Microwave-Enhanced Reactivity of Non-Activated Dienophiles Towards Pyrazine *o*-Quinodimethanes

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Abstract: Microwave irradiation in solvent-free conditions induces cycloaddition reactions of pyrazine *o*-quinodimethane intermediates with electron-rich dienophiles within 10–15 min to afford quinoxaline derivatives in acceptable yields.

Key words: alkynes, heterocycles, Diels–Alder reactions, microwaves, *o*-quinodimethanes

o-Quinodimethane derivatives are reactive dienes and can be generated in situ by a number of methods. The inter- and intramolecular Diels–Alder reactions of these compounds form the basis of the synthesis of a wide range of target molecules.[1]

Traditionally, heterocyclic *o*-quinodimethanes have received much less attention. However, the generation and synthetic applications of these materials have been recently reviewed[2] and interest in them is growing rapidly. Generation of *o*-quinodimethane derivatives involves harsh reaction conditions under which the reagents are heated to very high temperatures (frequently up to 200 ºC). Moreover, *o*-quinodimethanes are very reactive and unstable intermediates that rapidly decompose or undergo intramolecular reactions in the absence of an activated dienophile.

Microwave irradiation in solvent-free conditions has been widely demonstrated as a useful energy source in synthetic reactions. The rapid heating induced by the radiation avoids the decomposition of the reagents and/or products, reactions are cleaner and yields are in many cases higher than those obtained by classical heating.[3] For these reasons, microwave technology is a very promising technique to generate *o*-quinodimethane derivatives. These reactive intermediates react under classical heating conditions, with activated electron-poor dienophiles in Diels–Alder cycloadditions and, in many cases, good yields are obtained. However, their reactivity towards non-activated dienophiles has received much less attention, perhaps because these reactions fail under classical conditions.

As a continuation of our previous studies on microwave-induced cycloaddition reactions,[4] we report here the Diels–Alder reaction of pyrazine *o*-quinodimethane derivative **2** with non-activated dienophiles, such as aromatic alkynes or enamines, under microwave irradiation in solvent-free conditions.

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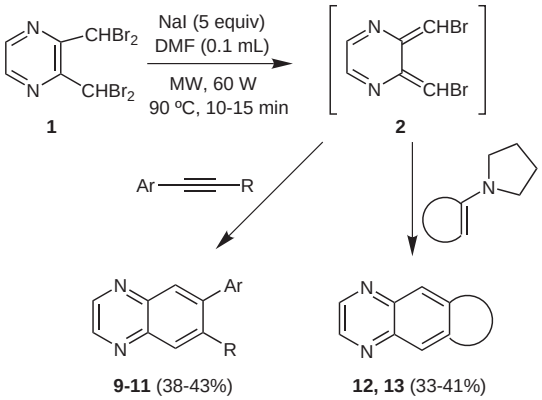
Pyrazine *o*-quinodimethane derivatives can be generated from 2,3-bis(dibromomethyl)pyrazine (**1**) by a 1,4-elimination reaction.[5] These intermediates react under classical heating with *N*-phenylmaleimide or cyclohexa-2,5-diene-1,4-dione to give good yields of products.[5] However, the reactivity of pyrazine *o*-quinodimethanes with electron-rich dienophiles has not been reported. As Lewis stated: 'poorer reacting systems tend to show a greater effect under microwave irradiation than reacting systems'.[6] For this reason, we studied the Diels–Alder reaction of pyrazine *o*-quinodimethanes with non-activated dienophiles under microwave irradiation.

Thus, when 2,3-bis(dibromomethyl)pyrazine (**1**) is irradiated in solvent-free conditions in the presence of NaI and a small amount of DMF (0.1 mL, the presence of a small amount of DMF is necessary to dissolve the sodium salt), the *o*-quinodimethane **2** is generated. Subsequent cycloadditions with aromatic alkynes **3**–**5** or enamines **6**–**7** afford the corresponding cycloadducts **9**-**13** within 10–15 minutes in 33–43% yield (see Scheme 1 and Table 1).[7]

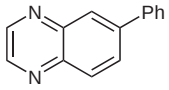
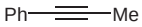
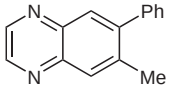
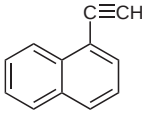
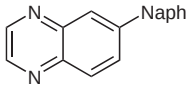
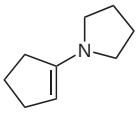
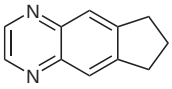
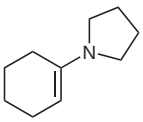
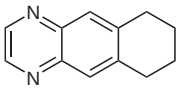
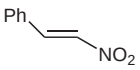
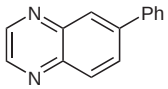
The rate of disappearance of tetrabromide **1** is greater under microwave irradiation than by classical heating. However, at this moment, we cannot affirm if the microwave induced elimination of **1** lead to an 'activated' *o*-quinodimethane which is more reactive in cycloaddition or the microwaves affect the reactivity of the dienophile.



Scheme 1

All the quinoxaline derivatives – prepared in acceptable yields via this microwave technology reported here for the first time – were characterised on the basis of their spectroscopic and analytical data. Reaction conditions have not been optimised, although a higher reaction

Table 1 Diels–Alder Cycloadditions between Pyrazine *o*-Quinodimethane **2** and Dienophiles **3**–**8** under Microwave Irradiation

Entry	Dienophile	Time (min)	Product[a]	Yield (%)
1	 **3**	13	 **9**	38
2	 **4**	15	 **10**	43
3	 **5**	15	 **11**	41
4	 **6**	15	 **12**	41
5	 **7**	15	 **13**	33
6	 **8**	10	 **9**	69

[a] Naph = 1-naphthyl

temperature (up to 100 ºC) leads to decomposition of the *o*-quinodimethane intermediate **2** before reaction with the dienophile and a corresponding decrease in the yield is observed.

Logically, when a reactive electron-poor dienophile – such as β-nitrostyrene (**8**) – is employed, the cycloaddition is much easier and the yield of the corresponding adduct increases to near 70% (entry 6). On the other hand, as one would predict, classical heating using an oil bath in conjunction with similar reaction conditions (time and temperature) gives only traces of the cycloadducts **9**–**13** (less than 3%) in all cases. This fact provides further evidence for the efficiency of microwave radiation.

In conclusion, Diels–Alder cycloadditions of pyrazine *o*-quinodimethanes with electron-poor dienophiles can proceed in good yields either under microwave irradiation or by classical heating. However, with electron-rich dienophiles these reactions can only be successfully performed under microwave irradiation providing the corresponding quinoxaline compounds to be obtained in acceptable yields.

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(7) Experimental procedure: A mixture of 2,3-bis(dibromomethyl)pyrazine[5](**1**) (150 mg, 0.35 mmol), NaI (265 mg, 1.77 mmol), DMF (0.1 mL) and the corresponding dienophile (1.25 mmol) was placed in an open vessel and irradiated at 60 W in a focused microwave reactor (CixMO model RF46280)[8] for 10–15 min (final temperature 90 ºC). The crude reaction product was purified by flash column chromatography (silica gel, Merck type 60 230–400 mesh) using hexane/ethyl acetate as the eluent to obtain the adduct. For example:
Data for **13**: yellow oil; IR (film, cm^{-1}) 2950, 2850, 1580, 1490, 1460; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.90 (m, 4 H, H-7 and -8), 3.06 (m, 4 H, H-6 and -9), 7.79 (s, 2 H, H-5 and -10), 8.73 (s, 2 H, H-2 and -3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 22.7 (C-7 and -8), 29.8 (C-6 and -9), 127.8 (C-5 and -10), 141.3 and 141.5 (C-4a, -5a, -9a and -10a), 144.1 (C-2 and -3); EM (EI) *m/z* 184 (M^+).
(8) Focused microwave reactor model RF46280 has total control of the power and temperature by an infrared sensor and has been developed by CixMO (www.cixmo.com).