Microwave-assisted addition of azomethines to isatoic anhydride

E DOMINIC JACOB,[a,*] LOPEZ MATHEW[b] and BABY THOMAS[c]

[a]Department of Chemistry, Research Centre, Nirmala College, Muvattupuzha 686 661
[b]Department of Chemistry, Union Christian College, Aluva 683 102
[c]Department of Chemistry, St. Dominics College, Kanjrapally 686 512
e-mail: ejdominic@rediffmail.com

Abstract. Diels–Alder addition of azomethines to isatoic anhydride in a solvent-free and eco-friendly condition is investigated using a microwave oven. The product is exclusively 2,3-diaryl-2,3-dihydroquinazolin-4(1H)-ones **4a–d**. HOMO–LUMO energy of the iminoketene and the dienophiles were calculated using semi-empirical AM1 calculations.

Keywords. Microwave-assisted additions; solvent-free reaction; synthesis; dihydroquinazolinones; AM1 calculations.

1. Introduction

Chemical reactions brought about by microwave irradiation gathered momentum in recent years.[1–8] The elegance of the reaction, high yield, short time span, simplified work-up procedure and eco-friendly conditions are the main advantages of the method. Although microwave reactions were begun in domestic microwave ovens, they are conducted in more sophisticated chemical microwave ovens now-a-days.[9] The existence of 'hot spots', inhomogeneity of the microwave field in the region to be heated the handicap in measuring the temperature of reaction, possibility of explosion, are some of the main defects of microwave oven reactions.[10] However, rotating the reaction platform that averages the field can decrease the inhomogeneity of the field. The temperature can be measured by taking out the sample at interval as required. The reproducibility of the result was also checked by repeating the experiment several times. We used the domestic version, as we are unable to use chemical ovens at present. Many quinazolinones, which are well known as choleretic and antidiabetic agents,[11] were prepared by treating anthranilic acid[12–15] with thionyl chloride in dry benzene.

2. Experimental section

Isatoic anhydride was purchased from Aldrich and used as received. Azomethines were prepared according to literature procedure, purified by column chromatography and recrystallised from methanol before application.[16] IR spectra were recorded on a Bomem MB Serier FT-IR spectrophotometer and absorbencies are reported in cm^{-1}. The NMR spectra were recorded in Bruker 300 MHz FT-NMR spectrometer on samples dissolved in $CDCl_3$ and chemical shifts are reported in δ(ppm) relative to Me_4Si as internal standard. Mass spectra were obtained by EIMS technique at 70 eV on an AutoSpec mass spectrometer. CHN analyses were carried out using Elementar Vario EL III. Melting points were recorded on Mel–Temp II Laboratory Devices, USA and are uncorrected. All reactions were monitored by thin layer chromatography (TLC); All TLC were carried out on Alugram SIL G/K plates. Visualization was effected with a UV lamp.

Microwave oven reactions were performed on a Kenstar domestic, multimode, without on and off mode, microwave oven, with rotating platform tray, with a power source of 230 V, 50 Hz, and microwave energy output 800 W, microwave input power 1200 W and microwave frequency 2450 MHz.

A mixture of isatoic anhydride **1** (593·3 mg, 3·64 mmol) and azomethine **3a–d** (3·64 mmol) were ground together in a mortar and transferred into a 50 mL beaker. The reaction mixture was then micro-

*For correspondence

wave-irradiated without solvent for 2 min at a temperature of 60°C. After cooling to room temperature, the reaction mixture was extracted with dichloromethane (20 mL), filtered to remove all unreacted and insoluble materials. The clear solution was concentrated and cooled. The 2,3-diaryl-2,3-dihydroquinazolin-4(1H)-ones **4a–d** recrystallised from 2 : 1 petroleum ether dichloromethane mixture. The structure of **4a–d** was confirmed based on spectral data.

The temperature of the reaction mixture at the time of reaction was measured by microwave irradiation of the same mass of reactants taken in a Borosil open test tube of 7·0 cm length, 0·9 cm diameter and 3·5 mL capacity. The test tube was kept in a 100 mL beaker and then microwave-irradiated for 2 min. The test tube was taken out, the temperature of the molten material was noted immediately with a thermometer and found to be 60°C.

Spectral data for **(4a)** *– 2,3-diphenyl-2,3-dihydroquinazolin-4(1H)-one:*
IR (KBr, cm^{-1}): 3299 (NH stretch), 1640 (C=O stretch), 1512, 1485, 1391, 1310, 1256, 1162, 1034, 872, 751, 703, 629, 548.
Anal. Calcd for $C_{20}H_{16}N_2O$: C, 80·00; H, 5·33; N, 9·33; O, 5·33%. Found: C, 80·02; H, 5·32; N, 9·35; O, 5·31%.

Spectral data for **(4b)** *– 3-(4-chlorophenyl)-2-phenyl-2,3-dihydroquinazolin-4(1H)-one:*
IR (KBr, cm^{-1}): 3305·51 (NH stretch), 1638·79 (C=O stretch), 1513, 1245·79, 1164·5, 1095·73, 1020·87, 833·591, 764·825, 702·399.

Anal. Calcd for $C_{20}H_{15}ClN_2O$: C, 71·85; H, 4·49; Cl, 10·48; N, 8·38; O, 4·79%. Found: C, 71·87; H, 4·48; Cl, 10·48; N, 8·39; O, 4·78%.

Spectral data for **(4c)** *– 3-(4-methylphenyl)-2-phenyl-2,3-dihydroquinazolin-4(1H)-one:*
IR (KBr, cm^{-1}): 3305·75 (NH stretch), 1638·79 (C=O stretch), 1507·84, 1395·42, 1314·22, 1251·79, 1152·00, 1020·87, 821·154, 758·728, 696·302.
Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80·25; H, 5·73; N, 8·92; O, 5·10%. Found: C, 80·27; H, 5·74; N, 8·90; O, 5·09%.

Spectral data for **(4d)** *– 3-(2-methoxyphenyl)-2-phenyl 2,3-dihydroquinazolin-4(1H)-one:*
IR (KBr, cm^{-1}): 3293 (NH stretch), 1635 (C=O stretch), 1510, 1483, 1398, 1312, 1272, 1166, 1034, 764, 711.
Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76·37; H, 5·45; N, 8·48; O, 9·7%. Found: C, 76·38; H, 5·44; N, 8·50; O, 9·68%.

3. Results and discussion

In the present studies we have found that in the absence of solvents and in time intervals of less than 3 min equimolar mixtures of isatoic anhydride[17–21] and azomethines react readily under microwave irradiation to give 2,3-diaryl-2,3-dihydroquinazolin-4(1H)-ones **4a–d**, as shown in scheme 1 with yields of 71 to 90%.

The 8π component of the unisolable heterodiene combines with the 2π component of heterodienophile
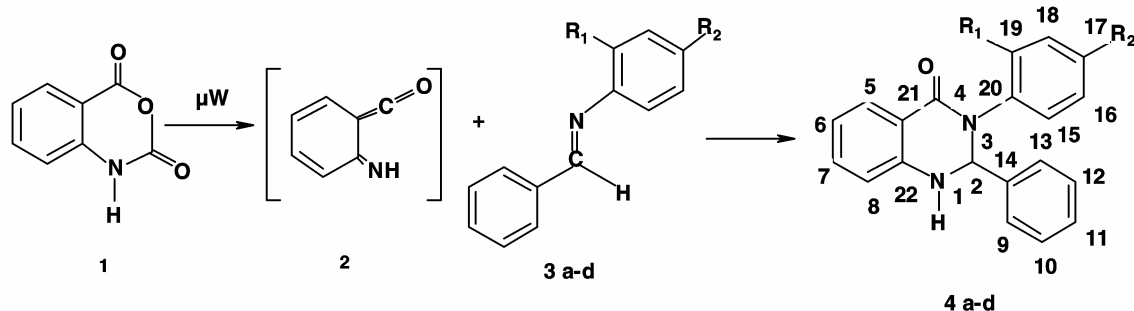
Compound	R	Yield of product **4a–d** (%)
3a, 4a	$R_1 = H$, $R_2 = H$	90
3b, 4b	$R_1 = H$, $R_2 = Cl$	90
3c, 4c	$R_1 = H$, $R_2 = CH_3$	90
3d, 4d	$R_1 = OCH_3$, $R_2 = H$	71

Scheme 1.

Table 1. Characterization data of compounds **4a–d**.

Compd. (colour)	m.p. (°C)	Yield (%)	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)	MS m/z (%)
4a (Cream)	210	90	7·99 (*d*, 1H, *J* = 8·2 Hz), 7·97 (*t*, 1H, *J* = 7·1 Hz), 7·33 (*d*, 1H, *J* = 8·3 Hz), 7·30–7·21 (*m*, 5H), 7·14–7·01 (*m*, 5H)), 6·86 (*t*, 1H, *J* = 7·0 Hz), 6·07 (*s*, 1H), 4·73 (*s*, broad, 1H, D$_2$O exchangeable)	163·0 (C4), 146·5 (C20), 136·2 (C22), 134·3 (C21), 132·8 (C14), 129·4 (C8), 129·2 (C5), 129·0 (C7), 128·9 (C6), 128·7 (C16, C18), 126·8 (C17), 126·2 (C15, C19), 119·4 (C10, C12), 116·9 (C9, C13), 116·7 (C11), 54·3 (C2)	300 (M^+, 18), 223 (50), 209 (15), 208 (100), 77 (20)
4b (Cream)	221	90	7·99 (*d*, 1H, *J* = 8·2 Hz), 7·97 (*t*, 1H, *J* = 7·1 Hz), 7·33 (*d*, 1H, *J* = 8·3 Hz), 7·25 (*d*, 2H, *J* = 8·0 Hz), 7 23 (*d*, 2H, *J* = 8 0 Hz), 7·14–7·01 (*m*, 5H), 6·87 (*t*, 1H, *J* = 7·0 Hz), 6·06 (*s*, 1H), 4·59 (*s*, broad, 1H, D$_2$O exchangeable)	164·5 (C4), 133·9 (C20), 130·3 (C22), 129·1 (C21) 129·0 (C14), 128·9 (C17), 128·7 (C8), 128·3 (C5), 128·1 (C7), 127·2 (C6), 126·7 (C16, C18), 119·7 (C15, C19), 114·7 (C10, C12), 113·6 (C9, C13), 113·5 (C11), 54·3 (C2)	334 (M^+, 12), 336 (4), 257 (34), 209 (48), 208 (100), 77 (12)
4c (Pale yellow)	188	90	8·00 (*d*, 1H, *J* = 8·2 Hz), 7·97 (*t*, 1H, *J* = 7·1 Hz), 7·33 (*d*, 1H, *J* = 8·3 Hz), 7·27 (*d*, 2H, *J* = 8·0 Hz), 7·14–7·01 (*m*, 5H), 6·86 (*t*, 1H, *J* = 7·0 Hz), 6·61 (*d*, 2H, *J* = 9·0 Hz), 6·04 (*s*, 1H), 4·63 (*s*, broad, 1H, D$_2$O exchangeable), 2·26 (*s*, 3H, CH$_3$)	163·0 (C4), 145·3 (C20), 140·1 (C22), 138·0 (C21), 136·4 (C14), 133·7 (C17), 129·5 (C8), 129·1 (C5), 128·9 (C7), 128·7 (C6), 126·9 (C16, C18), 126·8 (C15, C19), 119·5 (C10, C12), 116·9 (C9, C13), 114·7 (C11), 54·3 (C2), 21·1 (Me at C17)	314 (M^+, 15), 237 (30), 209 (15), 208 (100), 77 (20)
4d (Cream)	190	71	8·03 (*d*, 1H, *J* = 8·2 Hz), 8·00 (*t*, 1H, *J* = 7·2 Hz), 7·93 (*d*, 1H, *J* = 8·00 Hz), 7·90 (*d*, 1H, *J* = 8·3 Hz), 7·36 (*t*, 1H, *J* = 7·20 Hz), 7·30 (*t*, 1H, *J* = 7·2 Hz), 7·25–7·15 (*m*, 5H), 7·05 (*t*, 1H, *J* = 7·00 Hz), 6·78 (*d*, 1H, *J* = 8·00 Hz), 6·19 (*s*, 1H), 3·77 (*s*, 3H, CH$_3$), 4·58 (*s*, broad, 1H, D$_2$O exchangeable)	164·5 (C4), 146·5 (C20), 140·5 (C19), 134·4 (C22), 132·5 (C21), 129·7 (C14), 129·4 (C8), 129·2 (C5), 129·0 (C7), 128·2 (C6), 127·8 (C15), 123·6 (C17), 121·2 (C16), 120·5 (C18), 117·4 (C10, C12), 116·7 (C9, C13), 114·5 (C11), 57 (Me of MeO at C19), 55·7 (C2)	330 (M^+, 30), 253 (33.8), 209 (12.5), 208 (100), 77 (15)

to form heterocyclic system. The polar nature of the dienophile facilitates the reaction exclusively in a way that the negative site is connected to the ketene part of the diene and positive site to the imino part. It has been found that the yield of the product **4a–c** is almost constant irrespective of the various substituents on the azomethine part. Therefore, the effect of the substituent on the dienophile part is insignificant. A very interesting observation is that azomethine addition is completely regiospecific in which the nitrogen is oriented towards the ketene part.

The results are presented in table 1.

The HOMO-LUMO energies of **2** and **3a–d** have been calculated using the semiempirical AM1 theory. These values are tabulated in table 2. Inspection of the data given in table 2 reveals that the energy difference between the HOMO of diene and the LUMO of dienophile is smaller than that of the difference between the LUMO of the diene and the HOMO of the dienophile. Therefore it is concluded that the reaction between iminoketene and azomethine takes place *via* the interaction of HOMO of the former with the LUMO of the latter.

Electron-withdrawing chlorine lowers LUMO energy whereas electron-donating –CH$_3$ and –OCH$_3$ groups increase LUMO energy, the effect being more pronounced for the –OCH$_3$ group. However, the HOMO–LUMO energy difference is nearly constant lending support to the conclusion that substituents have only minimal effect on the reaction.

Table 2. HOMO and LUMO energies in hartrees.

Structure	HOMO	LUMO	HOMO(**2**)–LUMO (**3a–d**)	LUMO (**2**)–HOMO (**3a–d**)
2	–0·31039	–0·02545		
3a	–0·32700	–0·01844	0·29195	0·30155
3b	–0·32849	–0·02554	0·28485	0·30304
3c	–0·32109	–0·01817	0·2922	0·29564
3d	–0·31624	–0·01394	0·2965	0·34169

2 HOMO **3a** LUMO
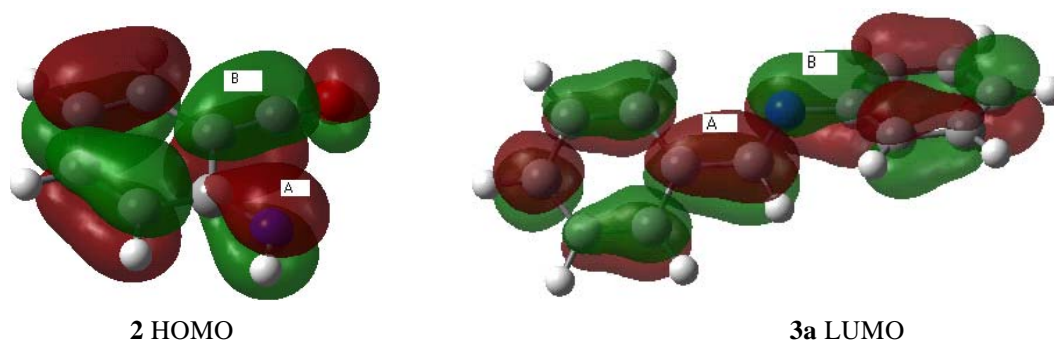
Figure 1. Lobes marked A and B on **2** interact with lobes marked A and B in **3a** respectively.

2 HOMO **3a** LUMO
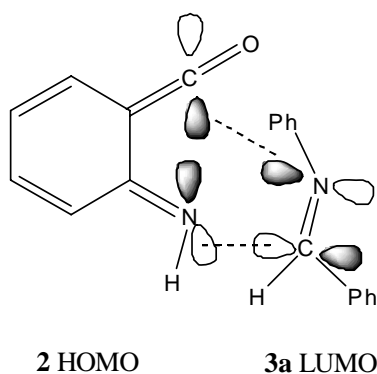
Figure 2. Only the relevant portions of orbitals are shown for clarity.

The HOMO of **2** and LUMO of **3a** are given in figure 1. A schematic sketch of the HOMO–LUMO interaction is given in figure 2. The orbital on the ketene carbon is in phase with the LUMO on the N of the dienophile, while the orbital on the imino part of the diene is in phase with the orbital on the carbon on the dienophile. Thus the reaction proceeds exclusively in the indicated direction.

4. Conclusion

The *in situ* generation of diene from isatoic anhydride followed by Diels–Alder addition of azomethines is a novel microwave-assisted reaction. It is an elegant method of synthesis in a short time duration, with good yield and maximum atom efficiency. The work up of the reaction mixture is also very simple. The compounds **4a–d** were unambiguously identified by clear spectral data and elemental analyses.

References

1. Bogdal D, Lukasiewicz M, Pielichowski J, Miciale A and Bednarz Sz 2003 *Tetrahedron* **59** 649
2. Leadbeater N E 2005 *J. Chem. Soc.*, *Chem. Commun.* 2881
3. Dominic E J and Lopez M 2004 *Curr. Sci.* **86** 1368
4. Bari S S, Bose A K, Chaudhary A G, Manhas M S, Raju V S and Robb E W 1992 *J. Chem. Educ.* **69** 938
5. Shui-Tein Chen, Shyh-Horng Chiou and Kung-Tsung Wang 1990 *J. Chem. Soc. Chem.*, *Commun.* 807

6. Gedye R N, Smith F E and Westaway K C 1988 *Can. J. Chem.* **66** 17

7. Gedye R N, Rank W and Westaway K C 1991 *Can. J. Chem.* **69** 706

8. Giguere R J, Bary T L and Duncan S M 1986 *Tetrahedron Lett.* **27** 4945

9. Brittany L H 2002 *Microwave synthesis*: *Chemistry at the speed of light* (New York: CEM Publishing)

10. Loupy A 2002 *Microwave in organic synthesis* (Weinheim: Wiley-VCH)

11. Koizumi M 1977 *Japan Kokai* 77,07,978 *Chem. Abst.* **87** 53366b

12. Kametani T, Loc C V, Higa T, Koizumi M, Ihara M and Fukumoto K 1977 *J. Am. Chem. Soc.* **99** 2306

13. Kametani T, Loc C V, Higa T, Koizumi M, Ihara M and Fukumoto K 1977 *J. Chem. Soc.*, *Perkin Trans I* **21** 2347

14. Kametani T, Higa T, Loc C V, Ihara M, Koizumi M and Fukumoto K 1976 *J. Am. Chem. Soc.* **98** 6186

15. Garin J, Merino P, Orduna J, Tejero T and Uriel S 1991 *Tetrahedron Lett.* **32** 3263

16. (a) Furniss B S, Hannaford A J, Rogers V, Smith P W G and Tatchell A R 1980 In *Vogel's textbook of practical organic chemistry* 4th edn (London: ELBS) p. 672; (b) Baliah V and Chandrasekharan V 1970 *Indian J. Chem.* **8** 1096; (c) Tanaka M and Kobayasha T 1985 *Synthesis* **10** 967; (d) Kiss P Aushas 1948 *Acta Phys. Chem.* **2** 8386

17. Crabtree H E, Smalley R K and Suschitzky H 1968 *J. Chem. Soc (C)* 2730

18. Rao V B and Ratnam C V 1979 *Indian J. Chem.* **B18** 409

19. Reddy C H K, Reddy P S N and Ratnam C V 1987 *Indian J. Chem.* **B26** 882

20. Steiger R P and Wagner E C 1953 *J. Org. Chem.* **18** 1427

21. Archer J A, Barker A J and Smalley R K 1973 *J. Chem. Soc.*, *Perkin Trans I* 1169