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One-pot solvent-free synthesis of symmetrical azines under microwave irradiation

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Dedicated to Academician Ivan Juchnovski on the occasion of his 70th birthday

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Fast, efficient and environmentally benign solvent-free one-pot procedures for the synthesis of symmetrical aryl and heteroaryl azines under microwave irradiation were developed. The main advantages of these synthetic approaches are the serious energy saving in comparison with the conventional heating and that they avoid the use of the toxic and dangerous for the environment hydrazine. The transformations go *via* semicarbazone or carbazate intermediates, which convert to azine with different rate depending on the conditions and the type of aromatic substituents. It was shown that the methods are effective when aryl aldehydes without substituents or with electrodonating ones are used. In contrast, if an electrowithdrawing group exists in the aldehyde molecule, no azine formation was observed and the intermediately formed semicarbazone or carbazate are the only reaction product. It was found that the carbazate route is preferable, particularly when a hydroxyl group exists in the aromatic subunit. The two-step procedure applied to the semicarbazone path was shown to be unfavourable in general. The *E,E*-configuration of the products was confirmed by X-ray analysis of a selected sample.

Key words: Azine, semicarbazone, carbazate, microwaves, solventless, X-ray.

INTRODUCTION

Compounds having azine moiety have displayed a broad spectrum of biological activity profiles such as antitumor [1–4], antibacterial [5–8], anti-inflammatory [9], antimalarial dyes (Janus Green B, Indoline Blue, etc.) [10], anticonvulsant [11], selective allosteric modulators of the metabotropic glutamate receptors subtype 5 (mGluR5) [12], insect growth regulators [13] and many others. Polynuclear platinum complexes with bridging linkers are described as cisplatin analogues, which are expected to overcome the resistance problem of the latter due to a significantly different way of binding DNA adducts. Among the complexes possessing rigid bridging ligands, azines have shown induction of apoptosis, implying considerable anticancer potential [14, 15]. They are important sintons for various cycloaddition reactions [16–20] and ligands in coordination chemistry [21–30]. In addition, both azines and transformation intermediates described in this paper (semicarbazones and carbazates) are widely used for the isolation and characterisation of carbonyl compounds and for their protection during synthesis [31].

Azines are well-known compound ever since 19th century but only a limited number of synthetic pathways is applied for their preparation. The classical scheme is based on a reaction of aldehydes with the highly toxic hydrazine [32, 33]. Semicarbazide has been also applied as a reagent in a two-step procedure involving thermolysis of the intermediately formed semicarbazones at high temperature, above 250ºC [34, 35]. It was found [35] that the reaction occurs through reactive *N*-substituted isocyanate intermediates which undergo $\pi^{2s}+\pi^{2a}$ cycloaddition to the relatively unstable isocyanate dimmer followed by threefold extrusion. The proposed mechanism has been supported by detection of the decomposition products and by trapping the reactive isocyanate intermediates with nucleophiles. The hard conditions of semicarbazone pathway have been overcome by performing the transformation *via* a *t*-butyl carbazate intermediate and using HCl/AcOH in the second step [36].

Microwave-assisted reactions achieve rate enhancement, higher yields and better selectivity with respect to the conventional heating [37–46]. The efficient, clean and economic solvent-free technique [47–51], which avoids hazards of solution phase reactions, is an environmentally benign condition preventing release of reaction products into the environment. To the best of our knowledge, there are no records in the literature on the one-pot procedure for conversion of aldehydes to azines *via* semicarbazones and carbazates and only one record on microwave-assisted azine synthesis by applying hydrazine sulfate as a reagent [52].

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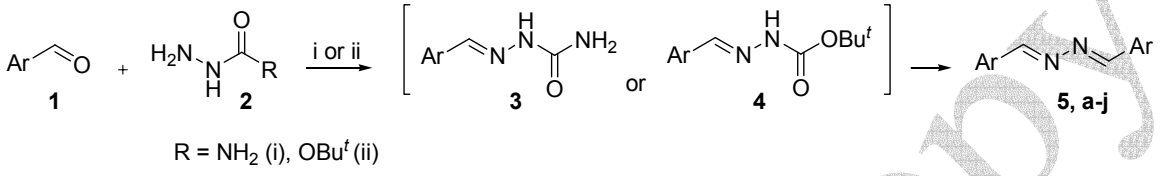
One-pot solvent-free protocols for the preparation of symmetrical azines under microwave irradiation are presented herein. The methods are fast, efficient, and avoid the use of the toxic and dangerous for the environment hydrazine.

RESULTS AND DISCUSSION

A series of symmetrically aryl-substituted azines (**5a**–**5j**) were prepared from aromatic aldehydes in a solvent-free protocol under microwave irradiation (MWI). In an attempt to avoid the use of the toxic and environmentally hazardous hydrazine, two different reagents were applied, namely semicarbazide hydrochloride (**2**, R=NH_2) and *t*-butyl carbazate (**2**, R = OBu^t). In a typical reaction, mixtures of an aromatic aldehyde (**1**) and a reagent (**2**) were irradiated in a domestic household microwave oven in open vessels yielding the target azines, as shown in Scheme 1.



R = NH_2 (i), OBu^t (ii)

Ar = 2-OH-1-naphthyl (**a**), 4-OHPh (**b**), 2-OHPh (**c**), 2-OH-3-MeOPh (**d**), 3,4-$(MeO)_2$Ph (**e**), 4-MePh (**f**), 4-Me_2NPh (**g**), 2-furfuryl (**h**), 2-thiophenyl (**i**), ferrocenyl (**j**)

Scheme 1. Synthesis of azines **5a**-**5j**. i) Method A: **2** hydrochloride, R = NH_2 (2 equiv), MWI; ii) Method B: **2**, R = OBu^t (2 equiv), MWI.

The target azines **5** were obtained with different rates depending on the reagent used, the power and the type of aromatic substituents as shown in Table 1. The reaction duration and the power were selected according to the concrete transformation behaviours followed by TLC; overheating and decomposition being detected in many cases. The products were separated from the reaction inter-mediates or decomposition products by high performance flash chromatography.

Semicarbazide hydrochloride (2, R=NH_2), an inexpensive commercially available material, was first used as a reagent. An overheating was detected by TLC at 800 W resulting in complex reaction mixtures, while a slow graduate azine formation was observed at varying the power (Table 1, method A). However, a complete and clean conversion cannot be achieved on a reasonable time-scale. Nevertheless, the method is very fast and thus leads to a serious energy saving in comparison with the conventional heating, where high temperatures are required to reach azine formation above 250ºC.

In an attempt to increase the reaction yields, the transformation was carried out with immobilized on solid support reagents. Different solids were tested as supports, such as silica gel, alumina oxides, celite, but better conversion was not achieved.

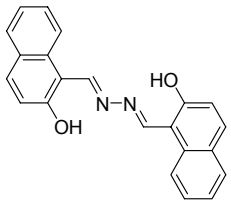
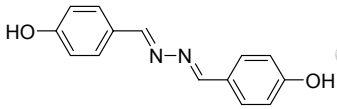
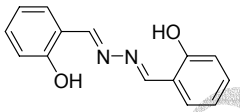
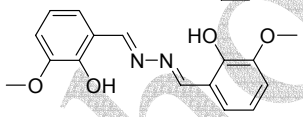
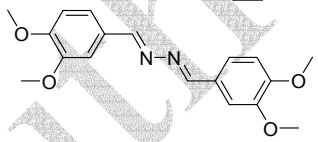
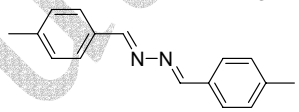
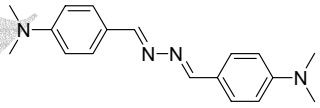
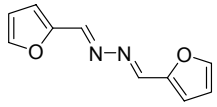
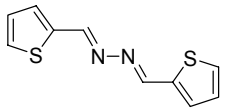
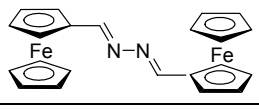
Tert-butyl carbazate (**2**, R = OBu^t) was also tested in the transformation studied. As can be seen from Table 1 (method B), good to excellent yields were achieved for most of the examples, in contrast to the conversion *via* semicarbazone. The results show that in general carbazate is preferred over semicarbazide as a reagent in this reaction. The latter conclusion is effectively illustrated on an example of 2-hydroxy substituted aldehydes. While the corresponding azines **5a**, **5c** and **5d** were obtained in good to excellent yields *via* carbazates, much lower conversions were achieved by method A (72–98%, entries 2, 6, 8 *vs* 17–63%, entries 1, 5, 7). The formation of 4-hydroxy azine **5b** appears as a frontier case. It was obtained quantitatively *via* carbazate (entry 4), while no product was isolated by method A (entry 3). No conversion was detected at low power and the intermediately formed semicarbozone was isolated, while decomposition took place above 440 W.

The results in Table 1 show that the presence of a polar electrodonating group seems to be essential for the reactivity, the effect being most clearly exhibited if the substituent is at *p*-position with respect to the aldehyde function. A possible explanation of the latter could be an increasing of the energy absorption caused by the polar group and/or electronic effects of the substituents. As can be seen, quantitative conversions were achieved *via* carbazate with aldehydes **1b** and **1g** possessing a single polar substituent in *p*-position (entries 4 and 14), while the *o*-substituted products **5a** and **5c** were isolated in a bit lower yield (entries 2 and 6). The better conversion to disubstituted product **5d** in comparison with **5a** and **5c** (entry 8 *vs* entries 2 and 6) could be due to a surplus energy absorbed by the second polar group. The behaviour of aldehyde **1e**, where the extra energy absorbed resulted in an overheating and decomposition even at relatively low power (entry 10), is

in accordance with the given suggestion. The product **5e** contains an additional polar group with respect to **5b** and *p,m*-substituents instead of *o,m*- in comparison with **5d**. The results *via* semicarbazone intermediate are in agreement with that pattern; an overheating for **5b** and **5e** and graduate formation of **5a**, **5c** and **5d**.

The presence of a hydroxyl group in *o*-position leads to serious lack of solubility of azines **5a** and **5c** thus creating problems in their isolation. This very low solubility is due to H-bonding between *o*-hydroxyl group and nitrogen, which is clearly demonstrated by the absence of a band for OH in their IR spectra. In the case of **5d** the H-bonding between OH and OMe is stronger than OH…N, while a strong band for free OH group exists in the IR spectrum of **5b**. The NMR data for O*H* and C*H*=N protons present an additional confirmation of the presence and direction of the H-bonding. The downfield shifting of the O*H* proton resonances of **5a**, **5c** and **5d** with respect to **5b** (11.08 ppm, 10.61 ppm and 11.57 ppm *vs* 9.70 ppm, respectively) show that the hydroxyl groups are H-bonded. On the other side, the C*H*=N resonances are downfielded only in the case of **5a** and **5c** (9.70 ppm and 9.88 ppm, respectively) indicating that the nitrogen in **5d** (C*H*=N of 8.44 ppm) is not H-bonded.

Table 1. Microwave synthesis of symmetrical aryl azines **5**.

Entry		Aryl azine	Synthetic scheme [a]	Reaction time, min	MWI power, W	Yield, [b] %
1	**5a**		A	5	800	45
2			B	5	800	81
3	**5b**		A	2-15	300-800	-
4			B	5	800	99
5	**5c**		A	5	600	17
6			B	5	800	72
7	**5d**		A	10	800	63
8			B	5	800	98
9	**5e**		A	2	600	49
10			B	5	600	35
11	**5f**		A	2	440	55
12			B	5	800	67
13	**5g**		A	2	600	75
14			B	5	800	99
15	**5h**		A	1	800	11
16			B	5	800	43
17	**5i**		A	2	440	34
18			B	5	600	70
19	**5j**		A	2-5	440-800[c]	<10
20			B	2-5	440-800	<5

[a] Method A: Preparation *via* semicarbazone **3**; Method B: Preparation *via* carbazate **4**. [b] After high performance flash chromatography on silica gel.
[c] In consecutive 30 sec intervals.

Ferrocenyl azine **5j** presents an exception of the general pattern of behaviour. An overheating was observed even at low power by both methods (entries 19, 20) resulting in complex mixtures. Moreover, the yields of the product were not reproducible. These facts are most probably due to the presence of iron in the molecule.

No azine formation was detected from 4-cyanobenzaldehyde and 4-nitrobenzaldehyde by both methods even at 800 W and the corresponding intermediates, semicarbazones or carbazates, were isolated. These results are an indication that no transformation takes place if electrowithdrawing substituents exist in the aromatic ring of the starting aldehyde. When 3,4-dihydroxybenzaldehyde was used even at low power, the corresponding azine was detected as a component of a complex polymers-containing reaction mixture, which shows that polyphenols are not stable enough upon the reaction conditions used.

The slower conversion rate of method A compared to method B gave us the idea to transform the former scheme as a two-step protocol for the synthesis of the selected products. Semicarbazones **3** were obtained in high yields (above 90%) by irradiating aqueous solutions of an aldehyde and semicarbazide hydrochloride in a microwave oven applying 800 W power for 5 min. After simple filtration the products were irradiated with microwaves in the absence of a solid support but no transformation was detected. The reaction vessels were only slightly warmed up at the end of the treatment, which is an indication that semicarbazones **3** do not absorb sufficient energy. When performing the reaction with pre-immobilized on silica gel or basic alumina semicarbazones, azine formation was observed but at much slower reaction rate compared to the direct protocol (Scheme 1, Table 1: method A), which makes the latter a preferable reaction scheme in all cases. In an attempt to obtain ferrocenyl azine **5j** in a reasonable scale and reproducible results, the two-step protocol was applied on both pathways A and B by using silica gel and basic alumina as solid supports. However, an overheating was again observed and no product was isolated.

X-ray Crystallography and Structure Description

Crystals of bis(3,4-dimethoxyphenyl)azine **5e** suitable for X-ray analysis were grown by slow diffusion of hexane into chloroform solutions of the product. The asymmetric unit of **5e** consists of two crystallographically independent $C_{18}H_{20}N_2O_4$ molecules, Figure 1, which are arranged in slabs parallel to the *ac* plane, Figure 2. No solvent molecules have been identified and located in the structure. All atoms fully occupy general (2a: x,y,z) positions. The C–C, C–N and C–O distances are typical for such compounds and range between 1.365(2)–1.457(3) Å (C–C), 1.359(2)–1.438(2) Å (C–O), 1.278(2)–1.285(2) Å (C–N) and 1.410(2)–1.412(2) Å (N–N), respectively.

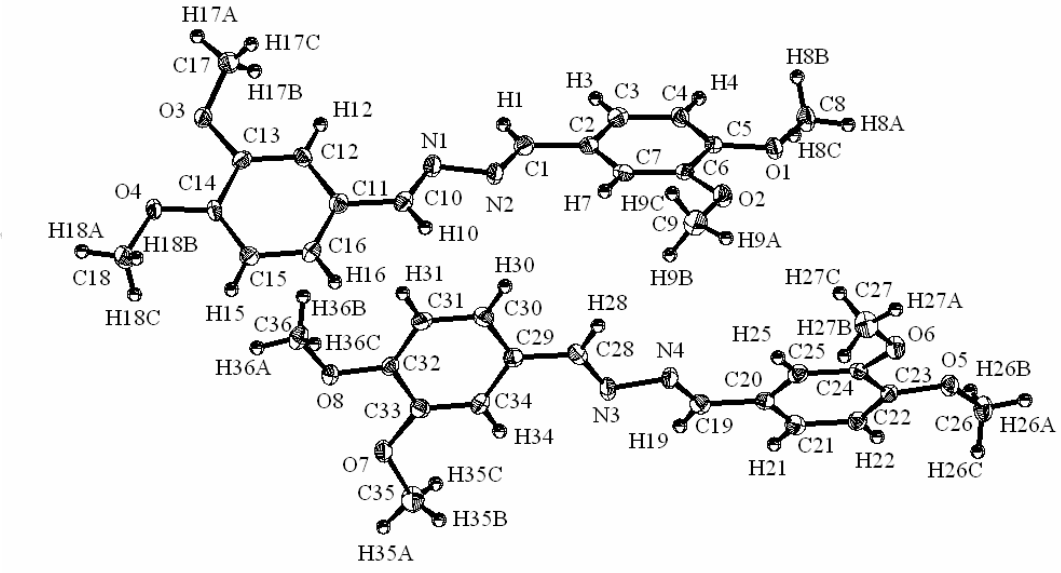


Fig. 1. Asymmetric unit, thermal ellipsoids (50% probability level) and labeling scheme of **5e**.

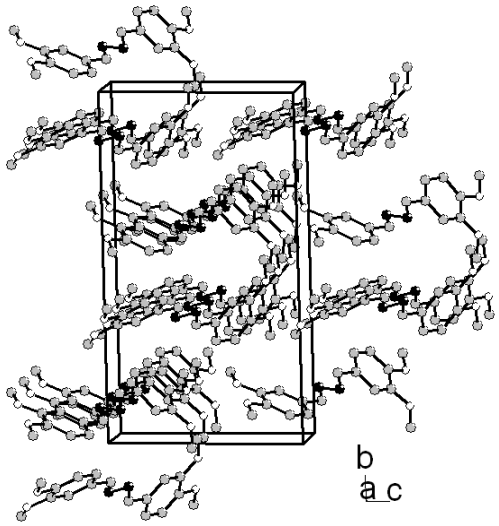


Fig. 2. Unit cell and space filling of 5e.

CONCLUSIONS

In conclusion, a series of symmetrical aryl and heteroaryl azines was obtained in solvent-free one-pot protocols under microwave irradiation. Semicarbazide hydrochloride and *t*-butyl carbazate were applied as reagents, thus avoiding the use of the toxic and dangerous for the environment hydrazine. The methods are very fast, which leads to a serious energy saving in comparison with the conventional heating. It was found that the rate of the azine formation is strongly dependent on the conditions and the type of aromatic substituents. It has been shown that the methods are effective when aryl aldehydes without substituents or with electro-donating ones are used. In contrast, if an electro-withdrawing group exists in the aldehyde molecule, no azine formation has been observed and the inter-mediately formed semicarbazone or carbazate are the only reaction products. It was observed that the carbazate route is preferable, particularly when a hydroxyl group exists in the aromatic moiety. The two-step procedure applied to the semicarbazone path was shown to be unfavourable in general. The *E,E*-configuration of the products was confirmed by X-ray analysis of a selected sample.

EXPERIMENTAL SECTION

General Procedures

All reagents were purchased from Aldrich, Merck and Fluka and were used without any further purification. The microwave irradiated reactions (MWI) were performed in a domestic household oven Panasonic NN-S255W. Merck silica gel 60 (0.040–0.063 mm) and BDH basic active aluminium oxide Brockmann grade 1 were employed as solid supports. Fluka silica gel/TLC-cards 60778 with fluorescent indicator 254 nm were used for TLC chromatography and R_f-values determination. The purifications were carried out on a Biotage Horizon^{TM} HPFC system on silica gel. The melting points were determined in capillary tubes on a MEL-TEMP 1102D-230 VAC apparatus without corrections. The IR spectra were taken on a Bruker IFS 113v as KBr discs and were quoted in cm^{-1}. The NMR spectra were recorded on a Bruker AVANCE DRX 250 spectrometer, the chemical shifts were quoted in ppm in δ-value against tetramethylsilane (TMS) as internal standard and the coupling constants were calculated in Hz. The low-resolution mass spectra were carried out on a HP 5973 Mass Selective Detector.

Synthesis of aryl azines ***5***

General procedure: A mixture of an aldehyde (1 mmol) and semicarbazide hydrochloride (2 mmol, method A) or *t*-butyl carbazate (2 mmol, method B) was irradiated in a microwave oven. The crude product was purified by high performance flash chromatography on silica gel without work-up.

The reaction conditions and yields are summarized in Table 1.

Azine ***5a*** [53]. Flash chromatography (CH_2Cl_2), R_f 0.86; m. p. 290–293ºC decomp. (Ref. [53] > 290 ºC); IR: 421.2, 755.4, 788.4, 797.8, 834.2, 871.2, 956.0, 1143.0, 1167.6, 1184.7, 1215.6, 1242.8, 1283.2, 1321.4, 1418.3, 1467.6, 1580.6, 1604.8, 1622.1, 2923.6, 3055.2; ^{1}H NMR ($CDCl_3$:CF_3COOH 3:1): 7.30 (d, 2H, J 9.0, C*H*-3 of Ar), 7.50 (dd, 2H, J 7.1, 8.1, C*H*-7 of Ar), 7.68 (ddd, 2H, J 1.2, 7.1, 8.5, C*H*-6 of Ar), 7.81 (d, 2H, J 8.1, C*H*-8 of Ar), 8.07 (d, 2H, J 9.0, C*H*-4 of Ar), 8.23 (d, 2H, J 8.5, C*H*-5 of Ar), 9.70 (s, 2H, C*H*=N), 11.08 (bs, O*H*, overlapped with COO*H* of CF_3COOH); ^{13}C NMR ($CDCl_3$:CF_3COOH 3:1): 106.43 (C_{quat}-1), 118.08 (*C*H of Ar), 120.11 (*C*H of Ar), 126.13 (*C*H of Ar), 128.98 (C_{quat}), 130.27 (*C*H of Ar), 130.69 (*C*H of Ar), 132.79 (C_{quat}), 141.76 (*C*H of Ar), 157.90 (*C*H=N), 163.29 (C_{quat}-2); MS: (EI+) m/z 340 (M^+, 72) , 323 (M-OH, 34), 170 (½ M^+, 100), 115 (Ar, $C_9H_7^+$, 52).

Azine ***5b*** [54]. Flash chromatography (CH_2Cl_2:MeOH 95:5), R_f 0.36 (CH_2Cl_2:MeOH 90:10); m. p. 258–259ºC (Ref. [55] 268ºC); IR: 516.3, 521.4, 625.1, 812.7, 827.9, 841.8, 1167.1, 1230.4, 1264.4, 1285.1, 1303.6, 1382.3, 1393.7, 1449.0, 1514.3, 1563.9, 1592.3, 1607.9, 1623.3, 2526.0, 2591.9, 2943.9, 3338.0; ^{1}H NMR ($CDCl_3$:DMSO 2:1): 6.79 (d, 4H, J 8.6, C*H*-2 and C*H*-6 of Ar), 7.58 (d, 4H, J 8.6, C*H*-3 and C*H*-5 of Ar), 8.45 (s, 2H, C*H*=N), 9.69 (bs, 2H, O*H*,

exchangeable signal); ^{13}C NMR ($CDCl_3$:DMSO 2:1): 115.52 (*C*H-2 and *C*H-6 of Ar), 125.09 (C_{quat}-4), 129.70 (*C*H-3 and *C*H-5 of Ar), 159.85 (C_{quat}-1), 160.52 (*C*H=N).

Azine ***5c*** [34]. Flash chromatography (CH_2Cl_2), R_f 0.14; m. p. 209–211ºC (Ref. [34] 213–214ºC); IR: 459.2, 683.6, 751.9, 785.3, 894.3, 1198.0, 1207.1, 1223.2, 1237.6, 1278.4, 1317.0, 1331.1, 1388.1, 1488.0, 1572.6, 1624.8, 2639.1, 2752.9, 3043.9; ^{1}H NMR ($CDCl_3$:CF_3COOH 10:1): 7.02 (m, 4H, C*H* of Ar), 7.56 (m, 4H, C*H* of Ar), 9.88 (d, 2H, J 0.6, C*H*=N), 10.61 (bs, 2H, O*H*, exchangeable signal); ^{1}H NMR ($CDCl_3$:CF_3COOH 3:1): 7.18 (m, 4H, *C*H-3 and *C*H-5 of Ar), 7.57 (dd, 2H, J 1.6, 8.0, C*H*-6 of Ar), 7.69 (ddd, 2H, J 1.6, 7.3, 8.7, C*H*-4 of Ar), 8.98 (s, 2H, C*H*=N), 11.69 (bs, O*H*, overlapped with COO*H* of CF_3COOH); ^{13}C NMR ($CDCl_3$:CF_3COOH 10:1): 117.76 (*C*H-3 or *C*H-5 of Ar), 120.26 (*C*H-3 or *C*H-5 of Ar), 120.71(C_{quat}-1), 134.18(*C*H-4 or *C*H-6 of Ar), 137.59 (*C*H-4 or *C*H-6 of Ar), 161.77 (C_{quat}-2), 197.39 (*C*H=N); ^{13}C NMR ($CDCl_3$:CF_3COOH 3:1): 114.23 (C_{quat}-1), 118.03 (*C*H-3 or *C*H-5 of Ar), 122.69 (*C*H-3 or *C*H-5 of Ar), 136.06 (*C*H-4 or *C*H-6 of Ar), 139.94 (*C*H-4 or *C*H-6 of Ar), 160.49 (C_{quat}-2), 164.58 (*C*H=N).

Azine ***5d*** [56]. Flash chromatography (CH_2Cl_2), R_f 0.47; m. p. 192–193ºC (Ref. [56] 196ºC); IR: 733.0, 745.4, 778.3, 838.7, 963.8, 1077.6, 1092.4, 1219.9, 1250.6, 1263.2, 1321.1, 1440.0, 1469.6, 1491.8, 1578.2, 1623.1, 2229.4, 2840.8, 2928.6, 3421.4; ^{1}H NMR ($CDCl_3$): 3.93 (s, 6H, OC*H*$_3$), 6.88–7.03 (m, 6H, 6C*H* of Ar), 8.70 (s, 1H, C*H*=N), 11.57 (bs, 1H, O*H*, exchangeable); ^{13}C NMR ($CDCl_3$): 56.16 (OCH_3), 110.59 (*C*H of Ar), 115.03 (*C*H of Ar), 117.29 (C_{quat}-1), 119.40 (*C*H of Ar), 124.01 (*C*H of Ar), 148.30 (C_{quat}), 149.63 (C_{quat}), 164.80 (*C*H=N); after addition of KOH: ^{1}H NMR ($CDCl_3$:DMSO-d_6 5:1): 3.75 (s, 6H, OC*H*$_3$), 6.50 (dd, 2H, J 7.5, 7.8, C*H*-5 of Ar), 6.75 (d, 2H, J 7.5, C*H* of Ar), 7.04 (d, 2H, J 7.8, C*H* of Ar), 8.81 (s, 1H, C*H*=N); ^{13}C NMR ($CDCl_3$:DMSO-d_6 5:1): 55.63 (OCH_3), 78.68 (*C*H of Ar), 113.28 (*C*H of Ar), 114.96 (C_{quat}), 118.54 (C_{quat}), 122.06 (*C*H of Ar), 127.61 (C_{quat}), 149.98 (C_{quat}), 161.92 (*C*H=N), 217.83 (*C*=O); HMQC cross-peaks: 3.752/55.63, 6.496/116.65, 6.750/113.28, 7.043/122.06, 8.811/161.92; MS (EI+) m/z 300 (M^+, 100), 283 (M-OH, 38), 150 (½ M^+, 100), 135 (½ M^+-CH_3, 28), 108 (½ M^+-CH_3-CHN, 27), 65 (Ar, $C_5H_5^+$, 27).

Azine ***5e*** [57]. Flash chromatography (CH_2Cl_2:NH_4OH 100:0.1), R_f 0.27; m. p. 189–190ºC (Ref. 195ºC [58], 193ºC [59]); IR: 617.5, 650.1, 753.9, 810.4, 866.1, 957.4, 1015.9, 1034.6, 1140.8, 1157.1, 1238.0, 1258.5, 1270.4, 1312.9, 1343.3, 1420.1, 1442.0, 1463.7, 1507.8, 1579.2, 1597.9, 1622.7, 2019.5, 2838.9, 2928.4, 2961.0, 3000.7, 3420.1; ^{1}H NMR ($CDCl_3$): 3.94 (s, 6H, OC*H*$_3$), 3.975 (s, 6H, OC*H*$_3$), 6.91 (d, 2H, J_{56} 8.3, C*H*-5 of Ar), 7.25 (dd, 2H, J_{26} 1.9, J_{56} 8.3, C*H*-6 of Ar), 7.54 (d, 2H, J_{26} 1.9, C*H*-2 of Ar), 8.60 (s, 2H, C*H*=N); ^{13}C NMR ($CDCl_3$): 55.90 (OCH_3), 108.65 (*C*H of Ar), 110.59 (*C*H of Ar), 123.90 (*C*H of Ar), 127.19 (C_{quat}), 149.31 (C_{quat}), 151.74 (C_{quat}), 161.14 (*C*H=N).

Azine ***5f*** [60]. Flash chromatography (CH_2Cl_2), R_f 0.66; m. p. 146–148ºC (Ref. [61] 153ºC); IR: 505.8, 817.8, 864.2, 969.2, 1176.1, 1211.1, 1290.3, 1303.5, 1321.0, 1511.7, 1568.6, 1608.6, 1621.5, 2857.9, 2915.0, 2939.6, 2996.4, 3030.3; ^{1}H NMR ($CDCl_3$): 2.40 (s, 6H, C*H*$_3$), 7.25 (d, 4H, J 8.1, C*H*-3 and C*H*-5 of Ar), 7.73 (d, 4H, J 8.1, C*H*-2 and C*H*-6 of Ar), 7.74 (s, 1H, C*H*=N); ^{13}C NMR ($CDCl_3$): 21.61 (CH_3), 128.47 (*C*H of Ar), 129.50 (*C*H of Ar), 131.40 (C_{quat}), 141.57 (C_{quat}), 161.88 (*C*H=N).

Azine ***5g*** [62]. Flash chromatography (CH_2Cl_2), R_f 0.59; m. p. 231–232ºC (Ref. [62] 226–228ºC); IR: 522.5, 814.4, 948.2, 1064.3, 1178.8, 1228.1, 1302.0, 1365.6, 1430.2, 1443.4, 1522.6, 1551.8, 1602.7, 2802.0, 2911.7; ^{1}H NMR ($CDCl_3$): 3.03 (s, 12H, NC*H*$_3$), 6.72 (d, 4H, J 8.9, C*H*-2 and C*H*-6 of Ar), 7.70 (d, 4H, J 8.9, C*H*-3 and C*H*-5 of Ar), 8.57 (s, 2H, C*H*=N); ^{13}C NMR ($CDCl_3$): 40.16 (N*C*H$_3$), 111.67 (*C*H-2 and *C*H-6 of Ar), 128.18 (C_{quat}-4), 129.85 (*C*H-3 and *C*H-5 of Ar), 152.07 (C_{quat}-1), 160.77 (*C*H=N); MS (EI+): m/z 294 (M^+, 100), 266 (M^+-2N, 31), 250 (M^+-$N(CH_3)_2$, 17), 206 (M^+-$2N(CH_3)_2$, 46), 147 (½ M^+, 47), 132 (½ M^+-CH_3, 29), 117 (½ M^+-$2CH_3$, 27), 105 (½ M^+-CHN-CH_3, 17), 65 (Ar, $C_5H_5^+$, 16).

Azine ***5h*** [63]. Flash chromatography (CH_2Cl_2), R_f 0.36; m. p. 87–90ºC (Ref. [63] 111–112ºC); IR: 515.1, 591.4, 735.6, 750.6, 805.3, 882.1, 888.0, 929.4, 950.5, 1023.2, 1077.8, 1098.8, 1147.1, 1153.3, 1217.6, 1263.2, 1271.7, 1291.1, 1392.9, 1470.5, 1547.3, 1575.6, 1641.9, 2963.0, 3077.5, 3101.4, 3136.0, 3149.8; ^{1}H NMR ($CDCl_3$): 6.50 (dd, 2H, J 1.8, 3.5, C*H*-4 of Ar), 6.86 (dd, 2H, J 0.6, 3.5, C*H*-3 of Ar), 7.56 (d, 2H, J 1.8, C*H*-5 of Ar), 8.49 (s, 2H, C*H*=N); ^{13}C NMR ($CDCl_3$): 112.18 (*C*H-3 of Ar), 116.73 (*C*H-4 of Ar), 145.71 (*C*H-5 of Ar), 149.26 (C_{quat}-2 of Ar), 150.82 (*C*H=N).

Azine ***5i*** [64]. Flash chromatography (CH_2Cl_2), R_f 0.42; m. p. 150–152ºC (Ref. 154ºC [65], 151–152ºC [66], 157.5–158.5ºC [67]); IR: 498.7, 724.1, 765.1, 833.7, 858.0, 950.4, 1041.6, 1166.0, 1212.5, 1235.5, 1253.8, 1273.5, 1327.0, 1368.2, 1420.9, 1511.7, 1537.8, 1609.2, 1696.8, 2966.5, 3007.8, 3081.0, 3099.7, 3248.3; ^{1}H NMR (DMSO): 7.21 (dd, 2H, J 3.7, 5.1, C*H*-4 of Ar), 7.63 (dd, 2H, J 1.0, 3.7, C*H*-5 of Ar), 7.56 (ddd, 2H, J 1.0, 1.0, 4.9 C*H*-3 of Ar), 8.86 (s, 2H, C*H*=N); ^{13}C NMR (DMSO):

128.18 (*C*H of Ar), 130.91 (*C*H of Ar), 133.71 (*C*H of Ar), 138.32 (C_{quat}-2 of Ar), 155.72 (*C*H=N).

Azine ***5j*** [68]. Flash chromatography (CH_2Cl_2), R_f 0.55; m. p. 243–244ºC (Ref. [68] 245ºC); ^{1}H NMR (DMSO-d_6:$CDCl_3$ 5:1): 4.18 (s, 10H, C*H* of ferrocene), 4.42 (t, 4H, J 1.8, C*H* of ferrocene), 4.65 (t, 4H, J 1.8, C*H* of ferrocene), 7.98 (s, 2H, C*H*=N); ^{13}C NMR (DMSO-d_6:$CDCl_3$ 5:1): 67.04 (2×*C*H of ferrocene), 68.83 (5×*C*H of ferrocene), 69.65 (2×*C*H of ferrocene), 79.74 (C_{quat} of ferrocene), 143.74 (*C*H=N); MS (EI+): m/z 424 (M^+, 100), 396 (M^+-2N, 16), 212 (½ M^+, 74), 198 (½ M^+-NH, 79), 185 (ferrocene$^+$, 47), 56 (Fe, 57).

Two-step protocols for the preparation of azines ***5***

A mixture of ferrocene carbaldehyde (1 mmol) and semicarbazide hydrochloride **2** (R = NH_2, 2 mmol) or *t*-butyl carbazate **2** (R = OBu^t, 2 mmol) in water (30 ml) was irradiated in a microwave oven for 2–5 min with a power of 440 W. The crystals formed after cooling were filtered off and dried in air. To a solution of thus prepared semicarbazone **3** or carbazate **4** (1 mmol) in acetone (5 ml) silica gel (2 g) or basic alumina (2 g) was added and the solvent was removed *in vacuo*. The mixture was irradiated in a microwave oven. The product was purified by high performance flash chromatography on silica gel.

Crystal structure determination of compound ***5e***

A prismatic colourless crystal 0.41×0.12×0.08 mm in size was mounted on a SMART X-ray diffractometer with a 1K CCD area detector. Data were collected at room temperature using graphite-monochromatized Mo-K_α radiation (λ = 0.71073 Å). A hemisphere of data (1271 frames at 5 cm detector distance) was collected using a narrow-frame method with scan widths of 0.30º in ω and an exposure time of 30 s/frame. The first 50 frames were measured again at the end of the data collection to monitor instrument and crystal stability. Analysis of the frames showed negligible decay during data collection. The data were integrated using a Bruker SAINT software package with a narrow frame algorithm [69] yielding a total of 10262 reflections of which 4650 independent and 3641 with I > 10σ(I). The SADABS program was used for the absorption correction [70]. The final cell constants were based on 1562 reflections with *I* > 10σ(I). The structure was solved by direct methods and refined by full matrix least-squares techniques with the SHELX97 software package [71]. The observed reflection conditions (h0l; 00l: l = 2n) indicated Pc (#7) and P2/c (#13) as the only possible space groups. The initial solution in the higher symmetry S.G. resulted in an unsatisfactory model. Initial solution in Pc resulted in R-factor of c.a. 10% and the refinement was consequently carried out in the lower symmetry S.G. First, all non-hydrogen atoms have been found and assigned from the Fourier maps and their thermal parameters refined anisotropically. Next, the hydrogen atoms have been added to the refinement as riding models and their thermal parameters refined isotropically. After the refinement con-verged, a close examination of the solution as well as a test using the PLATON program confirmed the lack of possible higher symmetry [72]. Main crystallographic details are listed in Table 2. Full crystallographic data for this paper in cif-format can be obtained free of charge from the Cambridge Crystallographic Data Centre [73].

Table 2. Crystal data and structure refinement for **5e**.

Empirical formula	$C_{18}H_{20}N_2O_4$
Formula weight	328.35
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, S.G.	Monoclinic, P1c1 (#7)
Unit cell dimensions	a = 11.3601(10) Å α = 90 deg. b = 18.8367(17) Å β = 92.858(4) deg. c = 8.4068(8) Å γ = 90 deg.
Volume, Z	1690.8(3) Å^3, 4
Calculated density	1.290 g/cm^3
Absorption coefficient	0.092 mm^{-1}
F(000)	696
Crystal size	0.41×0.12×0.08 mm
θ range for data collection	1.91 to 22.98 deg.
Limiting indices	–9 ≤ h ≤ 9, –20 ≤ k ≤ 19, –12 ≤ l ≤ 12
Reflections collected/unique	10262/4650 [R(int) = 0.0202]
Refinement method	Full-matrix least-squares on F^2
Data / parameters	4650/431
Goodness-of-fit on F^2	1.023
Final R indices [I>2σ(I)]	^{a}R1 = 0.0303, ^{b}Rw2 = 0.0763
R indices (all data)	R1 = 0.0337, Rw2 = 0.0785
Largest diff. peak and hole	0.151 and –0.144 e·Å^{-3}

[a] $R1 = \Sigma \mid |F_o| - |F_c| / \Sigma |F_o|$ (based on reflections with I > 2σ(I));
[b] $R_w = [\Sigma w(|F_o| - |F_c|)^2 / \Sigma w |F_o|^2]^{1/2}$;
$w = 1/[\sigma^2(F_o^2) + (0.0511P)^2 + 0P]$; $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$ (all data).

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ЕДНОСТАДИЕН СИНТЕЗ НА СИМЕТРИЧНИ АЗИНИ ПОД ДЕЙСТВИЕ НА МИКРОВЪЛНИ В ОТСЪСТВИЕ НА РАЗТВОРИТЕЛИ

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Посветена на акад. Иван Юхновски по повод на 70-та му годишнина

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Разработени са бързи, ефикасни и благоприятни за околната среда едностадийни процедури за синтез на симетрични арил и хетероарил азини под действие на микровълни в отсъствие на разтворители. Основните предимства на тези синтетични схеми са сериозната икономия на енергия в сравнение с реакциите при конвенционално нагряване и избягването на употребата на токсичния и вреден за околната среда хидразин. Трансформациите протичат през семикарбазонен или карбазатен междинен продукт, който се превръща в азин с различна скорост в зависимост от реакционните условия и вида на заместителите в ароматното ядро. Показано е, че методите са ефективни при използване на ароматни алдехиди без заместители или с електронодонорни заместители. Обратно, при наличие на електроно-акцепторни групи в молекулите на алдехидите не се наблюдава образуване на азини, а се изолират единствено междинно образуваните семикарбазони или карбазати. Намерено е, че карбазатният път е предпочетен, особено при наличие на хидроксилна група в ароматната част. Семикарбазонният път е проведен и по двустадийна процедура и е показано, че едностадийната е предпочетен като цяло. *E,E*-Конфигурацията на продуктите е потвърдена посредством рентгеноструктурен анализ на подбрана проба.