1,3-DIPOLAR CYCLOADDITION OF NITRILES UNDER MICROWAVE IRRADIATION IN SOLVENT-FREE CONDITIONS

Angel Díaz-Ortiz*[a], Enrique Díez-Barra[a], Antonio de la Hoz[a], Andrés Moreno[a], María J. Gómez-Escalonilla[a], and André Loupy[b]

a) Facultad de Química, Universidad de Castilla-La Mancha, E-13071, Ciudad Real, Spain b) Laboratoire des Réactions Sélectives sur Supports, CNRS UA 478, Université Paris-Sud. 91405, Orsay, France

Abstract - Several nitriles were allowed to react with nitrones or nitrile oxides in the absence of solvent under microwave irradiation within 2-10 min to give 2,3-dihydro-1,2,4-oxadiazoles or 1,2,4-oxadiazoles, respectively.

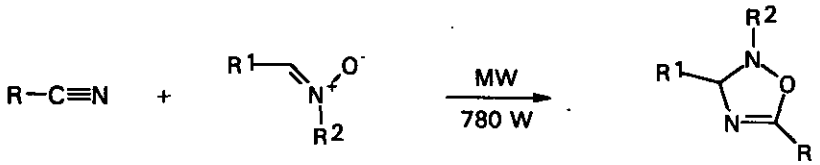
1,3-Dipolar cycloaddition reaction is a versatile method to prepare five-membered heterocyclic compounds. The cycloadditions involve a 1,3-dipole and a multiple bond as dipolarophile.[1] The use of nitriles as hetero-dipolarophiles in 1,3-dipolar cycloadditions is uncommon due to their low reactivity.[2] However, the importance of five-membered nitrogen heterocycles as precursors of many natural and pharmaceutical compounds is well known.[3] Recently, several cycloadditions of nitrones with nitriles have been reported,[4,5] although these reactions require very drastic conditions, high pressures[4] or long reaction times at high temperatures,[5] to obtain acceptable or good yields.

Microwave irradiation in solvent-free conditions has well demonstrated, in the last years, as non-classic energetic source to improve dramatically many synthetic processes.[6]

In connection with our studies related to the Diels-Alder and/or 1,3-dipolar cycloaddition of cyclic ketene acetals,[7,8] fluorinated alkenes[9] or activated alkynes[10] with several 1-hetero-1,3-dienes or 1,3-dipoles under microwave irradiation, we report now a new procedure to perform 1,3-dipolar cycloadditions of nitriles with nitrones and nitrile oxides.

We found that microwave irradiation induces the 1,3-dipolar cycloadditions of aliphatic and aromatic nitriles (**1a-f**) with nitrones or nitrile oxides under solvent-free conditions within 2-10 min to give the corresponding 2,3-dihydro-1,2,4-oxadiazoles (**3a-g**) or 1,2,4-oxadiazoles (**5a-e**). These results are summarized in the Tables 1 and 2.

Table 1. 1,3-Dipolar cycloaddition of nitriles (**1a-c**) with nitrones under microwave irradiation

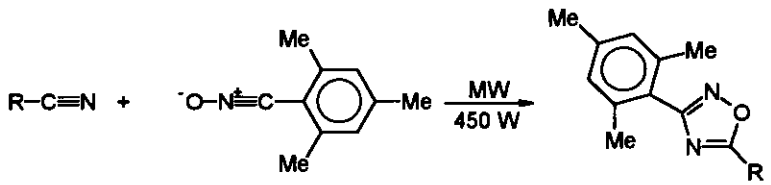


1a-c **2a-d** **3a-g**

Entry	R	R^1	R^2	Reaction conditions time/min, final temp./°C	Product [yield(%)]	Classical heating [yield(%)][a]
1	CCl_3	C_6H_5	Me	3, 115	**3a** (82)	61
2	CCl_3	C_6H_5	C_6H_5	2, 120	**3b** (40)	24
3	CCl_3	*p*-$CF_3C_6H_4$	Me	2, 115	**3c** (91)	79
4	CO_2Et	C_6H_5	C_6H_5	5, 195	**3d** (39)	4
5	CO_2Et	*p*-$CF_3C_6H_4$	C_6H_5	3, 155	**3e** (41)	17
6	CO_2Et	*p*-$CF_3C_6H_4$	Me	3, 135	**3f** (50)	17
7	C_6H_5	*p*-$CF_3C_6H_4$	C_6H_5	10, 180	**3g** (29)	traces

[a] Reactions were carried out under the same indicated reaction conditions (time and temperature) without solvent.

Table 2. 1,3-Dipolar cycloaddition of nitriles (**1a,b,d-f**) with nitrile oxide (**4**) under microwave irradiation



1a,b,d-f **4** **5a-e**

Entry	R	Reaction conditions time/min, final temp./°C	Product [yield(%)]	Classical heating [yield(%)][a]
1	Me	5, 125	**5a** (29)	traces
2	CCl_3	5, 120	**5b** (96)	83
3	CO_2Et	4, 100	**5c** (81)	60
4	*p*-$MeOC_6H_4$	8, 145	**5d** (98)	85
5	*p*-$NO_2C_6H_4$	8, 135	**5e** (68)	48

[a] Reactions were carried out under the same indicated reaction conditions (time and temperature) without solvent.

Reaction times are dramatically reduced, and reaction conditions are milder than other methods described, while cycloadditions were carried out in a simple domestic microwave oven.

To compare the yields obtained, we performed the cycloadditions by classical heating in an oil bath under the same indicated reaction conditions (time and temperature) in the absence of solvent. The results are also summarized in the Tables 1 and 2. The most important differences, in favour of microwaves, were observed in the most difficult reactions. The same kind of conclusions was drawn from saponification[11] and alkylation reactions under microwaves in solvent-free procedures when considering the substrate influence. Such an observation is coherent with a remark of Lewis[12] stating that "slower reacting systems tend to show a greater effect under microwave irradiation than reacting systems".

When the cycloaddition was a facile process resulting an stable cycloadduct, the differences of yields between microwaves or classical heating were not very important (e.g., Table 1 Entry 3, or Table 2 Entries 2 and 4). However, when yields were moderates, microwave irradiation permitted to obtain cycloadducts that classical heating afforded in very low yields (e.g., Table 1 Entries 4 and 7, or Table 2 Entries 1 and 5). Therefore, the good results attained under microwave irradiation perhaps are not a consequence of the temperature achieved.

Non-activated nitriles afforded moderate yields in their cycloadditions. However, these results suggest that yields may be related to the stability of the 1,3-dipoles and the heterocyclic cycloadducts. Nitrile oxides are less stable than nitrones, but they are more reactive as 1,3-dipole and their resulting adducts, 1,2,4-oxadiazoles, are more stable than their 2,3-dihydro derivatives. These facts could explain the good yields shown in the Table 2. 2,3-Dihydro-1,2,4-oxadiazoles decompose or revert to reagents at the reaction temperature, thus reducing the final yields.

In conclusion, microwave irradiation in solvent-free conditions induces cycloadditions of nitriles in a few minutes with easy work-up and acceptable yields and using a simple, cheap, accessible and safe equipment: a domestic microwave oven.

EXPERIMENTAL

All nitriles were of commercial quality from freshly opened containers. Nitrones and nitrile oxides were prepared by reported methods. Microwave irradiations were conducted in a Miele Electronic M720 domestic oven. Column chromatographies were performed on silica gel 60 Merck (230-400 mesh). Elemental analyses were performed on a Perkin-Elmer PE2400 CHN elemental analyser. ^{1}H-Nmr spectra were recorded in chloroform-d_1 (TMS) solutions using a Varian Unity 300 spectrometer.

General Procedure.- The adequate nitrile (3 equiv.) and the nitrone or nitrile oxide (1 equiv.) were mixed in a teflon vessel placed into an alumina-magnetite (Fe_3O_4) (5:1) bath.[13] The mixture was irradiated for

the indicated time (see Tables 1 and 2) and products were isolated from the crude mixture by flash chromatography.

5-Trichloromethyl-2-methyl-3-phenyl-2,3-dihydro-1,2,4-oxadiazole (3a)

From trichloroacetonitrile (0.3 ml, 2.88 mmol) and *N*-benzylidenemethylamine *N*-oxide[14] (130 mg, 0.96 mmol).

Flash chromatography [light petroleum-ethyl acetate (1:1)] afforded 219 mg (82%) of the compound (**3a**), mp 66-67 °C (from chloroform-hexane). (Anal. Calcd for $C_{10}H_9N_2OCl_3$: C, 43.15; H, 3.25; N, 10.05. Found: C, 43.1; H, 3.25; N, 10.0). ^{1}H-Nmr δ (ppm): 2.98 (br s, 3H, CH_3), 5.76 (br s, 1H, CH), 7.35-7.44 (m, 5H, H_{arom}). ^{13}C-Nmr δ (ppm): 46.6 (CH_3), 85.1 (CCl_3), 93.9 (CH), 126.5, 128.7, 129.0, 137.5 (C_{arom}), 160.0 (O-C=N).

5-Trichloromethyl-2,3-diphenyl-2,3-dihydro-1,2,4-oxadiazole (3b)

From trichloroacetonitrile (0.2 ml, 1.98 mmol) and *N*-benzylidenephenylamine *N*-oxide[15] (130 mg, 0.66 mmol).

Flash chromatography [light petroleum-ethyl acetate (5:1)] afforded 90 mg (40%) of the product (**3b**), mp 137-138 °C (from chloroform-hexane). (Anal. Calcd for $C_{15}H_{11}N_2OCl_3$: C, 52.95; H, 3.25; N, 8.25. Found: C, 53.0; H, 3.2; N, 8.25). ^{1}H-Nmr δ (ppm): 7.19-7.59 (m, 11H, CH and H_{arom}). ^{13}C-Nmr δ (ppm): 95.7 (CCl_3), 123.5 (CH), 126.7, 128.5, 128.8, 129.2, 129.3, 132.0, 132.7, 137.2 (C_{arom}), 168.3 (O-C=N).

5-Trichloromethyl-3-(4-trifluoromethylphenyl)-2-methyl-2,3-dihydro-1,2,4-oxadiazole (3c)

From trichloroacetonitrile (0.2 ml, 1.92 mmol) and *N*-trifluoromethylbenzylidenemethylamine *N*-oxide[14] (130 mg, 0.64 mmol).

Flash chromatography [light petroleum-ethyl acetate (2:1)] afforded 201 mg (91%) of the product (**3c**), mp 92-93 °C (from chloroform-hexane). (Anal. Calcd for $C_{11}H_8N_2OCl_3F_3$: C, 38.15; H, 2.35; N, 8.1. Found: C, 38.1; H, 2.3; N, 8.15). ^{1}H-Nmr δ (ppm): 3.02 (s, 3H, CH_3), 5.83 (s, 1H, CH), 7.58-7.66 (m, 4H, H_{arom}). ^{13}C-Nmr δ (ppm): 46.7 (CH_3), 84.8 (CCl_3), 92.9 (CH), 123.9 (CF_3), 125.7, 126.9, 131.1, 141.3 (C_{arom}), 160.5 (O-C=N).

5-Ethoxycarbonyl-2,3-diphenyl-2,3-dihydro-1,2,4-oxadiazole (3d)

From ethyl cyanoformate (0.2 ml, 2 mmol) and *N*-benzylidenephenylamine *N*-oxide (130 mg, 0.66 mmol). Flash chromatography [light petroleum-ethyl acetate (5:1)] afforded 76 mg (39%) of the compound (**3d**), mp 118-119 °C (from chloroform-hexane). (Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.9; H, 5.45; N, 9.45. Found: C, 68.8; H, 5.5; N, 9.6). ^{1}H-Nmr δ (ppm): 1.46 (t, 3H, J = 7.1 Hz, CH_3), 4.50 (q, 2H, J = 7.1 Hz, CH_2), 7.43 (s, 1H, CH), 7.28-7.62 (m, 10H, H_{arom}). ^{13}C-Nmr δ (ppm): 14.2 (CH_3), 61.9 (CH_2), 127.4, 128.6, 128.8, 130.2, 130.3, 130.4, 132.6, 133.0, 143.8 (CH and C_{arom}), 163.1, 163.2 (O-C=N and COO).

4-Ethoxycarbonyl-3-(4-trifluoromethylphenyl)-2-phenyl-2,3-dihydro-1,2,4-oxadiazole (3e)

From ethyl cyanoformate (0.14 ml, 1.47 mmol) and *N*-4-trifluoromethylbenzylidenephenylamine *N*-oxide[15] (130 mg, 0.49 mmol).

Flash chromatography [light petroleum-ethyl acetate (5:1)] afforded 73 mg (41%) of the product (**3e**), mp 100-101 °C (from chloroform-hexane). (Anal. Calcd for $C_{18}H_{15}N_2O_3F_3$: C, 59.3; H, 4.15; N, 7.7. Found: C, 59.4; H, 4.2; N, 7.6). ^{1}H-Nmr δ (ppm): 1.46 (t, 3H, J = 7.1 Hz, CH_3), 4.50 (q, 2H, J = 7.1 Hz, CH_2), 7.31-7.65 (m, 10H, CH and H_{arom}). ^{13}C-Nmr δ (ppm): 14.2 (CH_3), 62.1 (CH_2), 123.7 (CF_3), 125.5, 127.6, 128.7, 130.4, 130.5, 131.8, 132.4, 136.4, 141.9 (CH and C_{arom}), 162.9, 163.2 (COO and O-C=N).

5-Ethoxycarbonyl-3-(4-trifluoromethylphenyl)-2-methyl-2,3-dihydro-1,2,4-oxadiazole (3f)

From ethyl cyanoformate (0.2 ml, 1.92 mmol) and *N*-4-trifluoromethylbenzylidenemethylamine *N*-oxide (130 mg, 0.64 mmol).

Flash chromatography [light petroleum-ethyl acetate (2:1)] afforded 97 mg (50%) of the product (**3f**), mp 39-40°C (from chloroform-hexane). (Anal. Calcd for $C_{13}H_{13}N_2O_3F_3$: C, 51.65; H, 4.35; N, 9.25. Found: C, 51.6; H, 4.5; N, 9.2). ^{1}H-Nmr δ (ppm): 1.36 (t, 3H, J = 7.0 Hz, CH_3), 2.95 (s, 3H, NCH_3), 4.37 (q, 2H, J = 7.0 Hz, CH_2), 5.84 (s, 1H, CH), 7.56-7.62 (m, 4H, H_{arom}). ^{13}C-Nmr δ (ppm): 13.8 (CH_3), 46.8 (NCH_3), 63.4 (CH_2), 93.0 (CH), 123.8 (CF_3), 125.5, 126.9, 131.4, 141.7 (C_{arom}), 153.0, 156.0 (COO and O-C=N).

3-(4-Trifluoromethylphenyl)-2,5-diphenyl-2,3-dihydro-1,2,4-oxadiazole (3g)

From benzonitrile (0.15 ml, 1.47 mmol) and *N*-4-trifluromethylbenzylidenephenylamine *N*-oxide (130 mg, 0.49 mmol).

Flash chromatography [light petroleum-ethyl acetate (5:1)] afforded 52 mg (29%) of the product (**3g**), mp 158-159 °C (from light petroleum-ethyl acetate). (Anal. Calcd for $C_{21}H_{15}N_2OF_3$: C, 68.5; H, 4.1; N, 7.6. Found: C, 68.35; H, 4.0; N, 7.6). ^{1}H-Nmr δ (ppm): 6.39 (s, 1H, CH), 6.90-7.83 (m, 14H, H_{arom}). ^{13}C-Nmr δ (ppm): 123.6 (CF_3), 113.7, 121.4, 125.4, 127.1, 128.6, 128.7, 129.2, 130.3, 132.4, 136.4, 141.9, 147.9 (CH and C_{arom}), 167.7 (O-C=N).

5-Methyl-3-(2,4,6-trimethylphenyl)-1,2,4-oxadiazole (5a)

From acetonitrile (0.12 ml, 2.4 mmol) and 2,4,6-trimethylbenzonitrile oxide[16] (130 mg, 0.8 mmol).

Flash chromatography [toluene] afforded 47 mg (29%) of the product (**5a**), mp 103-104 °C (from chloroform-hexane). (Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.25; H, 7.0; N, 13.85. Found: C, 71.4; H, 6.9; N, 13.75). ^{1}H-Nmr δ (ppm): 2.02 (s, 3H, CH_3), 2.24 (s, 6H, *o*-CH_3), 2.32 (s, 3H, *p*-CH_3), 6.96 (s, 2H, H_{arom}). ^{13}C-Nmr δ (ppm): 14.0 (CH_3), 20.1 (*o*-CH_3), 21.1 (*p*-CH_3), 122.1, 128.7, 137.6, 140.5 (C_{arom}), 168.2 (N-C=N), 176.3 (O-C=N).

5-Trichloromethyl-3-(2,4,6-trimethylphenyl)-1,2,4-oxadiazole (5b)

From trichloroacetonitrile (0.24 ml, 2.4 mmol) and 2,4,6-trimethylbenzonitrile oxide (130 mg, 0.8 mmol).

Flash chromatography [light petroleum-ethyl acetate (15:1)] afforded 233 mg (96%) of the compound (**5b**), mp 62-63 °C (from hexane). (Anal. Calcd for $C_{12}H_{11}N_2OCl_3$: C, 47.4; H, 3.65; N, 9.2. Found: C, 47.3; H, 3.7; N, 9.0). ^{1}H-Nmr δ (ppm): 2.23 (s, 6H, *o*-CH_3), 2.33 (s, 3H, *p*-CH_3), 6.96 (s, 2H, H_{arom}). ^{13}C-Nmr δ (ppm): 20.2 (*o*-CH_3), 21.2 (*p*-CH_3), 83.5 (CCl_3), 122.1, 128.7, 137.8, 140.5 (C_{arom}), 169.1 (N-C=N), 174.0 (O-C=N).

5-Ethoxycarbonyl-3-(2,4,6-trimethylphenyl)-1,2,4-oxadiazole (5c)

From ethyl cyanoformate (0.23 ml, 2.4 mmol) and 2,4,6-trimethylbenzonitrile oxide (130 mg, 0.8 mmol).

Flash chromatography [light petroleum-ethyl acetate (15:1)] afforded 168 mg (81%) of the compound (**5c**), mp 50-51 °C (from chloroform-hexane). (Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.6; H, 6.2; N, 10.8. Found: C, 64.7; H, 6.2; N, 10.95. ^{1}H-Nmr δ (ppm): 1.48 (t, 3H, J = 7.2 Hz, $C\underline{H}_3$-CH_2), 2.18 (s, 6H, *o*-CH_3), 2.32 (s, 3H, *p*-CH_3), 4.56 (q, 2H, J = 7.2 Hz, CH_2), 6.95 (s, 2H, H_{arom}). ^{13}C-Nmr δ (ppm): 13.9 ($\underline{C}H_3$-CH_2), 20.0 (*o*-CH_3), 21.1 (*p*-CH_3), 63.8 (CH_2), 122.6, 128.5, 137.8, 140.2 (C_{arom}), 154.2 (N-C=N), 166.3, 169.4 (O-C=N and COO).

5-(4-Methoxyphenyl)-3-(2,4,6-trimethylphenyl)-1,2,4-oxadiazole (5d)

From 4-methoxybenzonitrile (319 mg, 2.4 mmol) and 2,4,6-trimethylbenzonitrile oxide (130 mg, 0.8 mmol).

Flash chromatography [hexane-ethyl acetate (3:1)] afforded 230 mg (98%) of the compound (**5d**), mp 114-115°C (from chloroform-hexane). (Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.15; N, 9.5. Found: C, 73.3; H, 6.1; N, 9.6). ^{1}H-Nmr δ (ppm): 2.24 (s, 6H, *o*-CH_3), 2.32 (s, 3H, *p*-CH_3), 3.86 (s, 3H, OCH_3), 6.95-8.14 (m, 6H, H_{arom}). ^{13}C-Nmr δ (ppm): 20.0 (*o*-CH_3), 21.1 (*p*-CH_3), 55.4 (OCH_3), 114.4, 116.8, 123.9, 128.4, 129.9, 137.6, 139.5, 163.0 (C_{arom}), 168.6 (N-C=N), 175.2 (O-C=N).

3-(2,4,6-Trimethylphenyl)-5-(4-nitrophenyl)-1,2,4-oxadiazole (5e)

From 4-nitrobenzonitrile (355 mg, 2.4 mmol) and 2,4,6-trimethylbenzonitrile oxide (130 mg, 0.8 mmol).

Flash chromatography [light petroleum-ethyl acetate (15:1)] afforded 168 mg (68%) of the product (**5e**), mp 152-153 °C (from chloroform-hexane). (Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.0; H, 4.9; N, 13.6. Found: C, 65.85; H, 4.85; N, 13.5). ^{1}H-Nmr δ (ppm): 2.23 (s, 6H, *o*-CH_3), 2.34 (s, 3H, *p*-CH_3), 6.96 (s, 2H, H_{arom}), 8.38 (s, 4H, H_{arom}). ^{13}C-Nmr δ (ppm): 20.1 (*o*-CH_3), 21.1 (*p*-CH_3), 123.1, 124.2, 128.6, 129.0, 129.4, 137.6, 140.0, 149.9 (C_{arom}), 169.2 (N-C=N), 173.3 (O-C=N).

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