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N-Hydroxyphthalimide/Cobalt(II) Catalyzed Low Temperature Benzylic Oxidation Using Molecular Oxygen

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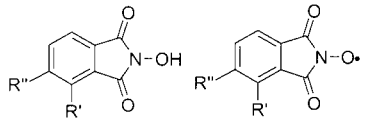
Abstract—A variety of (substituted) aryl glyoxylates is formed in good to excellent yield under very mild conditions by direct oxidation of the corresponding arylacetic esters or mandelic acid esters with molecular oxygen and *N*-hydroxyphthalimide/cobalt(II) acetate as catalyst. Heteroaromatic analogs are more difficult to oxidize with this system. The effect of substitution in the aromatic ring of *N*-hydroxyphthalimide on the oxidation of ethylbenzene has been studied. Electron withdrawing substituents accelerate the oxidation of ethylbenzene and promote the formation of acetophenone. Electron donating substituents lead to decreased rates of oxidation and enhance the selectivity for 1-phenylethanol.

Introduction

The selective oxidation of organic substrates using dioxygen (molecular oxygen) as the ultimate oxidant is a very important synthetic and industrial goal. With respect to its use in the manufacture of organic chemicals, catalytic oxidation with dioxygen traditionally holds a very prominent place in the petrochemical industry, where it is by far the most important technology for the upgrading of hydrocarbons.[1] The dominant position of dioxygen as the oxidant for bulk chemical oxy-functionalizations is due to the fact that it is the only economically and environmentally feasible oxidant for large scale processing. In contrast, even though dioxygen is ideal from an economic and environmental point of view and the need for the development of sustainable processes steadily increases, the fine-chemical business is still heavily dependent on *stoichiometric* oxidants, such as permanganate and dichromate. One of the reasons for the lack of fine-chemical applications of catalytic oxy-functionalizations is that the high molecular complexity of fine-chemical substrates is usually not compatible with the rather forcing reaction conditions (high temperature and pressure) required for traditional oxidations with dioxygen. These processes are generally not very selective and accordingly only suitable for the oxidation of relatively simple substrates. Another problem associated with traditional dioxygen oxidations which hampers its application in fine-chemical manufacture is the low conversion that is usually required in order to obtain acceptable selectivities. Such low conversion processes are generally best carried out in dedicated, continuous plants commonly found in the bulk industry, but they are rarely compatible with the batch production facilities that are common in the fine-chemical industry. Thus, within the fine-chemical industry there is a need for selective, high conversion dioxygen based oxy-functionalizations that can be operated under mild conditions.

Recently, an efficient catalytic method for the low-temperature oxygenation of organic substrates with dioxygen was developed by Ishii et al.[2] using *N*-hydroxyphthalimide (2-hydroxy-1*H*-isoindole-1,3-dione, NHPI, **1a**) as a catalyst and a metal salt as co-catalyst. With this system, organic compounds containing sufficiently reactive C–H bonds, e.g. (cyclic) alkanes,[3] sulfoxides,[4] alkylbenzenes[5] and aromatic compounds containing benzylic functions[2,6] have been oxidized at moderate temperatures up to high conversion.



1 2

	R'	R''		R'	R''
a	H	H	**e**	OMe	H
b	Me	H	**f**	H	OMe
c	H	Me	**g**	NO_2	H
d	F	H	**h**	H	NO_2

The cobalt salt/NHPI system of Ishii resembles the classical

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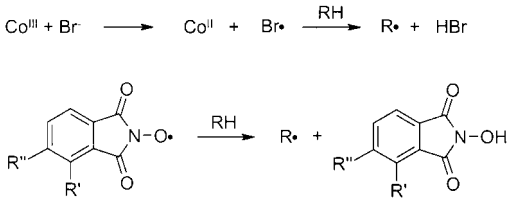


Figure 1. Classical cobalt/bromide oxidation versus NHPI mediated oxidation of hydrocarbons.

Co/Br^- catalyzed oxidation of hydrocarbons[1] in the sense that under oxidative conditions, NHPI is converted into its corresponding radical phthalimide-*N*-oxyl (PINO **2**), which, like bromine atoms formed from bromide in the Co/Br system, is able to abstract hydrogen from C–H bonds, thus propagating the radical oxidation chain (Fig. 1). However, in contrast to bromide catalysis, *N*-hydroxyphthalimide-based oxidation catalysis offers the possibility to tune the catalyst performance by modifying NHPI via introduction of substituents on the aryl ring. We have investigated this possibility and report our findings here.

In addition to studying variations of the NHPI catalyst, we wished to study different substrates in order to investigate the scope and limitations of the oxidation procedure. We started our research by studying the oxidation of substrates that are challenging for industrial purposes such as benzylic oxidation of phenylacetic esters and heteroaromatic compounds. Around 1950 the preparation of phenylglyoxalic acid by oxidation of methyl phenylacetate with air and with the aid of a cobalt(II) salt, at 110°C was reported in the Russian literature. After 36 h 86% of the glyoxylate was obtained.[7] Only very recently was NHPI in combination with dioxygen used to oxidize ethyl phenylacetate to ethyl phenylglyoxylate (ethyl 2-oxophenylacetate).[8] With *n*-Bu_4NBr as additive, moderate conversions (65%) were achieved. With bis(acetylacetonato)cobalt(II) ($Co(acac)_2$), a low conversion was reported. Only one other example in which an arylacetate is oxidized using molecular oxygen is known in the literature, viz. in one of the steps of the synthesis of (±)-clavizepine.[9] To oxidize ethyl 2-[2(benzyloxy)phenoxy]-4,5-dimethoxyphenylacetate, lithium diisopropylamine (LDA) and molecular oxygen were used in combination with hexamethylphosphoric triamide (HMPA) in THF to obtain the corresponding glyoxylate in 63% yield, with concomitant formation of 14% of the hydroxyketone. Finally, oxidations of arylacetic esters to arylglyoxylic esters using hydroperoxides instead of molecular oxygen in combination with for example a vanadium catalyst have been reported in the literature.[10] The yields of these oxidations vary from 24% (*p*-nitro substituted) to 88% (*p*-methoxy substituted) glyoxylate.

In this paper, the oxidation of a variety of substrates catalyzed by NHPI and cobalt(II) is described, followed by a study in which different substituted NHPI catalysts are tested. We end with a discussion of the reaction mechanism.

Table 1. Benzylic oxidation of arylacetic esters by NHPI/Co^{II} and O_2 (Reaction conditions: 10 mmol substrate in 10 mL of acetic acid, 10% NHPI, 0.5% $Co^{II}(OAc)_2{\cdot}4H_2O$, O_2-filled balloon, 40°C)

Entry	Substrate	Product	Conversion[a]	Yield[a]
1	**3a**	**4a**	15	0
2	**3b**	**4b**	100	99
3	**3c**	**4c**	9	0
4	**3d**	**4d**	12	0
5	**5a**	**6a**	100	73[b]
6	**5b**	**6b**	11	0
7	**5c**	**6c**	100	99
8	**5d**	**6d**	100	64[c]
9	**7b**	**8b**	87	87
10	**7c**	**8c**	100	99

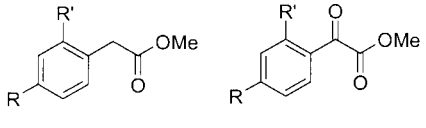
[a] Conversion and yields in % after 24 h, determined by GC.
[b] Yield calculated from ^1H NMR spectra after isolation of the crude product.
[c] Sole other product is (4-carboxyphenyl)acetic ester (36%).

Results

Oxidation of arylacetic esters

We investigated the aerobic oxidation of a range of arylacetic esters, using NHPI/cobalt(II) acetate ($Co(OAc)_2{\cdot}4H_2O$) as the catalytic system. The results are presented in Table 1. It can be seen from this table that the benzylic position of arylacetic esters can be oxidized very efficiently. Remarkably, the conversion and selectivity towards glyoxylate exceed those obtained with the NHPI/$Co(acac)_2$ aided system used by Matsunaka et al.[8] It is important to note that, while the reaction time is longer, the temperature is much lower in our case (40 instead of 80°C).

Yoshino et al. have investigated the possible influence of aryl substituents on the reactivity of the substrate.[5] In the reaction of substituted toluenes with 5% NHPI, 0.5% Co^{II} and molecular oxygen, they found that a *p*-Cl substituent retards the oxidation with respect to unsubstituted toluene (47% conversion after 24 h instead of 52%), whereas a *p*-methoxy substituent greatly accelerates it (89% conversion after 24 h). As can be seen in Table 1, also in this study an electron donating substituent such as a methoxy group at the *para* position of the substrate is shown to have a positive effect on the yield of glyoxylate (entry 2 versus entry 5). It is interesting to note that oxidation of **5a** using 3-F-NHPI (**1d**) yields **6a** in 81%, which is higher than with NHPI itself (73%). An electron withdrawing substituent (i.e. Br) in the *para* position of the substrate suppresses the oxidation of the benzylic position very effectively (entries 3 and 4). Any substituent *ortho* with respect to the acetic ester functionality inhibits oxidation completely. Steric influences are probably the reason for this effect, since both electron withdrawing and donating substituents display the same effect.[1,11]



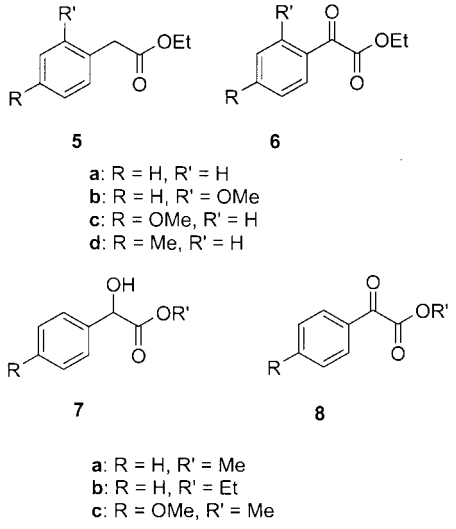
3 **4**

a: R = H, R' = OMe
b: R = OMe, R' = H
c: R = H, R' = Br
d: R = Br, R' = H

Table 2. Benzylic oxidation of heterocyclic acetic esters with NHPI/Co^{II} and O_2

Entry	Substrate	Reaction conditions[a]	Product (Yield, %)
1	**9**	0.8% Co^{II}, 16% NHPI, 72 h	–
2	**10**	3% Co^{II}, 15% NHPI, 48 h	–
3	**11**	0.5% Co^{II}, 10% NHPI	**12** (18)
4	**11**	0.5% Co^{II}, 20% NHPI	**12** (22)
5[b]	**13**	3% Co^{II}, 10% NHPI, 16 h, 40°C	**14** (21)
6[b]	**13**	0.5% Co^{II}, 10% NHPI, 16 h	**14** (14)
7[b]	**13**	0.5% Co^{II}, 10% NHPI, 40°C, 16 h	**14** (6)

[a] The following general reaction conditions were applied: 10 mL of acetic acid, 10 mmol of substrate, and the indicated of NHPI and $Co^{II}(OAc)_2{\cdot}4H_2O$ (in mol%) were vigourously stirred under an oxygen atmosphere at 80°C for 24 h.
[b] Other oxygen variations in reaction conditions were applied, but none were successful in increasing the yield of the oxidized product from **13**.

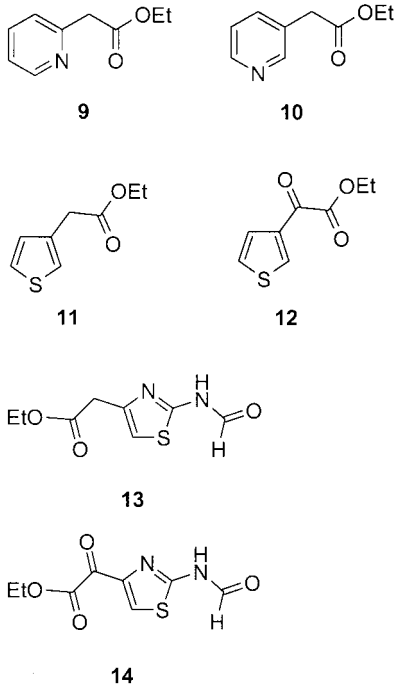


Virtually no difference was found in the reactivity of otherwise identical methyl and ethyl esters (entries 2 and 7). A methyl group on the aromatic ring can itself be oxidized but entry 8 in Table 1 shows that the benzyl-CH_2 in **5d** is more easily oxidized (64%) than the aromatic methyl substituent (36%). Doubly oxidized products were not found.

Mandelic esters were also used as substrates to investigate the oxidation of a possible side product or intermediate in the formation of the glyoxylates. Entries 9 and 10 show that mandelates can be oxidized very efficiently to glyoxylates, and may thus be intermediates in the oxidation of aryl acetates towards these compounds.

Oxidation of heteroaromatic substrates

Nitrogen or sulfur in a five membered aromatic ring may be regarded as an electron donating substituent, and facile benzylic oxidation may be expected. In a six-membered ring (e.g. pyridine), the electron withdrawing effect of the heteroatom makes the ring positively polarized and hydrogen abstraction will be more difficult (see also the Discussion section). Since we were interested in expanding the scope of the catalytic system, especially towards heteroaromatic compounds, four industrially relevant heteroaromatic substrates related to arylacetic esters (**9**–**11** and **13**) were chosen.



The results of their reactions with NHPI/Co^{II}/O_2 are shown in Table 2. It is indeed observed that a pyridine ring deactivates the benzylic position to an extent that no conversion takes place, as was predicted. The thiophene and thiazole heterocycles, however, were also found to be relatively unreactive towards benzylic oxidation when compared to the carbocycles such as ethyl phenyl acetate. It is possible

Table 3. Oxidation of ethylbenzene by Co^{II} and O_2 in the presence of different *N*-hydroxy-phthalimides as co-catalysts (Reaction condition: 10 mmol ethylbenzene, 0.5 mmol (5%) **1**, 0.05 mmol (0.5%) $Co^{II}(OAc)_2{\cdot}$ $4H_2O$, 10 mL of acetic acid, O_2-filled balloon, 80°C, 24 h, vigorous stirring)

Entry	Catalyst	Conversion (%)	Yield of acetophenone (%)	Yield of 1-phenylethanol (%)
1	**1a**	94	85	2
2	**1b**	95	87	2
3	**1c**	93	82	3
4	**1d**	96	88	2
5	**1e**	82	68	4
6	**1f**	80	59	5
7	**1g**	10	3	0
8	**1h**	7.5	4	2

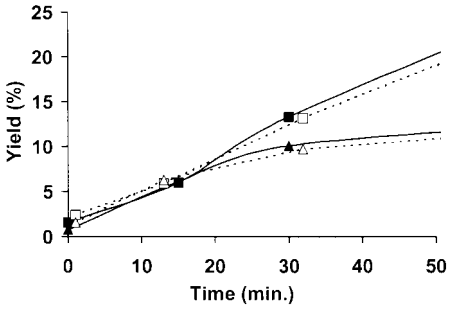


Figure 2. Formation of acetophenone and 1-phenylethanol at low conversions with two different NHPI catalysts. for reaction conditions see Table 3. Explanation of symbols: (—) **1a** as co-catalyst, (- - -) **1e** as co-catalyst, (□) acetophenone, (△) 1-phenylethanol.

that a nitroxide or sulfoxide is formed which deactivates the substrate for oxidation. Also, coordination of the sulfur or nitrogen atoms of the substrate to the cobalt catalyst can occur, which will have a detrimental effect.

Catalytic activity of substituted NHPI's

The substituted *N*-hydroxyphthalimides **1a**–**h** were used as catalysts together with $Co(II)(OAc)_2{\cdot}4H_2O$ in the oxidation of the model substrate ethylbenzene. In Table 3 the yields of the reaction products after 24 h, when conversion is essentially complete, are presented. It can be seen that the NO_2-substituted NHPI's are inactive. A possible explanation may be the ability of a nitro group to act as a radical scavenger. As the reaction is believed to be radical in nature this quenches the oxidation. Similarly, Yoshino et al.[5] have observed a negative influence of nitro groups on their reaction system when substrates with NO_2-groups were used. Blank reactions were run with only Co^{II} or only NHPI (**1a**) as catalysts. The former reaction yielded 2% of ketone and 1% of alcohol, the latter 5% and 2% of these products, respectively.

Since the differences in catalyst activity do not stand out very well at high conversions, we decided to investigate the product distribution at low conversions, to study possible effects of the substituents in the NHPI co-catalysts. The formation of 1-phenylethanol and acetophenone during the first 50 min of the reaction is plotted in Fig. 2 and during the first five hours of the reaction in Fig. 3. Several NHPI co-catalysts were used. A number of interesting observations can be made from these plots. First, it can be seen that both 1-phenylethanol and acetophenone are formed in a 1:1 ratio (ketone to alcohol ratio (K/A) of 1.0) in the first 20 min of the oxidation reaction (Fig. 2). This means that the ketone does not only evolve from the oxidation of the alcohol (as was shown by using mandelic esters as substrates, which were oxidized to the corresponding glyoxylates, vide infra), but is also formed directly. In a later stage of the reaction the ketone is formed from 1-phenylethanol as can be concluded from the decreasing amount of alcohol after about one hour reaction time (Fig. 3). Secondly, the fluorinated NHPI is a more active co-catalyst than the other NHPI's. With this co-catalyst, acetophenone is produced at the cost of the yield of 1-phenylethanol.

Overall, the electron withdrawing fluorine substituent enhances the catalytic activity of the NHPI and thus the rate of the reaction. On the other hand, the methoxy substituted NHPI's **1e** and **1f** decrease the reaction rate and at the same time favor the formation of alcohol in the early stage of the reaction. The mildly donating methyl substituent in **1b** and in **1c** slightly decreases the reaction rate with respect to the unsubstituted catalyst, as expected.

Discussion

A mechanism for the catalytic oxidation of toluene with NHPI, Co^{II} and O_2 has been proposed by the group of Ishii.[5,6] It involves the formation of the phthalimide-*N*-oxyl radical **2**, and the subsequent abstraction by this radical of a hydrogen atom from the substrate as the initiating steps. After this, the substrate radical R· reacts rapidly with O_2, forming an alkylperoxy radical. Two molecules of the latter rearrange to the ketone (K) and alcohol (A); the well-known Russell termination (Scheme 1).[1,12] It is expected from this mechanism that the K/A ratio is 1.0. During the first 20 min of the reaction, ketone and alcohol formation takes place only via Russell termination (see Fig. 2), but at higher conversions it is clear that other mechanisms play an important role. Also, it is not immediately clear from the Russell termination mechanism what the influence of aryl substituents in NHPI and the substrate is on the reaction rate and selectivity. We would like to further specify the proposed mechanism so that it explains these issues.

A relatively simple explanation for the substituent effect is possible using the polar transition state model which has been proposed for related reactions (Fig. 4).[13,14] It is obvious

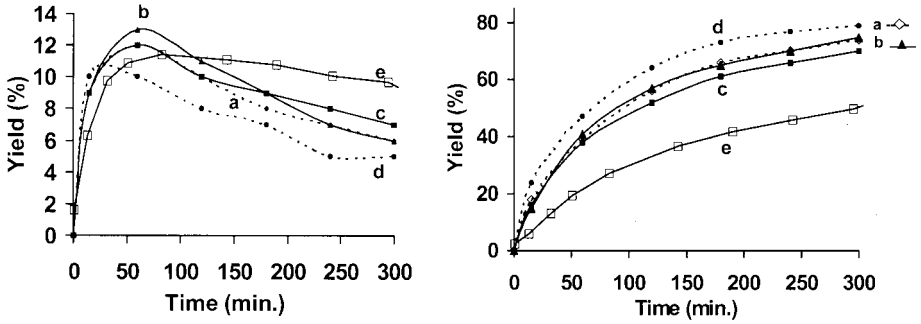
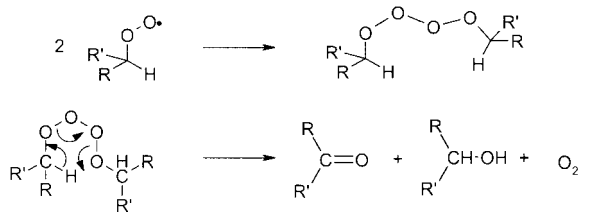


Figure 3. Oxidation of ethylbenzene using different substituted NHPI catalysts. Left: formation of 1-phenylethanol; right: formation of acetophenone. For reaction conditions see Table 3. a: NHPI, b: 3-Me-NHPI, c: 4-Me-NHPI, d: 3-F-NHPI, e: 3-OMe-NHPI.



Scheme 1.

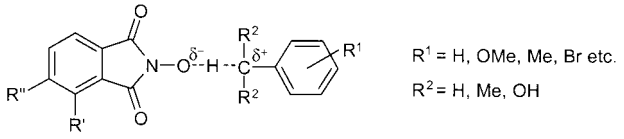
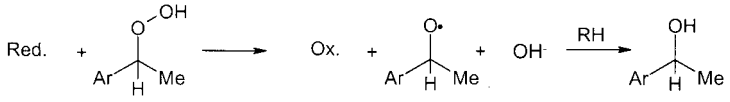
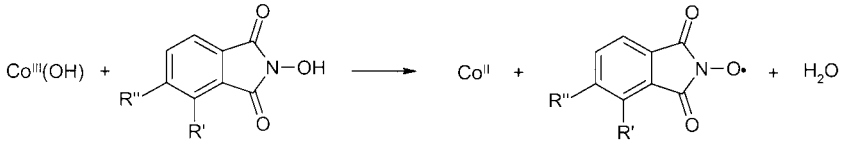


Figure 4. Transition state for the abstraction of a hydrogen atom from ethylbenzene by the PINO radical.

Haber–Weiss mechanism. More alkoxy radical is formed when more Co^{II}, generated through reduction of Co^{III} by NHPI, is present. This process is enhanced when NHPI is more negatively charged, i.e. when its reduction potential is higher. Thus, more alcohol is produced when NHPI has a more electron donating substituent. The $E_{1/2}$ values of a series of 4-substituted NHPI's were measured by Gorgy et al.[15] and were found to correlate linearly with the Hammett parameter σ of the substituent, a more positive σ-value (a more electron withdrawing substituent) corresponding to a higher $E_{1/2}$. The NHPI's with a more electron donating ligand have a higher reduction potential ($E_{1/2}$). Thus, the reducing power of the NHPI co-catalyst may indeed play an important role in the distribution of products formed with the NHPI/cobalt(II) system described here. For the electrooxidation of borneol with only NHPI as the catalyst, Gorgy and co-workers also found that a higher oxidizing character of the catalyst (which is the driving



Scheme 2.



Scheme 3.

that an electron donating substituent on the aromatic ring of the substrate (R^1) will stabilize the partial positive charge on the benzylic carbon atom, just as an electron withdrawing ring substituent on NHPI (R^2) will stabilize a partially negatively charged hydroxyl oxygen atom. Thus, 3-F-NHPI (**1d**) will oxidize ethylbenzene at a higher rate than 3-OMe-NHPI (**1e**) as is observed (see Fig. 3). A comparison may be made with the benzylic oxidation of substituted toluenes for which the same observations have been reported in the literature. Thus, *p*-chlorotoluene is more difficult to oxidize than *p*-methoxytoluene.[5] Furthermore, the polar transition state model explains the high reactivity of 1-phenylethanol compared to ethylbenzene (see entries 9 and 10, Table 1). The benzylic OH-group of 1-phenylethanol stabilizes the partial positive charge on the benzylic carbon atom by resonance, and thus favors further oxidation to ketone, as is observed.

Although the influence of the NHPI aryl substituents on the reaction rate can be understood with the polar transition state model, it does not clarify the favored formation of the alcohol product (lower K/A ratio) when the NHPI substituent is electron donating (e.g. methoxy). An explanation may be given on the basis of the reduction potential of NHPI. As shown in Scheme 2, the dissociation of the alkylperoxide into an alkoxy radical may be aided by a reductant if we regard this dissociation as a one-electron reduction process. The reductant may be Co^{II}, analogous to the force in their reaction) gave a more efficient catalytic process in agreement with our observations (Scheme 3).

In conclusion, we have found that the catalytic system presented here provides a very active, selective and mild method for benzylic oxidations with molecular oxygen as the final oxidant. While such oxidations usually take place at temperatures over 100°C, the Co^{II}/NHPI system is active at almost ambient temperatures, making it much more feasible for application in industrial processes. It has been possible to tune the NHPI co-catalyst with respect to the reaction rate and the ketone–alcohol ratio (K/A) by using different substituents on its aromatic ring. An electron withdrawing substituent increases the rate and the K/A ratio, whereas an electron donating substituent on NHPI induces a slower reaction and leads to a lower K/A ratio, especially at low conversions.

Experimental

General

All chemicals were purchased from Acros Chimica or Aldrich and were used as received. NMR spectra were taken on a Bruker AM-300 (300 MHz) or Bruker ACF-200 (200 MHz) spectrometer, chemical shifts are given in ppm with TMS as internal standard. FT-IR measurements in

KBr tablets were performed on a Perkin–Elmer 298 spectrometer. Elemental analyses were measured on a Carlo Erba Instruments CHNSO 1108. Mass spectra (EI) were taken on a Fisons VG7070E instrument.

Syntheses

The substituted *N*-hydroxyphthalimides **1a–d**, **1g** and **1h** were synthesized by reacting the corresponding phthalic anhydrides with hydroxylamine in solution, according to modified literature procedures.[16–18] Due to solubility problems, the methoxy substituted compounds **1e** and **1f** could not be obtained in this way. These were synthesized by heating methoxy substituted phthalic acid in vacuo at 170°C in a sublimation apparatus, with an excess (2–3 equiv.) of hydroxylamine HCl salt, until elimination of water and HCl could no longer be observed. The light yellow sublimate was recrystallized together with the residue, which also contained phthalimide product, to obtain 3-methoxy-NHPI or 4-methoxy-NHPI (>99% pure). Detailed procedures and analyses are described below.

3- and 4-Methyl-*N*-hydroxyphthalimide, 1b and 1c. $NH_2OH{\cdot}HCl$ (0.67 g, 9.6 mmol) and $N(Et)_3$ (1.3 mL, 9.5 mmol) were dissolved in ethanol (60 mL). After stirring for 10 min 3- or 4-methyl phthalic anhydride (1.59 g, 9.8 mmol) was added. The mixture was refluxed overnight. The clear solution was concentrated to 10 mL. The resulting yellow oil was poured into 100 mL of water. The product precipitated as a white powder, which was filtered and dried under vacuum. **3-Me-NHPI, 1b:** White powder; yield: 49% (0.84 g, 4.7 mmol); mp 221°C; [Found: C, 60.91; H, 3.97; N, 7.77. $C_9H_7NO_3$ requires C, 61.02; H, 3.98; N, 7.91%]; δ_H (300 MHz DMSO-d_6): 10.74 (1H, bs, N–O*H*), 7.68 (3H, m, Ar*H*), 2.62 (3H, s, C*H*$_3$); δ_C (75.4 MHz DMSO-d_6): 164.9 (*C*=O), 164.0 (*C*=O), 137.2 (Ar), 136.7 (Ar), 134.1 (Ar), 129.2 (Ar), 125.4 (Ar), 120.8 (Ar); ν_{max} (KBr): 1791, 1725; 1704 cm^{-1}. *m/z* (EI) 177 (100 M^+), 161 (31), 147 (7), 132 (10), 118 (23), 103 (20), 89 (40). **4-Me-NHPI, 1c:** White powder; yield: 47% (0.81 g, 4.6 mmol); mp 202°C; [Found: C, 60.74; H, 4.23; N, 7.71. $C_9H_7NO_3$ requires C, 61.02; H, 3.98; N, 7.91%]; δ_H (300 MHz $CDCl_3$): 7.71 (1H, d, *J*=7.6 Hz, Ar*H*), 7.63 (1H, s, Ar*H*), 7.53 (1H, d, *J*=7.6 Hz, Ar*H*), 2.50 (3H, s, C*H*$_3$); δ_C (75.5 MHz DMSO-d_6): 168.2 (*C*=O), 149.4 (Ar), 138.7 (Ar), 133.0 (Ar), 130.0 (Ar), 127.5 (Ar), 126.9 (Ar), 25.4 (*C*H$_3$); ν_{max} (KBr): 1788, 1741, 1704 cm^{-1}; *m/z* (EI) 177 (65 M^+), 161 (27), 147 (70), 133 (42), 118 (99), 104 (38), 89 (100).

3-Fluoro-*N*-hydroxyphthalimide, 1d. $NH_2OH{\cdot}HCl$ (0.84 g, 12.1 mmol) and K_2CO_3 (0.84 g, 6.1 mmol) were dissolved in water (20 mL). The solution was stirred for 20 min and 3-fluorophthalic anhydride (2.0 g, 12.0 mmol) was added. The solution was stirred overnight at room temperature. The resulting white suspension was filtered and the residue dried under vacuum to give **1d** (1.12 g, 6.2 mmol, 51%) as a white powder, mp 216°C; [Found: C, 49.21; H, 2.76; N, 7.12. $C_8H_4NO_3F{\cdot}0.8H_2O$ requires C, 49.14; H, 2.89; N, 7.16%]; δ_H (200 MHz DMSO-d_6): 10.93 (1H, bs, N–O*H*), 7.88 (1H, m, Ar*H*), 7.68 (2H, m, Ar*H*); δ_C (50.3 MHz DMSO-d_6): 163.3 (d, J_{C-F}=3.2 Hz, *C*=O), 161.2 (s, C=O), 156.4 (d, J_{C-F}=261.3 Hz, Ar), 137.5 (d, J_{C-F}=8.0 Hz, Ar), 131.4 (s, Ar), 122.9 (d, J_{C-F}=19.9 Hz, Ar), 119.6 (d, J_{C-F}=3.2 Hz, Ar), 114.7 (d, J_{C-F}=12.5 Hz, Ar), ν_{max} (KBr): 1789, 1744, 1707 cm^{-1}; *m/z* (EI) 181 (100 M^+); 165 (10), 151 (33), 122 (41), 108 (6), 94 (41).

3- and 4-Methoxy-*N*-hydroxyphthalimide, 1e and 1f. 2,3-Dimethylanisole or 3,4-dimethylanisole (3.4 g, 25 mmol) and a large excess of $KMnO_4$ (25 g, 0.16 mol) were dissolved in 140 mL of a water/*t*-BuOH mixture (70/30% v/v). The reaction mixture was refluxed overnight, 50 mL of EtOH was added to destroy unreacted $KMnO_4$ and the alcohols were distilled off. The resulting brown suspension was filtered over Celite. The colorless solution was concentrated to 100 mL, acidified with conc. HCl after which the phthalic acid crystallized as a white solid. The obtained phthalic acid (10 mmol, and 12.3 mmol resp. of 3- and 4-methoxyphthalic acid) was placed in a sublimation apparatus with a cold finger, which could be heated with a high temperature silicon oil bath under 1 mbar pressure. 3 equiv. of powdered $NH_2OH{\cdot}HCl$ (2.1 g, 30 mmol and 2.6 g, 36.9 mmol, resp.) were added. The mixture was heated to 170°C under reduced pressure, with occasional stirring. The evaporation of water could be observed, after which a light yellow solid started to form. After 5 h no further reaction could be observed, and the reaction was stopped. The resulting yellow-brown solids were recrystallized from boiling water (75 mL) or toluene–EtOH (20:1 v/v, 50 mL). **3-OMe-NHPI, 1e:** Yellow powder, yield: 21% (0.41 g, 2.1 mmol); mp 232°C; [Found: C, 51.03; H, 4.23; N, 6.61. $C_9H_7NO_4{\cdot}H_2O$ requires C, 51.04; H, 4.32; N, 6.61%]; δ_H (300 MHz DMSO-d_6): 10.65 (1H, bs, N–O*H*), 7.76 (1H, dd, *J*=8.4 Hz, *J*=7.2 Hz, Ar*H*), 7.45 (1H, d, *J*=8.4 Hz, Ar*H*), 7.35 (1H, d, *J*=7.2 Hz, Ar*H*), 3.97 (3H, s, OC*H*$_3$); δ_C (75.5 MHz DMSO-d_6): 167.7 (*C*=O), 166.9 (*C*=O), 160.0 (Ar), 140.7 (Ar), 134.6 (Ar), 122.9 (Ar), 119.0 (Ar), 117.3 (Ar), 60.3 (O*C*H$_3$); ν_{max} (KBr): 1788, 1766, 1718, *m/z* (EI) 193 (100 M^+), 176 (71), 158 (41), 145 (65), 133 (39), 117 (20), 104 (53), 92 (29). **4-OMe-NHPI, 1f:** Light yellow powder, yield: 29% (0.69 g, 3.6 mmol); mp 213°C; [Found: C, 55.65; H, 3.64; N, 7.17. $C_9H_7NO_4$ requires C, 55.96; H, 3.65; N, 7.25%]; δ_H (300 MHz DMSO-d_6): 10.74 (1H, bs, N–O*H*), 7.78 (1H, d, *J*=8.2 Hz, Ar*H*), 7.38 (1H, d, *J*=2.3 Hz, Ar*H*), 7.28–7.24 (1H, dd, *J*=8.2 Hz, *J*=2.3 Hz, Ar*H*), 3.93 (3H, s, OC*H*$_3$); δ_C (75.5 MHz DMSO-d_6): 168.4 (*C*=O), 147.4 (Ar), 135.3 (Ar), 129.0 (Ar), 124.0 (Ar) 123.3 (Ar), 112.7 (Ar), 60.3 (O*C*H$_3$); ν_{max} (KBr): 1787, 1731 cm^{-1}; *m/z* (EI) 193 (100 M^+), 177 (4), 163 (30), 134 (56), 120 (5), 106 (23), 92 (9).

3- and 4-Nitro-*N*-hydroxyphthalimide, 1g and 1h. To toluene (80 mL) were added 3- or 4-nitrophthalic anhydride (3.81 g, 19.7 mmol), $NH_2OH{\cdot}HCl$ (1.34 g, 19.2 mmol) and triethylamine (2.66 mL, 19 mmol). The mixture was refluxed overnight. Water was removed during the reaction by azeotropic distillation. The yellow solution was then concentrated and the resulting yellow oil was purified by column chromatography on silica gel (eluent: hexane–ethylacetate=4:1). **3-NO_2-NHPI, 1g:** Yellow powder; yield: 9% (0.37 g, 1.8 mmol); mp 209–213°C; [Found: C, 42.76; H, 2.55; N 12.34. $C_8H_4N_2O_5{\cdot}H_2O$ requires C, 42.49; H, 2.67; N, 12.39%]; δ_H (200 MHz DMSO-d_6): 11.81 (1H, bs, N–O*H*), 8.18 (3H, m, Ar*H*); δ_C (75.5 MHz DMSO-d_6): 171.2 (*C*=O), 168.6 (*C*=O), 148.3 (Ar), 140.0 (Ar), 138.6

(Ar), 132.1 (Ar), 130.8 (Ar), 127.8 (Ar); ν_{max} (KBr): 1773, 1734, 1709, 1540 cm^{-1}; *m/z* (EI) 208 (M^+); 192, 178. **4-NO_2-NHPI, 1h:** This compound has been described in the literature,[16] Registry No. 105969-98-0

Arylacetic esters and mandelic esters

General procedure for ethylbenzene oxidations. A solution of 10 mmol of ethylbenzene in 10 mL of acetic acid containing 0.5 mmol (5%) of NHPI catalyst **1** and 0.05 mmol (0.5%) of $Co(OAc)_2 \cdot 4H_2O$ was placed in a three-necked flask equipped with a rubber balloon filled with 100% O_2 (Hoek Loos, 99.9%) and heated to 80°C with vigorous stirring. 1,2,4-Trichlorobenzene was added to the reaction mixture as an internal standard for GC analysis. Regularly taken aliquots were analyzed with a Chrompack Packard 438A chromatograph (FFAP CB column, 15 m, 0.32 mm internal diameter, d_f=1.0 μm or a CPSIL 5 CB column, 25 m, 0.32 mm internal diameter, d_f=1.2 μm), or a Hewlett Packard 5890 Series II chromatograph (CP-SIL 5 CB column, 25 m, 0.32 mm internal diameter, d_f=1.2 μm). The commercially available phenylacetic acids or mandelic acids were esterified by standard procedures in 80–91% yield.

General procedure for the oxidation of arylacetic esters and mandelic esters. The reaction was performed in a similar way as described for the oxidation of ethylbenzene, with the exception that 1 mmol (10%) of NHPI catalyst was used. The mixture was stirred at 40°C. The reaction was followed by GC analysis as described above. The crude products were isolated by evaporating the solvent and washing with hot heptane, and were analyzed by NMR. Purification was performed by crystallization from hot pentane or by column chromatography (silica gel, eluent: chloroform or petroleumether–ethylacetate 7:3 v/v). The analyses of the products were identical to the following literature references: **4-Methoxyphenylglyoxylate methyl ester (4b) and ethyl ester (6c)**[19] **Ethyl phenylglyoxylate (6a)**[20,21] **Ethyl *p*-tolylglyoxylate (6d)**[22,23] **Ethyl 3-thiopheneglyoxylate (12)**[24] **Ethyl 2-(formylamino)-4-thiazoleglyoxylate (14).**[25,26] Registry No. **4b** 32766-61-3; **6a** 1603-79-8; **6c** 40140-16-7; **6d** 5524-56-1; **12** 53091-09-1; **14** 64987-03-7.

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