Microwave Irradiation as an Efficient Tool for the Generation of N-Heterocyclic *o*-Quinodimethanes: Synthesis of Polyheterocyclic Compounds by Diels–Alder Reactions

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Received 13 December 2005

Abstract: Microwave irradiation provides a general methodology for the generation of *o*-quinodimethanes derived from 1,2,4-triazine, pyrazole and 1,2,3-triazole. The cycloaddition reactions of such compounds with electron-deficient dienophiles allow the corresponding heteropolycyclic adducts to be obtained within 15 minutes in 51–87% yield.

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

Heterocyclic *o*-quinodimethanes are unstable and reactive dienes that must be generated in situ.[1] In solution and in the presence of a dienophile the *o*-quinodimethanes can be intercepted in a Diels–Alder reaction.[2] This is the basis for the synthesis of a wide range of polycyclic natural products.[3] Most of the papers in this area describe the generation of *o*-quinodimethanes in situ and trapping with dienophiles to obtain the Diels–Alder adduct. In this regard, the general application of these reactions has not been fully explored.

The generation of *o*-quinodimethane derivatives generally involves harsh reaction conditions under which the reagents are heated to very high temperatures (frequently up to 200 °C). Moreover, *o*-quinodimethanes rapidly decompose or undergo intramolecular reactions in the absence of an activated dienophile.

In the last decade, microwave irradiation under solvent-free conditions has been shown to be a useful energy source in a wide range of synthetic reactions. The rapid heating induced by the radiation avoids decomposition of reagents and/or products, reactions are cleaner and yields are in many cases higher than those obtained by classical heating.[4] For these reasons, the microwave approach represents a very promising methodology to generate *o*-quinodimethane derivatives.

Recently, we studied the microwave-enhanced reactivity of non-activated dienophiles (aromatic alkynes and enamines) towards a pyrazine *o*-quinodimethane. This methodology allowed the corresponding quinoxalines to be obtained in 33–43% yield.[5]

SYNLETT 2006, No. 4, pp 0579–0582
Advanced online publication: 20.02.2006
DOI: 10.1055/s-2006-932460; Art ID: G38205ST

We wish to report here a microwave-assisted approach for the generation and Diels–Alder reactions of *o*-quinodimethane derivatives of 1,2,4-triazine, pyrazole and 1,2,3-triazoles. These heterocyclic systems have not been as widely studied as other systems (e.g., indole) and a general synthetic application of *o*-quinodimethanes derived from these nitrogen-bearing heterocycles is lacking – perhaps owing to the modest results achieved by classical methods.

The 1,2,4-triazine ring system is a key component of commercial dyes, herbicides and insecticides.[6] In addition, some derivatives have shown wide antibiotic and antitumor activities.[7] Pyrazoles have long been of pharmacological interest as antianxiety,[8] antipyretic, analgesic and antiinflammatory drugs[9] as well as antimicrobials.[10] 1,2,3-Triazole is the essential structural unit in a number of drugs and some of these materials are also potent HIV-1 inhibitors,[11] antimicrobial agents,[12] or selective β_3-adrenergic receptor agonists.[13]

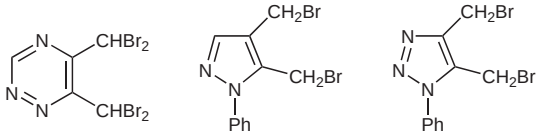
In the last decade, Stephanidou-Stephanatou and coworkers have studied the generation of *o*-quinodimethanes derived from pyrazole and 1,2,3-triazole.[14] The Diels–Alder reactions with electron-deficient dienophiles afforded the corresponding adducts in 11–52% yield.

We report here a general microwave-assisted synthetic methodology to prepare, in good yields and within a few minutes, heteropolycyclic compounds derived from 1,2,4-triazine, pyrazole and 1,2,3-triazole.

Irradiation of bromoderivatives **1**, **2** or **3** under 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) gave the corresponding *o*-quinodimethane. Subsequent cycloadditon with electron-deficient dienophiles afforded the corresponding cycloadducts within 15 minutes in 51–87% yield (Figure 1 and Scheme 1).[15] The results are given in Table 1.

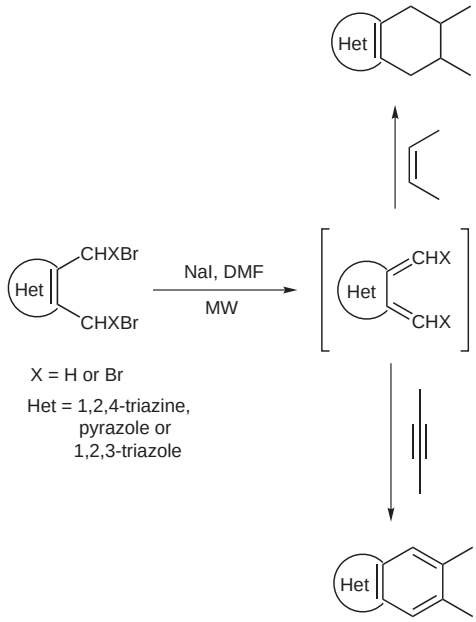
These findings clearly demonstrate that microwave irradiation provides an excellent way to induce the generation and Diels–Alder cycloaddition of heterocyclic *o*-quinodimethane derivatives.

All of the products were characterised on the basis of their spectroscopic and analytical data. Reactions were conducted until the starting bromoderivative had completely



1 2 3

Figure 1 Bromoderivatives **1**–**3** used as precursors in the generation of *o*-quinodimethanes



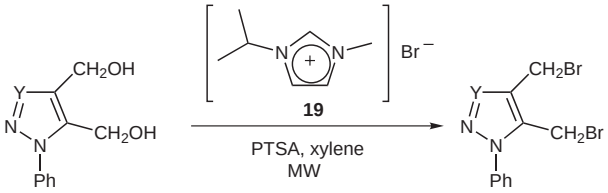
Scheme 1

disappeared. It should be noted, however, that reaction conditions have not been optimised.

The use of precursor **1** and subsequent elimination of two equivalents of HBr allowed aromatic products to be obtained.[16] Precursors **2** and **3** afforded aromatic cycloadducts with triple-bonded dienophiles (such as DMAD) and *p*-benzoquinone. However, other double-bonded dienophiles (*N*-methylmaleimide and DEAD) led to non-aromatic adducts.

Bromoderivatives **2** and **3** were prepared from the corresponding diols **17** and **18**, respectively, through a nucleophilic substitution reaction. In order to increase the sustainability of the methodology, we performed these transformations using an ionic liquid under microwave irradiation.

In accordance with a recent study by Leadbeater,[17] we prepared and used the ionic liquid **19** to obtain **2** and **3**. Irradiation of a mixture of the diol, TsOH, the ionic liquid and xylene (1 mL) at 150 °C for 3.5 minutes afforded the bromoderivatives **2** and **3** in 66 and 61% yield, respectively (Scheme 2).[18] In the classical procedure, treatment of the diol with PBr_3/DMAP in CH_2Cl_2 at room temperature for 24 hours gave compounds **2** and **3** in 51% and 40% yield, respectively. These results again demonstrate the synergy between ionic liquids and microwave irradiation to accelerate reactions and increase product yields. This work also constitutes the first application of this reaction in heterocyclic compounds.



17 Y = CH
18 Y = N

2 Y = CH
3 Y = N

Scheme 2

In conclusion, in this work we have applied microwave irradiation in the generation and Diels–Alder cycloaddition of several heterocyclic *o*-quinodimethanes. The results represent a general synthetic procedure to prepare, within a few minutes, a wide range of heterocyclic compounds in good yields. The novelty of this work is not the synthetic approach employed but the application of microwave heating in the development of a general synthetic procedure to prepare interesting heteropolycyclic products in good yields.

Table 1 Cycloaddition Reactions between Bromoderivatives **1**–**3** and Electron-Deficient Dienophiles **4**–**7** under Microwave Irradiation

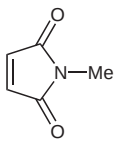
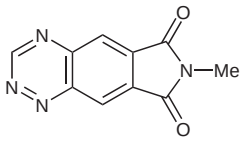
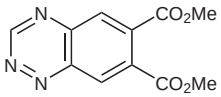
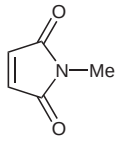
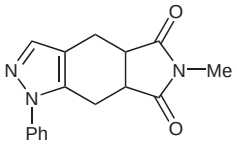
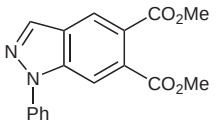
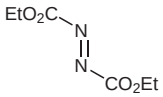
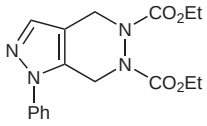
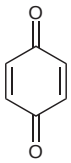
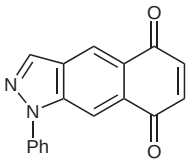
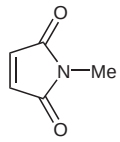
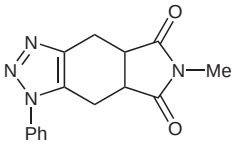
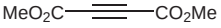
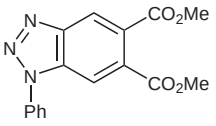
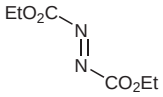
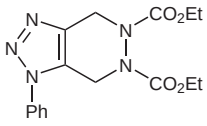
Entry	Substrate	Dienophile	Temp (°C)	Product	Yield (%)
1	**1**	 **4**	90	 **8**	68
2	**1**	 **5**	90	 **9**	55

Table 1 Cycloaddition Reactions between Bromoderivatives **1**–**3** and Electron-Deficient Dienophiles **4**–**7** under Microwave Irradiation (continued)

Entry	Substrate	Dienophile	Temp (°C)	Product	Yield (%)
3	**2**	 **4**	150	 **10**	80
4	**2**	 **5**	110	 **11**	51
5	**2**	 **6**	110	 **12**	62
6	**2**	 **7**	115	 **13**	58
7	**3**	 **4**	150	 **14**	87
8	**3**	 **5**	140	 **15**	68
9	**3**	 **6**	120	 **16**	66

Acknowledgment

Financial support from the Spanish DGCyT (Project CTQ2004-01177/BQU) and Junta de Comunidades de Castilla-La Mancha (Project PAI05-019) is gratefully acknowledged. One of us (M.A.H.) wishes to acknowledge a grant from JJCC.

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(15) **Experimental Procedure.**
A mixture of bromoderivative (1 equiv), NaI (5 equiv if **1** is employed or 3 equiv in the case of **2** and **3**), DMF (0.1 mL) and the corresponding dienophile (2 equiv) was placed in an open vessel and irradiated at 10 W in a focused microwave reactor (Discover®, CEM) for 15 min. The crude product was purified by flash column chromatography (silica gel, Merck type 60, 230–400 mesh) using hexane–EtOAc as the eluent to obtain the adduct.
Data for **8**: mp 204–205 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.35 (s, 3 H, CH_3), 8.60 (s, 1 H, H-5), 9.05 (s, 1 H, H-9), 10.14 (s, 1 H, H-3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.0 (CH_3), 126.0 (C-5), 126.3 (C-9), 132.2, 135.7 (C-9a and -4a), 143.9, 149.6 (C-8a and -5a), 165.6 (C=O). MS (EI): *m/z* = 214 [M^+].
Data for **10**: mp 165.5–166.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.86 (dd, 1 H, *J* = 7.3, 15.4 Hz, H-4), 2.90 (s, 3 H, CH_3), 2.93 (dd, 1 H, *J* = 7.3, 16.1 Hz, H-10), 3.23 (dd, 1 H, *J* = 1.6, 15.4 Hz, H-4), 3.34 (dd, 1 H, *J* = 1.6, 7.3 Hz, H-5), 3.36 (dd, 1 H, *J* = 1.8, 7.3 Hz, H-9), 3.55 (dd, 1 H, *J* = 1.8, 16.1 Hz, H-10), 7.37 (t, 1 H, *J* = 6.3 Hz, *p*-H Ph), 7.44 (t, 2 H, *J* = 6.3 Hz, *m*-H Ph), 7.46 (t, 2 H, *J* = 6.3 Hz, *o*-H Ph), 7.47 (s, 1 H, H-3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1 (C-4), 21.7 (C-10), 25.3 (CH_3), 39.6, 39.9 (C-5 and -9), 123.5 (*m*-C), 127.5 (*p*-C), 129.3 (*o*-C), 137.7 (C-3), 179.0, 179.4 (C=O), 115.2, 135.9, 139.1 ppm. MS (EI): *m/z* 281 [M^+].
Data for **16**: yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (m, 6 H, 2 × CH_3), 4.21 (m, 4 H, 2 × CH_2), 4.51 (br s, 2 H, H-4a and -7a), 5.30 (br s, 2 H, H-4b and -7b), 7.54 (m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4 (CH_3), 42.0, 44.3 (C-4 and -7), 63.2 (COO***C***H_2), 122.3 (*p*-C), 129.3 (*m*-C), 129.9 (*o*-C), 140.7 (*ipso*-C), 155.3, 155.6 (COO), 136.3 ppm. MS (EI): *m/z* = 345 [M^+].
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(18) **Experimental Procedure.**
A mixture of hydroxyderivative **17** or **18** (1 equiv), ionic liquid **19** (2.8 equiv), PTSA (2 equiv) and xylene (1 mL) was placed in an closed vessel and irradiated at 15 W in a focused microwave reactor (Discover®, CEM) for 3.5 min (final temperature 150 °C). The organic layer was separated from this two-phase system. The ionic liquid was washed with xylene (2 × 1 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed at reduced pressure. The resulting bromoderivatives, **2** or **3**, can be directly employed or purified by flash column chromatography (silica gel, Merck type 60, 230–400 mesh) using hexane–EtOAc 2:1 as the eluent.