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# The Effect of Focused Microwaves on the Reaction of Ethyl *N*-Trichloroethylidenecarbamate with Pyrazole Derivatives

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**Abstract:** Under microwave irradiation vinylpyrazoles react with ethyl *N*-trichloroethylidenecarbamate **1** to give the addition to the imine system through the conjugated vinyl group. Likewise, compound **1** react with the NH group of pyrazolylhydrazones, if present. To the best of our knowledge this reaction type has not been described before and only can be performed under microwave irradiation. By classical heating, in the absence of microwaves, only dimerization or decomposition of the pyrazole derivatives is observed in these reactions. 

*Keywords:* Microwave heating; imines; pyrazoles; substitution.

## INTRODUCTION

In the course of an investigation on the reactivity of pyrazolyl derivatives as dienes in cycloaddition reactions [1-3], we have studied the reaction of vinylpyrazoles, pyrazolylhydrazones and imines derived from aminopyrazoles towards ethyl *N*-trichloroethylidenecarbamate **1** [4] in order to obtain valuable pyrazole derivatives condensed with heterocyclic systems such as pyrazolo pyrimidines [5].

*N*-Acylimines and *N*-acyliminium species are the most thoroughly studied and widely used class of imino dienophiles [6]. *N*-Trichloroethylidenecarbamate participates in cycloaddition reactions as a dienophile [7-9] as a dipolarophile [10] and even as a heterodiene [11].

Pyrazole derivatives are very unreactive dienes due to the loss of aromaticity of the pyrazole ring on [4+2] cycloadduct formation.

Microwave irradiation has shown its utility in many reactions [12-16] including cycloadditions [17]. Cycloaddition reactions sometimes require harsh conditions (long reaction times, high temperatures and inconvenient procedures), which are not compatible with sensitive compounds. Moreover, when long reaction times are required, reversibility of Diels-Alder reactions is favoured. These problems have been nicely solved by the heating rate induced by microwaves. In fact, we have shown that microwave irradiation may induce the cycloaddition of very unreactive systems towards electron deficient dienophiles [1-3].

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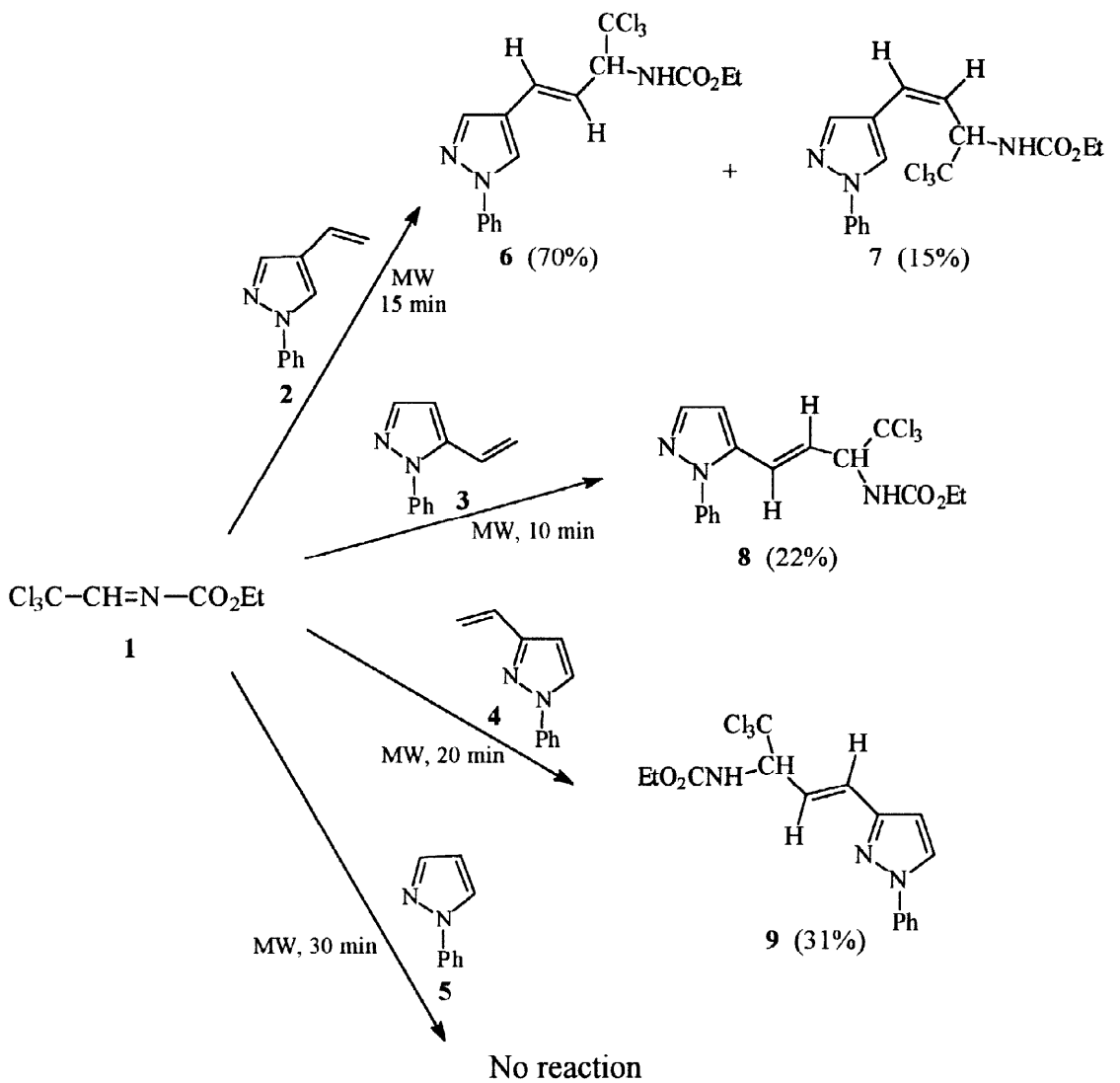
## RESULTS AND DISCUSSION

On the basis of these reasons, the reactions of pyrazolyl derivatives with ethyl *N*-trichloroethylidencarbamate were conducted under focused microwaves in solvent-free conditions [12-16] in our laboratory. However, we did not observe any cycloaddition reaction. The result of the reaction depends on the nature of the diene system and the substitution of the pyrazole ring.

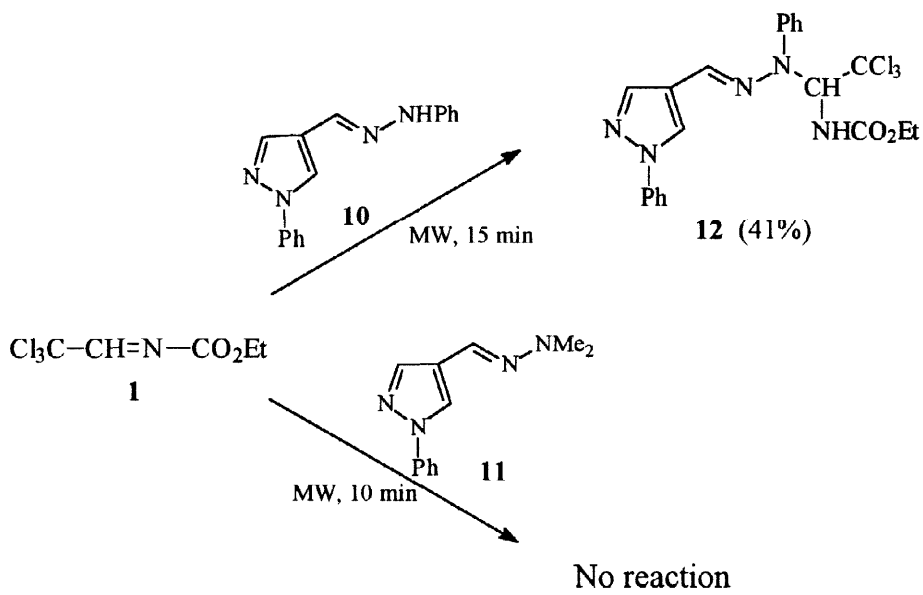
4- And 5-vinylpyrazoles **2** and **3** react with normal dienophiles under microwave irradiation to give indazole derivatives in good yield [1]. However, reaction of vinylpyrazoles **2-4** with **1** occurs through the exocyclic double bond to give Michael addition to the conjugated imine system (Scheme 1).




**Scheme 1**

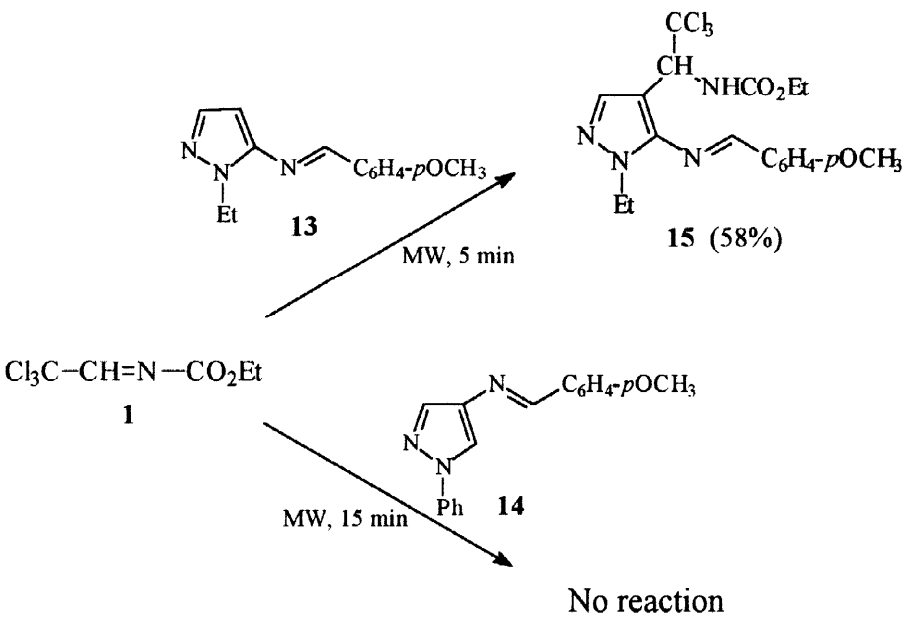
This reaction must be considered as an electrophilic substitution of the exocyclic double bond which is activated by conjugation with the pyrazole ring. It is remarkable that even in the 5- and 3-substituted pyrazoles **3** and **4**, reaction occurs at the double bond and not in the activated 4-position of the pyrazole ring. Moreover, when there is no vinyl substituent in the ring, as in 1-phenylpyrazole **5**, no reaction occurs after 30 min of irradiation at 165 °C and reagents are recovered. The thermodynamic *trans* isomer is the only product observed in the reaction of pyrazoles **3** and **4**. Reaction conditions (irradiation time and temperature) were optimised until complete consumption of the pyrazolyl derivative. In the reactions with low yield, vinylpyrazole is not recovered owing to its high tendency to polimerize. Under conventional heating in an oil bath no reaction occurs under similar conditions of temperature and time, and the starting vinylpyrazoles dimerize and are not recovered in these conditions.

Aromatic 1-azadienes are very unreactive hetero-dienes. For this reason hydrazones are used instead, because electrondonation by the second nitrogen favours the cycloaddition reaction [18]. We have shown that pyrazolyl hydrazones give a thermal 1,2-hydrogen shift under microwaves to afford bipyrazoles by 1,3-dipolar cycloaddition of the *in situ* formed azomethineimine [2]. Reaction of the pyrazolyl hydrazone **10** with **1** produces the Michael addition to the conjugated imine through the NH group. When a second *N*-substituent is introduced and there is no NH group, as in hydrazone **11**, no reaction occurs.




**Scheme 2**

Pyrazolylimines **13** and **14** react as azadienes in Diels-Alder reactions with electron poor dienophiles. In this context we have described the first cycloaddition of a 2-azadiene involving a pyrazole ring [3]. Pyrazolylimine **13** reacts with **1** by an electrophilic substitution at the activated 4-position of the pyrazole ring. The unreacted pyrazolyl derivative decomposes and 1-ethyl-5-aminopyrazole can be isolated. Again, under conventional heating no reaction occurs in similar conditions and decomposition of the starting material takes place. However, imine **14** in which position 4 is blocked does not react after 15 min of microwave irradiation and the only process observed is the decomposition of the reagents.




**Scheme 3**

These results show that the introduction of a nitrogen in the exocyclic double bond reduces its nucleophilicity. Addition through the double bond in hydrazones **10** and **11** is a reversible process and addition occurs only through the NH group of the hydrazone, if present. In the imines **13** and **14** no reaction occurs through the exocyclic double bond and the electrophilic aromatic substitution is observed if position 4 is not blocked.

## CONCLUSIONS

We have shown that vinylpyrazoles may react with activated imines to give the addition to the imine system through the conjugated vinyl group. To the best of our knowledge this reaction type has not been described before.

With activated alkenes where no alternative to the Diels-Alder cycloaddition is likely (e.g., β-nitrostyrene) the products obtained are stable cyclic compounds and do not undergo ring opening [1-3]. In consequence, it do not seem probable that the products described derive from initial cycloadducts followed by ring opening.

**The use of microwave irradiation as an energy source is crucial to produce the reaction and to avoid the dimerization or decomposition of the starting pyrazole, the only processes observed in the absence of microwaves**. Again, the rapid heating induced by the microwave irradiation modifies the course of a reaction to produce a transformation which is not performed by classical heating.

Lastly, this reaction could be extended to other azoles and specially to other activated imines in order to obtain valuable derivatives such as heterocyclic aminoacids. These aspects are currently under active investigation in our laboratory and the results will be published in due course.

## EXPERIMENTAL

All m.p. were determined on a Gallenkamp apparatus and are uncorrected. $^1$H NMR spectra were recorded at 299.94 MHz and $^{13}$C NMR spectra 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. Column chromatography was carried out with $SiO_2$ (silica gel, Merck type 60 230-400 mesh). Microwave irradiations were conducted in a focused microwave reactor Prolabo MX350 with measurement and control of power and temperature by infrared detection. Elemental analyses were determined on a Perkin-Elmer PE2400 CHN apparatus. Reagents were prepared following reported procedures.

*General Procedure*. A mixture of the pyrazolyl derivative (1 mmol) and ethyl *N*-trichloroethylidenecarbamate (**1**) (1.5 mmol) was irradiated at atmospheric pressure in a focused microwave reactor for the time and at the power indicated. The crude mixture, composed of the product and compounds derived from decomposition or polymerization of the pyrazolyl derivative, was purified by flash chromatography on using hexane/ethyl acetate 1:3 or 1:5 as the eluent.

*4-(2-Ethoxycarbonylamino-4,4,4-trichloro-1-trans-buten-1-yl)-1-phenylpyrazole (6) and 4-(2-ethoxycarbonylamino-4,4,4-trichloro-1-cis-buten-1-yl)-1-phenylpyrazole (7)*. From ethyl *N*-trichloroethylinedecarbamate (**1**) [4] (385 mg, 1.76 mmol) and 1-phenyl-4-vinylpyrazole (**2**) [19,20] (200 mg, 1.17 mmol) with irradiation at 255 W for 15 min (final temperature 125 °C) derivatives **6** (318 mg, 70%) and **7** (68 mg, 15%) were isolated.

Data for **6**: yellow oil; $^1$H-NMR δ 1.29 (t, *J* 7, 3 H, $CH_3$), 4.21 (q, *J* 7, 2 H, $OCH_2$), 5.21(ddd, *J* 10, 6.6, 1.2, 1 H, $CHCCl_3$), 5.5 (d, *J* 10, 1 H, NH), 6.16 (dd, *J* 15.8, 6.6, 1 H, =*CH*-$CHCCl_3$), 6.70 (dd, *J* 15.8, 1.2, 1 H, =CH-pyrazole), 7.29 (t, *J* 7.6, 1 H, H-4' phenyl), 7.43 (t, *J* 7.6, 2 H, H-3' and -5' phenyl), 7.64 (d, *J* 7.6, 2

H, H-2' and -6' phenyl), 7.82 (s, 1 H, H-3 pyrazole), 7.95 (s, 1 H, H-5 pyrazole). $^{13}$C-NMR δ 14.5 ($CH_3$), 61.8 ($CH_2$), 67.8 (*CH*-$CCl_3$), 101.9 ($CCl_3$), 119.0 (C-2' and -6' phenyl), 120.6 (C-4 pyrazole), 121.0 (=*CH*-$CHCCl_3$), 125.0 (C-5 pyrazole), 125.7 (=CH-pyrazole), 126.7 (C-4' phenyl), 129.4 (C-3' and -5' phenyl), 139.1 (C-3 pyrazole), 139.6 (C-1' phenyl), 155.5 (C=O). Anal. Calc for $C_{16}H_{16}Cl_3N_3O_2$: C, 49.45; H, 4.15; N, 10.8. Found C, 49.35; H, 4.25; N, 10.65%.

Data for 7: m.p. 80-81 °C (methanol); $^1$H-NMR δ 1.26 (t, *J* 7.1, 3 H, $CH_3$), 4.15-4.26 (m, 2 H, $OCH_2$), 5.38 (d, *J* 9, 1 H, NH), 5.59-5.71 (m, 2 H, =*CH-CH*$CCl_3$), 6.63 (d, *J* 10.5, 1 H, =CH-pyrazole), 7.29 (t, *J* 7.6, 1 H, H-4' phenyl), 7.47 (t, *J* 7.6, 2 H, H-3' and -5' phenyl), 7.79 (m, 3 H, H-3 pyrazole, H-2' and -6' phenyl), 8.52 (s, 1 H, H-5 pyrazole). $^{13}$C-NMR δ 14.4 ($CH_3$), 62.0 ($OCH_2$), 63.7 (*CH*-$CCl_3$), 102.2 ($CCl_3$), 118.5 (C-4 pyrazole), 118.9 (C-2' and -6' phenyl), 121.2 (=*CH*-$CHCCl_3$), 125.4 (=CH-pyrazole), 126.1 (C-5 pyrazole), 126.6 (C-4' phenyl), 129.4 (C-3' and -5' phenyl), 139.7 (C-1' phenyl), 141.9 (C-3 pyrazole), 156.1 (C=O). Anal. Calc for $C_{16}H_{16}Cl_3N_3O_2$: C, 49.45; H, 4.15; N, 10.8. Found C, 49.3; H, 4.3; N, 10.7%.

*5-(2-Ethoxycarbonylamino-4,4,4-trichloro-1-trans-buten-1-yl)-1-phenylpyrazole (8)*. From compound **1** (385 mg, 1.76 mmol) and 1-phenyl-5-vinylpyrazole (**3**) [21] (200 mg, 1.17 mmol) with irradiation at 285 W for 10 min (final temperature 130 °C) derivative **8** (100 mg, 22%) was isolated as a yellow oil. $^1$H-NMR δ 1.23-1.31 (m, 3 H, $CH_3$), 4.14-4.24 (m, 2 H, $OCH_2$), 5.15 (dd, *J* 10.2, 6.6, 1 H, *CH*$CCl_3$), 5.34 (d, *J* 10.2, 1 H, NH), 6.30 (dd, *J* 15.9, 6.6, 1 H, =*CH*-$CHCCl_3$), 6.60 (d, *J* 1.9, 1 H, H-4 pyrazole), 6.63 (d, *J* 15.9, 1 H, =CH-pyrazole), 7.40-7.52 (m, 5 H, phenyl), 7.65 (d, *J* 1.9, 1 H, H-3 pyrazole). $^{13}$C-NMR δ 14.4 ($CH_3$), 61.9 ($OCH_2$), 67.6 (*CH*-$CCl_3$), 83.2 ($CCl_3$), 105.3 (C-4 pyrazole), 120.1 (C-5 pyrazole), 123.6 (=CH-pyrazole), 125.3 (C-2' and -6' phenyl), 125.6 (=*CH*-$CHCCl_3$), 128.3 (C-4' phenyl), 129.2 (C-3' and -5' phenyl), 139.1 (C-1' phenyl), 140.2 (C-3 pyrazole), 155.4 (C=O). Anal. Calc for $C_{16}H_{16}Cl_3N_3O_2$: C, 49.45; H, 4.15; N, 10.8. Found C, 49.25; H, 4.3; N, 10.65%.

*3-(2-Ethoxycarbonylamino-4,4,4-trichloro-1-trans-buten-1-yl)-1-phenylpyrazole (9)*. From compound **1** (385 mg, 1.76 mmol) and 1-phenyl-3-vinylpyrazole (**4**) [22] (200 mg, 1.17 mmol) with irradiation at 285 W for 20 min (final temperature 160 °C) derivative **9** (141 mg, 31%) was isolated as a yellow oil. $^1$H-NMR δ 1.29 (t, *J* 7.1, 3 H, $CH_3$), 4.21 (q, *J* 7.1, 2 H, $OCH_2$), 5.28 (dd, *J* 10.2, 5.4, 1 H, *CH*$CCl_3$), 5.38 (d, *J* 10.2, 1 H, NH), 6.51 (dd, *J* 15.9, 5.3, 1 H, =*CH*-$CHCCl_3$), 6.60 (d, *J* 2.6, 1 H, H-4 pyrazole), 6.91 (d, *J* 15.9, 1 H, =CH-pyrazole), 7.29 (t, *J* 7.5, 1 H, H-4' phenyl), 7.45 (dd, *J* 8.5, 7.5, 2 H, H-3' and -5' phenyl), 7.67 (d, *J* 8.5, 2 H, H-2' and -6' phenyl), 7.87 (d, *J* 2.6, 1 H, H-5 pyrazole). $^{13}$C-NMR δ 14.5 ($CH_3$), 61.8 ($CH_2$), 67.4 (*C*H-$CCl_3$), 101.7 ($CCl_3$), 105.5 (C-4 pyrazole), 119.0 (C-2' and -6' phenyl), 124.1 (=*C*H-$CHCCl_3$), 126.5 (C-4' phenyl), 127.8 (=CH-pyrazole), 127.9 (C-5 pyrazole), 129.4 (C-3' and -5' phenyl), 139.8 (C-1' phenyl), 150.2 (C-3 pyrazole), 155.5 (C=O). Anal. Calc for $C_{16}H_{16}Cl_3N_3O_2$: C, 49.45; H, 4.15; N, 10.8. Found C, 49.35; H, 4.2; N, 10.75%.

*1-Phenylpyrazole-4-carbaldehyde* N-*(1-ethoxycarbonylamino-2,2,2-trichloroethyl)* N-*phenylhydrazone (12)*. From compound **1** (250 mg, 1.14 mmol) and 1-phenylpyrazole-4-carbaldehyde *N*-phenylhydrazone (**10**) (200 mg, 0.76 mmol) with irradiation at 285 W for 15 min (final temperature 90 °C) derivative **12** (150 mg, 41%) was isolated, m.p. 152-4 °C (methanol). $^1$H-NMR δ 1.31 (t, *J* 7.1, 3 H, $CH_3$), 4.24 (m, 2 H, $OCH_2$), 5.03 (d, *J* 10, 1 H, *CH*NH), 6.47 (d, *J* 10, 1 H, NH), 7.26-7.37 (m, 5 H, CH, H-2", -6'', -4' and -4" phenyl), 7.42-7.50 (m, 4 H, H-3', -5', -3'' and -5" phenyl), 7.66 (d, *J* 7.6, 2 H, H-2' and -6' phenyl), 7.86 (s, 1 H, H-3 pyrazole), 7.98 (s, 1 H, H-5 pyrazole). $^{13}$C-NMR δ 14.5 ($CH_3$), 61.9 ($OCH_2$), 80.34 (*CH*-$CCl_3$), 101.9 ($CCl_3$), 119.1 (C-1' phenyl), 121.0 (C-4 pyrazole), 124.6 (C-5 pyrazole), 126.7, 127.9, 128.0, 130.7 (=CH, C-4', -4", -2'' and -6" phenyl), 129.4, 130.1 (C-3', -5', -3'' and -5" phenyl), 139.3 (C-3 pyrazole), 139.7, 143.6 (C-1' and -1" phenyl) 155.3 (C=O). Anal. Calc for $C_{21}H_{20}Cl_3N_5O_2$: C, 52.45; H, 4.2; N, 14.55. Found C, 52.25; H, 4.3; N, 14.45%.

*4-(1-Ethoxycarbonylamino-2,2,2-trichloroethyl)-1-ethyl-5-*p*-methoxylbenzyliminopyrazole (15)*. From compound **1** (190 mg, 0.87 mmol) and 1-ethyl-5-*p*-methoxybenzyliminopyrazole (**13**) (132 mg, 0.58 mmol) with irradiation at 255 W for 5 min (final temperature 85 °C) derivative **15** (151 mg, 58%) was isolated as a colorless oil. $^1$H-NMR δ 1.23-1.29 (m, 3 H, $CH_3CH_2O$), 1.40 (t, *J* 7.3, 3 H, $CH_3CH_2N$), 3.89 (s, 3 H, $OCH_3$), 4.13-4.20 (m, 4 H, $OCH_2$), 5.59 (d, *J* 10, 1 H, $CHCCl_3$), 5.83 (d, *J* 10, 1 H, NH), 7.01 (d, *J* 8.7, 2 H, H-2' and -6' phenyl), 7.71 (s, 1 H, H-3 pyrazole), 7.94 (d, *J* 8.7, 2 H, H-3' and -5' phenyl), 8.59, (s, 1 H, N=CH). $^{13}$C-NMR δ 14.2 ($CH_3CH_2O$), 14.5 ($CH_3CH_2N$), 43.4 ($NCH_2$), 55.5 ($OCH_3$), 61.7 ($OCH_2$ and *CH*-$CCl_3$), 102.6, 103.6 (C-4 pyrazole and $CCl_3$), 114.3 (C-2' and -6' phenyl), 128.3 (C-5 pyrazole), 131.2 (C-3' and -5' phenyl), 148.0 (C-1' phenyl), 155.4 (C=O), 163.2 (CH=N), 164.8 (C-4' phenyl). Anal. Calc for $C_{18}H_{21}Cl_3N_4O_3$: C, 48.3; H, 4.75; N, 12.5. Found C, 48.05; H, 4.9; N, 12.35%.

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