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A comparison of green chemistry metrics for two methods of bromination and nitration of bis-pyrazolo[3,4-b;4′,3′-*e*]pyridines

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Abstract

Green chemistry metrics (E-factor, atom economy, reaction mass efficiency) and the EcoScale have been compared for conventional heating and microwave assisted bromination and nitration of bis-pyrazolo[3,4-b;4′,3′-*e*]pyridines. The major advantages in microwave-assisted reactions in relation to traditional evaluation of the process have encompassed higher yields, shorter reaction time and higher selectivity. The microwave-assisted reactions have shown better green chemistry parameters and EcoScale ranks than those in conventionally heated reactions. Mass reaction efficiency values have been critical for considering 'green' the reactions conducted under traditional conditions. Additional advantages of using microwaves, not considered in calculated parameters, include easier purification of the reaction mixture and isolation of the product.

Keywords: bis-pyrazolo[3,4-b;4′,3′-*e*]pyridines; EcoScale; green chemistry metrics; microwave-assisted electrophilic substitution.

Introduction

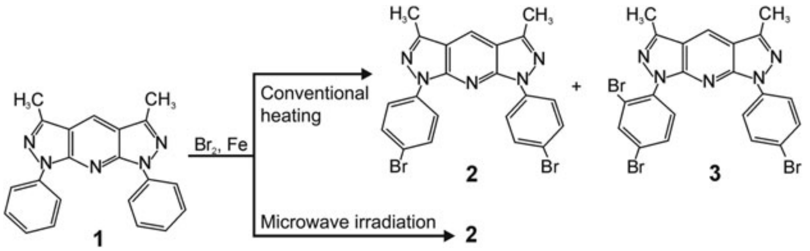
Bis-pyrazolo[3,4-b;4′,3′-*e*]pyridines (BPPs) exhibit antibacterial (Joshi et al., 1981) and moderate antifungal (Quiroga et al., 2005) activities and their conjugated π-systems are highly fluorescent under the white light, in both solid and liquid states (Rechthaler et al., 1999; He et al., 1997; Parusel et al., 1997). BPPs are useful as blue luminophores for electroluminescent devices, e.g., for OLEDs (organic light emitting diodes). These compounds are photoemitters when doped into polymeric matrices as well as copolymerized with corresponding monomers, such as *N*-vinylcarbazole. Brominated and nitrated BPPs may also be important compounds for their possible use as synthetic intermediates and for their potential as pharmacological and fluorescent agents, but the detailed study of their properties and applications has not been reported so far.

Over the past few years there has been a growing interest in application of the concept of green chemistry to different fields of chemistry (Armenta et al., 2008; Anastas and Eghbali, 2010; Deligeorgiev et al., 2010; Tobiszewski et al., 2010). We have calculated green metrics and the EcoScale to evaluate the greenness of bromination of five BPPs **1, 4a–c, 10** and nitration of three BPPs **4a,b, 10** conducted under conventional heating and microwave reactor. Recently, the energy efficiency of microwave-assisted transformations at laboratory scale organic preparations has been critically assessed (Moseley and Kappe, 2011). The major objective of this study was to find the optimal reaction conditions from both environmental and economical points of view.

Results and discussion

All BPPs that have been used as substrates for bromination and nitration (Schemes 1–3) have been synthesized in the Organic Chemistry Laboratory, Jan Kochanowski University in Kielce, according to standard procedures (Puchała et al., 1997; Puchała, 2003). The structures of all reaction products were checked by ^{1}H NMR, as well as their mass and IR spectra.

The percent yield of microwave-assisted bromination reactions varied from 76% to 97% and the time of all reactions was 10 min, except for bromination of **1** for which the reaction time was 7 min. The same reactions were conducted under conventional heating. The percent yield was almost twice as much lower than that for microwave-induced bromination reactions (43–56%) and the reaction time varied from 10 to 18 h. Another disadvantage of conventional heating was low selectivity. Different products were obtained in conventional and microwave heating. Microwave irradiation lead to one less substituted product. In bromination of tetra-substituted BPP **1** two products were obtained for the conventional procedure: dibrominated **2** (43%) and tribrominated **3** (37%) BPPs, and in the microwave irradiation procedure the only product was **2**. Bromination of pentasubstituted BPP **4a** led to formation of octabrominated BPP **5** in conventional heating conditions and tribrominated BPP **6** in microwave-assisted reaction. Higher selectivity was also obtained for bromination of BPP with methoxy group **10**. Heptabrominated BPP **11** was the product of conventional heating reaction and tribrominated BPP **12** of microwave-assisted reaction, respectively. Microwave-assisted bromination lead to formation of products with 4-substituted phenyl ring. The full conversion of the substrate in time shorter than in conventional heating is the evidence of activational effect of microwave irradiation.



Scheme 1 Products of conventional and microwave-assisted bromination of **1**.

The reaction yields and reaction times for conventional and microwave-assisted bromination of BPPs have been discussed by the present authors (Marcinkowska et al., 2010).

Three BPPs **4a,b, 10** were substrates for nitration (Schemes 2 and 3). The two products of conventionally heated nitration of **4a,b** encompassed tri- and tetranitrated BPPs **8a,b** and **9a,b**. The product ratio was 2:1 for nitration of **4a** and 12:1 for nitration of **4b**.

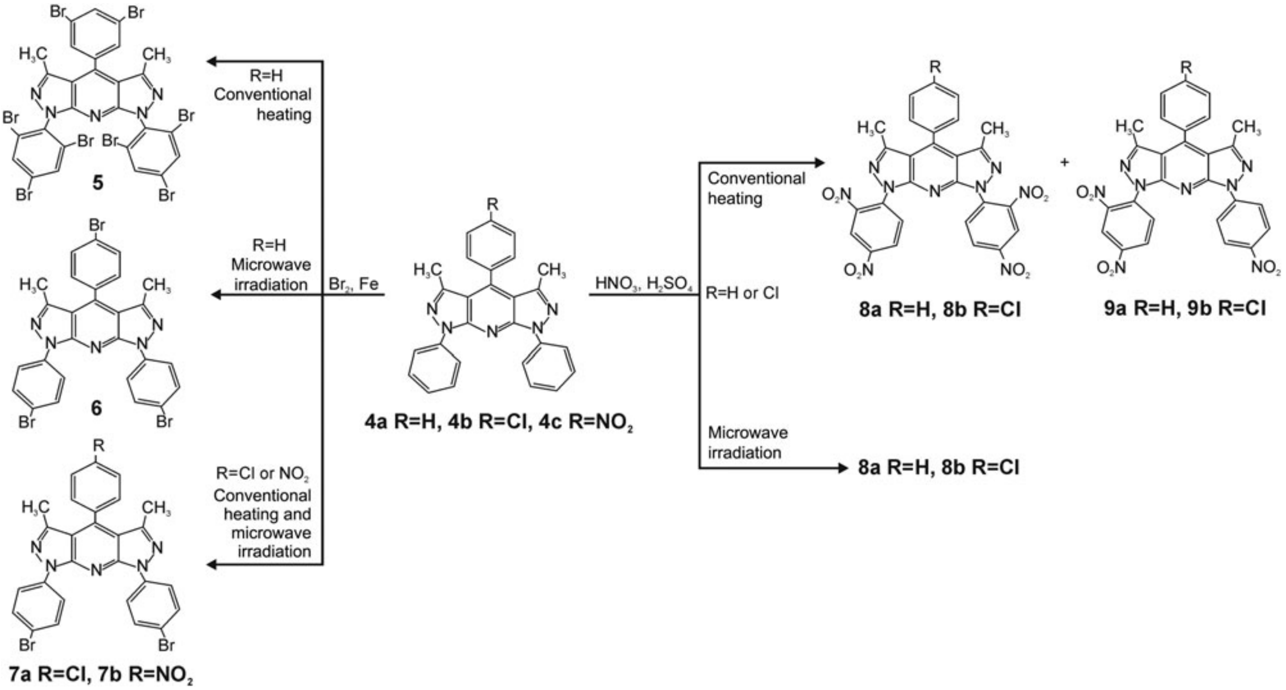
For the microwave-assisted nitration, the reaction time was 45–50 min and the power of the reactor was set to 150 W. The only product of **4a** nitration was **8a** and the product of **4b** nitration was **8b**, respectively. Both conventionally heated and microwave-assisted nitration of **10** produced a hexa-substituted nitro compound **13**, in which each phenyl ring contained two nitro groups. Nitronium ion is a stronger electrophile compared to bromonium ion, and thus electrophilic strength plays an important role in nitration reaction. In the presence of nitronium ion, the product is substituted even in position 2, which remains inactive in bromination reaction.

Green chemistry metrics and the EcoScale

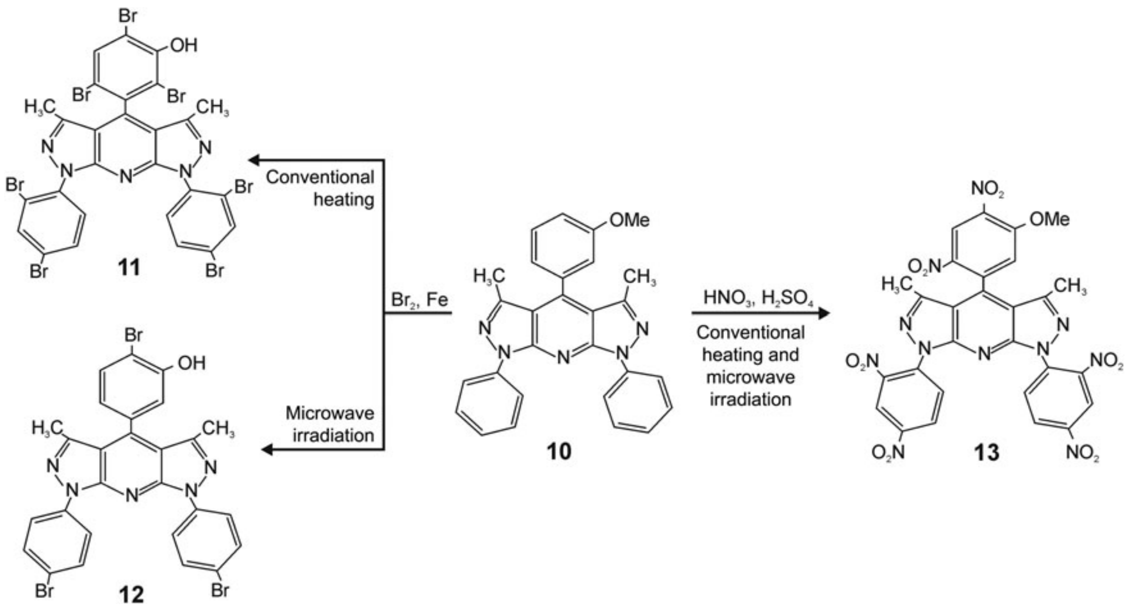
For an evaluation of the greenness of chemical processes, different metrics have been applied. Most of them refer to minimization of waste (E-factor, atom economy, mass intensity), cleanness of individual reaction (reaction mass efficiency, carbon efficiency) and elimination of hazardous chemicals (effective mass yield, environmental quotient) (Curzons et al., 2001; Constable et al., 2002; Andraos, 2005). The concept of EcoScale was introduced to combine both ecological and economical parameters of organic preparations (Van Aken et al., 2006).

E-factor

The environmental factor, which is one of the most often used green chemistry parameters, especially in chemical and pharmaceutical industry, expresses the ratio of the total waste generated in reaction (in one-step) or reactions (in multi-step)



Scheme 2 Products of conventional and microwave-assisted bromination and nitration of **4a–c**.



Scheme 3 Products of conventional and microwave-assisted bromination and nitration of **10**.

preparation to the weight of the end product (Sheldon, 1992). The following formula is used for calculations:

$$\text{E-factor}=\frac{\text{mass of total waste}}{\text{mass of product}}$$

The E-factor values for bromination of BPPs were very low (0.2–0.6), indicating a small waste amount produced. The values of E-factor did not differ for nitration reactions (0.1) and for bromination reactions of **4b** (0.3) and **4c** (0.2) conducted with different energy sources. In bromination, E-factor values for reactions of **4a** and **10** are 1.5 times higher than those for conventional heating (0.6) compared with microwave irradiation (0.4). E-factor of reaction of **1** is three times higher for conventional conditions (0.6) than that for microwave-induced reaction (0.2).

Atom economy

Atom economy shows how much of the reagents are incorporated in the final product. For reaction: A+B→C:

$$\text{AE}=\frac{\text{molecular weight of product C}}{\text{molecular weight of A}+\text{molecular weight of B}}\times 100\%$$

The highest atom economy is 100%; the closer it is to 100, the higher percentage of reactants appears in the final product.

According to Andraos (2005), over 40% of 36 analyzed substitution reactions meet the ‘golden atom economical’ reaction criteria. Constable et al. (2002) have provided the average atom economy value for bromination reaction as 84%. A threshold value of atom economy for ‘green’ reaction is 61.8% (Andraos, 2005).

Our bromination reactions of **1, 4a–c, 10** showed atom economy values in the range of 27.8–79.2% for conventional conditions and 72.1–99.5% for microwave irradiation. Only conventionally heated reaction 1 showed atom economy <61.8%, which excluded it from being ‘green’. Atom economies for all nitration reactions (65.9–98.7%) met the green reaction criteria according to Andraos (2005). The comparison of the atom economy, mass reaction efficiency and EcoScale values is presented in Table 1.

Reaction mass efficiency

For a general reaction: A+B→C,

$$\text{RME}=\frac{\text{molecular weight of product C}\times\text{percent yield}}{\text{molecular weight of A}+\left(\text{molecular weight of B}\times\text{molar ratio}\,\frac{\text{B}}{\text{A}}\right)}$$

This parameter takes into account the percentage yield of the reaction, which is a traditional metrics in organic synthesis. For reactions of bromination of BPPs, the yields for conventional conditions were: 43% **1**, 45% **4a**, 56% **4b**, 54% **4c** and 47% **10**, whereas for microwave-assisted reactions: 79% **1**, 76% **4a**, 97% **4b**, 87% **4c** and 84% **10** (Table 1). The values of the same parameter for conventional nitration were: 57% **4a**, 70% **4b; 10** and microwave-assisted nitration: 26% **4a** and 70% **4b; 10**.

The average value of the reaction mass efficiency, cited from the literature, is 63% for bromination reactions (Curzons et al., 2001). This value is close to the threshold reaction mass efficiency for ‘green reaction’, which is 61.8% (Andraos, 2005).

The reaction mass efficiency values calculated for bromination and nitration of BPPs were rather poor, especially for

Table 1 Reaction conditions and green chemistry metrics for bromination and nitration of BPPs.

Substrate	Method	E-factor	Atom economy	Reaction mass efficiency (%)	EcoScale	Yield (%)	Time (h)	Products
Bromination								
1	Conventional	0.6	27.8	32.4	53.5	43	10	**2** and **3**
	Microwave-assisted	0.2	99.5	67.2	72.5	79	0.1	**2**
4a	Conventional	0.6	61.8	39.9	54.5	45	12	**5**
	Microwave-assisted	0.4	72.9	67.4	71.0	76	0.2	**6**
4b	Conventional	0.3	78.9	44.2	60.0	56	12	**7a**
	Microwave-assisted	0.3	78.9	76.6	81.5	97	0.2	**7a**
4c	Conventional	0.2	79.2	37.3	59.0	54	12	**7b**
	Microwave-assisted	0.2	79.2	69.0	76.5	87	0.2	**7b**
10	Conventional	0.6	62.8	47.1	55.5	47	18	**11**
	Microwave-assisted	0.4	72.1	73.3	75.0	84	0.2	**12**
Nitration								
4a	Conventional	0.1	91.0	51.8	60.4	57	45	**8a** and **9a**
	Microwave-assisted	0.1	89.2	70.4	77.4	26	0.7–0.8	**8a**
4b	Conventional	0.1	91.5	64.5	67.2	70	45	**8b** and **9b**
	Microwave-assisted	0.1	89.7	68.4	71.1	70	0.7–0.8	**8b**
10	Conventional	0.1	87.1	55.4	64.5	70	45	**13**
	Microwave-assisted	0.1	87.1	55.4	65.5	70	0.7–0.8	**13**

conventional reaction conditions (Table 1). In bromination of BPPs, the reaction mass efficiency values obtained for reactions with a conventional energy source are approximately twice as much lower (32.4–47.1%) than those received for reactions under microwave irradiation (67.2–76.6%). The lowest reaction mass efficiency values were calculated for bromination of **1**. The nitration reactions showed low reaction mass efficiency values, especially for conventional reaction of **4a** (51.8%) and both conventional and microwave-assisted reaction of **10** (55.4%). These reactions, as well as bromination, conducted under conventional heating could not be regarded as ‘green’ according to Andraos (2005).

EcoScale

The concept of EcoScale was introduced by Van Aken et al. (2006) to evaluate the quality of the organic preparation on a laboratory scale. Parameters that are included in the evaluation encompass: yield, cost, safety, conditions and ease of workup/purification. An ‘ideal’ reaction, which has a score of 100 in the EcoScale, uses inexpensive compounds and is conducted at room temperature. Moreover, its yield is 100%, and it is safe for both the operator and for the environment. For each of the parameters that differ from ‘the ideal value’, the penalty points are assigned, lowering the total score. The penalty point values to calculate the EcoScale are published by Van Aken et al. (2006). The higher the score, the greener and more economical organic preparation is. The EcoScale can be calculated with the following formula:

EcoScale=100-sum of individual penalties

Based on the EcoScale value, the ranking of reaction conditions is given as: >75, excellent; 50–75, acceptable; and <50, inadequate.

The EcoScale values for bromination of BPPs were in the range of 53.5–60.0 (conventional reactions) and 71.0–81.5 (microwave-assisted reactions). The excellent conditions, according to the EcoScale, were achieved for microwave-assisted bromination of **4b,c, 10** (Table 1). Both conventional and microwave-assisted nitration reactions were acceptable in terms of the EcoScale. Only for nitration of **4a**, conducted under microwave irradiation, the excellent rank can be assigned (score 77.4 in EcoScale).

Conclusions

Evaluation of laboratory-scale novel bromination and nitration reactions of bis-pyrazolo[3,4-b;4′3′-*e*]pyridines with respect to the different green chemistry metrics and EcoScale has allowed to assess the greenness of these reactions. All the reactions could be considered ‘green’ on the basis of their E-factor, atom economy (except for bromination of **1** conducted under conventional heating) and EcoScale. The mass reaction efficiency values were the lowest for almost all conventionally heated bromination and nitration reactions. Microwave-assisted bromination and nitration (except for nitration of **10**) meet the criteria of ‘green’ reaction with respect to all calculated parameters. Microwave irradiation, although controversial from the point of view of energy efficiency at laboratory scale, as recently discussed by Moseley and Kappe (2011), has many advantages. The most important ones include shorter reaction time, usually higher selectivity and easier preparation.

Experimental section

Microwave-assisted reactions were conducted in Teflon vessels. For bromination, 0.001 mol of BPP and 2.5 ml (0.049 mol) of bromine were placed with 0.07 g (0.001 mol) of iron (catalyst) in a vessel and irradiated with 240 W of the reactor power in the temperature range of 60–65°C for 7–10 min. After that time, the mixture was added to 15 ml (0.833 mol) of H_2O and filtrated. The residue was washed with ethanol. The final products were chromatographically purified with the use of dichloromethane as an eluent.

Three BPPs were subjected to nitration with the use of 0.005 mol of 65% HNO_3 and 0.01 mol of 95% H_2SO_4 (1:2). These reactions were conducted under conventional heating and microwave irradiation. First, substrates were dissolved in sulfuric acid and then a nitrating mixture was added. Nitration in conventional conditions took 24 h. The substrates were heated to 50–60°C in the conventional procedure and to 60–65°C in the microwave procedure. The reactions were controlled using thin-layer chromatography. The reaction mixture was neutralized with saturated aqueous Na_2CO_3. The two products **8a,b** and **9a,b** of conventionally heated reactions of **4a,b** could not be separated with the use of column chromatography and dichloromethane as an eluent due to their poor solubility.

Infrared spectra were obtained using a SPECORD M-80 spectrometer CARL ZEISS JENA in KBr disks. ^{1}H NMR spectra were recorded for solutions in $CDCl_3$ with the Bruker AMX 400 spectrometer at a frequency of 400 MHz. Mass spectra were recorded by the Finnigan MAT 95 spectrometer at the ionization potential of 70 eV. Microwave reactions were carried out in the microwave reactor PLAZMATRONIKA (Poland). Column chromatography was performed on silica gel 60 (230–400 mesh, Merck). Elemental analysis of compounds **2, 7a** and **12** was performed with elemental analyzer Perkin/Elmer 2400 CHN.

Characterization of the products of bromination of BPPs

1,7-Bis(4-bromophenyl)-3,5-dimethyl-bis-pyrazolo[3,4-b;4′,3′-*e*]pyridine (2) m.p. 238–240°C; IR: 1616, 1584, 1552, 1488, 1408, 1376, 1336, 1316, 1168, 1100, 840, 820, 776 cm^{-1}; ^{1}H NMR: δ, 2.61 (s, 6H, 3/5-CH_3), 7.21–7.33 (m, 2H, H_{Ar}), 7.52 (t, J=7.9 Hz, 4H, H_{Ar}), 8.14 (s, 1H, H_{Ar}), 8.37 (d, J=7.8 Hz, 4H, H_{Ar}); MS: *m/z* 339 (M^+, 100), 338 (31), 340 (51), 341 (5), 170 (9), 77 (20), 51 (6). Anal. calcd. for $C_{21}H_{15}N_5Br_2$: C, 50.73; H, 3.04; N, 14.08; Br, 32.15. Found: C, 49.08; H, 2.68; N, 13.44; Br, 33.80.

1,4,7-Tris(4-bromophenyl)-3,5-dimethyl-bis-pyrazolo[3,4-b;4′,3′-e]pyridine (6) m.p. 230–239°C; IR: 1590, 1575, 1523, 1500, 1450, 1391, 1346, 1027, 840, 743, 515 cm^{-1}; ^{1}H NMR: δ, 2.08 (s, 6H, 3/5-CH_3), 7.45 (dd, J=6.8 Hz, J=1.8 Hz, 2H, H_{Ar}), 7.58 (d, J=6.7 Hz, 2H, H_{Ar}), 8.30 (dd, J=8.8 Hz, J=2.8 Hz, 4H, H_{Ar}), 7.65 (dd, J=8.8 Hz, J=2.8 Hz, 4H, H_{Ar}); MS: 573 (M^+, 100), 575 (58), 576 (24), 572 (31), 571 (43), 492 (3).

1,7-Bis(4-bromophenyl)-4-(4-chlorophenyl)-3,5-dimethyl-bis-pyrazolo[3,4-b;4′,3′-e]pyridine (7a) m.p. 272–274°C; IR: 1597, 1500, 1452, 1345, 1250, 1101, 1015, 845, 575, 510 cm^{-1}; ^{1}H NMR: δ, 2.12 (s, 6H, 3/5-CH_3), 7.41 (d, J=8.2 Hz, 2H, H_{Ar}), 7.58 (d, J=8.2 Hz, 2H, H_{Ar}), 7.65 (d, J=8.8 Hz, 4H, H_{Ar}), 8.28 (d, J=8.8 Hz, 4H, H_{Ar}); MS: 607 (M^+, 100), 608 (57), 609 (80), 606 (42), 605 (44), 573 (2), 526 (2). Anal. calcd. for $C_{27}H_{18}N_5ClBr_2$: C, 53.36; H, 2.98; N, 11.52; Br, 26.30. Found: C, 53.53; H, 2.89; N, 11.46; Br, 26.42.

1,7-Bis(4-bromophenyl)-3,5-dimethyl-4-(4-nitrophenyl)-bis-pyrazolo[3,4-b;4′,3′-*e*]pyridine (7b) m.p.>350°C; IR: 1590, 1581, 1500, 1395, 1350, 1250, 1100, 1080, 590 cm^{-1}; ^{1}H NMR: δ, 2.09 (s, 6H, 3/5-CH_3), 7.67 (d, J=8.8 Hz, 4H, H_{Ar}), 7.71 (d, J=8.5 Hz, 2H, H_{Ar}), 8.29 (d, J=8.8 Hz, 4H, H_{Ar}), 8.48 (d, J=8.5 Hz, 2H, H_{Ar}); MS: *m/z* 618 (M^+, 100), 619 (50), 620 (56), 617 (33), 616 (48), 572 (12), 492 (3).

4-(4-Bromo-3-hydroxyphenyl)-1,7-bis(4-bromophenyl)-3,5-dimethyl-bis-pyrazolo[3,4-b;4′,3′-*e*]pyridine (12) m.p.>350°C; IR: 3456, 1664, 1576, 1476, 1432, 1352, 1288, 1104, 1040, 1008, 864, 812, 784, 696, 588 cm^{-1}; ^{1}H NMR: δ, 2.18 (s, 6H, 3/5-CH_3), 6.20 (s, 1H, OH), 7.67 (d, J=8.8 Hz, 4H, H_{Ar}), 7.70 (d, J=8.9 Hz, 1H, H_{Ar}), 7.97 (s, 1H, H_{Ar}), 8.32 (d, J=8.8 Hz, 4H, H_{Ar}), 8.36 (d, J=8.9 Hz, 1H, H_{Ar}). Anal. calcd. for $C_{27}H_{14}N_5Br_7O$: C, 32.97; H, 1.43; N, 7.12; Br, 56.86. Found: C, 33.07; H, 1.39; N, 7.23; Br, 56.84.

Characterization of the products of nitration of BPPs

3,5-Dimethyl-1,7-bis(2,4-dinitrophenyl)-4-phenyl-bis-pyrazolo[3,4-b;4′,3′-*e*]pyridine (8a) m.p.>350°C; IR: 1602, 1584, 1576, 1448, 1406, 1138, 918, 748 cm^{-1}; ^{1}H NMR: δ, 2.15 (s, 6H, 3/5-CH_3), 7.47–7.52 (m, 3H, H_{Ar}), 7.61–7.67 (m, 2H, H_{Ar}), 8.21 (d, J=8.9 Hz, 2H, H-5″), 8.62 (dd, J=8.9 Hz, J=1.7 Hz, 2H, H_{Ar}), 8.91 (s, 1H, H_{Ar}).

4-(4-Chlorophenyl)-3,5-dimethyl-1,7-bis(2,4-dinitrophenyl)-bis-pyrazolo[3,4-b;4′,3′-e]pyridine (8b) m.p.>350°C; IR: 1604, 1590, 1562, 1496, 1402, 1376, 1244, 1132, 1104, 844, 832, 742 cm^{-1}; ^{1}H NMR: δ, 2.14 (s, 6H, 3/5-CH_3), 7.46 (d, J=8.6 Hz, 2H, H_{Ar}), 7.62 (d, J=8.6 Hz, 2H, H_{Ar}) 8.21 (d, J=9.01 Hz, 2H, H_{Ar}), 8.63 (dd, J=9 Hz, J=2.4 Hz, 2H, H_{Ar}), 8.92 (s, 1H, H_{Ar}).

3,5-Dimethyl-1-(2,4-dinitrophenyl)-7-(4-nitrophenyl)-4-phenyl-bis-pyrazolo[3,4-b;4′,3′-*e*]pyridine (9a) IR: 1604, 1576, 1560, 1504 1460, 1408, 1336, 1168, 1080, 928, 740, 716 cm^{-1}; ^{1}H NMR: δ, 2.09 (s, 6H, 3/5-CH_3), 7.78–7.82 (m, 3H, H_{Ar}), 7.87–7.92 (m, 2H, H_{Ar}), 8.28–8.32 (m, 3H, H_{Ar}), 8.56–8.61 (m, 3H, H_{Ar}), 8.81 (s, 1H, H_{Ar}).

4-(4-Chlorophenyl)-3,5-dimethyl-1-(2,4-dinitrophenyl)-7-(4-nitrophenyl)-bis-pyrazolo[3,4-b;4′,3′-*e*]pyridine (9b) IR: 1604, 1592, 1524, 1504, 1440, 1384, 1260, 1112, 1028, 912,848, 728 cm^{-1}; ^{1}H NMR: δ 2.11 (s, 6H, 3/5-CH_3), 7.49 (d, J=8.3 Hz, 2H, H_{Ar}), 7.59 (d, J=8.3 Hz, 2H, H_{Ar}), 8.25–8.31 (m, 3H, H_{Ar}), 8.57–8.61 (m, 3H, H_{Ar}), 8.82 (s, 1H, H_{Ar}).

4-(3-Metoxy-2,4-dinitrophenyl)-3,5-dimethyl-1,7-di(2,4-dinitrophenyl)-bis-pyrazolo[3,4-b;4′,3′-*e*]pyridine (13) m.p.>350°C; IR: 1595, 1500, 1445, 1381, 1350, 1320, 1252, 1104, 1075, 1020, 960 cm^{-1}; ^{1}H NMR: δ, 2.13 (s, 6H,3/5-CH_3), 4.13 (s, 3H, OCH_3), 7.20 (s, 1H, H_{Ar}), 8.21 (d, J=8.9 Hz, 2H, H_{Ar}), 8.66 (dd, J=8.9 Hz, J=2.4 Hz, 2H, H_{Ar}), 8.90 (s, 2H, H_{Ar}), 8.99 (s, 1H, H_{Ar}); MS: *m/z* 715 (M^+, 59), 716 (20), 714 (43), 710 (27), 700 (16), 670 (19), 669 (16).

References

Anastas, P.; Eghbali, N. Green chemistry: principles and practice. *Chem. Soc. Rev.* **2010**, *39*, 301–312.

Andraos, J. Unification of reaction metrics for green chemistry ii: evaluation of named organic reactions and application to reaction discovery. *Org. Process Res. Dev.* **2005**, *9*, 404–431.

Armenta, S.; Garrigues, S.; de la Guardia, M. Green analytical C. *Anal. Chem.* **2008**, *27*, 497–511.

Constable, D.J.C.; Curzons, A.D.; Cunningham, V.L. Metrics to ‘green’ chemistry – which are the best? *Green Chem.* **2002**, *4*, 521–527.

Curzons, A. D.; Constable, D. J.C.; Mortimer, D. N.; Cunningham, V. L. So you think your process is green, how do you know? Using principles of sustainability to determine what is green – a corporate perspective. *Green Chem.* **2001**, *3*, 1–6.

Deligeorgiev, T.; Gadjev, N.; Vasilev, A.; Kaloyanova, S.; Vaquero, J. J.; Alvarez-Builla, J. Green chemistry in organic synthesis. *Mini-Rev. Org. Chem.* **2010**, *7*, 44–53.

He, Z.; Milburn, G.; Danel, A.; Puchała, A.; Tomasik, P.; Rasała, D. Blue electroluminescence of novel pyrazoloquinoline and bispyrazolopyridine derivatives in doped polymer matrices. *J. Mater. Chem.* **1997**, *7*, 2323–2325.

Joshi, K. C.; Dubey, K.; Dandia, A. Studies in potential organofluorine antibacterial agents. Part 6: synthesis and antibacterial activity of some new fluorine containing 1,3,4,5,7-pentasubstituted dipyrazolo[3,4-b;4,3-3]pyridines. *Pharmazie* **1981**, *36*, 336–337.

Marcinkowska, M.; Puchała, A.; Rasała, D. Zastosowanie promieniowania mikrofalowego w reakcji bromowania bis-pirazolo[3,4-b;4′-3′-e]pirydyn. *Aparatura Badawcza i Dydaktyczna* **2010**, *4*, 109–115.

Moseley, J.D.; Kappe, C.O. A critical assessment of the greenness and energy efficiency of microwave-assisted organic synthesis. *Green Chem.* **2011**, *13*, 794–806.

Parusel, A.B.J.; Schamschule, R.; Piorun, D.; Rechthaler, K.; Puchała, A.; Rasała, D.; Rotkiewicz, K.; Kohler, G. Semiempirical characterisation of substituted bis-pyrazolopyridines as new bulky electron donor-acceptor systems in their electronic ground state. *J. Mol. Struct.(TEOCHEM)* **1997**, *419*, 63–75.

Puchała, A. Synthesis and properties of bis-pyrazolo[3,4-b;4′,3′-e] pyridines. Doctors thesis. Jan Kochanowski University, Kielce, 2003 (in Polish).

Puchała, A.; Rasała, D; Kolehmainen, E.; Prokesova, M. An improved general method for the preparation of 4-aryl substituted *bis*pyrazolo[3,4-b;4,3′-e]pyridines. *Org. Prep. Proc. Int.* **1997**, *29*, 212–216.

Quiroga, J.; Portilla, J.; Insuasty, B.; Abonia, R.; Nogueras, M.; Sortino, M.; Zacchino, S. Solvent-free microwave synthesis of bis-pyrazolo[3,4-*b*:4′,3′-*e*]-pyridines and study of their antifungal properties. *J. Heterocyclic Chem.* **2005**, *42*, 61–66.

Rechthaler, K.; Schamschule, R.; Parusel, A.B.J.; Rotkiewicz, K.; Piorun, D.; Köhler, G. Fluorescence properties of an electron acceptor substituted bis-pyrazoloquinoline derivatives: NO_2-DMPP. *Acta Phys. Polonica A* **1999**, *95*, 321–334.

Sheldon, R.A. Organic synthesis; past, present and future. *Chem. Ind.* (*Lond.*) **1992**, *23*, 903–906.

Tobiszewski, M.; Mechlińska, A.; Namieśnik, J. Green analytical chemistry – theory and practice. *Chem. Soc. Rev.* **2010**, *39*, 2869–2878.

Van Aken, K.; Strekowski, L.; Patiny, L. EcoScale, a semiquantitative tool to select an organic preparation based on economical and ecological parameters. *Beilstein J. Org. Chem.* **2006**, *2*, 3.

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