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MICROWAVE-ASSISTED SYNTHESIS OF PYRAZOLES BY 1,3-DIPOLAR CYCLOADDITION OF DIAZO COMPOUNDS TO ACETYLENE DERIVATIVES

Irena Zrinski, Marina Juribasic, and Mirjana Eckert-Maksic*

Division of Organic Chemistry and Biochemistry, Rudjer Boskovic Institute, P.O.B. 180, HR-10002 Zagreb, Croatia; *Corresponding author. Tel.:+385 1 4680 197 fax:+385 1 4680 195; e-mail:mmaksic@emma.irb.hr

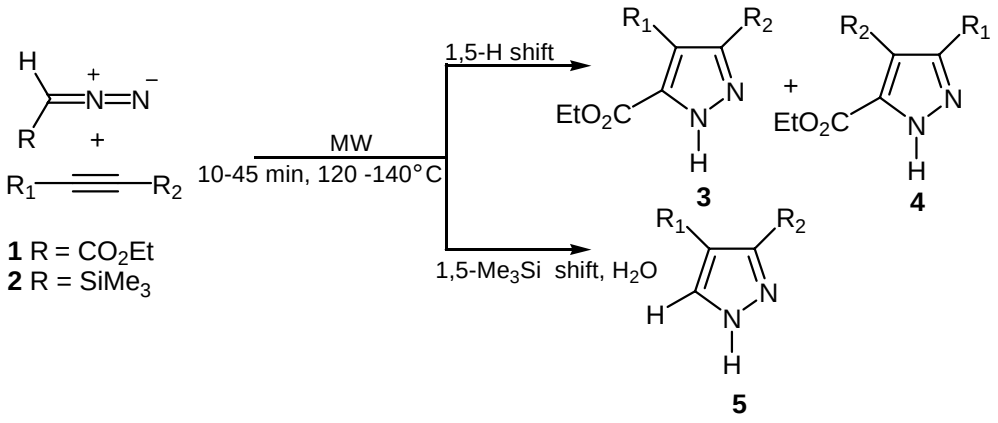
Abstract – Microwave-assisted preparation of a wide range of 5-ethoxycarbonylpyrazoles and 3-pyrazoles by 1,3-dipolar cycloaddition of diazo compound to acetylenes is described. All reactions were carried out using high throughput sequential technique.

INTRODUCTION

Pyrazole derivatives have been subject of broad interest due to their wide application in pharmaceutical and agrochemical industry.[1] The most widely used method of their synthesis has been the reaction between 1,3-dicarbonyl compounds and hydrazines.[2,3] Its usage is, however, somewhat limited due to the harsh reaction conditions or the multistep sequences usually required to access the starting materials. Another popular method involves 1,3-dipolar cycloaddition of diazo compounds or some other 1,3-dipoles to the triple bond.[2,4] These reactions lead to formation of *3H*-pyrazoles that can be isolated when di-substituted diazomethanes are employed. In case of the parent diazomethane and monosubstituted diazomethanes unstable *3H*-pyrazoles are formed, which subsequently undergo 1,5-sigmatropic shift yielding pyrazoles as the final product.[2] In last few years, several new approaches to synthesis of pyrazoles derivatives, including the microwave-assisted synthesis by Vilsmeier cyclization of hydrazones[5a] and pyrazole libraries obtained by imine cycloaddition to the polymer-supported vinylsulfone[5b] have been developed.[5]

Herewith, we report on preparation of some substituted pyrazoles by 1,3-dipolar cycloaddition of diazo compounds (**1**) and (**2**) to variety of acetylene derivatives assisted by controlled microwave (MW) heating in a high-throughput fashion (Scheme 1 and Table 1). To the best of our knowledge the effect of microwave heating on reactivity of ethyl diazoacetate (**1**) has been reported only towards alkenes, while reactivity of acetylene derivatives has not been explored so far.[6] We were particularly interested in exploring possibility

of obtaining derivatives of pyrazoles of type **(5)** by replacing diazomethane with more stable trimethylsilyl derivative.[7] Given the high tendency of the TMS for migration, we anticipated that the TMS group will undergo 1,5-shift more easily than H-atom giving rise to formation of 1-trimethylsilyl-derivative of **5**[8] followed by hydrolytic cleavage of the N-Si bond to pyrazole (**5**).[9]



Scheme 1

RESULTS AND DISCUSSION

We first explored reactivity of **1** towards a series of acetylene derivatives as summarized in Table 1(Entries 1 – 11). The reaction was carried out using neat reaction conditions. All the alkynes reacted smoothly with ethyl diazoacetate to give the target pyrazole product in good to high yields with high regioselectivity with one notable exception provided by 3-hexyne, which failed to give the desired product even in trace amount (Entry 9). Instead, at higher temperature (140 °C) decomposition of the reaction mixture was observed. In the case of reactions of **1** and mono(*n*-alkyl) substituted acetylenes, a mixture containing two regioisomeric products (**3**) and (**4**) were formed, with the former product being predominant (Entries 1 and 3). In all other cases the 3(5)-ethoxycarbonylpyrazoles (**3**) were the only products formed.

We next investigated reactivity of (trimethylsilyl)diazomethane (**2**) using the same acetylenic derivatives as in the first set of experiments (Table 1, Entries 12 – 19). These reactions were carried out by irradiating a mixture of 2.0 M solution of (trimethylsilyl)diazomethane (**2**) in hexane and acetylene derivatives. As expected, in each case except with 3-hexyne (Entry 17), the only product formed was the corresponding derivative of 3-pyrazole (**5**). This conclusion was corroborated by carrying out GC-MS analysis of the reaction products obtained by reacting phenylacetylene and **2** immediately after completion of reaction and after keeping it in an open vessel during night. In case of the former experiment the GC-MS analysis exhibited only one signal with molecular ion mass of 216 dalton (which corresponds to the 3-(phenyl)-1-trimethylsilyl-pyrazole), whereas in the latter presence of a new signal with molecular ion

mass of 144 dalton (which corresponds to the hydrolyzed product (**5**)) was observed.[10] Based on ^{1}H NMR analysis the structure of the 3-(phenyl)-1-trimethylsilyl-pyrazole could be unequivocally assigned to the isomer with the TMS group at the nitrogen atom.[10]

Table 1. 1,3-Dipolar cycloaddition reaction of diazo compounds (1), (2) and mono(di)-substituted acetylenes

Entry	R_1	R_2	Reaction condition	Ratio of isomers (**3**) : (**4**)[c]	Yield (%)[d]
1[a]	H	*n*-Bu	MW, 140 °C, 30 min	9.1: 0.9	60[e]
2[a]	H	*n*-Bu	Δ, 48 h	8.7 : 1.3	38[e]
3[a]	H	*n*-Hex	MW, 140 °C, 30 min	8.5 : 1.5	65
4[a]	H	CMe_3	MW, 140 °C, 45 min	1 : 0	58
5[a]	H	$SiMe_3$	MW, 120 °C, 15 min	1 : 0	95
6[a]	H	$SiMe_3$	Δ, 48 h	1 : 0	67
7[a]	H	Ph	MW, 120 °C, 10 min	1 : 0	97[e]
8[a]	H	Ph	Δ, 24 h	1 : 0	81[e]
9[a]	Et	Et	MW, 140 °C, 20 min	-	-
10[a]	$SiMe_3$	$SiMe_3$	MW, 140 °C, 20 min	-	98[e]
11[a]	Ph	Ph	MW, 140 °C, 20 min	-	96[e]
				products (**5**)	
12[b]	H	*n*-Bu	MW, 140 °C, 30 min	-	58[e]
13[b]	H	*n*-Hex	MW, 140 °C, 30 min	-	60
14[b]	H	CMe_3	MW, 140 °C, 45 min	-	55[e]
15[b]	H	$SiMe_3$	MW, 120 °C, 15 min	-	97[e]
16[b]	H	Ph	MW, 120 °C, 10 min	-	96[e]
17[b]	Et	Et	MW, 140 °C, 20 min	-	-
18[b]	$SiMe_3$	$SiMe_3$	MW, 140 °C, 45 min	-	55[e, f]
19[b]	Ph	Ph	MW, 140 °C, 45 min	-	61[e, f]

[a]Reaction with ethyl diazoacetate (**1**). [b]Reaction with (trimethylsilyl)diazomethane (**2**). [c]The ratio of the regioisomeric products was determined by ^{1}H NMR analysis of crude reaction mixture. [d]Isolated yields. [e]NMR data were identical to those reported previously in literature. [f]The product (**5**) was accompanied by small amount of the starting acetylene derivative.

Closer analysis of the results in Table 1 shows that all MW reactions, irrespective of the diazo compound employed, were accomplished within 10 – 45 minutes. Another point worth of noting is that reactions of acetylenes substituted with one electron-withdrawing group (Me_3Si, Ph) (Entries 5, 7, 15 and 16) proceeded at lower temperature and with higher yields than those substituted with one electron-accepting group (Entries 1, 3, 4 and 12 - 14). We note in passing that the above mentioned trends are consistent with changes in HOMO-LUMO energy gaps between diazocarbonyl compounds and employed alkynes calculated using DFT method.[11] Furthermore, the rate of reactions was found to be dependent on steric effects, as evidenced by comparing reactions of mono- and di-substituted acetylenes.[4]

Finally, it is of some interest to compare results described above with those obtained by conventional synthesis.[2,12] For this purpose we have carried out several reactions using ethyldiazoacetate as a starting dipole under conventional heating (Table 1, Entries 2, 6 and 8). In each case the reaction time was considerably longer and work up more difficult than in MW syntheses. The same holds for comparison of the present results with those obtained by alternative methods, e.g. with diazomethane as the starting compound being typical example.[2,12] In addition, as mentioned above, both ethyl diazoacetate (**1**) and trimethylsilyl-substituted diazomethane (**2**) used in this work are more stable and less toxic and thus safer for practical use than diazomethane itself.[7]

To summarize, we have prepared a variety of pyrazoles of type (**3**), (**4**) and (**5**) in a high-throughput fashion using microwave assisted 1,3-dipolar cycloaddition of substituted diazo compounds and corresponding mono- and di-substituted acetylene derivatives. This opens a simple route to a wide range of polyfunctionalized pyrazoles in a short reaction times, offering at the same time efficient way of generating a library of pyrazoles starting from various diazo compounds and acetylene derivatives. Finally, it should be emphasized that the synthesis of 5-ethoxycarbonylpyrazoles (**3**) and (**4**) presents one of few examples of intermolecular 1,3-dipolar cycloaddition of electron-deficient diazocarbonyl compounds with alkynes described in literature so far.[2,5g,13] This is of considerable importance since 3(5)-alkoxycarbonyl pyrazoles and their derivatives have been often used as precursors to a variety of five- and six-membered heterocyclic compounds.[5,14]

EXPERIMENTAL

Microwave Irradiation Experiments. All microwave irradiation experiments were carried out using CEM Discover® LabMateTH/Explorer$_{PLS}$® monomode reactor in a high-throughtput sequential fashion. All experiments were performed in sealed microwave process vials with MW power from 150 - 250 W depending on MW absorbing capability of reaction mixture. Reaction time under MW conditions

corresponds to actual reaction time at given temperature without ramp time needed to reach desired temperature (see Table 1).

The crude products were purified by radial chromatography using Harrison Research 7924T Chromatotron and Merck silica gel 60 PF_{254} containing $CaSO_4$. GC analyses were carried out on Varian 3300 gas chromatograph. Infrared spectra (IR) were recorded on Perkin-Elmer FT 2000 infrared spectrometer. ^1H and ^{13}C NMR spectra were measured on a Bruker AV-300. Chemical shifts are reported in parts per million (δ/ppm) downfield from tetramethylsilane using the residual solvent signal as an internal standard. GC–MS analyses were measured on Hewlett-Packard 5890 Series II gas chromatograph. Elemental analyses of new compounds (Table 1, Entries 3 and 13) were carried out using a PerkinElmer 2400 Series II CHNS/O analyser.

(a) **Synthesis of 5-ethoxycarbonyl pyrazoles (3) and (4). General procedure:** A mixture of diazo compound (**1**) (1 mmol) and acetylene (10 mmol) in 5 mL (large) microwave process vial was irradiated in the MW reactor with magnetic stirring for 10 – 45 min at 120 – 140 °C (see Table 1). The excess of acetylene was recovered by distillation under reduced pressure (10 mmHg/25 °C). The reaction mixture was treated with CH_2Cl_2 and than concentrated in vacuo. In reactions giving less than 95 % purity (GC) of product after CH_2Cl_2 evaporation the residue was further purified by radial chromatography on SiO_2 (eluent: petrol ether and AcOEt).

3-*n*-Hexyl-5-ethoxycarbonyl-*1H*-pyrazole (Entry 3): ^1H NMR (300 MHz, $CDCl_3$), δ/ppm: 0.81-0.85 (m, 3H), 1.25-1.34 (m, 9H), 1.57-1.62 (m, 2H), 2.66-2.77 (t, *J*=7.6 Hz, 2H), 4.33 (q, *J*=7.1 Hz, 2H), 6.55 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$), δ/ppm: 14.0, 14.2, 22.5, 26.8, 28.7, 29.1, 31.5, 60.8, 106.1, 141.6, 147.9, 162.0. IR ($CHCl_3$), υ/cm^{-1}: 1719, 3443. Anal. Calcd for $C_{12}H_{20}N_2O_2$: C 64.26, H 8.99, N 12.49. Found: C 64.0, H 9.04, N 12.64.

3-*t*-Butyl-5-ethoxycarbonyl-*1H*-pyrazole (Entry 4):[15] ^1H NMR (300 MHz, $CDCl_3$), δ/ppm: 1.24-1.39 (m, 12 H), 4.34 (q, *J*=7.1 Hz, 2H), 6.61 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$), δ/ppm: 14.2, 30.14, 31.3, 60.77, 104.24, 141.0, 156.90, 161.92.

3-Trimethylsilyl-5-ethoxycarbonyl-*1H*-pyrazole (Entry 5):[12a] ^1H NMR (300 MHz, $CDCl_3$), δ/ppm: 0.22 (s, 9H), 1.17-1.21 (t, 3H, *J* = 7.18 Hz), 4.27 (q, 2H, *J* = 7.05 Hz), 6.87 (s, 1H), 12.94 (br. s. NH). ^{13}C NMR (300 MHz, $CDCl_3$), δ/ppm: -1.74 (q), 13.79 (q), 60.37 (t), 114.98 (d), 143.47 (s), 144.35 (s), 162.74 (s).

(b) **Synthesis of 3-pyrazoles (5). General procedure:** A mixture of 2 M solution of diazo compounds (**2**) (1 mL, 2 mmol) and acetylenes (2 mmol) in 5 mL (large) microwave process vial was irradiated in the MW reactor with magnetic stirring for 10 – 45 min at 120 – 140 °C (see Table 1). Reaction mixture was diluted wiht CH_2Cl_2 and than concentrated in vacuo. In reactions giving less than 95 % purity (GC) of products after CH_2Cl_2 evaporation the residue was further purified by radial chromatography on silica gel (eluent: petrol ether and AcOEt).

3-*n*-Hexyl-*1H*-pyrazole (Entry 13): ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm: 0.92-0.97 (t, 3H, *J*=7.1 Hz), 1.20-1.30 (m, 6H), 1.60-1.65 (m, 2H), 2.69-2.73 (t, *J*=7.6 Hz, 2H), 6.1 (d, J=1.3, 1H), 7.51 (d, *J*=1.7 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$), δ/ppm: 13.82, 22.5, 26.4, 28.7, 29.1, 32.0, 103.30, 135.10, 147.81. Anal. Calcd for $C_9H_{16}N_2$: C 71.01, H 10.60, N 18.40. Found: C 71.16, H 10.49, N 18.54.

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