Synthesis of Substituted Phenanthrenes via Intramolecular Condensation Based on Temperature-Dependent Deprotonation Using a Weak Carbonate Base

Katrien Monsieurs,[a] Geert Rombouts,[a] Pál Tapolcsányi,[b] Péter Mátyus,*[b] Bert U. W. Maes*[a]

[a] Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, 2020 Antwerp, Belgium
Fax +32(3)2653233; E-mail: bert.maes@ua.ac.be

[b] Department of Organic Chemistry, Semmelweis University, Högyes E. u. 7., 1092 Budapest, Hungary
Fax +36(1)217085; E-mail: matypet@szerves.sote.hu

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This paper is dedicated to Professor Miha Tišler on the occasion of his 80th birthday.

Abstract: Construction of substituted phenanthrenes via intramolecular condensation of 2′-methylbiphenyl-2-carbaldehydes using a mild base at 200 °C is described. The required high temperature can be quickly reached and easily maintained using microwave flash heating.

Key words: phenanthrene, Suzuki reaction, condensation, carbonate base, microwave irradiation, 11*H*-benzo[*a*]carbazole

Within the chemical class of polycyclic aromatic compounds phenanthrene is an important core structure. The phenanthrene moiety can not only be found in several natural products, of which many exhibit interesting biological activity,[1] but more recently phenanthrenes have also been shown as interesting ligands for novel catalyst systems.[2] Therefore, the development of new short synthetic methods for this important class of organic compounds has regained importance. Thanks to the progress made during the past two decades in the field of biphenyl synthesis by palladium-catalyzed carbon–carbon bond-formation reactions,[3,4] the synthesis of phenanthrenes starting from biphenyls became a straightforward approach. Formation of the C9–C10 bond can be carried out in multiple ways, depending on the substitution pattern of the biphenyl compound. Recently reported synthetic procedures include ring-closing metathesis,[5,6] electrophile-induced[7–9] or transition-metal-catalyzed cyclization[10,11] of 2-alkynylbiphenyl compounds, oxidative coupling of in situ generated ylides,[12] ring closure via chromium–carbene complexes[13–15] and palladium-catalyzed annulation reactions.[16–18] The work of three research groups came into our specific attention due to the parallels with our ongoing research concerning the synthesis of azapolycyclic aromatic compounds via a combination of a Suzuki and a subsequent ring-closure reaction.[19] Snieckus described a combination of his Directed *ortho*-Metalation (DoM) methodology (arylboronic acid preparation) with a Suzuki cross-coupling reaction for the synthesis of a *N*,*N*-diethyl 2′-methylbiphenyl-2-carboxamide substrate. Subsequent ring closure was achieved by Directed remote Metalation (DreM) in which the deprotonation of the 2′-methyl hydrogen by lithium diisopropylamide initiates the mechanism.[20,21] The resulting 9-phenanthrols could be easily converted into the corresponding phenanthrenes. Secondly, de Koning and co-workers adopted a comparable strategy, also starting with a Suzuki cross-coupling reaction for the synthesis of the starting material, i.e. a 2′-methylbiphenyl-2-carbaldehyde. This substrate type undergoes a ring-closure reaction when treated with potassium *tert*-butoxide under simultaneous irradiation with a 400 watt high-pressure mercury lamp.[22] The suggested mechanisms for this cyclization reaction include a photochemical pathway based on photoenolization and a simultaneous anionic mechanism starting with deprotonation of the methyl substituent. Finally, Kraus and coworkers recently used a similar ring-closure reaction for the synthesis of the natural product Denbinobin.[23] As in the case of de Koning, a 2′-methylbiphenyl-2-carbaldehyde served as the starting compound, but in this case P_4-*t*-Bu was used as a base, and irradiation with light was omitted.

Clearly, the deprotonation of the methyl group is the crucial step in the abovementioned reaction sequences. Not unexpectedly, all three research groups used a strong base to accomplish this deprotonation since the pK_a value of the benzylic methyl protons is very high. However, the use of strong (and often nucleophilic) bases imposes a serious limitation on the functional group compatibility. We reasoned that the acidity should be greatly influenced by the chosen solvent and reaction temperature.[24,25] Moreover, even if the deprotonation equilibrium is still very unfavorable, the occurring aromatization in the cyclization might still drive the reaction to completion.

Based on this argument, we decided to examine the possibility of using only a weak, non-nucleophilic base for the ring closure of 2′-methylbiphenyl-2-carbaldehydes. Since the need of applying a high temperature could be foreseen (pK_a is temperature-dependent),[24] the use of microwave heating in a closed vessel was an obvious choice. After all, microwave irradiation is known to be highly efficient for rapid and safe heating of reaction mixtures and temperatures far above the boiling point of the solvent can be easily reached and maintained.[26,27] Interestingly, to the best of our knowledge temperature

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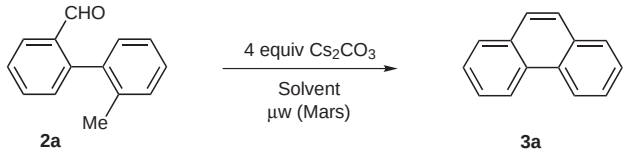
dependence of pK_a, involving high-temperature chemistry, has not yet been exploited synthetically.

For the first test and the subsequent optimization of the reaction conditions unsubstituted 2′-methylbiphenyl-2-carbaldehyde was chosen as the substrate and cesium carbonate was selected as the weak non-nucleophilic base. The starting compound **2a** could be easily prepared in excellent yield via Suzuki coupling of 2-bromotoluene with 2-formylphenylboronic acid under standard Gronowitz reaction conditions.[28] The subsequent ring-closure reaction was carried out in an industrial multimode microwave oven (Mars) with four equivalents of base. The crude reaction mixtures were worked up by extraction and subsequently analyzed by TLC and ^{1}H NMR. In the cases where the reaction did not reach completion, the ratio of reaction product (RP) to starting material (SM) was deduced from the ^{1}H NMR spectrum.

In the first part of the optimization study different solvents were tested. The results are summarized in Table 1. Tetrahydrofuran, dioxane and 1,2-dimethoxyethane (Table 1, entries 1–3) did not give any conversion, while in dimethyl sulfoxide or *N*-methyl-2-pyrrolidinone (Table 1, entries 4 and 5) the starting compound decomposed. Only when *N*,*N*-dimethylformamide was chosen as the solvent, the starting material was successfully converted into the desired phenanthrene. A reaction time of 30 minutes turned out to be insufficient for complete conversion (Table 1, entry 6), but after 90 minutes all the starting compound was consumed, and the product could be isolated in 54% yield after column chromatography (Table 1, entry 7).

Table 1 Effect of the Solvent on the Ring Closure of **2a**[29]



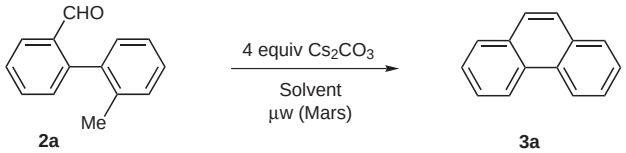
2a **3a**

	Solvent	Temp (°C)	Time (min)	RP/SM	Yield (%)	Comment
1	THF	130	90			Only SM
2	Dioxane	200	90			Only SM
3	DME	193[30]	30			Only SM
4	DMSO	200	30			Decomposition
5	NMP	200	30			Decomposition
6	DMF[a]	200	30	3.19		
7	DMF[a]	200	90		54[31]	SM was consumed

[a] Anhyd DMF was used.

Secondly, the role of the reaction temperature in the ring-closure reaction was examined (Table 2). The results clearly show that the temperature must be raised to around 180 °C to get the reaction started (Table 2, entry 4). Moreover, heating the mixture to 200 °C accelerated the reaction to a considerable extent, as can be seen from the significantly improved reaction product/starting material ratio (Table 2, entry 5).

Table 2 Effect of the Temperature on the Ring Closure of **2a**[29]



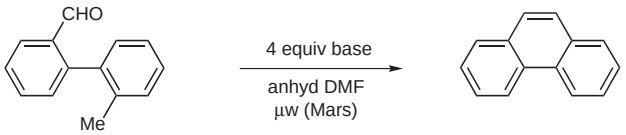
2a **3a**

	Solvent	Temp (°C)	Time (min)	RP/SM
1	DMF[a]	150	30	Only SM
2	DMF[a]	160	30	Only SM
3	DMF[a]	170	30	Only SM
4	DMF[a]	180	30	0.35
5	DMF[a]	200	30	3.19

[a] Anhyd DMF was used

Finally, the effect of some other weak bases on the ring-closure reaction was tested. The results are summarized in Table 3. The importance of the cation was investigated by substituting cesium carbonate by potassium carbonate (Table 3, entry 2). As could be expected from the HSAB principle, the harder potassium counterion has a stronger interaction with the hard carbonate base, making the latter less 'available' for the deprotonation of the substrate. Likewise, after deprotonation of the substrate, the potassium counterion will be less dissociated from the formed carbanion than the softer cesium ion. Therefore the nucleophilic attack of the carbanion on the carbonyl group is hampered when potassium carbonate is used instead of cesium carbonate. This characteristic is reflected in the decreasing reaction product/starting material ratio. In line with this observation, when sodium carbonate was used, no conversion to the reaction product was observed (Table 3, entry 3).

Table 3 Effect of the Base on the Ring Closure of **2a**[29]



2a **3a**

	Base	Temp (°C)	Time (min)	RP/SM
1	Cs_2CO_3	200	30	3.19
2	K_2CO_3	200	30	0.05
3	Na_2CO_3	200	30	Only SM
4	CsOAc	200	30	Only SM
5	K_2CO_3 + 18-crown-6	200	30	0.05

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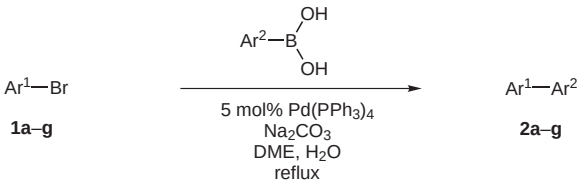
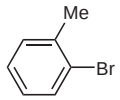
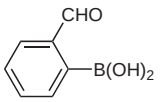
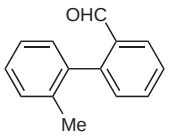
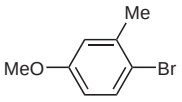
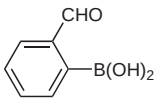
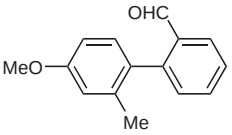
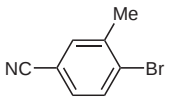
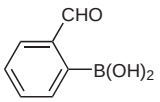
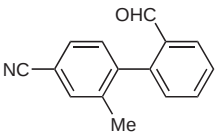
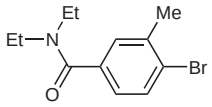
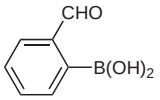
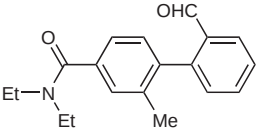
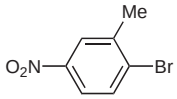
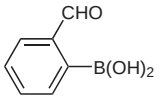
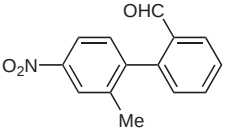
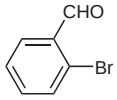
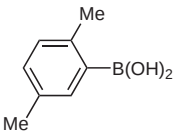
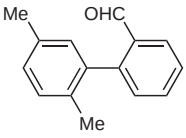
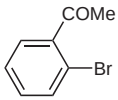
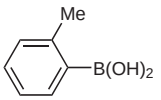
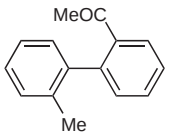
Table 4 Synthesis of 2′-Methylbiphenyl-2-carbaldehydes and 1-(2′-Methylbiphenyl-2-yl)ethanone[32]



1a–g **2a–g**

	Phenylbromide **1a–g**	Boronic acid	Product **2a–g**	Yield (%)
1				90% **2a**
2				49% **2b**
3				70% **2c**
4				80% **2d**
5				72% **2e**
6				93% **2f**
7				95% **2g**

The possibility of using an even weaker base was also examined. Therefore, the experiment was repeated with four equivalents of cesium acetate (Table 3, entry 4), but no reaction product was formed after 30 minutes at 200 °C. As a final experiment in this set we tested if the basic character of the anion could be enhanced by complexation of the counterion with a crown ether. 18-Crown-6 was selected due to its efficiency in capturing potassium ions. On comparing the ring-closure reaction using four equivalents of potassium carbonate and 0.5 equivalents of 18-crown-6 (Table 3, entry 5) with the reaction in which the crown ether was omitted (Table 3, entry 2), the conversion remained unchanged. This observation can be explained by taking into account that the potassium ion is already solvated by the *N*,*N*-dimethylformamide and its complexation with the crown ether does not improve the 'availability' (basicity) of the carbonate ion or carbanion any further, thus emphasizing the importance of the solvent. From the above described experiments it is clear that the best results for the ring-closure reaction were obtained with cesium carbonate as base in *N*,*N*-dimethylformamide at 200 °C.

In the next part of the investigation the functional group compatibility of the new reaction conditions was tested. Therefore a diverse set of substituted 2′-methylbiphenyl-2-carbaldehydes was synthesized via Suzuki cross-coupling reaction of the properly substituted phenylbromide and phenylboronic acid under Gronowitz conditions. Table 4 shows that the corresponding biphenyl compounds were isolated in good to excellent yields. The resulting substrates were then subjected to the optimized

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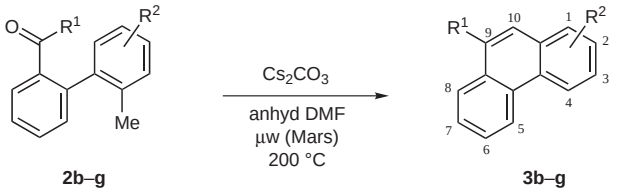
conditions for ring closure (Table 5). A methoxy group (Table 5, entry 1) was the first challenging substituent investigated since its electron-releasing property makes the methyl group less acidic. Nevertheless, the ring-closure reaction was completed after 90 minutes, and the phenanthrene **3b** could be isolated in a very good yield. Subsequently, some functional groups that are sensitive to strong nucleophilic bases were screened, namely, a cyano group, an amide group and a nitro group (Table 5, entries 2–4). Interestingly, the biphenyl compounds **2c**–**2e** could be converted into the corresponding phenanthrenes **3c**–**3e** under our optimized reaction conditions without any problem. To enable the comparison of our weak base/high temperature approach with the classical procedures based on the use of a strong base, the ring-closure reactions of the biphenyl compounds **2c**–**2e** were repeated with potassium *tert*-butoxide (4 equiv) as the base at a reaction temperature of 80 °C with *N*,*N*-dimethylformamide as the solvent. TLC analysis of the reaction mixtures revealed that in all three cases the starting compound was completely consumed after ten minutes. For the cyano and the amide functionalities, the presence of the strong base resulted in a more complex reaction mixture and the chromatographic purification was consequently more problematic and time-consuming. In accordance with this observation, the isolated yields of **3c** (60%) and **3d** (70%) were lower than those obtained with our weak base/high temperature approach. Interestingly, when the nitro-substituted compound **2e** was subjected to potassium *tert*-butoxide in *N*,*N*-dimethylformamide at 80 °C, no expected 2-nitrophenanthrene **3e** was formed. Instead, the main reaction product was identified as 1-hydroxy-2-nitrophenanthrene (33%).[33] This result demonstrates that in some cases the choice of the base can even influence the outcome of the reaction.

Finally, two substrates bearing an extra methyl group (**2f**, **2g**) were subjected to the new ring-closure reaction conditions. The resulting phenanthrenes **3f** and **3g** could be isolated in moderate to good yields. For 1-(2′-methylbiphenyl-2-yl)ethanone (**2g**) a longer reaction time was required, probably due to competitive deprotonation of the extra, substantially more acidic, methyl group of the acetyl group that slowed down the desired cyclization reaction.

Table 5 Synthesis of Substituted Phenanthrenes via Ring Closure of **2b**–**g**[29]

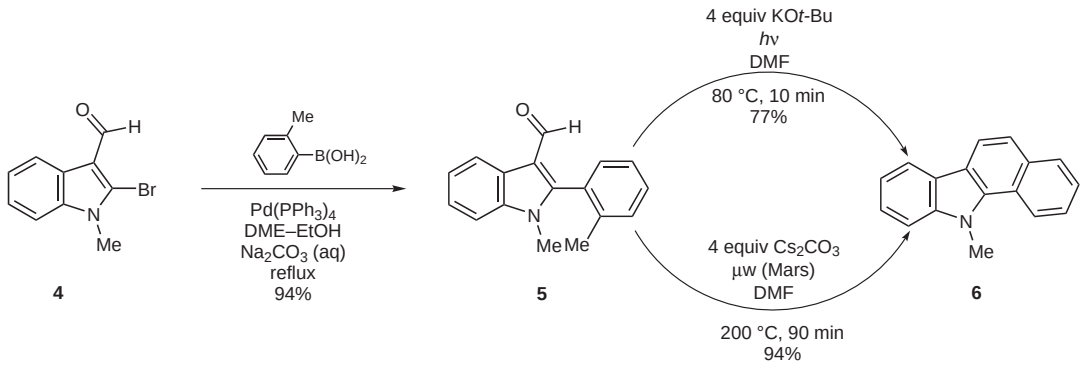


2b–g **3b–g**

	R^1	R^2	Time (min)	Yield (%)	Product
1	H	2-MeO	90	84	**3b**
2	H	2-CN	90	70	**3c**
3	H	2-$CON(Et)_2$	45	82	**3d**
4	H	2-NO_2	45	91	**3e**
5	H	3-Me	90	40[31]	**3f**
6	Me	H	420	89	**3g**

In order to test the further scope of this new ring-closure strategy, we decided to apply the method for the synthesis of a heterocyclic compound. 11-Methyl-11*H*-benzo[*a*]carbazole (**6**) was selected as the target since it permits a comparison with the method of de Koning et al. (Scheme 1).[34] Starting compound **5** could easily be prepared via Suzuki cross-coupling reaction of 2-bromo-1-methyl-1*H*-indole-3-carbaldehyde (**4**) with 2-methylphenylboronic acid. Subsequently, **5** could be smoothly converted into 11-methyl-11*H*-benzo[*a*]carbazole (**6**), which was isolated in excellent yield. On comparing our condensation reaction with the result obtained by de Koning, it is clear that although with cesium carbonate as the base a longer reaction time is needed, the yield is significantly higher.

In summary, the obtained results reveal that a careful choice of solvent in combination with the application of a high temperature opens the possibility of using a weak base for a deprotonation reaction that normally would require addition of a strong base. This new strategy was illustrated by the conversion of 2′-methylbiphenyl-2-carbaldehyde into phenanthrene by using the weak non-nucleophilic base cesium carbonate in *N*,*N*-dimethylformamide as the solvent at a reaction temperature of 200 °C.



Scheme 1

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The reaction conditions were successfully applied on substrates bearing different types of challenging substituents, and additionally as an example of the applicability of our new protocol in heterocyclic chemistry a 11*H*-benzo[*a*]carbazole was synthesized.

Acknowledgment

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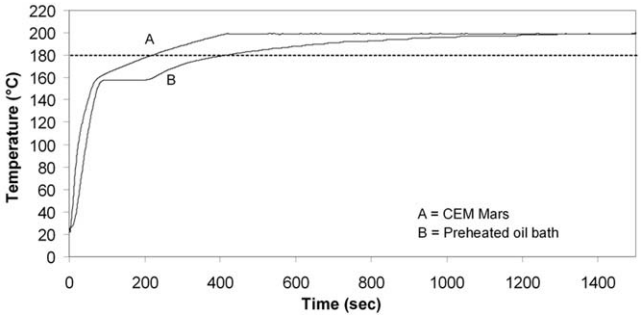

Figure 1

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(27) Figure 1 shows the heating profiles of a mixture of DMF (5 mL) and Cs_2CO_3 (3 mmol) in an 80 mL vessel, when heated by microwave irradiation on one hand and conventional heating in a preheated oil bath (oil-bath temperature: 220 °C) on the other hand. It is clear that the mixture reaches the set temperature of 200 °C considerably faster in the case of microwave heating. For an experimental set-up to compare reactions under conventional (oil bath) and microwave heating, see: Hostyn, S.; Maes, B. U. W.; Van Baelen, G.; Gulevskaya, A.; Meyers, C.; Smits, K. *Tetrahedron* **2006**, *62*, 4676.
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(29) **General Procedure for the Synthesis of Phenanthrenes 3a–g and 11-Methyl-11*H*-benzo[*a*]carbazole (6)**: An 80-mL Greenchem vessel was charged with biphenyl compound **2a–g** (0.75 mmol), Cs_2CO_3 (3 mmol) and anhyd DMF (5 mL). The vessel was flushed with argon under magnetic stirring for a few minutes. Subsequently, the vessel was sealed and heated to 200 °C in a Mars multi-mode microwave oven (CEM). The set power was 300 W. The total irradiation time (including the ramp time to the set temperature) was 90 min, unless indicated otherwise. After cooling the reaction mixture was poured into H_2O (100 mL) and was extracted with EtOAc (3 × 100 mL). The combined organic fractions were dried over $MgSO_4$, evaporated to dryness and purified via flash column chromatography on silica gel.
(30) It was not possible to reach 200 °C when DME was used as the solvent. At a temperature of 193 °C the autogenic pressure rose to the maximum allowed value of 200 psi. The safety settings of the microwave apparatus stopped microwave irradiation of the vessel. The reaction mixture was subsequently held at 193 °C not to exceed 200 psi. Figure 2 shows the heating profile.

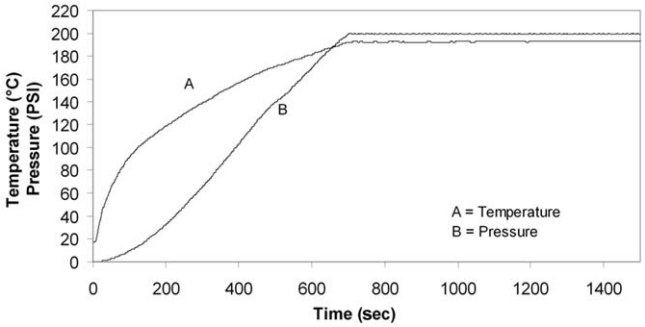

Figure 2

(31) The isolation of unsubstituted phenanthrene and 3-methylphenanthrene was hampered by their volatility. It is possible that this also contributes to the lower yields obtained for these compounds.
(32) **General Procedure for the Synthesis of Biphenyls 2a–g**: A two-necked flask was charged with phenylbromide **1a–g**, arylboronic acid (1.5 equiv), $Pd(PPh_3)_4$ (5 mol%), and DME

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(6 mL/mmol **1**). The flask was connected to a reflux condenser and flushed with nitrogen (via the second neck) for 2 min under magnetic stirring. Subsequently, an aq solution of 10% Na_2CO_3 (1 mL/mmol **1**) was added and the reaction mixture was stirred and refluxed overnight in an oil bath under a N_2 atmosphere. After cooling, the reaction mixture was poured into H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, evaporated to dryness and purified by flash column chromatography on silica gel.

(33) 1-Hydroxy-2-nitrophenanthrene: mp 160 °C (Lit.[35] 161–162 °C). ^{1}H NMR: (acetone-d_6): δ = 8.82–8.88 (m, 1 H), 8.44 (d, *J* = 9.5 Hz, 1 H), 8.38 (d, *J* = 9.2 Hz, 1 H), 8.27 (d, *J* = 9.5 Hz, 1 H), 8.07–8.12 (m, 1 H), 8.03 (d, *J* = 9.1 Hz, 1 H), 7.77–7.83 (m, 2 H). A derivatization of this compound was carried out to provide an extra confirmation of its structure. 1-Methoxy-2-nitrophenanthrene was synthesized by methylation of 1-hydroxy-2-nitrophenanthrene; mp 120–121 °C (Lit.[35] 122–123 °C).

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