **7** by oxidation due to the presence of air.[13,14,19a] Elimination of $HNO_2$[21] allowed the bipyrazoles **8**, **12** and **13** to be isolated as aromatic compounds. When ethyl propiolate or β-nitrostyrene were employed as dipolarophiles, two isomeric cycloadducts resulted from the two possible approaches of the reagents in the transition state.




**14** **15**

The regiochemistry of the cycloadducts obtained using unsymmetrical dipolarophiles, **8-13**, was inferred by a combined consideration of the broadband decoupled $^{13}C$ spectra, the gated decoupling $^{13}C$ spectra, and heteronuclear correlation and NOE difference experiments. These proved that the structure of the [4,3']-bipyrazoles is that indicated in Table 1.

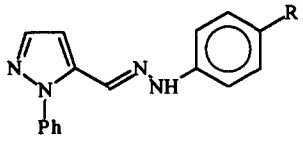



**8** **9** **10**

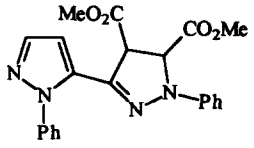
**11** **12** **13**

**Figure 1.** Selected NOEs for compounds **8-10** and **11-13**

In the same way, microwave irradiation for 15-45 min, of the 5-pyrazolyl hydrazone **16** or **17** and an electron-poor dipolarophile, such as **3-5**, afforded the [5,3']-bipyrazoles **18-23** (Table 2). No intermediates were isolable except in the cycloaddition with dimethyl fumarate **3** from which **24** could be isolated with shorter reaction times.

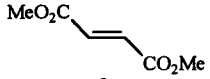
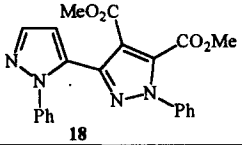
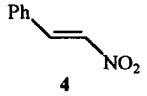
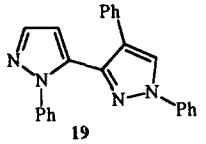
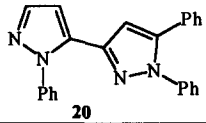
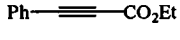
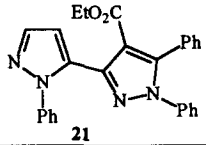
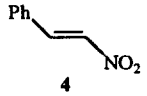
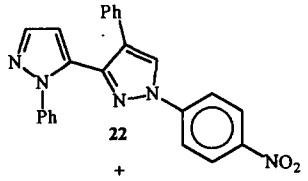
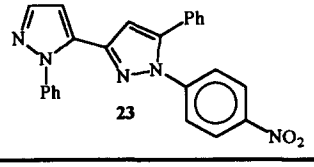


**16**, R = H
**17**, R = $NO_2$



**24**

**Table 2.** 1,3-Dipolar Cycloaddition Reaction of 1-Phenylpyrazole-5-carbaldehyde hydrazones **16** and **17**

| Hydrazone | Dipolarophile | Reaction conditions | Product | Yield (%) |
|---|---|---|---|---|
| **16** |  **3** | MW, 255 W, 155°C, 45 min |  **18** | 56 |
| **16** |  **4** | MW, 90 W, 130°C, 15 min |  **19** +  **20** | 45<br>22 |
| **16** |  **5** | MW, 240 W, 180°C, 30 min |  **21** | 40 |
| **17** |  **4** | MW, 255 W, 130°C, 12 min |  **22** +  **23** | 33<br>29 |

The regiochemistry of the bipyrazoles **19-23** was confirmed by spectroscopic experiments (Fig. 2).

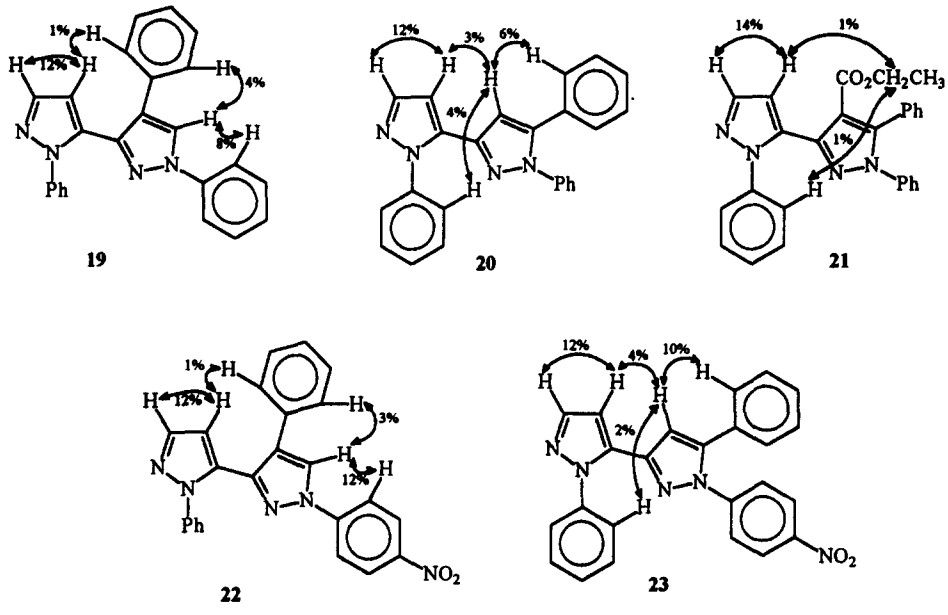
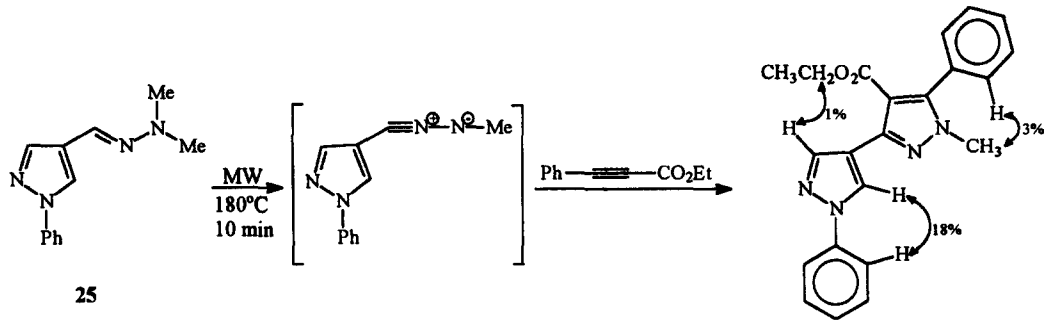



**Figure 2** Selected NOEs for compounds **19-23**

The 1,3-dipolar cycloaddition of the hydrazones **1** or **16** with dimethyl fumarate was also performed by classical heating in an oil bath under the same reaction conditions (temperature and reaction time) described above. We obtained the corresponding bipyrazoles, **7** and **18**, in 17 and 25% yield, respectively. These results showed the utility of the microwave radiation in organic synthesis and its advantages in comparison with classical heating, specially in processes that need strong heating and/or vigorous reaction conditions, such as the thermal hydrazone-azomethine imine isomerization.

The cycloaddition reactions of the dimethylhydrazone **25** were also analyzed. This hydrazone cannot undergo a thermal 1,2-hydrogen shift to afford an azomethine imine, as does **1** or **2**. We found that microwave irradiation of a mixture of the dimethylhydrazone **25** and ethyl phenylpropiolate **5** for 10 min gave the [4,3']-bipyrazole **26** in 80% yield. By classical heating under these reaction conditions compound **26** was not obtained. The structure and regiochemistry of this adduct were confirmed by its analytical and spectroscopic data and NOE difference experiments. A similar reaction with dimethyl fumarate as dipolarophile did not afford the corresponding bipyrazole but 1-phenyl-4-cyanopyrazole, generated from **25** by loss of dimethylamine.[22] In view of this reactivity, these reactions could occur through a Michael type intermediate. A competition between cyclisation and fragmentation of the intermediate could lead to different products.[23]




25

26 (80%)

## CONCLUSIONS

The thermal isomerization hydrazone-azomethine imine can be easily and efficiently performed under microwave irradiation to give good yields, in a few min, of bipyrazole derivatives. **However, the effect of microwave irradiation is not only a reaction acceleration but it induces the cycloaddition of dipolarophiles that do not react by classical heating under comparable reaction conditions**. Microwaves also induce dimethylhydrazone **25** to react with ethyl phenylpropiolate. The structure of the adducts obtained from unsymmetrical dipolarophiles has been inferred by a combined consideration of the broadband decoupled $^{13}C$ spectra, the gated decoupling $^{13}C$ spectra, and heteronuclear correlation and NOE difference experiments.

## ACKNOWLEDGEMENTS

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## EXPERIMENTAL

*General.*- All m.p. were determined on a Gallenkamp apparatus and are uncorrected. $^1H$ NMR spectra were recorded at 299.94 MHz on a Varian Unity 300 spectrometer. $^{13}C$ NMR spectra were recorded at 75.429 MHz on a Varian Unity 300 machine. Chemical shifts are reported in ppm (δ) using $Me_4Si$ as standard, and coupling constants *J* are given in Hz. Percentage NOE enhancements were obtained by integrating the affected resonance relative to the irradiated resonance in the difference spectrum in each case. Column chromatography was carried out with $SiO_2$ (silica gel, Merck type 60 230-400 mesh). Microwave irradiations were conducted in a Miele Electronic M720 domestic oven or a focused microwave reactor Prolabo MX350 with measurement and control of power and temperature by infrared detection. Elemental analysis were

determined on a Perkin-Elmer PE2400 CHN apparatus. Mass spectra were obtained on a VG Autospec instrument (70 eV). Reagents were purchased from commercial suppliers or prepared by literature methods.

*General Procedures*.- **Method A** : A mixture of hydrazone (1 equiv.) and dipolarophile (2 equiv.) was charged to a commercial 25 ml Teflon PTFE vessel, closed and irradiated in a Miele Electronic M720 microwave oven at 780 W for the indicated time. The crude reaction was purified by flash chromatography on silica gel.

**Method B** : A mixture of hydrazone (1 equiv.) and dipolarophile (2 equiv.) was irradiated in a focused microwave reactor Prolabo MX350 for the time and at the power indicated. The crude reaction was purified by flash chromatography on silica gel.

*Dimetyl 1,1'-diphenyl-[4,3']-bipyrazole-4',5'-dicarboxylate 7.* (Method B) From 1-phenylpyrazole-4-carbaldehyde phenylhydrazone **1** (200 mg, 0.76 mmol) and dimethyl fumarate **3** (218 mg, 1.52 mmol) with irradiation at 255 W for 45 min (final temperature 155 °C). Flash chromatography (hexane-ethyl acetate 3 :1) allowed bipyrazole **7** to be isolated as white needles (256 mg, 84%), m.p. 97-98 °C (from methanol) ; $^1$H-NMR ($CDCl_3$) δ 3.85 and 3.88 (2 x s, 6 H, 2 x $OCH_3$), 7.25 (t, *J* 7.3, 1 H, *p*-H 1-Ph), 7.40-7.48 (m, 5 H, $H_{arom}$), 7.54 (d, *J* 6.8, 2 H, *o*-H 1-Ph), 7.76 (d, *J* 7.5, 2 H, *o*-H 1'-Ph), 8.35 (s, 1 H, H-3), 8.81 (s, 1 H, H-5) ; $^{13}$C-NMR ($CDCl_3$) δ 52.0 and 53.2 ($OCH_3$), 114.7 (C-4'), 118.8 (*o*-C 1-Ph), 123.7 (*o*-C 1'-Ph), 126.3 and 128.8 (*p*-C 1- and 1'-Ph), 129.0 and 129.1 (*m*-C 1- and 1'-Ph), 127.1 and 140.6 (C-3 and -5), 137.7 and 144.9 (C-3' and -5'), 138.4 and 139.6 (*ipso*-C 1- and 1'-Ph), 161.0 and 162.4 (COO). Anal. Calcd. for $C_{22}H_{18}N_4O_4$ : C, 65.65 ; H, 4.5 ; N, 13.9. Found : C, 65.75 ; H, 4.5 ; N, 13.8% ; MS (EI) m/z 402 ($M^+$).

Data for **14** : yellow oil ; $^1$H-NMR ($CDCl_3$) δ 3.71 and 3.86 (2 x s, 6 H, 2 x $OCH_3$), 3.77 (dd, *J* 6.1 and 8.9, 1 H, H-4'), 4.32 (br s, 1 H, NH), 4.43 (d, *J* 8.9, 1 H, H-3'), 4.82 (d, *J* 6.1, 1 H, H-5'), 6.91 (t, *J* 7.8, 1 H, *p*-H 1'-Ph), 7.21-7.32 (m, 5 H, $H_{arom}$), 7.47 (t, *J* 7.8, 2 H, *m*-H 1-Ph), 7.70 (d, *J* 7.8, 2 H, *o*-H 1-Ph), 7.84 (s, 1 H, H-3), 8.07 (s, 1 H, H-5).

Data for **15** : m.p. 131-133 °C (from methanol) ; $^1$H-NMR ($CDCl_3$) δ 3.77 and 3.79 (2 x s, 6 H, 2 x $OCH_3$), 4.47 (d, *J* 5.3, 1 H, H-4'), 5.22 (d, *J* 5.3, 1 H, H-5'), 6.91 (t, *J* 7.8, 1 H, *p*-H 1'-Ph), 7.13 (d, *J* 7.8, 2 H, *o*-H 1'-Ph), 7.26-7.36 (m, 3 H, $H_{arom}$), 7.48 (t, *J* 7.8, 2 H, *m*-H 1-Ph), 7.71 (d, *J* 7.8, 2 H, *o*-H 1-Ph), 8.10 (s, 1 H, H-3), 8.30 (s, 1 H, H-5) ; $^{13}$C-NMR ($CDCl_3$) δ 53.1 and 53.3 ($OCH_3$), 57.0 (C-4'), 64.9 (C-5'), 113.2 (*o*-C 1'-Ph), 116.1 (C-4), 119.2 (*o*-C 1-Ph), 120.1 (*p*-C 1'-Ph), 125.2 (C-5), 129.5 (*m*-C 1-Ph), 137.0, 139.6 and 143.9 ($C_{arom}$), 139.7 (C-3), 168.5 and 170.2 (COO).

*1,1',5'-Triphenyl-[4,3']-bipyrazole 8.* (Method B) From 1-phenylpyrazole-4-carbaldehyde phenylhydrazone **1** (200 mg, 0.76 mmol) and β-nitrostyrene **4** (227 mg, 1.52 mmol) with irradiation at 135 W

for 10 min (final temperature 135 °C). Flash chromatography (hexane-ethyl acetate 5 :1) afforded the bipyrazole **8** as white needles (184 mg, 67%), m.p. 162-163 °C (from methanol) ; $^1$H-NMR ($CDCl_3$) δ 6.68 (s, 1 H, H-4'), 7.24-7.35 (m, 11 H, $H_{arom}$), 7.46 (d, *J* 7.6, 2 H, *m*-H 1-Ph), 7.75 (d, *J* 7.6, 2 H, *o*-H 1-Ph), 8.11 (s, 1 H, H-3), 8.38 (s, 1 H, H-5) ; $^{13}$C-NMR ($CDCl_3$) δ 105.3 (C-4'), 117.7 (C-4), 118.9 (*o*-C 1-Ph), 123.8 (C-5), 125.3, 126.4, 127.4, 128.3, 128.4, 128.6, 128.8 and 129.4 ($C_{arom}$), 130.3 (*ipso*-C 5'-Ph), 139.2 (C-3), 140.0 (*ipso*-C 1- and 1'-Ph), 144.1 and 144.9 (C-3' and -5'). Anal. Calcd. for $C_{24}H_{18}N_4$ : C, 79.5 ; H, 5.0 ; N, 15.5. Found : C, 79.0 ; H, 4.95 ; N, 15.5%.

*Ethyl 1,1',5'-triphenyl-[4,3']-bipyrazole-4'-carboxylate* ***9***. (Method A) From 1-phenylpyrazole-4-carbaldehyde phenylhydrazone **1** (200 mg, 0.76 mmol) and ethyl phenylpropiolate **5** (264 mg, 1.52 mmol) with irradiation for 15 min (final temperature 185 °C). Flash chromatography (hexane-ethyl acetate 5 :1) allowed bipyrazole **9** to be isolated as white needles (194 mg, 59%), m.p. 134-135 °C (from methanol) ; $^1$H-NMR ($CDCl_3$) δ 1.00 (t, *J* 7.1, 3 H, $CH_3$), 4.12 (q, *J* 7.1, 2 H, $CH_2$), 7.26-7.38 (m, 11 H, $H_{arom}$), 7.46 (t, *J* 6.6, 2 H, *m*-H 1-Ph), 7.79 (d, *J* 7.6, 2 H, *o*-H 1-Ph), 8.36 (s, 1 H, H-3), 8.81 (s, 1 H, H-5) ; $^{13}$C-NMR ($CDCl_3$) δ 13.7 ($CH_3$), 60.0 ($CH_2$), 112.1 (C-4), 117.2 (C-4'), 119.1, 125.6, 126.0, 127.1, 128.6, 128.7, 129.4, 130.8 ($C_{arom}$), 131.0, 139.9 and 140.8 (*ipso*-C 1-, 1'- and 5'-Ph), 141.8 (C-3), 146.5 and 146.6 (C-3' and -5'), 163.8 (COO). Anal. Calcd. for $C_{27}H_{22}N_4O_2$ : C, 74.65 ; H, 5.1 ; N, 12.9. Found : C, 74.55 ; H, 5.05 ; N, 12.9% ; MS (EI) m/z 434 ($M^+$).

*Ethyl 1,1'-diphenyl-[4,3']-bipyrazole-4'-carboxylate* ***10*** *and Ethyl 1,1'-diphenyl-[4,3']-bipyrazole-5'-carboxylate* ***11***. (Method A) From 1-phenylpyrazole-4-carbaldehyde phenylhydrazone **1** (200 mg, 0.76 mmol) and ethyl propiolate **6** (150 mg, 1.52 mmol) with irradiation for 15 min (final temperature 170 °C). Flash chromatography (hexane-ethyl acetate 5 :1) and then preparative TLC (silica gel, hexane-ethyl acetate 15 :1) afforded the adducts **10** (60 mg, 22%) and **11** (22 mg, 8%).

Data for **10** : white powder, m.p. 113-114 °C (from methanol) ; $^1$H-NMR ($CDCl_3$) δ 1.37 (t, *J* 7.1, 3 H, $CH_3$), 4.33 (q, *J* 7.1, 2 H, $CH_2$), 7.35 (s, 1 H, H-5'), 7.28-7.48 (m, 8 H, $H_{arom}$), 7.64 (d, *J* 8.6, 2 H, *o*-H 1-Ph), 8.17 (s, 1 H, H-3), 8.40 (s, 1 H, H-5) ; $^{13}$C-NMR ($CDCl_3$) δ 14.4 ($CH_3$), 60.2 ($CH_2$), 110.9 (C-4), 112.6 (C-4'), 119.2 (*o*-C 1-Ph), 126.2 (*o*-C 1'-Ph), 126.9 and 128.8 (*p*-C 1- and 1'-Ph), 128.9 (C-5), 129.3 and 129.4 (*m*-C 1- and 1'-Ph), 137.6 (C-3'), 139.6 and 139.7 (*ipso*-C 1- and 1'-Ph), 141.2 (C-5'), 142.9 (C-3), 163.2 (COO). Anal. Calcd. for $C_{21}H_{18}N_4O_2$ : C, 70.35 ; H, 5.05 ; N, 15.65. Found : C, 70.3 ; H, 4.95 ; N, 15.7% ; EM (EI) m/z 358 ($M^+$).

Data for **11** : yellow oil ; $^1$H-NMR ($CDCl_3$) δ 1.27 (t, *J* 7.1, 3 H, $CH_3$), 4.26 (q, *J* 7.1, 2 H, $CH_2$), 7.19 (s, 1 H, H-4'), 7.29-7.50 (m, 8 H, $H_{arom}$), 7.73 (d, *J* 7.6, 2 H, *o*-H 1-Ph), 8.08 (s, 1 H, H-3), 8.36 (s, 1 H, H-5) ; $^{13}$C-NMR ($CDCl_3$) δ 14.0 ($CH_3$), 61.2 ($CH_2$), 109.5 (C-4'), 124.0 (C-5), 126.1 (*m*-C 1'-Ph), 128.5 (*o*-C

1'-Ph), 128.8, 128.9, 129.4, 129.8, 137.0, 139.6, 139.8 ($C_{arom}$), 139.1 (C-3), 158.9 (COO). Anal. Calcd. for $C_{21}H_{18}N_4O_2$: C, 70.35 ; H, 5.05 ; N, 15.65. Found : C, 70.5 ; H, 4.95 ; N, 15.55% .

*1'-(p-Nitrophenyl)-1,5'-diphenyl-[4,3']-bipyrazole* **12** *and 1'-(p-nitrophenyl)-1,4'-diphenyl-[4,3']-bipyrazole* **13**. (Method B) From 1-phenylpyrazole-4-carbaldehyde (*p*-nitrophenyl)hydrazone **2** (200 mg, 0.65 mmol) and β-nitrostyrene **4** (194 mg, 1.3 mmol) with irradiation at 135 W for 10 min (final temperature 130 °C). Flash chromatography (hexane-ethyl acetate 5 :1) afforded bipyrazoles **12** (185 mg, 70%) and **13** (13 mg, 5%).

Data for **12** : white needles, m.p. 159-160 °C (from methanol) ; $^1$H-NMR ($CDCl_3$) δ 6.71 (s, 1 H, H-4'), 7.28-7.49 (m, 8 H, $H_{arom}$), 7.52 (d, *J* 9.2, 2 H, *o*-H 1'-Ph), 7.75 (d, *J* 7.6, 2 H, *o*-H 1-Ph), 8.11 (s, 1 H, H-3), 8.18 (d, *J* 9.2, 2 H, *m*-H 1'-Ph), 8.38 (s, 1 H, H-5) ; $^{13}$C-NMR ($CDCl_3$) δ 107.4 (C-4'), 119.0 (*o*-C 1-Ph), 124.1 (C-5), 124.3 (*o*-C 1'-Ph), 124.4 (*m*-C 1'-Ph), 139.2 (C-3), 117.0, 126.5, 126.6, 126.7, 128.8, 128.9, 129.1, 129.4, 139.8, 144.7, 145.7, 146.4 ($C_{arom}$). Anal. Calcd. for $C_{24}H_{17}N_5O_2$: C, 70.75 ; H, 4.2 ; N, 17.2. Found : C, 70.65 ; H, 4.15 ; N, 17.2%.

Data for **13** : white needles, m.p. 176-177 °C (from methanol) ; $^1$H-NMR ($CDCl_3$) δ 7.28-7.49 (m, 8 H, $H_{arom}$), 7.67 (d, *J* 8.3, 2 H, *o*-H 1-Ph), 7.90 (s, 1 H, H-3), 7.98 (d, *J* 9.2, 2 H, *o*-H 1'-Ph), 8.09 (s, 1 H, H-5'), 8.12 (s, 1 H, H-5), 8.37 (d, *J* 9.2, 2 H, *m*-H 1'-Ph) ; $^{13}$C-NMR ($CDCl_3$) δ 118.1 (*o*-C 1'-Ph), 119.1 (*o*-C 1-Ph), 125.2 (C-5), 125.4 (*m*-C 1'-Ph), 126.5 (C-5'), 126.7 and 128.0 (*p*-C 1- and 4'-Ph), 140.1 (C-3), 116.1, 119.9, 124.6, 128.3, 128.8, 129.0, 129.4, 129.7, 131.8 and 144.1 ($C_{arom}$). Anal. Calcd. for $C_{24}H_{17}N_5O_2$: C, 70.75 ; H, 4.2 ; N, 17.2. Found : C, 70.6 ; H, 4.2 ; N, 17.1%.

*Dimethyl 1,1'-diphenyl-[5,3']-bipyrazole-4',5'-dicarboxylate* **18**. (Method B) From 1-phenylpyrazole-5-carbaldehyde phenylhydrazone **16** (200 mg, 0.76 mmol) and dimethyl fumarate **3** (218 mg, 1.52 mmol) with irradiation at 255 W for 45 min (final temperature 155 °C). Flash chromatography (hexane-ethyl acetate 3 :1) allowed bipyrazole **18** to be isolated as white needles (171 mg, 56%), m.p. 114-115 °C (from methanol) ; $^1$H-NMR ($CDCl_3$) δ 3.56 and 3.84 (2 x s, 6 H, 2 x $OCH_3$), 6.75 (d, *J* 2, 1 H, H-4), 7.29-7.46 (m, 10 H, $H_{arom}$), 7.77 (d, *J* 2, 1 H, H-3) ; $^{13}$C-NMR ($CDCl_3$) δ 51.8 and 53.3 ($OCH_3$), 110.3 (C-4), 115.0, 123.7, 124.1, 127.2, 128.6, 129.1, 129.2, 140.1, 143.0 ($C_{arom}$), 132.9 (C-5), 137.3 and 138.4 (*ipso*-C 1- and 1'-Ph), 139.9 (C-3), 160.4 and 161.4 (COO). Anal. Calcd. for $C_{22}H_{18}N_4O_4$: C, 65.65 ; H, 4.5 ; N, 13.9. Found : C, 65.55 ; H, 4.5 ; N, 13.95%.

Data for the intermediate **24** : m.p. 116-117 °C (from methanol) ; $^1$H-NMR ($CDCl_3$) δ 3.71 and 3.75 (2 x s, 6 H, 2 x $OCH_3$), 4.30 (d, *J* 5.2, 1 H, H-4'), 5.10 (d, *J* 5.2, 1 H, H-5'), 6.66 (d, *J* 2, 1 H, H-4), 6.72 (d, *J* 7.6, 2 H, *o*-H 1'-Ph), 6.87 (t, *J* 7.6, 1 H, *p*-H 1'-Ph), 7.19 (t, *J* 7.6, 2 H, *m*-H 1'-Ph), 7.44-7.50 (m, 5 H, $H_{arom}$), 7.69 (d, *J* 2, 1 H, H-3) ; $^{13}$C-NMR ($CDCl_3$) δ 53.0 and 53.2 ($OCH_3$), 56.9 (C-4'), 64.8 (C-5'), 108.6

(C-4), 113.2 (*o*-C 1'-Ph), 120.6 (*p*-C 1'-Ph), 126.2 (*m*-C 1'-Ph), 128.2 (*p*-C 1-Ph), 128.7, 129.0, 129.3, 133.8, 143.1 ($C_{arom}$), 140.1 (C-3), 168.4 and 169.7 (COO).

*1,1',4'-Triphenyl-[5,3']-bipyrazole* **19** *and 1,1',5'-triphenyl-[5,3']-bipyrazole* **20**. (Method B) From 1-phenylpyrazole-5-carbaldehyde phenylhydrazone **16** (200 mg, 0.76 mmol) and β-nitrostyrene **4** (227 mg, 1.52 mmol) with irradiation at 90 W for 15 min (final temperature 130 °C). Flash chromatography (hexane-ethyl acetate 9 :1) afforded the adducts **19** (123 mg, 45%) and **20** (60 mg, 22%).

Data for **19** : white powder, m.p. 170-171 °C (from methanol) ; $^1$H-NMR ($CDCl_3$) δ 6.70 (d, *J* 2, 1 H, H-4), 6.90 (m, 2 H, *o*-H 4'-Ph), 7.08-7.16 (m, 8 H, $H_{arom}$), 7.33 (t, *J* 7.8, 1 H, *p*-H 1'-Ph), 7.48 (t, *J* 7.8, 2 H, *m*-H 1'-Ph), 7.72 (d, *J* 7.8, 2 H, *o*-H 1'-Ph), 7.78 (d, *J* 2, 1 H, H-3), 7.98 (s, 1 H, H-5') ; $^{13}$C-NMR ($CDCl_3$) δ 109.5 (C-4), 119.0 (C-3), 124.4, 124.8, 125.4, 126.8, 127.3, 128.2, 128.3, 129.5, 131.4, 139.9 ($C_{arom}$), 140.3 (C-5'). Anal. Calcd. for $C_{24}H_{18}N_4$ : C, 79.5 ; H, 5.0 ; N, 15.45. Found : C, 79.4 ; H, 5.05 ; N, 15.5%.

Data for **20** : yellow oil; $^1$H-NMR ($CDCl_3$) δ 6.06 (s, 1 H, H-4'), 6.84 (d, *J* 2, 1 H, H-4), 7.12 (d, *J* 7.6, 2 H, *o*-H 5'-Ph), 7.22-7.34 (m, 9 H, $H_{arom}$), 7.44 (t, *J* 8.1, 2 H, *m*-H 1-Ph), 7.53 (d, *J* 8.1, 2 H, *o*-H 1-Ph), 7.73 (d, *J* 2, 1 H, H-3) ; $^{13}$C-NMR ($CDCl_3$) δ 107.2 (C-4'), 107.3 (C-4), 126.0 (*o*-C 1-Ph), 128.4 (*o*-C 5'-Ph), 128.6 (*m*-C 1-Ph), 140.3 (C-3), 125.1, 127.6, 127.9, 128.0, 128.7, 128.8, 129.9, 136.4, 139.6, 140.4, 142.9, 143.6 ($C_{arom}$). Anal. Calcd. for $C_{24}H_{18}N_4$ : C, 79.5 ; H, 5.0 ; N, 15.45. Found : C, 79.6 ; H, 5.05 ; N, 15.4%.

*Ethyl 1,1',5'-triphenyl-[5,3']-bipyrazole-4'-carboxylate* **21**. (Method B) From 1-phenylpyrazole-5-carbaldehyde phenylhydrazone **16** (200 mg, 0.76 mmol) and ethyl phenylpropiolate **5** (265 mg, 1.52 mmol) with irradiation at 240 W for 30 min (final temperature 180 °C). Flash chromatography (hexane-ethyl acetate 5 :1) afforded the adduct **21** as white needles (132 mg, 40%), m.p. 138-139 °C (from methanol) ; $^1$H-NMR ($CDCl_3$) δ 0.92 (t, *J* 7.1, 3 H, $CH_3$), 3.84 (q, *J* 7.1, 2 H, $CH_2$), 6.76 (d, *J* 1.7, 1 H, H-4), 7.15 (d, *J* 7.3, 2 H, *o*-H 5'-Ph), 7.22-7.39 (m, 11 H, $H_{arom}$), 7.45 (d, *J* 7.3, 2 H, *o*-H 1-Ph), 7.79 (d, *J* 1.7, 1 H, H-3) ; $^{13}$C-NMR ($CDCl_3$) δ 13.6 ($CH_3$), 60.1 ($CH_2$), 109.9 (C-4), 124.0 (*o*-C 1-Ph), 125.2 (*o*-C 5'-Ph), 92.9, 126.6, 127.1, 128.0, 128.1, 128.6, 128.8, 129.3, 130.4, 134.6, 138.8, 140.4, 144.2, 146.3 ($C_{arom}$), 139.9 (C-3), 162.0 (COO). Anal. Calcd. for $C_{27}H_{22}N_4O_2$ : C, 74.6 ; H, 5.1 ; N, 12.9. Found : C, 74.6 ; H, 5.05 ; N, 13.0% ; EM (EI) m/z 434 ($M^+$).

*1'-(p-Nitrophenyl)-1,4'-diphenyl-[5,3']-bipyrazole* **22** *and 1'-(p-nitrophenyl)-1,5'-diphenyl-[5,3']-bipyrazole* **23**. (Method B) From 1-phenylpyrazole-5-carbaldehyde (*p*-nitrophenyl)hydrazone **17** (200 mg, 0.65 mmol) and β-nitrostyrene **4** (194 mg, 1.30 mmol) with irradiation at 240 W for 12 min (final temperature 170 °C). Flash chromatography (hexane-ethyl acetate 9 :1) afforded the adducts **22** (87 mg, 33%) and **23** (77 mg, 29%).

Data for **22** : white needles, m.p. 191-192 °C (from methanol) ; $^1$H-NMR ($CDCl_3$) δ 6.69 (d, *J* 1.8, 1 H, H-4), 6.91 (d, *J* 7.6, 2 H, *o*-H 4'-Ph), 7.06-7.20 (m, 8 H, $H_{arom}$), 7.78 (d, *J* 1.8, 1 H, H-3), 7.87 (d, *J* 9.1, 2 H, *o*-H 1'-Ph), 8.05 (s, 1 H, H-5'), 8.33 (d, *J* 9.1, 2 H, *m*-H 1'-Ph) ; $^{13}$C-NMR ($CDCl_3$) δ 109.5 (C-4), 118.4 (*o*-C 1'-Ph), 124.5 (*o*-C 1-Ph), 125.3 (*m*-C 1'-Ph), 125.5 (C-5'), 127.1 and 127.4 (*p*-C 1- and 4'-Ph), 127.5 (*o*-C 4'-Ph), 128.3 and 128.5 (*m*-C 1- and 4'-Ph), 140.4 (C-3), 126.3, 128.9, 129.4, 130.5, 134.2, 139.8, 143.7 ($C_{arom}$). Anal. Calcd. for $C_{22}H_{17}N_5O_2$ : C, 70.75 ; H, 4.2 ; N, 17.2. Found : C, 70.85 ; H, 4.25 ; N, 17.2.

Data for **23** : white needles, m.p. 176-177 °C (from methanol) ; $^1$H-NMR ($CDCl_3$) δ 6.15 (s, 1 H, H-4'), 6.85 (d, *J* 1.7, 1 H, H-4), 7.16 (d, *J* 7.8, 2 H, *o*-H 5'-Ph), 7.31-7.54 (m, 10 H, $H_{arom}$), 7.76 (d, *J* 1.7, 1 H, H-3), 8.15 (d, *J* 8.8, 2 H, *m*-H 1'-Ph) ; $^{13}$C-NMR ($CDCl_3$) δ 107.5 (C-4), 109.0 (C-4'), 124.4 (*m*-C 1'-Ph), 128.8 (*o*-C 5'-Ph), 140.3 (C-3), 124.3, 125.6, 126.1, 128.3, 128.9, 129.2, 129.4, 135.7, 144.1, 144.2, 144.3, 146.1 ($C_{arom}$). Anal. Calcd. for $C_{22}H_{17}N_5O_2$ : C, 70.75 ; H, 4.2 ; N, 17.2. Found : C, 70.6 ; H, 4.15 ; N, 17.3%.

*Ethyl 1'-methyl-1,5'-diphenyl-[4,3']-bipyrazole-4'-carboxylate* **26**. (Method B) From 1-phenylpyrazole-4-carbaldehyde dimethylhydrazone **25** (200 mg, 0.93 mmol) and ethyl phenylpropiolate **5** (325 mg, 1.86 mmol) with irradiation at 255 W for 10 min (final temperature 180 °C). Flash chromatography (hexane-ethyl acetate 3 :1) allowed the isolation of the bipyrazole **26** as white needles (277 mg, 80%), m.p. 147-148 °C (from methanol) ; $^1$H-NMR ($CDCl_3$) δ 0.94 (t, *J* 7.1, 3 H, $CH_3$), 3.72 (s, 3 H, N-$CH_3$), 4.06 (q, *J* 7.1, 2 H, $CH_2$), 7.27 (t, *J* 7.6, 1 H, *p*-H 5'-Ph), 7.32-7.51 (m, 7 H, $H_{arom}$), 7.80 (d, *J* 7.6, 2 H, *o*-H 1-Ph), 8.30 (s, 1 H, H-3), 8.79 (s, 1 H, H-5) ; $^{13}$C-NMR ($CDCl_3$) δ 13.6 ($CH_3$), 37.3 (N-$CH_3$), 59.8 ($CH_2$), 116.3 (C-4), 119.2 (*o*-C 1-Ph), 126.3 (*p*-C 5'-Ph), 127.2 (C-5), 109.7, 126.6, 128.2, 129.1, 129.3, 129.7 ($C_{arom}$), 144.8 and 147.3 (*ipso*-C 1- and 5'-Ph), 163.5 (COO). Anal. Calcd. for $C_{22}H_{20}N_4O_2$ : C, 70.95 ; H, 5.4 ; N, 15.05. Found : C, 71.0 ; H, 5.4 ; N, 15.0%.

## REFERENCES

1. Claisen, L. ; Roosen, P. *Justus Liebigs Ann. Chem.*, **1893**, *278*, 274.
2. Behr, L.C. ; Fusco, R. ; Jarboe, C.H. in *The Chemistry of Heterocyclic Compounds. Vol. 22. Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings* ; Wiley, R.H., Ed. ; John Wiley & Sons, New York, 1967.
3. (a) El-Khawass, E.S.M. ; Bistawroos, A.E. *Alexandria J. Pharm. Chem.*, **1990**, *4*, 77 ; (b) Bruno, O. ; Ramise, A. ; Bondavalli, F. ; Schenone, P. ; D'Amico, M. ; Filippelli, A. ; Filipelli, W. ; Rossi, F. *Farmaco*, **1993**, *48*, 949.
4. Cuadro, A.M. ; Elguero, J. ; Navarro, P. *Chem. Pharm. Bull.*, **1985**, *33*, 2535.
5. Tsuboi, S. ; Moriie, K. ; Hatsutori, Y. ; Wada, K. ; Sone, S. ; Oohigata, T. ; Ito, A. *Jpn. Kokai Tokkyo Koho JP 06,184,114*, **1994** [Chem. Abstr., **1995**, *122*, 105875].

6. Hartfiel, U. ; Dorfmeister, G. ; Franke, H. ; Geisler, J. ; Johann, G. ; Rees, R. *Eur. Pat. Appl. EP 542,388*, **1993** [Chem. Abstr., **1993**, *119*, 180774].
7. (a) Das, N.B. ; Mittra, A.S. *J. Indian Chem. Soc.*, **1978**, *55*, 829 ; (b) Nayak, A. ; Mittra, A.S. *J. Indian Chem. Soc.*, **1980**, *57*, 643 ; (c) Desbordes, P. ; Guigues, F. ; Peignier, R. *PCT Int. Appl. WO 94 29,300*, **1994** [Chem. Abstr., **1995**, *123*, 143884].
8. (a) Allen, C.F.H. ; Wilson, B.D. *U. S. Pat., 3106467*, **1963** [Chem. Abstr., **1964**, *60*, 2945] ; (b) Pearson, I. *U. S. Pat., 3883549*, **1975** [Chem. Abstr., **1975**, *84*, 81243] ; (c) Pragst, F. ; Stiefke, B. ; Schwertfeger, I. *East Ger. Pat., 113229*, **1975** [Chem. Abstr., **1976**, *84*, 137220] ; (d) Pfeiffer, W.D. ; Bulka, E. *Ger. (East) DD 293,347*, **1991** [Chem. Abstr., **1992**, *116*, 41452].
9. For example see : (a) Khan, M.A. ; Cosenza, A.G. *Afinidad*, **1988**, *414*, 173 : (b) Djerrari, B. ; Essassi, E. ; Fifani, J. *Bull. Soc. Chim. Fr.*, **1991**, *128*, 521 ; (c) Chary, T.J.M. ; Reddy, Ch.V.N. ; Murthy, A.K. *Indian J. Chem.*, **1992**, *31B*, 495 ; (d) Kuznetsov, M.A. ; Dorofeeva, Y.V. ; Semenovskii, V.V. ; Gindin, V.A. ; Studenikov, A.N. *Tetrahedron*, **1992**, *48*, 1269.
10. Padwa, A. (Ed.) *1,3-Dipolar Cycloaddition Chemistry, Vol. 1*, Wiley, New York, 1984.
11. (a) Oida, T. ; Tanimoto, S. ; Ikehira, H. ; Okano, M. *Bull. Chem. Soc. Jpn.*, **1983**, *56*, 1203 ; (b) Hassaneen, H.M. ; Shawali, A.S. ; Elwal, N.M. *Heterocycles*, **1990**, *31*, 1041 ; (c) Farag, A.M. ; Shawali, A.S. ; Abed, N.M. ; Dawood, K.M. *Gazz. Chim. Ital.*, **1993**, *123*, 467.
12. (a) Franck-Neumann, M. ; Geoffroy, P. ; Lohmann, J.J. *Tetrahedron Lett.*, **1983**, *24*, 1775 ; (b) Padwa, A. ; Meske, M. ; Rodriguez, A. *Heterocycles*, **1995**, *40*, 191.
13. (a) Grigg, R. ; Kemp, J. ; Thompson, N. *Tetrahedron Lett.*, **1978**, 2827 ; (b) LeFevre, G. ; Hamelin, J. *Tetrahedron Lett.*, **1978**, 4503 ; (c) Grigg, R.; Dowling, M.; Jordan, M.W.; Sridharan, V.; Thianpatanagui, S. *Tetrahedron*, **1987**, *43*, 5873.
14. (a) Sun, B. ; Adachi, K. ; Noguchi, M. *Tetrahedron*, **1996**, *52*, 901. (b) Sun, B. ; Adachi, K. ; Noguchi, M. *Synthesis*, **1997**, 53.
15. Grigg, R. *Chem. Soc. Rev.*, **1987**, *16*, 89.
16. (a) Caddick, S. *Tetrahedron*, **1995**, *51*, 10403 ; (b) Langa, F. ; De la Cruz, P. ; Díaz-Ortiz, A. ; Díez-Barra, E. ; De la Hoz, A. *Contemporary Org. Synth.*, **1997**, 373.
17. For example, see : (a) Díaz-Ortiz, A. ; Díez-Barra, E. ; De la Hoz, A. ; Prieto, P. ; Moreno, A. *J. Chem. Soc. Perkin Trans 1*, **1994**, 3595 ; (b) Lerestif, J.M. ; Perrocheau, J. ; Tonnard, F. ; Bazureau, J.P. ; Hamelin, J. *Tetrahedron*, **1995**, *51*, 6757 ; (c) Loupy, A. ; Petit, A. ; Bonnet-Delpon, D. *J. Fluor. Chem.*, **1995**, *75*, 215.
18. (a) Shimizu, T. ; Hayashi, Y. ; Kitora, Y. ; Teramura, K. *Bull. Chem. Soc. Jpn.*, **1982**, *55*, 2450 ; (b) Noguchi, M. ; Yamada, K. *Synthesis*, **1993**, 145.

19. (a) LeFevre, G. ; Hamelin, J. *Tetrahedron*, **1980**, *36*, 887 ; (b) Fouchet, B. ; Houch, M. ; Hamelin, J. *Tetrahedron Lett.*, **1981**, *22*, 1333 ; (c) Shimizu, T. ; Hayashi, Y. ; Nakano, M. ; Terashima, K. *Bull. Chem. Soc. Jpn.*, **1984**, *57*, 134 ; (d) Shimizu, T. ; Hayashi, Y. ; Miki, M. ; Terashima, K. *J .Org. Chem.*, **1987**, *52*, 2277 ; (e) Katayama, H. ; Takatsu, N. ; Kitano, H. ; Shimaya, Y. *Chem. Pharm. Bull.*, **1990**, *38*, 1129.

20. Díaz-Ortiz, A. ; Carrillo, J.R. ; Díez-Barra, E. ; De la Hoz, A. ; Gómez-Escalonilla, M.J. ; Moreno, A. ; Langa, F. *Tetrahedron*, **1996**, *52*, 9237.

21. For example, see : (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*, pages 7-8 ; Pergamon Press : Oxford, **1990** ; (b) Turchi, S. ; Giomi, D. ; Nesi, R. *Tetrahedron*, **1995**, *51*, 7085 ; (c) Nesi, R. ; Giomi, D. ; Papaleo, S. ; Quartara, L. *J. Chem. Soc. Chem. Commun.*, **1986**, 1536.

22. March, J. *Advanced Organic Chemistry, 4th ed.*, page 1039 ; John Wiley & Sons : New York, **1992**.

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