INTENSIFICATION OF A REACTION BY THE ADDITION OF A MINOR AMOUNT OF SOLVENT: DIELS–ALDER REACTION OF 2*H*-PYRAN-2-ONES WITH ALKYNES

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Diels–Alder transformation of substituted 3-benzoylamino-2*H*-pyran-2-ones **1** with a variety of alkynes **2** under microwave (MW) irradiation in a closed system can be intensified in a novel way by addition of a minor amount of butan-1-ol. When the reagents are not volatile under the used conditions, the reactions do not seem to be influenced by the addition of butan-1-ol, as demonstrated by the cycloaddition of a fused 2*H*-pyran-2-one **5** with *N*-ethylmaleimide (**6**) giving adduct **7**.

Keywords: Cycloadditions; Diels–Alder reactions; Alkynes; Microwaves; Green chemistry; Aniline derivatives; Benzenes; Pyranones.

Modern society demands that we move away from conventional chemical syntheses that heavily pollute or degrade the environment towards more sustainable processes that fall within the frame of green chemistry[1]. Recent developments have been focused on the use of methods and processes that use less toxic chemicals, produce smaller amounts of by-products and consume less energy[2]. For example, flammable and toxic organic solvents are substituted with more benign ones, but there is also great interest in conducting organic reactions without any solvents (solvent-free reactions). In addition, conventional forms of heating are often replaced by microwave heating[3].

In previous investigations of the Diels–Alder reactions of substituted 2*H*-pyran-2-ones and their fused derivatives[4], besides the reactions with alkenes[5a,5b] (maleic anhydride[5a] and *N*-substituted maleimides[5b]), we have already investigated the cycloadditions of alkynes under thermal and high-pressure conditions leading to a variety of multifunctionally substituted aniline and biphenyl derivatives[5c,5d]. The conditions employed were quite severe: high temperatures (e.g., reflux in tetralin[5c], b.p. 207 °C), long heat-

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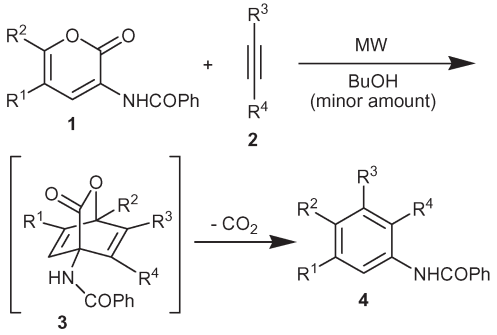
ing periods and excess of dienophiles were needed. Consequently, the yields of the products were lowered by isolation procedures. Therefore, we focused our investigation on keeping excess of alkynes as low as possible, on environmentally benign and simple procedures and on obtaining the highest possible yields.

The above requirements led us to the development of a novel, green approach to aniline, biphenyl and terphenyl derivatives **4a**–**4v** via the cycloadditions between differently substituted 3-benzoylamino-2*H*-pyran-2-ones **1a**–**1g**[5d,6] and various alkynes **2a**–**2f** (Scheme 1, Table I). We intended to carry out the reactions under microwave irradiation in aqueous environment or without using any solvent. Initially, we explored a test reaction between acetyl derivative **1a** and dimethyl acetylenedicarboxylate (**2a**) (cf. Table I, run 1) (molar ratio 1:1.2) in distilled water (1.5 ml/0.5 mmol of **1a**), which was previously shown to be a very efficient solvent in many transformations, including MW accelerated reactions[1,2f,7]. After irradiation of the reaction mixture in a closed vessel with microwaves in a focused-microwave reactor (CEM Discover) at 150 °C for 30 min (noncontact infrared sensor) the ^{1}H NMR analysis of the crude reaction mixture showed a very poor conversion to the corresponding product **4a** (ca. 5% conversion). We also detected some unreacted starting **1a** (5–10%), but the majority was unidentifiable decomposition products. The transformation of **1a** and phenylacetylene (**2d**) (Table I, run 4) (1:1.5) in aqueous suspension (1.5 ml



1a R^1 = COMe, R^2 = Me
1b R^1 = COPh, R^2 = Me
1c R^1 = CO_2Et, R^2 = Me
1d R^1 = CO_2Me, R^2 = CH_2CO_2Me
1e R^1 = H, R^2 = Me
1f R^1 = 4-$MeOC_6H_4$, R^2 = Me
1g R^1 = 3,4-$(MeO)_2C_6H_3$, R^2 = Me

2a R^3 = R^4 = CO_2Me
2b R^3 = R^4 = CO_2Et
2c R^3 = H, R^4 = CO_2Me
2d R^3 = H, R^4 = Ph
2e R^3 = H, R^4 = 4-MeC_6H_4
2f R^3 = H, R^4 = CO_2Et

SCHEME 1

of water/0.5 mmol of **1a**), irradiated at 170 °C for 1 h, revealed that nearly all starting **1a** reacted, but, in addition to the product **4d**, an appreciable amount of side and/or decomposition products was obtained. These results prompted us to explore the above reactions in the absence of any solvent[2b,3,8] as neat reactions, without any support or catalyst, by using the same equipment. A reaction mixture of **1a** and **2a** (1:1.2) was irradiated with microwaves at 150 °C for 90 min, and the estimated conversion deter-

TABLE I
Reaction times, temperatures and yields of products **4**

Run	Pyranone **1**	Alkyne **2**	*t*, h	Molar ration **1**:**2**	Product	Yield, %
1	**1a**	**2a**	3[a] (3)[b]	1:2.0[a] (1:5.0)[b]	**4a**	93[a] (90)[b]
2	**1a**	**2b**	1.5[a] (2.75)[b]	1:2.0[a] (1:2.5)[b]	**4b**[5c]	95[a,c] (93)[b,c]
3	**1a**	**2c**	1.5[a]	1:1.5	**4c**	88
4	**1a**	**2d**	0.17[a] (1.5)[b]	1:1.5[a] (1:2.0)[b]	**4d**[5c]	91[a,c] (91)[b,c]
5	**1a**	**2e**	0.33[a]	1:1.5	**4e**	87[c]
6	**1b**	**2a**	1.5[a]	1:2.5	**4f**	85
7	**1b**	**2c**	1.75[a]	1:1.5	**4g**	82
8	**1b**	**2d**	0.5[a]	1:1.5	**4h**[5c]	92[c]
9	**1b**	**2e**	1[a]	1:1.5	**4i**	92[c]
10	**1c**	**2a**	1.5[a]	1:2.5	**4j**	85
11	**1c**	**2b**	2[a] (3)[b]	1:2.0[a] (1:2.0)[b]	**4k**[5c]	90[a] (92)[b,c]
12	**1c**	**2c**	3[a]	1:2.0	**4l**	86
13	**1c**	**2d**	1.5[a]	1:1.5	**4m**[5c]	96[c]
14	**1d**	**2a**	2[a]	1:2.5	**4n**	80
15	**1d**	**2b**	3.5[a]	1:2.0	**4o**[5c]	92
16	**1d**	**2c**	3[a]	1:2.0	**4p**	93[c]
17	**1d**	**2f**	3[a]	1:2.0	**4q**	87[c]
18	**1e**	**2f**	2.5[a]	1:2.0	**4r**	86[c]
19	**1e**	**2d**	2.5[a]	1:2.0	**4s**	91[c]
20	**1f**	**2d**	2.5[d]	1:2.0	**4t**[5d]	89
21	**1f**	**2e**	2.5[d]	1:2.0	**4u**	89[c]
22	**1g**	**2e**	2.5[d]	1:2.0	**4v**	92[c]

[a] MW irradiation at 170 °C (with BuOH). [b] In an oil bath at 170–175 °C (without BuOH). [c] Conversion 100% (in all other cases ≥97%). [d] MW irradiation at 140 °C (with BuOH).

mined for the crude reaction mixture was around 60%. As we increased the reaction time to 3 h, no proportional increase in the conversion was observed (ca. 65%). To improve the yield we decided to increase the excess of dienophile **2a**. Indeed, with a 1:2 molar ratio the conversion after 90 min at 150 °C was already around 90%, and with a 1:4 molar ratio the reaction was completed in 90 min. On this basis one might erroneously conclude that the reaction could be driven to completion only with a large excess of alkyne **2a**.

During the above studies we noticed that after the reactions small droplets of condensed liquid (starting **2a**) appeared in the upper half of the reaction ampoule (where the surface was cooler during the reaction). Hence, a part of **2a** was not in contact with the substrate **1** during the reaction, and this might explain why the reaction without a large excess of the alkyne did not proceed to completion, and also why an increase in the reaction time did not bring the corresponding increase in the conversion. To avoid this problem we have decided to add a minimal amount of a liquid with appropriate boiling point, which could vaporise and hence prevent (at least partially) the deposition of alkynes in the upper part of the ampoule. Additionally, the liquid might also produce better contact between the reactants.

After some preliminary experiments we added 100 mg (1.35 mmol) of butan-1-ol (b.p. 116–118 °C) to our test reaction mixture (0.5 mmol of **1a** and 1.25 mmol of **2a**, molar ratio 1:2.5). Indeed, after 90 min of irradiation at 170 °C more than 99% of the starting **1a** reacted giving **4a** and no side product was detected. The same reaction without the addition of butan-1-ol, under otherwise identical conditions, resulted in the conversion of only around 87%. On the other hand, the reaction of **1a** and **2a** (1:2.5) carried out with butan-1-ol as a solvent (1.5 ml/0.5 mmol of **1a**) at 170 °C was found to be very inefficient (with only a 40% conversion after 90 min). Scaling-up the reaction of **1a** and **2a** to a 2-mmol scale, we examined two different possibilities: first we added the same weight of butan-1-ol (100 mg) as when working with 0.5 mmol of starting **1**, and in the next run we added 4 times more butan-1-ol than before (400 mg). Interestingly, after 90 min of microwave irradiation at 170 °C the conversion in the first case was nearly 100%, whereas in the second case some **1a** (ca. 5%) still remained unreacted. It seems that for each vessel a certain amount of the solvent is optimal. To compare the above conditions with conventional heating in an open vessel, we performed the test reaction of **1a** and **2a** (1:2.5) in a small glass tube equipped with a water condenser immersed in an oil bath at 170–175 °C. After 90 min heating, the conversion was

slightly below 90%, regardless of the addition of butan-1-ol. However, the conversions can exceed 97% with a considerable increase in the reaction time and an increased excess of alkynes. For example, for the reaction of **1a** and **2b** (1:2.5) under the same conditions as above (oil bath, 170–175 °C), we obtained a total conversion (without BuOH) after 2.75 h of heating (Table I, run 2). The results for the reaction of **1a** and **2d** (1:1.5) under the same conditions as above (oil bath, 170–175 °C) were similar: after 45 min of heating the conversion was around 90% (with or without BuOH), whereas an increase of excess of alkyne **2d** (to molar ratio 1:2.0) and an increase of reaction time (to 90 min) was necessary for the reaction to complete (Table I, run 4).

We employed the above method for the synthesis of various cycloadducts **4a**–**4v** starting from substituted 2*H*-pyran-2-ones **1** and alkynes **2**. We optimised the reaction conditions so that all these reactions had conversions of more than 97%, and many of them led to a 100% conversion; no side products were detected in any reaction. The products can be isolated by different procedures; we isolated them simply by adding a small amount of ethanol (or an ethanol–water mixture) to the crude reaction mixtures followed by filtration and washing the products with a small amount of ethanol to obtain 80–96% yields of the pure compounds. The syntheses studied here represent a significant improvement in comparison with the conventional thermal conditions. For example, the reaction producing **4t** (Table I, run 20) under 2.5 h microwave irradiation at 140 °C resulted in 98% conversion, whereas 15.5 h reflux in xylenes (b.p. ~ 140 °C) was required for the reaction completion; the isolated yield was 75% and the conversion after 90 min of heating was only about 13% [5d]. The conventional synthesis of **4p** (cf. Table I, run 16) required 18-h reflux in tetralin (the conversion after 90 min heating was less than 10%); the synthesis of **4r** (cf. Table I, run 18) required 31.5 h reflux in tetralin and the product could be isolated using column chromatography of the dark reaction mixture giving only 32% yield. All these data clearly reveal that the reactions under microwave irradiation generally require significantly lower reaction temperatures and/or shorter reaction times to give the corresponding products **4** in higher (or comparable) yields.

To additionally verify the necessity of adding butan-1-ol we decided to perform some of the above reactions in the absence of butan-1-ol. The data from Table II illustrate a significant intensification of the reaction in the presence of butan-1-ol. For example, the reaction of **1a** and **2c** yielding **4c** (run 2) at 170 °C under microwave irradiation, with addition of butan-1-ol,

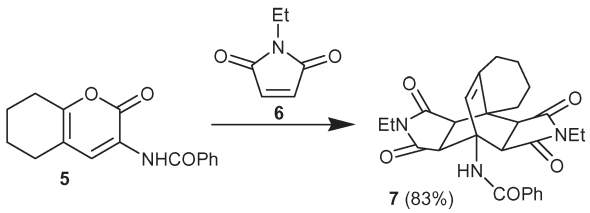
was nearly complete after 1 h (94% conversion), whereas the conversion without the alcohol was only 72%.

TABLE II
Comparison of the reactions producing **4** with and without the addition of butan-1-ol

Run	Pyranone **1**	Alkyne **2**	*t*, h	Molar ration **1**:**2**	Product	Conversion, %[a]	
						with BuOH	without BuOH
1	**1a**	**2a**	1.5[b]	1:2.5	**4a**	97	87
2	**1a**	**2c**	1[b]	1:1.5	**4c**	94	72
3	**1a**	**2e**	0.33[b]	1:1.5	**4e**	100	95
4	**1b**	**2c**	1.5[b]	1:1.5	**4g**	88	77
5	**1f**	**2d**	2.5[c]	1:2.0	**4t**	98	87

[a] From ^{1}H NMR spectra of the crude reaction mixtures. [b] At 170 °C. [c] At 140 °C.

In order to manifest the scope and limitation of the method, we decided to investigate the transformation between a fused pyran-2-one **5** and *N*-ethylmaleimide (**6**) (Scheme 2). The reaction in the presence or in the absence of butan-1-ol was complete (with 99% conversion of starting **5**) after 45 min microwave irradiation at 90 °C producing bicyclo[2.2.2]octene derivative **7**, which was isolated in 83% yield. After shorter reaction time (30 min) the conversion was also nearly the same (ca. 95%) in both cases. The logical explanation why butan-1-ol did not bring any improvement of the reaction progress might be that **6** were not enough volatile (m.p. 43–46 °C) under the used conditions (90 °C). Nevertheless, the microwave reaction represents a great improvement in comparison with the thermal reaction, where after 8.75 h reflux in decalin (using 10 mole % excess of **6**) product **7** was isolated in 56% yield[5b].



SCHEME 2
Conditions: 0.5 mmol of **5** and 1.04 mmol of **6**; MW, 45 min, 90 °C; 99% conversion, with or without butan-1-ol

It is also important to mention that comparable amounts of some other solvents tested in the synthesis of **4a** (ethanol, toluene, water, ionic liquid methylpyridinium tetrafluoroborate) were less efficient than butan-1-ol; water even caused preferential formation of decomposition products.

We have presented a new and efficient method of the intensification of Diels–Alder reaction, including the addition of a small amount of butan-1-ol, which diminished the required quantity of a volatile reactant and/or accelerated the reaction progress. The method seems to be especially useful for the closed systems used in modern MW equipments. It was applied for the preparation of different, highly substituted aniline, biphenyl and terphenyl derivatives.

EXPERIMENTAL

Melting points were determined on a Kofler hot microstage, and are uncorrected. ^{1}H NMR spectra (δ, ppm) were recorded with a Bruker Avance DPX 300 spectrometer at 29 °C (unless otherwise stated) at 300 MHz using TMS as an internal standard. ^{13}C NMR spectra were recorded on the same instrument at 75 MHz and are referenced to the central line of the solvent signal (DMSO-d_6 septet at δ 39.5 ppm and $CDCl_3$ triplet at δ 77.0 ppm). The coupling constants (*J*) are given in Hz. Deuteriochloroform was used as the solvent except for compounds **4a** and **4f** which were measured in DMSO-d_6. IR spectra were obtained with a Bio-Rad FTS 3000MX (KBr pellets), absorption maxima are given in cm^{-1}. Mass spectra were recorded with a VG-Analytical AutoSpec Q instrument. Elemental analyses (C, H, N) were performed with a Perkin–Elmer 2400 Series II CHNS/O Analyzer. TLC was carried out on Fluka silica gel TLC plates. The starting compounds **1** were prepared according to the published procedures[5d,6]; all other reagents and solvents were used as received from commercial suppliers.

Microwave reactions were conducted in air using a focused microwave unit (Discover by CEM Corporation, Matthews NC). The machine consists of a continuous, focused microwave power delivery system with an operator-selectable power output from 0 to 300 W. Reactions were performed in glass vessels (capacity 10 ml) sealed with a septum. The pressure was controlled with a load cell connected to the vessel via septum. The temperature of the vessel contents was monitored using a calibrated infrared temperature control mounted under the reaction vessel. The mixtures were stirred with a Teflon-coated magnetic stir bar in the vessel. Temperature, pressure and power profiles were recorded using commercially available software provided by the manufacturer of the microwave unit.

Syntheses of Products **4** (and **7**). General Procedure

A. Microwave conditions. A mixture of the starting 2*H*-pyran-2-one **1** or **5** (0.5 mmol), alkyne **2** (0.75–1.25 mmol) or *N*-ethylmaleimide (**6**; 130 mg, 1.04 mmol) and butan-1-ol (100 mg, 1.35 mmol) or alternatively without butan-1-ol was irradiated in the microwave equipment for the time specified (Tables I and II; Scheme 2). The final temperature was set to 170 °C for **4a**–**4s** or 140 °C for **4t**–**4v** or 90 °C for **7**; the power to 150 W or 80 W for **7**, and the ramp time to 5 min. For typical temperature, pressure and power profiles, see Fig. 1.

The reaction mixture was cooled, the oily residue was treated with ethanol or a mixture of ethanol–H_2O 1:1 (0.50–0.75 ml), the precipitated material was filtered off and washed with ethanol (0.5–1 ml).

B. Conventional thermal conditions. A mixture of the starting 2*H*-pyran-2-one **1** (0.5 mmol), alkyne **2** (0.75–1 mmol) and butan-1-ol (100 mg, 1.35 mmol) or alternatively without butan-1-ol, placed in a small glass tube fitted with reflux condenser, was immersed in an oil bath at 170–175 °C and heated for the specified time. The reaction mixture was cooled and the oily residue was analysed by ^{1}H NMR spectroscopy. For the isolation of products, the reaction mixture was treated as above.

Dimethyl 4-acetyl-6-(benzoylamino)-3-methylphthalate (**4a**). M.p. 149–150 °C (ethanol). For $C_{20}H_{19}NO_6$ (369.4) calculated: 65.03% C, 5.18% H, 3.79% N; found: 65.16% C, 5.25% H, 3.56% N. IR: 1740, 1688 br, 1602, 1583, 1524. ^{1}H NMR: 2.27 s, 3 H (Me); 2.59 s, 3 H (Me); 3.72 s, 3 H (CO_2CH_3); 3.83 s, 3 H (CO_2CH_3); 7.52–7.66 m, 3 H (Ph); 7.91–7.98 m, 2 H (Ph); 8.03–8.09 m, 1 H (5-H); 10.57 s, 1 H (NH). ^{13}C NMR (49 °C): 16.1, 30.0, 52.36, 52.43, 124.67, 124.71, 127.3, 128.4, 128.7, 131.8, 133.7, 134.8, 135.7, 142.5, 165.3, 165.4, 167.6, 201.5. FAB MS, *m/z* (rel.%): 370 (31) [MH^+], 105 (100).

Diethyl 4-acetyl-6-(benzoylamino)-3-methylphthalate (**4b**). M.p. 97–99 °C (diethyl ether). M.p. 97–99 °C (diethyl ether)[5c].

Methyl 4-acetyl-2-(benzoylamino)-5-methylbenzoate (**4c**). M.p. 108–111 °C (ethanol). For $C_{18}H_{17}NO_4$ (311.3) calculated: 69.44% C, 5.50% H, 4.50% N; found: 69.51% C, 5.64% H, 4.38% N. IR: 1690, 1679, 1587, 1523. ^{1}H NMR: 2.49 s, 3 H (Me); 2.67 s, 3 H (COMe); 4.00 s, 3 H (CO_2CH_3); 7.48–7.62 m, 3 H (Ph); 7.95 s, 1 H (6-H); 7.98–8.12 m, 2 H (Ph); 9.36 s, 1 H (3-H); 11.93 s, 1 H (NH). ^{13}C NMR: 20.4, 29.6, 52.6, 116.7, 120.7, 127.2, 128.8, 131.5, 132.0, 133.8, 134.4, 139.6, 142.4, 165.6, 168.3, 201.5. EI MS, *m/z* (rel.%): 311 (21) [M^+], 105 (100).

N-(4-Acetyl-5-methylbiphenyl-2-yl)benzamide (**4d**). M.p. 193–195 °C (ethanol). M.p. 193–195 °C (ethanol)[5c].

N-(4-Acetyl-4′,5-dimethylbiphenyl-2-yl)benzamide (**4e**). M.p. 164.5–166 °C (ethanol). For $C_{23}H_{21}NO_2$ (343.4) calculated: 80.44% C, 6.16% H, 4.08% N; found: 80.59% C, 6.35% H, 4.02% N. IR: 3360, 1685, 1648, 1499, 1474. ^{1}H NMR: 2.44 s, 3 H (Me); 2.55 s, 3 H (Me); 2.69 s, 3 H (Me); 7.17 s, 1 H (6-H); 7.31–7.36 m, 4 H; 7.38–7.46 m, 2 H; 7.47–7.55 m, 1 H;

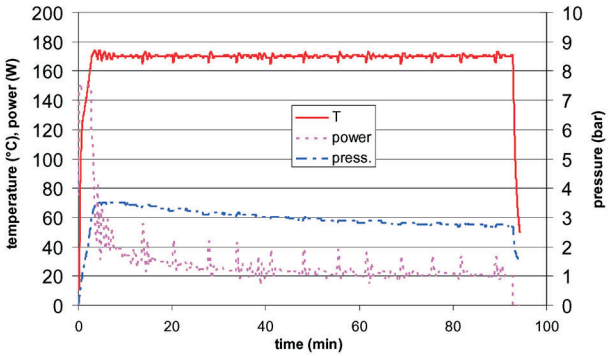


FIG. 1
Typical temperature (——), power (· · · ·) and pressure (– · – ·) profiles in the microwave-irradiated synthesis of **4b**

7.61–7.68 m, 2 H (Ph, C_6H_4); 8.06 s, 1 H (NH); 9.03 s, 1 H (3-H). ^{13}C NMR: 21.0, 21.2, 29.4, 122.5, 126.7, 128.7, 128.8, 129.9, 131.8, 132.7, 133.5, 134.0, 134.4, 134.5, 135.3, 136.5, 138.5, 165.1, 201.1. EI MS, *m/z* (rel.%): 343 (74) [M^+], 105 (100).

Dimethyl 4-benzoyl-6-(benzoylamino)-3-methylphthalate (**4f**). M.p. 160–161 °C (ethanol). HR MS for $C_{25}H_{21}NO_6$ calculated: 431.1368, found: 431.1376. For $C_{25}H_{21}NO_6$ (431.4) calculated: 69.60% C, 4.91% H, 3.25% N; found: 69.27% C, 5.04% H, 2.87% N. IR: 1711, 1694, 1682, 1669, 1599, 1580. ^{1}H NMR: 2.12 s, 3 H (Me); 3.76 s, 3 H (CO_2CH_3); 3.86 s, 3 H (CO_2CH_3); 7.50–7.64 m, 5 H; 7.71–7.84 m, 4 H; 7.88–7.95 m, 2 H (2 × Ph, 5-H); 10.60 s, 1 H (NH). ^{13}C NMR (59 °C): 15.8, 52.3, 52.4, 123.56, 123.62, 127.2, 128.1, 128.3, 128.9, 129.4, 131.8, 133.7, 134.0, 134.8, 135.4, 135.7, 142.4, 165.3, 165.5, 167.4, 195.8. EI MS, *m/z* (rel.%): 431 (23) [M^+], 105 (100).

Methyl 4-benzoyl-2-(benzoylamino)-5-methylbenzoate (**4g**). M.p. 150.5–153.5 °C (methanol). For $C_{23}H_{19}NO_4$ (373.4) calculated: 73.98% C, 5.13% H, 3.75% N; found: 74.08% C, 5.28% H, 3.64% N. IR: 1693, 1672, 1584, 1518. ^{1}H NMR: 2.29 s, 3 H (Me); 4.01 s, 3 H (CO_2CH_3); 7.43–7.64 m, 6 H (2 × Ph); 7.83–7.90 m, 2 H (Ph); 7.97–8.05 m, 3 H (Ph, 6-H); 8.93 s, 1 H (3-H); 11.96 s, 1 H (NH). ^{13}C NMR: 19.0, 52.6, 116.0, 119.5, 127.3, 128.7, 128.8, 130.0, 130.2, 132.0, 132.9, 133.7, 134.6, 136.5, 139.3, 144.7, 165.5, 168.6, 197.2. EI MS, *m/z* (rel.%): 373 (29) [M^+], 105 (100).

N-(4-Benzoyl-5-methylbiphenyl-2-yl)benzamide (**4h**). M.p. 193.5–195.0 °C (methanol–*N*,*N*-dimethylformamide). M.p. 193.5–195.0 °C (methanol–*N*,*N*-dimethylformamide)[5c].

N-(4-Benzoyl-4′,5-dimethylbiphenyl-2-yl)benzamide (**4i**). M.p. 154.5–155 °C (ethanol). For $C_{28}H_{23}NO_2$ (405.5) calculated: 82.94% C, 5.72% H, 3.45% N; found: 83.14% C, 5.80% H, 3.43% N. IR: 3289, 1669, 1648, 1578, 1522. ^{1}H NMR: 2.36 s, 3 H (Me); 2.44 s, 3 H (Me); 7.22 s, 1 H (6-H); 7.30–7.42 m, 6 H; 7.43–7.53 m, 3 H; 7.55–7.63 m, 3 H; 7.89–7.98 m, 2 H (2 × Ph, C_6H_4); 8.02 s, 1 H (NH); 8.51 s, 1 H (3-H). ^{13}C NMR: 19.3, 21.2, 121.6, 126.7, 128.4, 128.6, 128.9, 129.9, 130.2, 131.7, 132.2, 132.6, 132.7, 133.2, 134.2, 134.3, 134.5, 137.3, 138.1, 138.3, 164.9, 197.7. EI MS, *m/z* (rel.%): 405 (53) [M^+], 105 (100).

4-Ethyl 1,2-dimethyl 6-(benzoylamino)-3-methylbenzene-1,2,4-tricarboxylate (**4j**). M.p. 115–118 °C (methanol). For $C_{21}H_{21}NO_7$ (399.4) calculated: 63.15% C, 5.30% H, 3.51% N; found: 63.16% C, 5.44% H, 3.27% N. IR: 1744, 1721, 1702, 1678, 1582, 1527. ^{1}H NMR: 1.42 t, 3 H, *J* = 7.2 ($CO_2CH_2C\mathbf{H}_3$); 2.44 s, 3 H (Me); 3.92 s, 3 H (CO_2Me); 3.93 s, 3 H (CO_2Me); 4.41 q, 2 H, *J* = 7.2 ($CO_2C\mathbf{H}_2CH_3$); 7.48–7.65 m, 3 H (Ph); 7.96–8.02 m, 2 H (Ph); 9.24 s, 1 H (5-H); 11.23 s, 1 H (NH). ^{13}C NMR: 14.2, 16.9, 52.5, 53.2, 61.7, 116.6, 123.1, 127.3, 128.9, 130.1, 132.2, 134.3, 136.8, 137.0, 138.2, 165.5, 166.7, 167.4, 168.8. EI MS, *m/z* (rel.%): 399 (17) [M^+], 105 (100).

Triethyl 6-(benzoylamino)-3-methylbenzene-1,2,4-tricarboxylate (**4k**). M.p. 71–73 °C (diethyl ether–light petroleum). M.p. 71–73 °C (diethyl ether–light petroleum)[5c].

4-Ethyl 1-methyl 2-(benzoylamino)-5-methylterephthalate (**4l**). M.p. 127.0–130.5 °C (methanol). For $C_{19}H_{19}NO_5$ (341.4) calculated: 66.85% C, 5.61% H, 4.10% N; found: 66.85% C, 5.78% H, 3.91% N. IR: 1721, 1699, 1678, 1586, 1530. ^{1}H NMR: 1.43 t, 3 H, *J* = 7.2 ($CO_2CH_2C\mathbf{H}_3$); 2.56 s, 3 H (Me); 3.98 s, 3 H (CO_2Me); 4.40 q, 2 H, *J* = 7.2 ($CO_2C\mathbf{H}_2CH_3$); 7.43–7.63 m, 3 H (Ph); 7.94 s, 1 H (6-H); 7.98–8.15 m, 2 H (Ph); 9.39 s, 1 H (3-H); 11.84 s, 1 H (NH). ^{13}C NMR: 14.2, 20.6, 52.6, 61.3, 117.2, 121.9, 127.3, 128.8, 131.9, 133.1, 133.4, 134.6, 135.7, 139.3, 165.4, 166.8, 168.3. EI MS, *m/z* (rel.%): 341 (40) [M^+], 105 (100).

Ethyl 2-(benzoylamino)-5-methylbiphenyl-4-carboxylate (**4m**). M.p. 146–148 °C (ethanol). M.p. 146–148 °C (ethanol)[5c].

Trimethyl 6-(benzoylamino)-3-[(methoxycarbonyl)methyl]benzene-1,2,4-tricarboxylate (**4n**). M.p. 143.5–145.8 °C (methanol). For $C_{22}H_{21}NO_9$ (443.4) calculated: 59.59% C, 4.77% H, 3.16% N; found: 59.49% C, 4.80% H, 3.08% N. IR: 1739, 1720, 1703, 1685, 1583, 1526. ^{1}H NMR: 3.69 s, 3 H; 3.90 s, 3 H; 3.929 s, 3 H; 3.934 s, 3 H (4 × Me); 4.06 s, 2 H (CH_2); 7.49–7.64 m, 3 H (Ph); 7.95–8.03 m, 2 H (Ph); 9.46 s, 1 H (5-H); 11.17 s, 1 H (NH). ^{13}C NMR: 35.6, 52.1, 52.7, 52.8, 53.3, 117.9, 124.3, 127.3, 127.6, 128.9, 132.4, 134.1, 135.4, 137.2, 139.3, 165.5, 166.5, 167.3, 168.2, 170.8. EI MS, *m/z* (rel.%): 443 (10) [M^+], 105 (100).

1,2-Diethyl 4-methyl 6-(benzoylamino)-3-[(methoxycarbonyl)methyl]benzene-1,2,4-tricarboxylate (**4o**). M.p. 113.1–114.6 °C (methanol–water). M.p. 113.1–114.6 °C (methanol–water)[5c].

Dimethyl 2-(benzoylamino)-5-[(methoxycarbonyl)methyl]terephthalate (**4p**). M.p. 158–160 °C (ethanol). For $C_{20}H_{19}NO_7$ (385.4) calculated: 62.33% C, 4.97% H, 3.63% N; found: 62.38% C, 5.08% H, 3.55% N. IR: 1739, 1724, 1696, 1678, 1589, 1526. ^{1}H NMR: 3.71 s, 3 H; 3.93 s, 3 H; 3.99 s, 3 H (3 × CO_2Me); 4.01 s, 2 H (CH_2); 7.48–7.63 m, 3 H (Ph); 7.99 s, 1 H (6-H); 8.02–8.10 m, 2 H (Ph); 9.56 s, 1 H (3-H); 11.93 s, 1 H (NH). ^{13}C NMR: 39.6, 52.0, 52.5, 52.8, 117.6, 122.8, 127.4, 128.9, 129.5, 132.2, 134.3, 134.5, 135.1, 140.9, 165.6, 166.8, 168.2, 171.7. EI MS, *m/z* (rel.%): 385 (16) [M^+], 353 (44), 105 (100).

1-Ethyl 4-methyl 2-(benzoylamino)-5-[(methoxycarbonyl)methyl]terephthalate (**4q**). M.p. 156–158 °C (methanol). For $C_{21}H_{21}NO_7$ (399.4) calculated: 63.15% C, 5.30% H, 3.51% N; found: 63.39% C, 5.29% H, 3.38% N. IR: 1738, 1722, 1677, 1590, 1528. ^{1}H NMR: 1.45 t, 3 H, J = 7.1 ($CO_2CH_2C\mathbf{H}_3$); 3.71 s, 3 H (CO_2Me); 3.92 s, 3 H (CO_2Me); 4.02 s, 2 H (CH_2); 4.45 q, 2 H, J = 7.1 ($CO_2C\mathbf{H}_2CH_3$); 7.49–7.62 m, 3 H (Ph); 7.98 s, 1 H (6-H); 8.02–8.09 m, 2 H (Ph); 9.56 s, 1 H (3-H); 11.99 s, 1 H (NH). ^{13}C NMR: 14.1, 39.6, 52.0, 52.5, 62.0, 117.9, 122.7, 127.3, 128.8, 129.5, 132.1, 134.2, 134.4, 134.9, 140.8, 165.6, 166.7, 167.7, 171.7. EI MS, *m/z* (rel.%): 399 (20) [M^+], 105 (100).

Ethyl 2-(benzoylamino)-5-methylbenzoate (**4r**). M.p. 113–115.5 °C (light petroleum–ethyl acetate 20:1). For $C_{17}H_{17}NO_3$ (283.3) calculated: 72.07% C, 6.05% H, 4.94% N; found: 72.03% C, 6.25% H, 4.87% N. IR: 1691, 1668, 1606, 1596, 1533. ^{1}H NMR: 1.44 t, 3 H, J = 7.1 ($CO_2CH_2C\mathbf{H}_3$); 2.37 s, 3 H (Me); 4.42 q, 2 H, J = 7.1 ($CO_2C\mathbf{H}_2CH_3$); 7.42 dd, 1 H, J_1 = 8.5, J_2 = 2.0 (4-H); 7.46–7.60 m, 3 H (Ph); 7.89 dd, 1 H, J_1 = 2.0, J_2 = 0.5 (6-H); 7.98–8.10 m, 2 H (Ph); 8.82 deg dd, 1 H, J = 8.5 (3-H); 11.96 s, 1 H (NH). ^{13}C NMR: 14.2, 20.7, 61.4, 115.4, 120.4, 127.3, 128.7, 131.0, 131.8, 132.1, 135.0, 135.4, 139.5, 165.5, 168.6. EI MS, *m/z* (rel.%): 283 (54) [M^+], 105 (100).

N-(5-Methylbiphenyl-2-yl)benzamide (**4s**). M.p. 119–121 °C (ethanol). For $C_{20}H_{17}NO$ (287.4) calculated: 83.60% C, 5.96% H, 4.87% N; found: 83.84% C, 6.14% H, 4.73% N. IR: 3256, 1641, 1603, 1578, 1519. ^{1}H NMR: 2.38 s, 3 H (Me); 7.08–7.15 m, 1 H; 7.20–7.28 m, 1 H (3-H, 4-H); 7.32–7.54 m, 8 H; 7.56–7.64 m, 2 H (2 × Ph); 7.90 s, 1 H (NH); 8.38 d, 1 H, J = 8.4 (6-H). ^{13}C NMR: 20.9, 121.4, 126.8, 128.0, 128.6, 129.0, 129.1, 129.3, 130.5, 131.5, 132.3, 132.5, 134.0, 134.9, 138.2, 164.9. EI MS, *m/z* (rel.%): 287 (73) [M^+], 105 (100).

N-(4″-Methoxy-5′-methyl[1,1′:4′,1″-terphenyl]-2′-yl)benzamide (**4t**). M.p. 129–130 °C (ethanol). M.p. 129–130 °C (ethanol)[5d].

N-[4-(4-Methoxyphenyl)-4′,5-dimethylbiphenyl-2-yl]benzamide (**4u**). M.p. 174–176 °C (xylene). For $C_{28}H_{25}NO_2$ (407.5) calculated: 82.53% C, 6.18% H, 3.44% N; found: 82.76% C, 6.39% H, 3.33% N. IR: 3438, 1668, 1609, 1581, 1562, 1528, 1509. ^{1}H NMR: 2.31 s, 3 H (5-Me); 2.44 s, 3 H (4′-Me); 3.86 s, 3 H (MeO); 6.93–7.02 m, 2 H; 7.18 s, 1 H (6-H); 7.28–7.52 m, 9 H; 7.58–7.68 m, 2 H (Ph, 2 × C_6H_4); 7.98 s, 1 H (NH); 8.39 s, 1 H (3-H). ^{13}C NMR: 20.0, 21.2, 55.2, 113.4, 122.9, 126.7, 128.6, 129.1, 129.8, 130.3, 131.2, 131.49, 131.51, 131.9, 132.5, 133.8, 134.8, 134.9, 137.7, 141.4, 158.6, 164.8. EI MS, *m/z* (rel.%): 407 (100) [M^+], 105 (94).

N-[4-(3,4-Dimethoxyphenyl)-4′,5-dimethylbiphenyl-2-yl]benzamide (**4v**). M.p. 199–202 °C (xylene). For $C_{29}H_{27}NO_3$ (437.5) calculated: 79.61% C, 6.22% H, 3.20% N; found: 79.73% C, 6.26% H, 3.27% N. IR: 3231, 1637, 1605, 1577, 1557, 1522, 1510, 1494. ^{1}H NMR: 2.31 s, 3 H (5-Me); 2.44 s, 3 H (4′-Me); 3.91 s, 3 H (MeO); 3.94 s, 3 H (MeO); 6.89–7.02 m, 3 H; 7.19 s, 1 H (6-H); 7.27–7.53 m, 7 H; 7.58–7.68 m, 2 H (Ph, C_6H_4, C_6H_3); 7.99 s, 1 H (NH); 8.41 s, 1 H (3-H). ^{13}C NMR: 20.1, 21.2, 55.90, 55.91, 110.9, 112.7, 121.6, 122.7, 126.8, 128.6, 129.1, 129.8, 131.3, 131.5, 131.9, 132.5, 134.2, 134.86, 134.89, 137.8, 141.6, 148.1, 148.5, 164.9 (1 signal is hidden). EI MS, *m/z* (rel.%): 437 (100) [M^+], 105 (86).

N-(2,12-Diethyl-2,3,3a,6,7,8,9,9b,11,12,13,14-dodecahydro-1,3,11,13-tetraoxo-10H-4,9a[3′,4′]-endo-pyrrolo-9aH-benz[e]isoindol-4(1H)-yl)benzamide (**7**). M.p. 288–289 °C (toluene). M.p. 288–289 °C (toluene)[5b].

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REFERENCES

1. a) Sheldon R. A.: *Green Chem.* **2005**, *7*, 267; b) Matlack A.: *Green Chem.* **2003**, *5*, G7; c) Trost B. M.: *Acc. Chem. Res.* **2002**, *35*, 695; d) Anastas P. T., Kirchhoff M. M.: *Acc. Chem. Res.* **2002**, *35*, 686.
2. a) Adams D. J., Dyson P. J., Tavener S. J.: *Chemistry in Alternative Reaction Media*. Wiley, New York 2004; b) Tanaka K.: *Solvent-Free Organic Synthesis*. Wiley-VCH, Weinheim 2003; c) Wasserscheid P., Welton T. (Eds): *Ionic Liquids in Synthesis*. Wiley-VCH, Weinheim 2003; d) Jessop P. G., Leitner W. (Eds): *Chemical Synthesis Using Supercritical Fluids*. Wiley-VCH, Weinheim 1999; e) Li C.-J., Chan T.-H.: *Organic Reactions in Aqueous Media*. Wiley, New York 1997; f) Grieco P. A. (Ed.): *Organic Synthesis in Water*. Blackie Academic and Professional, London 1998.
3. a) Loupy A. (Ed.): *Microwaves in Organic Synthesis*. Wiley-VCH, Weinheim 2002; b) Hayes B. L.: *Microwave Synthesis: Chemistry at the Speed of Light*. CEM Publishing, Matthews (NC) 2002; c) Lidström P., Tierney J., Wathey B., Westman J.: *Tetrahedron* **2001**, *57*, 9225; d) Varma R. S.: *Green Chem.* **1999**, *1*, 43; e) Nüchter M., Ondruschka B., Bonrath W., Gum A.: *Green Chem.* **2004**, *6*, 128; f) Kappe C. O.: *Angew. Chem., Int. Ed.* **2004**, *43*, 6250; g) de la Hoz A., Díaz-Ortiz A., Moreno A.: *Chem. Soc. Rev.* **2005**, *34*, 164.
4. a) Afarinkia K., Vinader V., Nelson T. D., Posner G. H.: *Tetrahedron* **1992**, *48*, 9111; b) Woodard B. T., Posner G. H. in: *Advances in Cycloaddition* (M. Harmata, Ed.), Vol. 5, p. 47. JAI Press Inc., Greenwich 1999; c) Shusherina N. P.: *Russ. Chem. Rev.* **1974**, *43*, 851.
5. a) Kranjc K., Leban I., Polanc S., Kočevar M.: *Heterocycles* **2002**, *58*, 183; b) Kranjc K., Polanc S., Kočevar M.: *Org. Lett.* **2003**, *5*, 2833; c) Kranjc K., Štefane B., Polanc S., Kočevar M.: *J. Org. Chem.* **2004**, *69*, 3190; d) Kranjc K., Kočevar M.: *New J. Chem.* **2005**, *29*, 1027.
6. a) Kepe V., Kočevar M., Polanc S., Verček B., Tišler M.: *Tetrahedron* **1990**, *46*, 2081; b) Vraničar L., Polanc S., Kočevar M.: *Tetrahedron* **1999**, *55*, 271; c) Kepe V., Kočevar M.,

Petrič A., Polanc S., Verček B.: *Heterocycles* **1992**, *33*, 843; d) Kepe V., Kočevar M., Polanc S.: *J. Heterocycl. Chem.* **1996**, *33*, 1707.

7. a) Li C.-J.: *Chem. Rev.* **2005**, *105*, 3095; b) Leadbeater N. E., Marco M.: *Angew. Chem., Int. Ed.* **2003**, *42*, 1407; c) Arvela R. K., Leadbeater N. E.: *Org. Lett.* **2005**, *7*, 2101; d) Ju Y., Varma R. S.: *Org. Lett.* **2005**, *7*, 2409; e) Miyazawa A., Tanaka K., Sakakura T., Tashiro M., Tashiro H., Prakash G. K. S., Olah G. A.: *Chem. Commun.* **2005**, 2104; f) Ju Y., Varma R. S.: *Tetrahedron Lett.* **2005**, *46*, 6011; g) Martelanc M., Kranjc K., Polanc S., Kočevar M.: *Green Chem.* **2005**, *7*, 737; h) Kremsner J. M., Kappe C. O.: *Eur. J. Org. Chem.* **2005**, 3672; i) Leadbeater N. E.: *Chem. Commun.* **2005**, 2881.
8. a) Loupy A.: *C. R. Chim.* **2004**, *7*, 103; b) Varma R. S.: *Tetrahedron* **2002**, *58*, 1235; c) Varma R. S.: *Pure Appl. Chem.* **2001**, *73*, 193; d) Raunak, Kumar V., Mukherjee S., Poonam, Prasad A. K., Olsen C. E., Schäffer S. J. C., Sharma S. K., Watterson A. C., Errington W., Parmar V. S.: *Tetrahedron* **2005**, *61*, 5687; e) Pinto D. C. G. A., Silva A. M. S., Brito C. M., Sandulache A., Carrillo J. R., Prieto P., Díaz-Ortiz A., de la Hoz A., Cavaleiro J. A. S.: *Eur. J. Org. Chem.* **2005**, 2973; f) Dandia A., Arya K., Sati M., Gautam S.: *Tetrahedron* **2004**, *60*, 5253; g) Loupy A., Maurel F., Sabatié-Gogová A.: *Tetrahedron* **2004**, *60*, 1683; h) Pospíšil J., Potáček M.: *Eur. J. Org. Chem.* **2004**, 710; i) Ješelnik M., Varma R. S., Polanc S., Kočevar M.: *Green Chem.* **2002**, *4*, 35.