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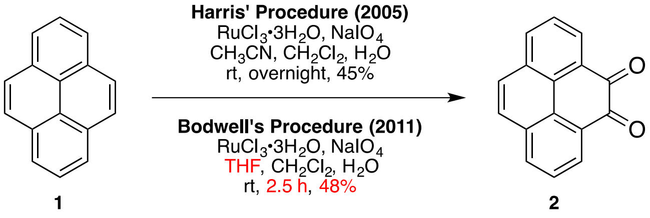
Synthesis of Pyrene-4,5-dione on a 15 g Scale

Joshua C. Walsh,[a] Kerry-Lynn M. Williams,[a] Dominik Lungerich,[b] and Graham J. Bodwell*[a]

Abstract: A scalable and efficient method for the synthesis of pyrene-4,5-dione has been developed. The addition of 5 mol% *N*-methylimidazole (NMI) to a known oxidation reaction was shown to marginally improve the yield and dramatically improve the ease of the workup and thus the amount of product isolable in a day using regular laboratory equipment.

Introduction

The use of pyrene as a key building block for the synthesis of designed π molecular systems, molecular sensors and carbon-based materials has increased dramatically over the past decade.[1] Not surprisingly, this has been accompanied by a number of new synthetic approaches to functionalized pyrenes.[2] One of the most heavily exploited pyrene derivatives over this time has been pyrene-4,5-dione (**2**). In 2016 alone, **2** has been used in such diverse areas as asymmetric synthesis,[3] supramolecular chemistry,[4] functional organic materials,[5] polycyclic heteroacenes,[6] and reactive intermediates.[7] The surge in popularity of **2** can be traced back to Harris' 2005 publication,[8,9] in which *in situ*-generated RuO_4 was shown to selectively oxidize pyrene's *K*-region to afford **2** directly in moderate yield on a *ca*. 1 g scale (Scheme 1). Although a larger scale (9 g) synthesis of **2** was reported in 1998,[10] it does not appear to have been utilized very often, possibly due to its relative length (three steps *vs*. one). In 2011, our group reported that replacing one of Harris' co-solvents (acetonitrile) with THF resulted in a significant reduction in the reaction time,[11] which allows for a reaction, the very messy workup (see below) and chromatography to be completed within a single day.



Scheme 1. Harris' synthesis of **2** and Bodwell's modification.

Harris' procedure employs 2 g of pyrene (**1**) and delivers roughly 1 g of **2**. In our hands, this was found to be the practical limit of the reaction. The major issue is the large amount of intensely colored (essentially black) intractable material that is produced in the reaction. Removal of this material by filtration is problematic because it quickly clogs filter paper, even with the addition of Celite. We previously reported that the use of paper towels instead of filter paper was beneficial,[11] but the filtration is still quite slow and does not completely remove the solid material. Moreover, 4–6 washes are required to remove the majority of the product from the solids and each wash brings more solid material through into the filtrate. The subsequent extraction is also challenging because the solid material that made it through the filtration step pervades both layers and adheres to the walls of the separatory funnel. With both layers already being deeply colored, it is very difficult to visualize the border between layers. All in all, the workup requires the use of a rather large volume of solvent for a reaction of its scale. While the reaction is certainly repeatable, it is bothersome from the perspective of the experimentalist and does not lend itself at all well to being performed on a scale beyond 2 g of pyrene.

Results and Discussion

The current broad interest in dione **2** led us to investigate how not only the yield, but also the ease of performing the *K*-region oxidation of pyrene (**1**) might be improved. Initial work showed that an increase or decrease in the temperature had a detrimental effect on the yield. Performing the reaction in an ice bath led to a marked decrease in the rate of consumption of pyrene (**1**) and afforded **2** in just 17% yield after 2.5 h. On the other hand, performing the reaction at 30 °C clearly resulted in an increase in the amount of solid byproduct and the yield fell to 32%. In this regard, it was found that overly rapid addition of $NaIO_4$, which dissolves exothermically in water, has the same effect.

The addition of nitrogen-containing heterocycles to transition metal-catalyzed oxidations has been shown to have a significant effect on the rate and outcome of certain reactions. For example, Sharpless reported that pyridine and various pyridine derivatives had a beneficial effect when added to the methylrhenium trioxide-mediated epoxidation of stilbenes.[12] The ligand was found to play three roles: (1) to speed up catalytic turnover, (2) to prevent the hydrolysis of the epoxides that were produced and, (3) above a threshold concentration, to increase the catalyst lifetime in solution. These results contrasted the effects observed when using nonaromatic tertiary amines, which were found to strongly inhibit catalyst activity.

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For the study of how additives affect the conversion of **1** to **2**, loadings of 5 mol% were chosen for initial screening (Table 1). The addition of pyridine resulted in a drop in the yield of **2** to 37%, but there was an immediately noticeable improvement in the “cleanliness” of the workup, which made it considerably easier to perform (Table 1, Entry 1). Of course, defining and assessing the level of cleanliness / messiness of a workup (a very important issue for an experimentalist) is a subjective matter. As such, the observed improvements in the workup in this and subsequent experiments were categorized only as good (A), moderate (B) or poor (C).

Table 1. Additive screening in the *K*-region oxidation of pyrene (**1**)[a] to afford dione **2**.

Entry	Additive[b]	Yield (%)[c]	Cleaning Effect[d]
1	pyridine	37	B
2	2.2’-bipyridine	43	B
3	1,10-phenanthroline	26	C
4	diethylene triamine	43	C
5	PPh_3	36	C
6	DBU	45	B
7	DavePhos	45	A
8	*N*-methylimidazole	52	A

[a] 2.0 g scale. [b] 5 mol%. [c] Isolated yield. [d] A = good (much cleaner workup), B = moderate (somewhat cleaner workup), C = poor (unchanged workup).

The use of the bidentate ligand 2,2’-bipyridine also resulted in a cleaner workup and the yield (43%) approached that of our modified procedure (Table 1, Entry 2).[11] Upon moving to 1,10-phenanthroline, the yield dropped to 26% and the workup was as problematic as before (Table 1, Entry 3). It may be that this ligand also undergoes *K*-region oxidation.[13] A reaction employing diethylene triamine (a nonaromatic, tridentate tertiary amine) also had virtually no effect on the yield or the workup (Table 1, Entry 4), whereas the use of triphenylphosphine resulted in a lower yield of **2** (36%) after an unimproved workup (Table 1, Entry 5). With the addition of the amidine base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, a relatively strong organic base) came the return of the noticeably improved workup (Table 1, Entry 6). Upon using DavePhos, a popular Buchwald-Hartwig ligand, the yield (45%) held steady and there was a pronounced improvement in the cleanliness of the workup to the point that it could be described as straightforward (Table 1, Entry 7). *N*-Methylimidazole (NMI) had an equally good cleaning effect on the workup and the yield (52%) improved slightly. All of these reactions were run for 2.5 h and, according to TLC analysis, there did not appear to be any pronounced differences in the rate of consumption of pyrene (**1**).

Since the best result was obtained with NMI, which also has the benefit of being inexpensive, it was selected for the investigation of how the loading affects the yield of **2** (Table 2). The cleaning effect of NMI was consistently good over the range of 1–100 mol%, but the yield was quite variable. The yield of **2** was greatest at the initially chosen loading of 5 mol% (Table 2, Entry 2), but still reasonably good at 1 mol% and 10 mol% (Table 2, Entries 1 and 3). Curiously, the yield fell off sharply as the loading was increased to 25 mol% (Table 2, Entries 4–6) and then recovered somewhat as the loading was increased to a full equivalent (Table 2, Entries 7 and 8).

Table 2. Optimization of the loading of NMI in the *K*-region oxidation of pyrene (**1**)[a] to afford dione **2**

Entry[	NMI (mol%)[b]	Yield (%)[b]
1	1	44
2	5	52
3	10	45
4	15	39
5	20	30
6	25	12
7	50	17
8	100	21

[a] 2.0 g scale. [b] Isolated yield.

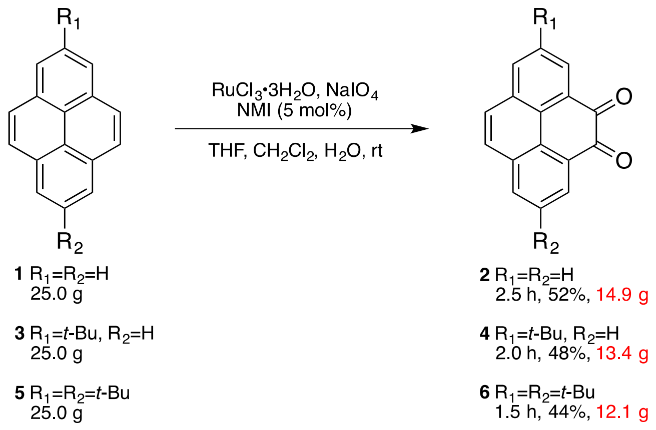
With an experimentally more manageable procedure in hand, attention was turned to increasing the scale of the reaction. Upon moving to 5, 10 and 25 g of pyrene (**1**), the work-up proved to be as straightforward as it was in the 2 g scale and the yield remained steady at 51-52% (Table 3, Entries 2–4). Each of these reactions has been repeated several times by different experimentalists with consistent outcomes. The 25 g scale reaction, which afforded 14.9 g of pyrene-4,5-dione (**2**), was the largest scale at which the reaction could be performed comfortably using the laboratory glassware that was available to us. The reaction was performed once on a 100 g scale, but this proved to be substantially more challenging from a practical perspective due to the large volumes of solvent and amounts of materials that had to be dealt with. In this regard, it is much more convenient to perform four reactions at the 25 g scale than one reaction at the 100 g scale.

Table 3. Scale-up of the *K*-region oxidation of pyrene (**1**) to afford dione **2** with 5 mol% NMI as an additive.

Entry	Pyrene (**1**) (g)	Yield (%)[a]
1	2	52
2	5	52
3	10	51
4	25	52
5	100	41

[a] Isolated yield.

Two pyrene derivatives, 2-*tert*-butylpyrene (**3**) and 2,7-di-*tert*-butylpyrene (**5**) were also subjected to the new reaction conditions and it was found that the oxidation smoothly converted them to the respective diones **4** and **6** in slightly lower yield on a 25 g scale (Scheme 2). Smaller scale reactions also proceeded smoothly. The times required for the reactions of **3** and **5** to go to completion (2.0 and 1.5 h, respectively) were shorter than for pyrene (**1**) (2.5 h),[14] which may be a reflection of increasing electron density in the pyrene system with each additional *tert*-butyl substituent. It may also that the *tert*-butyl groups add steric bulk, which disfavors aggregation and/or improves dissolution of starting materials. Paying attention to the reaction time is important because, for all three substrates, prolonged reaction resulted in the formation of several byproducts (TLC analysis), a messier workup and diminishing yields of the respective diones.



Scheme 2. *K*-Region oxidations of **1**, **3** and **5** on a 25 g scale.

The new procedure is advantageous not only in terms of convenience and scale, but also from a sustainability viewpoint. Using the new procedure described here, a single experimentalist can convert 25.0 g of pyrene (**1**) into 14.9 g of dione **2** in a period of 6 h (includes the reaction, workup and chromatography), during which *ca*. 6 L of solvent is used. The large majority of this solvent is dichloromethane for extraction and chromatography, which is largely recoverable.[15] By comparison, using our previous procedure, the same experimentalist was able to convert 2.0 g of pyrene (**1**) into 1.1 g of dione **2** in a period of 7 h, during which *ca*. 4 L of solvent was used.

In the case of pyrene-4,5-dione (**2**), column chromatography can be avoided through the use of precipitation. The brown solid obtained in this fashion is of lower purity than the bright orange solid obtained from column chromatography (TLC, ^1H NMR analysis), but is of sufficient quality for use in reactions such as reductive *O*-alkylation.[11] The precipitation method was not as effective for the isolation of **4** and **6**.

At this point in time, the role played by the NMI (and other additives) in cleaning up the reaction and the reason(s) why it is most effective at 5 mol% loading are unclear. No meaningful correlations between any structural or physical property of the additives (N-hybridization, denticity, pK_a of the conjugate acid) and the yield of the reaction leading to **2** or the cleaning effect could be identified. More extensive studies will be required to shed light on these issues.

Conclusions

The addition of 5 mol% NMI to the ruthenium-mediated *K*-region oxidation of pyrene (**1**) has a pronounced effect on the ease with which the reaction workup can be performed. This allows it to be performed comfortably on up to 25 g of pyrene (**1**) using standard laboratory equipment. Using this procedure, a single worker can easily generate *ca*. 15 g of dione **2** in one day.

Experimental Section

For general experimental information, please see ref. 11.[11]

Pyrene-4-5-dione (2). To a solution of pyrene (25.0 g, 124 mmol) in CH_2Cl_2 (500 mL) and THF (500 mL) were added $RuCl_3{\cdot}3H_2O$ (3.23 g, 12.4 mmol), *N*-methylimidazole (0.501 g, 6.18 mmol) and H_2O (625 mL). $NaIO_4$ (119 g, 555 mmol) was added in small portions over 20 min. The resulting slurry was stirred at room temperature for 2.5 h and the organic solvents were removed under reduced pressure. CH_2Cl_2 (500 mL) and H_2O (500 mL) were added to dissolve the solids and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (4 × 250 mL) and the combined organic layers were washed with H_2O (3 × 500 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a dark orange solid. Column chromatography (10 cm width × 15 cm height, CH_2Cl_2) gave pyrene-4,5-dione (**2**) as bright orange crystals (14.9 g, 52%) R_f (CH_2Cl_2) = 0.32: mp: >300 °C dec, Lit.[8] 299–302 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.46 (dd, *J* = 7.4, 1.3 Hz, 2H), 8.15 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.83 (s, 2H), 7.74 (t, *J* = 7.7 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 180.4, 135.7, 132.0, 130.2, 130.1, 128.4, 128.0, 127.3 ppm. HRMS [APCI(+)] calcd for $C_{16}H_8O_2$ 232.0524, found: 232.0523. **Alternative workup using precipitation**: Instead of evaporating the post-extraction solution (combined organic layers) to dryness, it was concentrated under reduced pressure to a volume of *ca*. 250 mL and then diluted with methanol (*ca*. 500 mL). The resulting suspension was then cooled to 0 °C for 1 h and the product was collected by suction filtration to yield **2** as a brown powder (40–45%).

2-*tert*-Butylpyrene-4,5-dione (4). To a solution of 2-*tert*-butylpyrene (25.0 g, 97.0 mmol) in CH_2Cl_2 (500 mL) and THF (500 mL) were added $RuCl_3{\cdot}3H_2O$ (2.59 g, 9.70 mmol), *N*-methylimidazole (0.398 g, 4.85 mmol) and H_2O (625 mL). $NaIO_4$ (93.5 g, 437 mmol) was added in small portions over 20 min. The resulting slurry was stirred at room temperature for 2 h and the organic solvents were removed under reduced pressure. CH_2Cl_2 (500 mL) and H_2O (500 mL) were added to dissolve the solids and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (4 × 250 mL) and the combined organic extracts were washed with H_2O (3 × 500 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a dark orange solid. Column chromatography (10 cm width × 25 cm height, CH_2Cl_2) gave 2-*tert*-butylpyrene-4,5-dione (**4**) as a bright orange solid (13.4 g, 48%): R_f (CH_2Cl_2) = 0.64: mp: >250 °C dec. ; ^1H NMR ($CDCl_3$, 300 MHz) 8.57 (d, *J* = 2.1 Hz, 1H), 8.44 (dd, *J* = 7.4, 1.3 Hz, 1H), 8.14 (dd, *J* = 8.0, 1.3 Hz, 1H), 8.14 (d, *J* = 2.1 Hz, 1H), 7.81 (s, 2H), 7.70 (t, *J* = 7.7 Hz, 1H), 1.49 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) 180.85, 180.81, 151.7, 135.6, 132.3, 131.9, 131.8, 130.2, 130.1, 130.0, 128.6, 128.5, 127.61, 127.55, 127.1, 126.6, 35.3, 31.2 ppm. MS [APCI(+)] *m/z* (%): 311 ($[M+Na]^+$, 100); HRMS [APCI(+)] calcd for $C_{20}H_{16}O_2$ 288.1153, found: 288.1150.

2,7-Di-*tert*-butylpyrene-4,5-dione (6). To a solution of 2,7-di-*tert*-butylpyrene (25.0 g, 81.2 mmol) in CH_2Cl_2 (500 mL) and THF (500 mL) were added $RuCl_3{\cdot}3H_2O$ (2.17 g, 8.11 mmol), *N*-methylimidazole (0.333 g, 4.06 mmol) and H_2O (625 mL). $NaIO_4$ (78.3 g, 365 mmol) was added in small portions over 20 min. The resulting slurry was stirred at room temperature for 1.5 h and the organic solvents were removed under reduced pressure. CH_2Cl_2 (500 mL) and H_2O (500 mL) were added to dissolve the solids and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (4 × 250 mL) and the combined organic layers were washed with H_2O (3 × 500 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a dark orange solid. Column chromatography (10 cm width × 25 cm height, CH_2Cl_2) gave 2,7-bis(*tert*-butyl)pyrene-4,5-dione (**6**) as a bright orange solid (12.1 g, 44%): R_f (CH_2Cl_2) = 0.48: mp: >250 °C dec, Lit.[8] 241–244 °C; ^1H NMR ($CDCl_3$, 300 MHz) 8.55 (d, *J* = 2.1 Hz, 2H), 8.12 (d, *J* = 2.1 Hz, 2H), 7.80 (s, 2H), 1.49 (s, 18H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) 181.1, 151.1, 131.9, 131.8, 129.8, 128.4, 127.3, 126.5, 35.2, 31.2 ppm. MS [APCI(+)] *m/z* (%): 367 ($[M+Na]^+$, 100); HRMS [APCI(+)] calcd for $C_{24}H_{24}O_2$ 344.1777, found: 344.1776.

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Keywords: pyrene • *K*-region • oxidation • ruthenium • *N*-methylimidazole

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[14] In all of the reactions, the starting material is never completely consumed (TLC analysis). Once the starting material has been reduced to just a faint fluorescent spot, the reaction should be terminated.

[15] The dichloromethane used for extraction and chromatography is collected from rotary evaporation with a pink (from chromatography) to purple (from extraction) coloring due to the presence of iodine. Shaking the recovered dichloromethane with aqueous sodium thiosulfate solution in a separatory funnel affords colorless solvent, which after drying over anhydrous Na_2SO_4, yields dichloromethane suitable for use in a subsequent experiment. The dichloromethane that was recovered during this work was used only for chromatography of *K*-region oxidation reactions. The use of sodium thiosulfate washes during the workup prior to chromatography did remove most of the iodine, but the dichloromethane in the receiving flask of the rotary evaporator was still pink during both the extraction stage and the chromatography. As such, it proved to be more expedient to perform a sodium thiosulfate wash on the recovered solvent.

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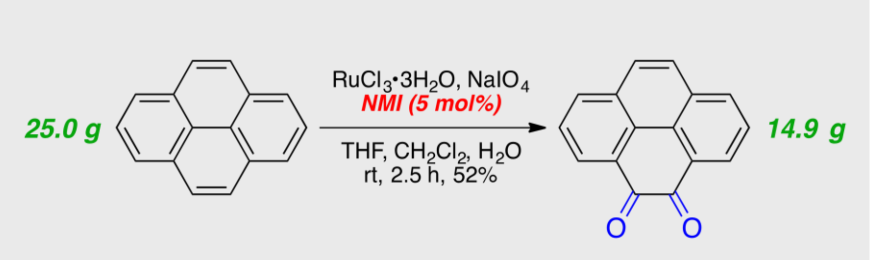
COMMUNICATION



Pyrene Oxidation*

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Synthesis of Pyrene-4,5-dione on a 15 g Scale

The addition of 5 mol% NMI to the ruthenium-mediated *K*-region oxidation of pyrene has a dramatic effect on the workup. The previously very messy and laborious workup that limited the scale of the reaction has thus become much easier to perform, which enables the reaction to be performed comfortably on up to 25 g of pyrene.