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Ultrasound Assisted Diels-Alder Reactions of 1-Azadienes with "Normal" Electronic Demand.

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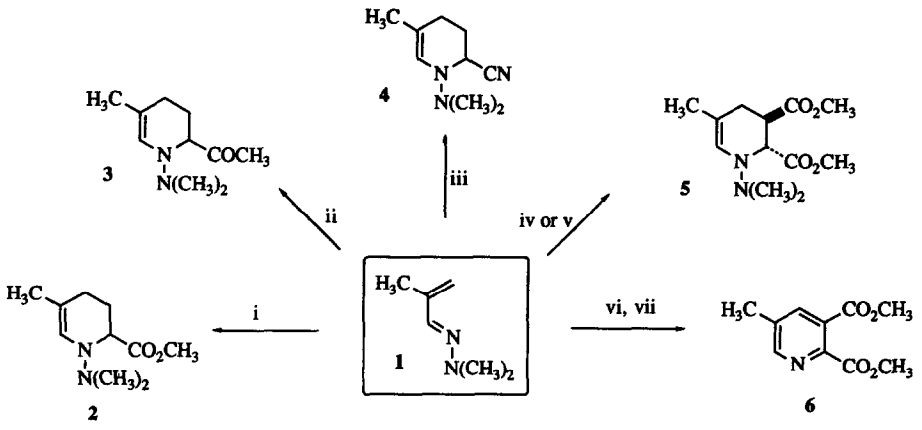
Abstract: Ultrasound irradiaton accelerates hetero Diels-Alder reactions between 1-dimethylamino-1-azadienes and electron-defficient dienophiles. Besides the lower reaction times and increased yields, other advantages of the sonicated reactions are the possibility of isolating previously unknown adducts due to the milder reaction conditions and, in some cases, the decrease in side reactions.

The Diels-Alder reaction plays a major role in the preparation of six-membered carbocycles. Although far less developed, Diels-Alder reactions of heterodienes are finding increasing use in heterocyclic synthesis.[1-4] 1-Azadienes are less studied than other heterodienes, due to several factors. In the first place, conformational (*s-cis* ⇌ *s-trans*)[5] and tautomeric (imine ⇌ enamine)[6] equilibria lower the concentration of the desired reactive species. Secondly, the pyridine derivatives obtained as reaction products are less stable than ordinary Diels-Alder adducts,[7] and thus the hetero Diels-Alder reaction is thermodynamically disfavoured.[8] Finally, 1-azadienes show poor reactivity, which, in the case of "normal" electron demand reactions,[9] can be assigned to the electron-withdrawing character of the nitrogen atom. In principle, this problem can be overcome by introduction of electron-releasing groups, and Ghosez[5,10] has shown that dimethylaminohydrazones of α,β-unsaturated aldehydes behave as 1-azadienes towards electron-defficient dienophiles.[11,12] However, the conditions required for many simple dienophiles are harsh, and involve heating at 100-120 °C for *ca.* 220 h, sometimes in a sealed tube and therefore their use may be impractical in many cases. The development of milder reaction conditions is desirable in order to broaden the scope of these powerful hetero Diels-Alder cycloadditions.

The effects of ultrasound on chemical reactions are usually ascribed to the phenomenon of cavitation, *i.e.*, the formation and subsequent collapse of small microbubbles inside the liquid phase, which is accompanied by the local generation of high temperatures and pressures of several kbar.[13] Since high pressures are known to enhance the rate of Diels-Alder reactions,[14] the same effect might in principle be achieved by sonication, with the advantage of a much more convenient experimental procedure. However, literature data on the sonochemistry of the Diels-Alder reaction are extremely scarce[15] and, to our knowledge, ultrasound has never been applied to an hetero Diels-Alder process. We report here the considerable improvements found upon sonication of Diels-Alder reactions between several 1-azadienes and dienophiles. The reactions were carried out using the neat dienes as solvents when this was possible and employing acetonitrile as solvent in other cases. The fact that these reactions were performed in solution makes them noteworthy, since the sonochemistry of homogeneous systems is relatively little studied in comparison with heterogeneous sonochemistry.[13]
Scheme 1 and Table 1 summarize the results obtained in the reaction between methacrolein dimethylhydrazone

(1)[16] and several α,β-unsaturated carbonyl compounds, showing that ultrasound irradiation allows to carry out the desired Diels-Alder reactions in good to excellent yields under very mild temperature conditions. Control experiments showed no progress when the same reactions were performed in the absence of ultrasound, proving that the improvements observed were not due to "macroscopic" heating. The formation of the *trans* tetrahydropyridine derivative (**5**) starting from either diethyl maleate or dimethyl fumarate was also observed by



Reagents: i. Methyl acrylate. ii. Methyl vinyl ketone. iii. Acrylonitrile. iv. Dimethyl fumarate. v. Dimethyl maleate. vi. Dimethyl acetylene dicarboxylate. vii. Air

Scheme 1

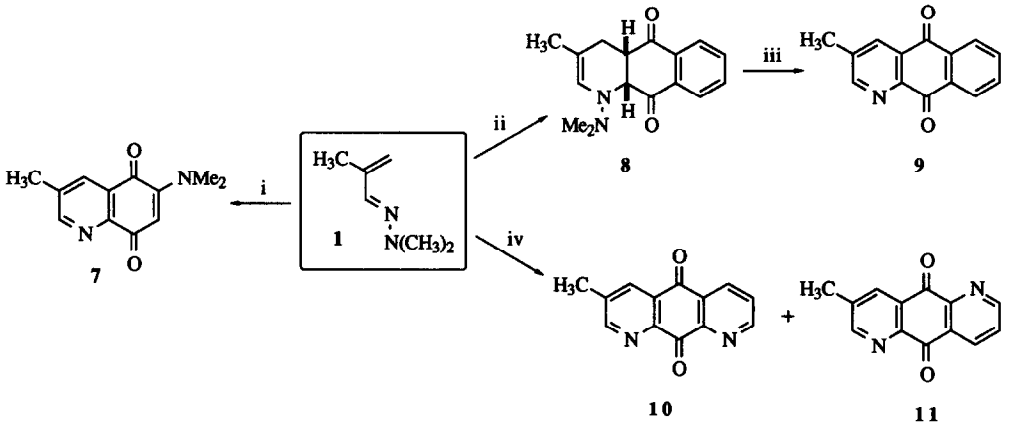
Product	Ultrasound		Heating[5,10]	
	Conditions	Yield[a], %	Conditions	Yield[a], %
2	Neat, 50 °C, 37 h	47 (87)	Benzene, 100 °C, 264 h	68
3	Neat, 50 °C, 50 h	35 (56)	Acetonitrile, 100 °C, 211 h (sealed tube)	70
4	Neat, 50 °C,	60 (98)	Benzene, 100 °C, 230 h (sealed tube)	53
5[b]	Neat, 50 °C, 16 h Neat, 50 °C, 49 h	55 (98) 99	Acetonitrile, 100 °C, 138 h	*c*
5[d]	Neat, 50 °C, 49 h	95	Acetonitrile, 100 °C, 166 h	*c*
6	1.- Neat, 50 °C, 50 h 2.- $CDCl_3$, reflux, 2 h	60	*c*	0

Notes: *a.*- Yields in brackets are based on unrecovered starting material. *b.*- From dimethyl fumarate. *c.*- Not described in the literature. *d.*- From dimethyl maleate.

Table 1

Ghosez[5,10] under thermal conditions. Some differences exist between the course of our sonicated reactions and those performed under no influence of ultrasound. Thus, this autor describes a complete absence of reaction between **1** and dimethyl acetylene dicarboxylate, which under our conditions gave compound **4** in 60% yield after Diels-Alder cycloaddition and air oxidation.

As regards the reactions between **1** and quinones (Scheme 2 and Table 2), the results obtained were also satisfactory. The products observed do not differ significantly from those obtained in the non-sonicated reactions. It is remarkable, however, that the mildness of the reaction conditions allowed the isolation in high



Reagents: i. Benzoquinone. ii. Naphthoquinone. iii. Air. iv. 5,8-Quinolinequinone

Scheme 2

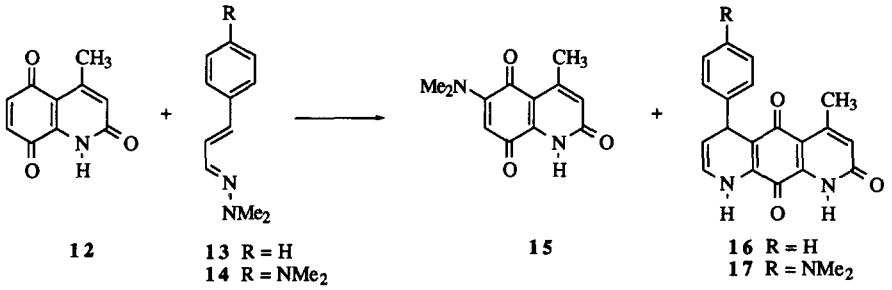
Product(s)	Ultrasound		Heating	
	Conditions	Yield[a], %	Conditions	Yield, %
7	Acetonitrile, 30 min, r.t.	50	*b*	44[16]
8	Acetonitrile, 30 min, r.t.	88 [94]	*c*	*c*
9	1.- Acetonitrile, 30 min, r.t. 2.- Air, 1 day, r.t.	92	Acetonitrile, 75 °C, 24 h	92[5,10]
10, 11	1.- Neat, 50 min, r.t. 2.- $CDCl_3$, air, 1 h, r.t.	67 (**10**) 33 (**11**)	1.- Benzene, r.t., 12 h 2.- EtOH, reflux, 2 h	74 (**10**)[17,d] 12 (**11**)[17]

Notes: *a*. Yields in square brackets are based on unrecovered starting material. *b*. Not described in the literature. *c*. This product could not be isolated under literature conditions. *d*. This reaction has been described to give **10** as the only product in 76 % yield (reference 16).

Table 2

yield of the unstable[17] Diels-Alder adduct **8**. A slight loss of regioselectivity is apparently observed in the reaction between **1** and 5,8-quinolinequinone, although it is difficult to establish a reliable comparison because conflicting reports exist on the regioselectivity of this reaction.[17,18]

Finally, and due to our current interest[19] in the synthesis of 1,8-diazaanthracene-2,9,10-triones as antitumour analogues of the antifolate antibiotic diazaquinomycin A,[20] we decided to study the influence of ultrasound on the reactions between 1-dimethylamino-1-azadienes and 4-methyl-2,5,8(1*H*)-quinolinetrione (**12**).[21] These reactions are usually very rapid unless the unreactive[22] 4-aryl-1-dimethylamino-1-azadienes are employed, and therefore we were interested in studying the influence of ultrasound in these cases. As shown on Scheme 3 and Table 3, sonication allows again to carry out the cycloaddition between **12** and dienes **13**, **14**[16,22] under much milder conditions and in dramatically shorter reaction times than under reflux. Another important advantage is the lower proportion of the undesired secondary product (**15**), arising from the liberation of dimethylamine from the initial Diels-Alder Adduct and its subsequent addition to the starting quinone.



12 **13** R = H, **14** R = NMe_2

Scheme 3

Ultrasound				Heating		
Diene	Conditions	Yield, %		Conditions	Yield, %	
		15	Adduct		**15**	Adduct
13	Neat, 10 min, r.t.	43	56 (**16**)	$CHCl_3$, 24 h, reflux	65	34 (**16**)
14	$CHCl_3$, 13 h, 50 °C	63	35 (**17**)	$CHCl_3$, 96 h, reflux	61	11 (**17**)

Table 3

In conclusion, we have shown that ultrasound increases the rate of Diels-Alder cycloadditions of 1-dimethylamino-1-azadienes. The main advantages of the use of sonication can be summarized as follows: a) Much lower reaction times and temperatures are required and the experimental protocol is simpler. b) Increased yields are obtained in many cases. c) The mildness of the conditions employed allows the preparation in high yield of unstable adducts (*e.g.*, the previously non-isolated compound **8**). d) Side reactions are sometimes

diminished, as in the reaction between 4-aryl-1-dimethylamino-1-azadienes **13** and **14** and 4-methyl-2,5,8(1*H*)-quinolinetrione.

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EXPERIMENTAL

Reactions under ultrasound irradiation were performed with a Branson 450 ultrasound probe, using the pulsed mode (pulse duration, 0.2 to 0.3 s), with output values between 30 and 40 Watt. Infrared spectra were recorded on Perkin-Elmer 577 and Buck Scientific 500 spectrophotometers, with all compounds compressed into KBr pellets. NMR spectra were obtained on Bruker AC-250 (250 MHz for ^{1}H, 63 MHz for ^{13}C) and Varian VXR-300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) spectrometers; $CDCl_3$, DMSO-d_6 and pyridine-d_5 were used as solvents, and TMS was added in all cases as an internal standard. ^{13}C-NMR spectra were assigned with the aid of DEPT experiments, when necessary. Elemental analyses of new compounds were determined by the Servicio de Microanálisis, Universidad Complutense, on a Perkin-Elmer 2400 CHN microanalyzer. Melting points were measured in open capillary tubes using a Büchi inmersion apparatus, and are uncorrected. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (Scharlau Cf 530) or by ^{1}H-NMR. Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230-400 mesh and Scharlau Ge 048). All reagents were of commercial quality (Aldrich, Fluka, Merck, SDS, Probus) and were used as received.

Diels-Alder Reactions of Methacrolein Dimethylhydrazone. General Procedure.

A solution of the suitable dienophile (0.3 to 2.9 mmol) in the minimum amount of methacrolein dimethylhydrazone (**1**) (0.9 to 10 equivalents), or (for the synthesis of compounds **8** and **9**) a solution of equimolecular amounts of the dienophile and compound (**1**) in the minimum amount of acetonitrile was irradiated with ultrasound for the times and at the temperatures indicated in tables 1 and 2. Excess diene was evaporated *in vacuo* and the residue, consisting of a mixture of the known[5,10,17] adducts and, in some cases, unreacted dienophile, was analyzed by ^{1}H-NMR to determine the yield. Spectral data for some of the compounds have not been previously reported and are given below.

Data for **2**. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 5.88 (s, 1H, H-6); 3.74 (s, 3H, CO_2CH_3); 3.65 (m, 1H, H-2); 2.43 (s, 6H, NMe_2); 2.16-1.93 and 1.89-1.74 (2 m, 4H, H-3,4); 1.62 (s, 3H, C_5-CH_3) ppm.

Data for **3**. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 5.89 (s, 1H, H-6); 3.43 (m, 1H, H-2); 2.41 (s, 6H, NMe_2); 2.19 (s, 3H, $COCH_3$); 2.14-1.89 and 1.84-1.69 (2 m, 4H, H-3,4); 1.62 (s, 3H, C_5-CH_3) ppm.

Data for **4**. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 5.81 (s, 1H, H-6); 4.03 (m, 1H, H-2); 2.49 (s, 6H, NMe_2); 2.18-1.94 (m, 4H, H-3,4); 1.61 (s, 3H, C_5-CH_3) ppm.

Data for **5**. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 5.89 (s, 1H, H-6); 3.85 (d, 1H, J = 8.8 Hz, H-2); 3.74 and 3.69 (2 s, 6H, 2 CO_2CH_3); 3.15 (m, 1H, H-3); 2.44 (s, 6H, NMe_2); 2.34 (m, 1H, H-4_{eq}); 2.07 (dd, 1H, J = 5.9 and 16.9 Hz, H-4_{ax}); 1.64 (s, 3H, C_5-CH_3) ppm.

Data for **6**. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.59 (d, 1H, J = 1.6 Hz, H-6); 7.93 (d, 1H, J = 1.4 Hz, H-4); 3.90 and 3.65 (2 s, 6H, 2 CO_2CH_3); 2.50 (s, 3H, C_5-CH_3) ppm.

Data for **7**. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.78 (s, 1H, H-2); 8.31 (s, 1H, H-4); 6.00 (s, 1H, H-7); 3.25 (s, 6H, NMe_2); 2.49 (s, 3H, C_2-CH3) ppm.

Data for **8**. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.04-7.99 and 7.94-7.89 (2 m, 4H, H-5,6,7,8); 5.86 (s, 1H, H-2); 4.11 (d, 1H, J = 2.0 Hz, H-9a); 3.36 (m, 1H, H-4a); 2.58 (d, 1H, J = 17.1 Hz, H-5_{eq}); 2.19 (s, 6H, NMe_2); 2.15 (dd, 1H, J = 5.8 Hz, H-5_{ax}; the other coupling was hidden by the dimethylamino resonance); 1.66 (s, 1H, C_3-CH_3) ppm.

Data for **9**. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.90 (s, 1H, H-2); 8.35 (s, 1H, H-4); 8.30-8.10 and 7.80-7.70 (2 m, 4H, H-5,6,7,8); 2.56 (s, 3H, C_3-CH_3) ppm.

Diels-Alder Reactions of 4-Aryl-1-dimethylamino-1-azadienes. General Procedure.

A solution of 4-methyl-2,5,8(1*H*)-quinolinetrione (**12**)[21] and the suitable azadiene (**13, 14**) in chloroform (*ca.* 30 ml per 100 mg of **12**) was refluxed in an oil bath (method A) or irradiated with ultrasound (method B) for the times and at the temperatures indicated in table 3. Evaporation of the solvent and column chromatography of the residue eluting with a gradient from net dichloromethane to 7:3 dichloromethane-ethyl acetate afforded a small amount of recovered starting diene, together with 6-dimethylamino-4-methyl-2,5,8(1*H*)-quinolinetrione (**15**)[18a] ,as a red solid, and the 5-aryl-1,8-diazaanthracenetriones (**16, 17**), as green solids.

4-Methyl-5-phenyl-5,8-dihydro-2,9,10(1*H*)-1,8-diazaanthracenetrione (16).

Starting from 127 mg (0.67 mmol) of quinone (**12**) and 234 mg (1.34 mmol) of azadiene (**13**), a yield of 101 mg (65 %) of quinone (**15**) and 72 mg (34 %) of compound (**16**) was obtained after reflux in chloroform for 24 h (method A). When a solution of 75 mg (0.0397 mmol) of quinone (**12**) in 2 g (11.49 mmol) of diene (**13**) was sonicated for 10 min at room temperature (method B), a yield of 40 mg (43 %) of (**15**) and 70 mg (56 %) of (**16**) was obtained. Melting point, 206 °C (dichloromethane-ethyl acetate). IR, ν_{max} (KBr): 3400 (NH), 1660, 1655, 1600 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, d_5-pyridine) δ: 10.40 (d, 1H, J = 4.0 Hz, H-8); 7.69 (dd, 2H, $J_{2',3'}$ = 8.0 Hz, $J_{2',4'}$ = 1.0 Hz, H-2', 6'); 7.41 (t, 2H, J = 8.0 Hz, H-3', 5'); 7.25 (tt, $J_{4',3'}$ = 7.8 Hz, $J_{4',2'}$ = 1.1 Hz, H-4'); 6.70 (m, 2H, H-3, H-7); 5.17 (m, 1H, H-6); 5.11 (d, 1H, J = 5.0 Hz, H-5); 2.46 (d, 3H, J = 1.0 Hz, C_4-CH_3) ppm. Found: C, 71.36; H, 8.41; N, 4.29. $C_{19}H_{14}N_2O_3$ requires C, 71.69; H, 8.80; N, 4.43.

5-(4-Dimethylaminophenyl)4-methyl-5,8-dihydro-2,9,10(1*H*)-1,8-diazaanthracenetrione (17).

Starting from 415 mg (2.2 mmol) of quinone (**12**) and 524 mg (2.4 mmol) of azadiene (**14**), a yield of 313 mg (61 %) of compound (**15**) and 80 mg (11%) of compound (**17**) was obtained after reflux in chloroform for 96 h (method A). Ultrasound irradiation (method B) of a chloroform solution of 150 mg (0.079 mmol) of quinone (**12**) and 189 mg (0.087 mmol) of azadiene (**14**) at 50 °C for 13 h afforded 116 mg (63 %) of compound (**15**) and 99 mg (35 %) of compound (**17**). Melting point: 252-256 °C (dichloromethane-ethyl acetate). IR (KBr): 3630-3100 (NH), 1650, 1640, 1635 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, d_5-pyridine): 10.24 (d, 1H, J = 3.0 Hz, H-8); 7.62 (d, 2H, J = 8.8 Hz, $C_{2'}$-H, $C_{6'}$-H); 6.85 (d, 2H, J = 8.8 Hz, H-3', 5'); 6.76 (m, H-7); 6.74 (s, 1H, H-3); 2.78 (s, 6H, $N(CH_3)_2$); 2.54 (s, 3H, C_4-CH_3) ppm.(The signal of H-6 was not

detected because it is included in the water signal). Found: C, 68.83; H, 5.47; N, 11.31. $C_{21}H_{19}N_3O_3$ requires C, 69.79; H, 5.29; N, 11.63.

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