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# A Way to Avoid Using Precious Metals: The Application of High-Surface Activated Carbon for the Synthesis of Isoindoles via the Diels–Alder Reaction of 2*H*-Pyran-2-ones

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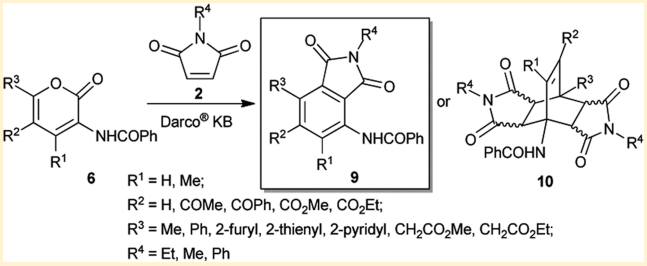
Supporting Information

**ABSTRACT:** The application of activated carbon (Darco KB) for the acceleration and direction of the transformation of various 2*H*-pyran-2-ones with *N*-substituted maleimides toward isoindole derivatives through the reaction sequence cycloaddition/elimination/dehydrogenation is described. In this reaction, the catalyst mainly influences the dehydrogenation step, which is essential to avoid the formation of bicyclo[2.2.2]octenes as the other possible products. We found that the combination of Darco KB, as the metal-free catalyst, and decalin, as the solvent in a closed vessel, represents the most successful conditions. A comparison of the effect of various dehydrogenation catalysts and reaction conditions is also presented. In addition, we have proven that the aromatization occurs via a hydrogen transfer from the cyclohexadiene intermediate to the maleimide derivative (therefore producing succinimides). This transfer is facilitated by the active surface of the heterogeneous carbon-based catalyst.

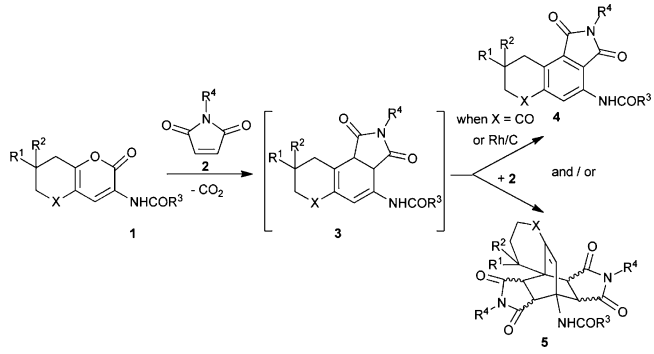



## INTRODUCTION

Isoindoles and their fused derivatives represent a very important class of compounds with a wide scope of applications and biological activity, ranging from effects on the cardiovascular and cerebral systems to dopamine agonist, anticancer, antibiotic, anticonvulsive, and anti-inflammatory effects.[1] One of the most notorious examples of such a biologically important isoindole compound is thalidomide,[2] which was licensed in the 1950s as a sedative drug, typically used to cure morning sickness, but withdrawn in 1961 because of its teratogenicity. Because of the importance of isoindoles, various synthetic approaches[1a,2e,3] were developed, further stimulating our interest in the Diels–Alder reactions of 2*H*-pyran-2-ones and their fused analogues, as they could represent attractive precursors for the synthesis of isoindole derivatives. Previously, we conducted a preliminary investigation of such a pathway, starting from the 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-ones **1** and various maleimides **2** leading to the formation of the fused isoindoles (i.e., benz[*e*]isoindoles) **4** or the bridged double cycloadducts (fused bicyclo[2.2.2]octene derivatives) **5** (Scheme 1).[4] It is worth mentioning that in a special case, where X = CO, the first efficient, substituent-driven aromatization of an intermediary-formed cycloadduct was observed, resulting in the substituted benz[*e*]isoindoles **4**. The same type of aromatization could also be achieved in an unprecedented catalysis with rhodium on activated carbon (Rh/C).

As a continuation of the above investigation, we planned to use the appropriately substituted 2*H*-pyran-2-ones **6** as dienes and react them in a Diels–Alder reaction with the *N*-substituted maleimides **2** in order to obtain the isoindoles **9** as single or predominant products (Scheme 2). In a close analogy with our previous results, the reaction sequence leading to the isoindoles **9** should include a primary cycloaddition step of an appropriate dienophile **2** (*N*-substituted maleimides) with the substituted 2*H*-pyran-2-ones **6** as the diene to give a $CO_2$-bridge-containing intermediate **7**. In the second step, a retro-Diels–Alder reaction (the elimination of $CO_2$) should give the next intermediate **8**, which could be either aromatized (dehydrogenated) to give the isoindole derivative **9** or a new cycloaddition takes place, yielding the bicyclic adduct **10**. The

**Scheme 1. Reaction Pathway Leading to the Benz[*e*]isoindoles 4**

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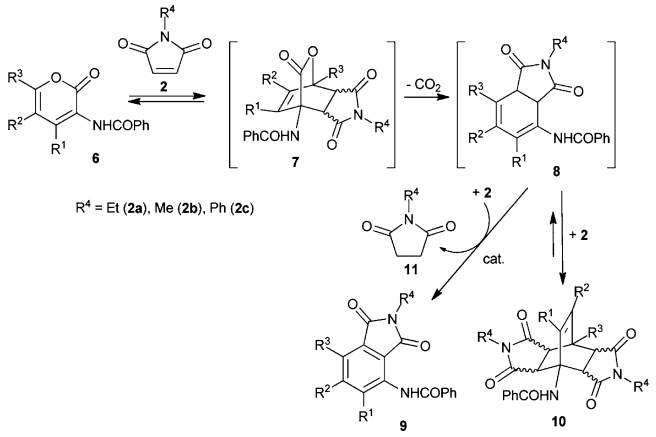
**Scheme 2. Reaction Pathway Leading to the Isoindoles 9a–s**



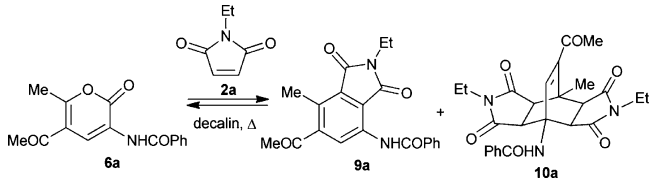

last reaction step toward **9** is the most crucial one, as it does not take place easily on its own but needs an appropriate catalyst. As already mentioned, we found that Rh/C is a successful heterogeneous dehydrogenation catalyst;[4] however, it has some major drawbacks, its high price being one of the most important ones. Therefore, the quest for more appropriate heterogeneous dehydrogenation catalysts continued.

On the basis of our experiences with such transformations,[4,5] we anticipated that the thermal reaction conditions necessary for the cycloaddition would also suffice for the second step, i.e., the retro-Diels–Alder reaction (the elimination of $CO_2$), yielding the key cyclohexadiene intermediates **8**. In the absence of a dehydrogenation catalyst, the compounds **8** would react with another molecule of a dienophile, leading to the bicyclo[2.2.2]octenes **10**. To prevent this second cycloaddition step, it is necessary to use a sink for the hydrogen and an appropriate catalyst that facilitates the formal transfer of a molecule of hydrogen from the cyclohexadiene intermediate, thus yielding the final aromatized isoindole product **9**.[4] To enable this transfer, we surmised that it should be necessary to have a catalyst with an active surface that is as large as possible. With this in mind and in accordance with some previous literature reports,[6,7] we were not completely convinced that a precious metal was indispensable. As a result, a plethora of relatively cheap carbon-based materials would suddenly seem to be an attractive choice for the dehydrogenation catalysis. In addition, it is important to note that in the case of fused pyran-2-ones, the second cycloaddition step is, in contrast to the aromatization (elimination of hydrogen), a reversible transformation.[4,8]

## RESULTS AND DISCUSSION

The transformation most probably starts with the cycloaddition between the appropriately substituted 2*H*-pyran-2-one **6** and the *N*-substituted maleimide **2**, yielding the primary $CO_2$-bridged 2-oxabicyclo[2.2.2]oct-5-ene derivative **7** (Scheme 2). With the thermally induced, spontaneous, retro-Diels–Alder elimination of the $CO_2$ from **7**, the cyclohexadiene intermediate **8** is obtained, which is further aromatized into the final isoindole product **9**. Alternatively, the intermediate **8** can act as a new diene system, and therefore, a new molecule of dienophile **2** can cycloadd to yield the undesired bicyclo[2.2.2]-octene **10**, representing the double cycloadduct. According to ref 4, both cycloaddition steps (**6** ⇆ **7** and **8** ⇆ **10**) should be reversible, but the irreversible elimination of $CO_2$ from **7** shifts

**Table 1. Comparison of the Reaction Conditions and Dehydrogenation Catalysts for the Transformation between the 2*H*-Pyran-2-one 6a ($R^1$ = H; $R^2$ = COMe; $R^3$ = Me) (1 mmol) and *N*-Ethylmaleimide (2a) (2 mmol) in Decalin (8 mL) Yielding 9a**




| run | catalyst | *m* (cat.)/mg | *t*/h | *T*/°C | conversion (%)[a] | ratio **9a**:**10a**[a] |
|---|---|---|---|---|---|---|
| 1 | Rh/C | 820 | 4[b] | 150 | 95 | 1:0.9 |
| 2 | Pd/C | 820 | 4[b] | 150 | 85 | 1:1 |
| 3 | activated carbon | 820 | 4[b] | 150 | 93 | 0.4:1 |
| 4 | MWNT | 820 | 4[b] | 150 | 77 | 0.5:1 |
| 5 | MWNT | 250 | 4[b] | 150 | 88 | 0.15:1 |
| 6 | SWNT | 250 | 4[b] | 150 | 95 | 0.1:1 |
| 7 | NDP | 820 | 4[b] | 150 | 81 | 1:0.2[c] |
| 8 | $TiO_2$ | 820 | 4[b] | 150 | 91 | 0.8:1 |
| 9 | Darco KB | 60 | 4[b] | 150 | 90 | 0.3:1 |
| 10 | Darco KB | 410 | 4[b] | 150 | 95 | 0.7:1 |
| 11 | Darco KB | 820 | 4[b] | 150 | 100 | 1:0.3 |
| 12 | Darco KB | 820[d] | 4[b] | 150 | 100 | 1:0 |
| 13 | Darco KB | 820 | 4[e] | 150 | 100 | 1:0.1 |
| 14 | Darco KB | 820 | 4[e] | 180 | 100 | 1:0.05 |
| 15 | activated carbon | 820 | 4[e] | 180 | 93 | 1:0.7 |
| 16 | Darco KB | 820 | 6[e] | 180 | 100 | 1:0.05 |
| 17 | | | 24[e] | 180 | >95 | 0.1:1 |

[a]The ratio was estimated from $^1$H NMR spectra of a crude reaction mixture. [b]Round-bottom flask with reflux condenser, decalin (8 mL) in an oil bath. [c]With the extensive formation of side products. [d]With 0.5 mmol of **6a** and 1 mmol of **2a** in decalin (4 mL). [e]Closed ACE pressure tube (15 mL), decalin (8 mL) in an oil bath.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the first cycloaddition reaction far away from the starting compound **6**. The second cycloaddition (i.e., **8** ⇆ **10**) should also be reversible, therefore enabling the eventually formed double cycloadduct **10** to be transformed back into the intermediate **8** and so having another chance for the aromatization into **9**; however, our studies with **6** show somewhat different results (see below).

**Comparison of the Efficiency of Various Dehydrogenation Catalysts and Reaction Conditions.** First, we decided to examine various materials with a large specific surface[7b] as potential dehydrogenation catalysts and also to study the effects of the changing reaction conditions on the model conversion of **6a** into the isoindole product **9a** and/or into the corresponding double cycloadduct **10a**. As potentially interesting catalysts, we selected two types of activated carbon (ordinary and Darco KB), Rh/C, and Pd/C, as well as multi- and single-wall carbon nanotubes (MWNTs and SWNTs),[9] nanodiamond powder (NDP), and titanium dioxide powder. On the basis of our previous experiences, we chose decalin as the most appropriate solvent; the preliminary reactions were carried out in an open, round-bottom flask equipped with a reflux condenser that was heated for 4 h in an oil bath at 150 °C (Table 1, runs 1−12). The crude reaction mixtures were analyzed by $^1$H NMR spectroscopy, and the results have shown that the conversion toward **9a** was the highest when the Darco KB was applied. Understandably, the best results were obtained with the largest amount of Darco KB (Table 1, run 12); however, with such a large amount of Darco KB (and without an increase in the volume of the solvent), the reaction mixture was exceedingly viscous, thus preventing efficient stirring and decreasing the yields. Therefore, as the most appropriate conditions for further optimization, we selected those presented as run 11 (Table 1). NDP was the only other catalyst also yielding an appreciable amount of isoindole **9a** (Table 1, run 7); however, its application was not appropriate, as it caused the extensive formation of side products. All the other combinations proved to be even less successful.

The observed activities of the various heterogeneous dehydrogenation catalysts correlate well with the values of the specific surface areas as measured by the surface-area analyzer,[10] for the catalysts we applied: the BET surface area as determined by the adsorption of nitrogen for the Darco KB was found to be above 1320 $m^2/g$, for the Rh/C it was around 832 $m^2/g$, and for the active carbon it was only 700 $m^2/g$. The better results for dehydrogenation obtained with the Rh/C might, therefore, be mainly attributed to the higher specific area of the carbon component of the Rh/C in comparison with the metal-free active carbon (Table 1, runs 1 and 3). This comparison clearly shows that there is no appreciable effect of metals (precious and others present on the carbon[7b]) on the dehydrogenation step; the results are also consistent with those from the literature.[7b,c]

Since the *N*-substituted maleimides **2** are prone to sublimation, we decided to examine the transformation between **6a** and **2a** in a closed vessel (ACE pressure tube) under the previously determined most successful conditions (with Darco KB). Indeed, the ratio **9a**:**10a** after 4 h of heating in a closed vessel in an oil bath at 150 °C was improved (Table 1, run 13). Furthermore, with an increase in the temperature to 180 °C, the results obtained were even better: the ratio between **9a** and **10a** was 1:0.05, and the conversion was again complete (Table 1, run 14). On the other hand, substituting Darco KB with activated carbon under otherwise identical conditions (Table 1, run 15) decreased the conversion to 93% and the ratio of **9a** to **10a** to 1:0.7, therefore showing that the activated carbon is a less effective dehydrogenation catalyst.

On the basis of some literature reports,[6,7,11] we decided to determine the effect of oxygen on these transformations. We carried out the reaction of **6a** with **2a** under inert conditions (bubbling argon through the reaction mixture) and also with the bubbling of oxygen, both in open vessels (for safety reasons). After 4 h at 180 °C, the conversion was, in the case of inert conditions, around 67%, and exclusively **9a** was detected. However, under the oxygen atmosphere, the conversion toward **9a** was around 23% (without any **10a**), albeit accompanied by a large quantity of degradation products. These results show that a larger amount of oxygen in our case does not enable selective oxidation (dehydrogenation of **8a** into **9a**): at most, it probably causes an unselective overoxidation. In contrast, the majority of the examples described in the literature[6,7,11] were accelerated by the application of an oxygen atmosphere.

**Insights into the Dehydrogenation Activity of Darco KB.** To elucidate the exact dehydrogenation activity of the activated carbon Darco KB, we first tried to isolate the *N*-substituted succinimide **11** that should have been formed if the dehydrogenation takes place as described above. Indeed, in the reaction of **6a** and **2a** (in the molar ratio 1:2) after 4 h at 180 °C, we could detect signals clearly belonging to the *N*-ethylsuccinimide (**11a**) in the $^1$H NMR spectrum of the crude reaction mixture. We also proved this by adding to the reaction mixture an authentic sample of **11a**. Unfortunately, we were not able to isolate **11a**, as it is prone to sublimation during the removal of the solvent (decalin) under reduced pressure. Additionally, in the same reaction, we managed to prove the quantitative formation of **11a** via an HPLC analysis of the crude acetone extract of the reaction mixture (molar ratio of **11a**:**9a** approximately 0.95:1, as determined by the addition of standard **11a**). These results clearly show that the *N*-substituted maleimides **2** really act as the scavengers for the hydrogen that is liberated by the aromatization of **8**. It means that oxygen is not (at least not predominantly) involved in the aromatization step.

This is further supported by the data obtained from the reaction of **6a** and **2a** (however in the molar ratio 1:1), where after 4 h at 180 °C in a closed vessel, an appreciable amount of the starting **6a** remained unreacted.

However, we were still somewhat perplexed as to why the increase of the reaction time (compare runs 14 and 16, Table 1) did not appreciably change the ratio between the isoindoles **9** and the double cycloadducts **10**, as previously reported.[4] Therefore, we decided to check the proposition that the last cycloaddition step (i.e., **8** → **10**) is not reversible (as opposed to the case of the fused pyran-2-ones)[4] under the reaction conditions applied, and **9** cannot form from **10** accordingly. In this regard, a solution of the double cycloadduct **10a** (0.5 mmol) was heated in decalin (8 mL) at 180 °C in a closed vessel and after 24 h analyzed by $^1$H NMR spectroscopy. Surprisingly, there was not even a trace of the aromatized isoindole **9a** (and also not of the cyclohexadiene intermediate **8a**). In the case of fused pyran-2-ones,[4] under comparable conditions there was an around 10% conversion to the corresponding aromatized product. In order to see if there might be an effect of the activated carbon on this transformation, we analogously heated a mixture of the double cycloadduct **10a** (0.5 mmol) and Darco KB (820 mg) in decalin (8 mL) at 180 °C in a closed vessel. After 24 h (and


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**Table 2. Reaction Conditions and Yields for the Synthesis of 9 Starting from 6a–j (1 mmol) and *N*-Substituted Maleimides 2**

| | starting compound **6** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| run | $R^1$ | $R^2$ | $R^3$ | | $t$/h[a] | **2** | product[b] | yield (%)[c] |
| 1 | H | COMe | Me | **6a** | 4 | **2a** | **9a** | 82 |
| 2 | H | COPh | Me | **6b** | 3 | **2a** | **9b** | 84 |
| 3 | H | $CO_2Me$ | Me | **6c** | 3 | **2a** | **9c** | 64 |
| 4 | H | $CO_2Et$ | Me | **6d** | 4 | **2a** | **9d** | 63 |
| 5 | H | $CO_2Me$ | $CH_2CO_2Me$ | **6e** | 4 | **2a** | **9e** | 59[d] |
| 6 | H | $CO_2Et$ | $CH_2CO_2Et$ | **6f** | 4 | **2a** | **9f** | 71 |
| 7 | H | H | Ph | **6g** | 4 | **2a** | **9g** | 52[d] |
| 8 | H | H | 2-furyl | **6h** | 11[e] | **2a** | **9h** | 41[d] |
| 9 | H | H | 2-thienyl | **6i** | 16[e] | **2a** | **9i** | 62[d] |
| 10 | Me | H | 2-pyridyl | **6j** | 6 | **2a** | **9j** | 73 |
| 11 | H | COMe | Me | **6a** | 4 | **2b** | **9k** | 76 |
| 12 | H | COPh | Me | **6b** | 4 | **2b** | **9l** | 80 |
| 13 | H | $CO_2Me$ | Me | **6c** | 4.5 | **2b** | **9m** | 73 |
| 14 | H | $CO_2Et$ | $CH_2CO_2Et$ | **6f** | 4 | **2b** | **9n** | 66 |
| 15 | Me | H | 2-pyridyl | **6j** | 6 | **2b** | **9o** | 70 |
| 16 | H | COMe | Me | **6a** | 4 | **2c** | **9p** | 85 |
| 17 | H | COPh | Me | **6b** | 4 | **2c** | **9q** | 87 |
| 18 | H | $CO_2Me$ | Me | **6c** | 5 | **2c** | **9r** | 73 |
| 19 | H | $CO_2Et$ | $CH_2CO_2Et$ | **6f** | 4 | **2c** | **9s** | 71 |

[a]Reaction times were optimized for each run separately. [b]Darco KB (820 mg), solvent decalin (8 mL) in a closed ACE pressure tube (15 mL) heated with oil bath (180 °C). [c]Yield of isolated product (crude products contained up to 4% of the corresponding **10**). [d]In this case, the crude products contained around 8–10% of the corresponding **10**.[5c,d] [e]At 200 °C.

also after 100 h), there were again no traces of the corresponding isoindole derivative **9a** (as above). However, as proved previously,[4] it might be necessary to have some additional 2*H*-pyran-2-one in the reaction mixture to scavenge the liberated maleimide. In the next experiment, therefore, we mixed an equimolar amount of **6a** and **10a** (0.5 mmol each) in decalin (8 mL) and heated the mixture at 200 °C under otherwise identical conditions as those above. After 24 h, there was again no sign of a conversion from **10a** to **9a**. Even with the addition of activated carbon Darco KB (820 mg) to the above-mentioned mixture of **6a** and **10a** (0.5 mmol each) in decalin (8 mL) after 24 h (at 200 °C), there was no trace of **9a** (and also not of **8a**); the starting compounds remained unchanged. Additional experiments analogous to those described above were also carried out with **10c**. All these results have clearly shown that in contrast to the results previously obtained with fused pyran-2-ones,[4] the double cycloadducts **10** of the bicyclo[2.2.2]octene type are far more stable and do not undergo the retro-Diels–Alder reaction at the reaction temperatures applied (180–200 °C) for their formation. On the other hand, in the case of **10h** the results were different: when an equimolar mixture of the double cycloadduct **10h** and the starting 2*H*-pyran-2-one **6h** (0.5 mmol each) with the addition of Darco KB (820 mg) in decalin (8 mL) was heated (for 24 h) in a closed vessel at 200 °C and analyzed by $^1$H NMR spectroscopy, the formation of the isoindole product **9h** was clearly proved (approximate ratio **9h**:**10h**:**6h** = 0.33:1:1; 25% of the starting **6h** and **10h** having reacted). For the same transformation at a lower temperature (180 °C) (under otherwise identical conditions as above), however, the results were completely different: just a negligible amount of **9h** could be observed in the $^1$H NMR spectrum of the crude reaction mixture. Analogous behavior was found for **9i** as well. Obviously, the temperature plays a crucial role, and the temperature threshold to achieve the reversibility for the transformation **8** → **10** is, in the cases of **9h**,**i**, somewhere between 180 and 200 °C, whereas in all the other cases it is above 200 °C.

Therefore, starting from the cyclohexadiene intermediate **8** at temperatures below 200 °C, there are two irreversible reaction pathways, one leading to the desired isoindoles **9** (**8** → **9**) and the other to the double cycloadducts **10** (**8** → **10**). Since both steps are irreversible, there is no way to influence their ratio **9**:**10** by just changing reaction time; when the products are formed, they cannot be transformed back into the intermediate **8** and therefore also not into the product **10**. To obtain the products **9** in a higher yield, it would be preferential to execute the syntheses of **9** (and not of **10**) at temperatures that would be above the temperature threshold necessary for the cycloaddition **8** → **10** to be reversible (and would therefore preferentially lead to the formation of the thermodynamically more stable isoindole products **9**). However, this is not viable in practice, as such high temperatures would cause the excessive degradation of the starting compounds and also the products.

As expected, in a separate experiment starting from the isoindole **9e** and the succinimide **11a** in decalin and in the presence of Darco KB, we also confirmed that the isoindoles **9**, when formed, cannot be reconverted (hydrogenated) into the intermediates **8**.

The importance of the dehydrogenation catalyst is, in these cases, even more important than in the series of fused pyran-2-ones, and it is obvious that the intermediate **8** has to be dehydrogenated as soon as it is formed to prevent its transformation into **10**. This conclusion also shows why it was necessary to employ such large amounts of the dehydrogenation catalyst and why the amount of isoindole **9** did not increase solely with a prolonged reaction time.

**Synthesis of Isoindole Products 9 from 6 and 2.** The selected conditions as found in run 14 (Table 1) using Darco KB as the dehydrogenation catalyst were further applied for the synthesis of a set of novel isoindoles **9a–s** from the variously substituted 2*H*-pyran-2-ones **6a–j** and *N*-substituted malei-


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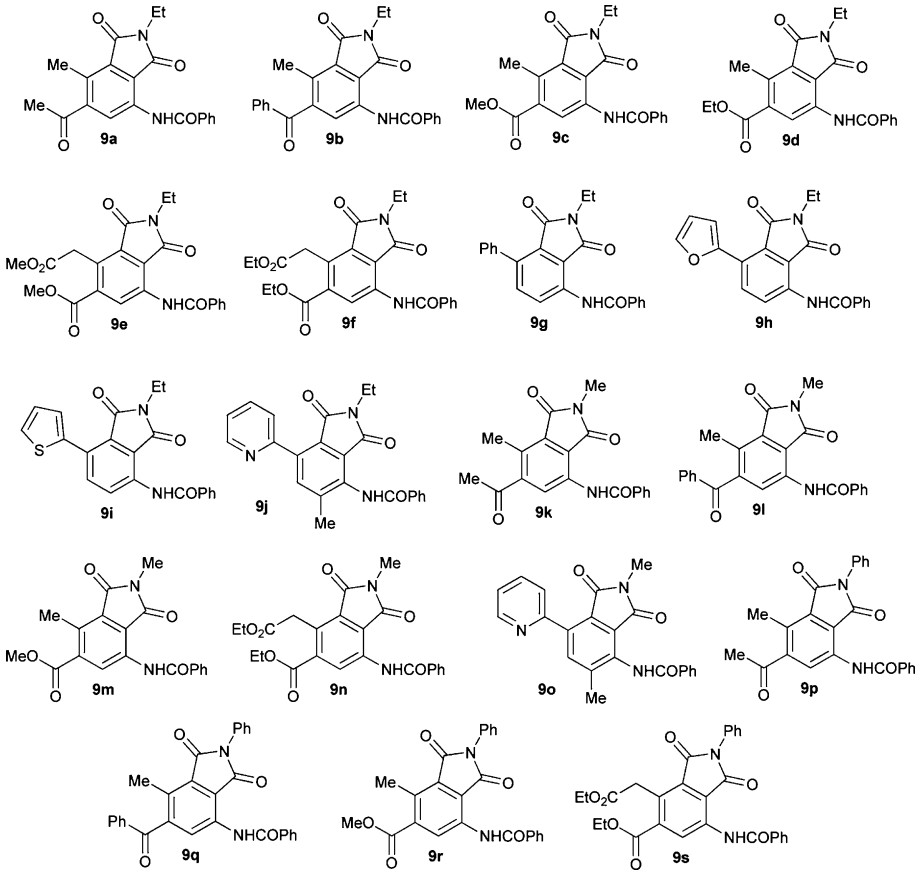
**Chart 1. Isoindole Products 9a–s**




mides **2a–c**. The reactions were carried out in closed vessels that were heated for 3–16 h in an oil bath at 180–200 °C (Table 2) followed by a continuous extraction with toluene from the dehydrogenation catalyst, yielding the products **9a–s** (Chart 1) in 41–87% isolated yields. The best results (the highest conversions and highest ratio **9**:**10**) were obtained with those 2*H*-pyran-2-ones **6** where $R^3$ is a mildly electron-donating substituent, such as a methyl (**6a–d**); similar results were also obtained with the alkoxycarbonylmethyl group (**6e,f**). On the other hand, when $R^3$ is an electron-withdrawing heterocyclic moiety (2-furyl, 2-thienyl) (**6h,i**), the reactions proceed far more slowly (Table 2, runs 8 and 9), whereas with $R^3$ being a phenyl or 2-pyridyl group (**6g,j**), intermediate results were obtained. These data, further supported by the fact that the double bond of the dienophiles **2** is electron-deficient (because of both carbonyl groups), point to the cycloaddition with a normal electron demand.[12] On this basis, cycloaddition of **2a** with electron-rich dienes (2*H*-pyran-2-ones) should proceed even faster; however, in this case also the second cycloaddition step (i.e., of **2** on the intermediate **8**) might be influenced. The effects of the groups $R^1$ and $R^2$ that are not bound to the terminal carbon atoms of the diene system **6**, as also suggested by the literature data,[12c] are far less pronounced.

## CONCLUSIONS

We have presented the application of activated carbon Darco KB as a very efficient dehydrogenation catalyst for the preparation of a set of novel isoindole derivatives **9a–s** via a one-pot Diels–Alder reaction starting from substituted 2*H*-pyran-2-ones and various *N*-substituted maleimides. Furthermore, to the best of our knowledge, our results represent some of the first examples of the use of activated carbon for a key dehydrogenation step, being part of a one-pot sequence incorporating various transformations (including a Diels–Alder cycloaddition forming C–C bonds and the elimination of $CO_2$ as a retro-Diels–Alder reaction followed by a dehydrogenation). Additionally, we have corroborated the results of Hayashi and others,[6,7c] which indicate that in many cases a precious-metal-free active-carbon surface suffices for an efficient dehydrogenation step. Finally, when a scale-up is desired and larger amounts of the catalyst are necessary, we believe that the catalyst could be easily reused.

## EXPERIMENTAL SECTION

Melting points were determined on a micro-hot-stage apparatus and are uncorrected. $^1$H NMR spectra were recorded at 29 °C and 300 or 500 MHz using $Me_4Si$ as an internal standard. $^{13}$C NMR spectra were recorded at 75.5 MHz and are referenced against the central line of the solvent triplet ($CDCl_3$ at 77.0 ppm). The coupling constants (*J*) are given in Hz. IR spectra were obtained as KBr pellets for all compounds (except for **11a**). The starting compounds **6** were prepared according to the published procedures.[13] All other reagents and solvents were used as received from commercial suppliers.

**Thermal Synthesis of the Products 9.** A suspension of the starting 2*H*-pyran-2-one **6** (1 mmol), maleimide **2** (2 mmol), and Darco KB (820 mg) in decalin (8 mL) was placed in a glass ACE pressure tube (15 mL), closed with a Teflon screwed stopper, and heated in an oil bath (at 180 °C for all cases, except for **9h,i** at 200 °C) for 3 h (for **9b,c**), 4 h (for **9a,d–g,k,l,n,p,q,s**), 4.5 h (for **9m**), 5 h (for **9r**), 6 h (for **9j,o**), 11 h (for **9h**), or 16 h (for **9i**). The entire mixture (in the cases of the preparation of **9e,g,h,i** containing around 8–10% of the corresponding bicyclo[2.2.2]octene adduct **10**, as shown by $^1$H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NMR of the crude mixture; in all other cases less than 4% of the corresponding **10** was detected) was transferred into a Soxhlet apparatus and continuously extracted with toluene (120 mL) for 8 h. The extract was evaporated under reduced pressure, and the crude product was treated with 3−4 mL of acetone and then filtered to obtain pure **9**.

***N*-(6-Acetyl-2-ethyl-7-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)benzamide (9a).** Yield: 287 mg (82%) as a very pale yellow solid; mp 204−206 °C (EtOH); IR (KBr) $\nu$ 1757, 1692, 1622, 1539 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 1.31 (t, $J$ = 7.2 Hz, 3H), 2.66 (s, 3H), 2.74 (s, 3H), 3.75 (q, $J$ = 7.2 Hz, 2H), 7.59 (m, 3H), 8.03 (m, 2H), 9.22 (s, 1H), 10.64 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 13.9, 14.3, 30.3, 33.0, 117.8, 124.1, 127.3, 129.1, 129.2, 131.8, 132.7, 133.2, 135.4, 146.9, 165.7, 167.7, 169.5, 201.2; MS (EI) $m/z$ (%) = 350 (26) [$M^+$], 105 (100). Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.29; H, 4.91; N, 8.13.

***N*-(6-Benzoyl-2-ethyl-7-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)benzamide (9b).** Yield: 346 mg (84%) as an off-white solid; mp 227−228 °C (acetone); IR (KBr) $\nu$ 3445, 1762, 1699, 1686, 1672, 1621, 1596, 1581, 1539, 1493 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 1.33 (t, $J$ = 7.2 Hz, 3H), 2.56 (s, 3H), 3.78 (q, $J$ = 7.2 Hz, 2H), 7.56 (m, 6H), 7.85 (m, 2H), 8.01 (m, 2H), 8.91 (s, 1H), 10.67 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 13.9, 14.2, 33.0, 117.1, 123.4, 127.3, 128.8, 129.0, 130.1, 130.7, 132.6, 133.3, 134.2, 135.3, 136.2, 147.9, 165.5, 167.8, 169.8, 196.1 (1 signal hidden); MS (ES−) $m/z$ (%) = 411 (100) [$M - H]^-$. Anal. Calcd for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.89; N, 6.79. Found: C, 72.83; H, 4.78; N, 7.09.

***N*-(2-Ethyl-6-methoxycarbonyl-7-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)benzamide (9c).** Yield: 234 mg (64%) as a pale yellow solid; mp 190−191 °C (acetone); IR (KBr) $\nu$ 3339, 1762, 1734, 1698, 1675, 1618, 1580, 1536 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 1.30 (t, $J$ = 7.2 Hz, 3H), 2.82 (s, 3H), 3.74 (q, $J$ = 7.2 Hz, 2H), 3.95 (s, 3H), 7.57 (m, 3H), 8.01 (m, 2H), 9.33 (s, 1H), 10.57 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 13.8, 14.5, 33.0, 52.6, 118.4, 126.4, 127.3, 128.8, 129.0, 132.6, 133.2, 134.0, 135.1, 138.5, 165.4, 166.4, 167.6, 169.4; MS (ES+) $m/z$ (%) = 367 (100) [$M + H]^+$. Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.47; H, 4.97; N, 7.65.

***N*-(2-Ethyl-6-ethoxycarbonyl-7-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)benzamide (9d).** Yield: 239 mg (63%) as a pale yellow solid; mp 164−166.5 °C (MeOH); IR (KBr) $\nu$ 1760, 1723, 1699, 1619, 1536 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 1.31 (t, $J$ = 7.2 Hz, 3H), 1.44 (t, $J$ = 7.2 Hz, 3H), 2.84 (s, 3H), 3.75 (q, $J$ = 7.2 Hz, 2H), 4.43 (q, $J$ = 7.2 Hz, 2H), 7.58 (m, 3H), 8.03 (m, 2H), 9.33 (s, 1H), 10.61 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 13.9, 14.2, 14.5, 33.0, 61.8, 118.3, 126.2, 127.3, 128.8, 129.0, 132.6, 133.4, 133.7, 135.2, 139.3, 165.5, 166.2, 167.8, 169.6; MS (EI) $m/z$ (%) = 380 (31) [$M^+$], 105 (100). Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.36. Found: C, 66.02; H, 5.11; N, 7.29.

***N*-(2-Ethyl-6-methoxycarbonyl-7-methoxycarbonylmethyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)benzamide (9e).** Yield: 224 mg (59%) as a yellow-green solid; mp 167−169.5 °C (EtOH); IR (KBr) $\nu$ 1761, 1737, 1692, 1626, 1541 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 1.31 (t, $J$ = 7.2 Hz, 3H), 3.74 (m, 5H), 3.94 (s, 3H), 4.60 (s, 2H), 7.59 (m, 3H), 8.04 (m, 2H), 9.55 (s, 1H), 10.63 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 13.8, 32.9, 33.2, 52.1, 52.8, 118.6, 127.2, 127.3, 129.1, 129.6, 129.7, 132.8, 133.2, 136.4, 137.8, 165.5, 166.0, 167.5, 169.3, 171.1; MS (EI) $m/z$ (%) = 380 (31) [$M^+$], 105 (100). Anal. Calcd for $C_{22}H_{20}N_2O_7$: C, 62.26; H, 4.75; N, 6.60. Found: C, 62.46; H, 4.66; N, 6.76.

***N*-(2-Ethyl-6-ethoxycarbonyl-7-ethoxycarbonylmethyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)benzamide (9f).** Yield: 321 mg (71%) as a yellow-orange solid; mp 183−185 °C (EtOH); IR (KBr) $\nu$ 1761, 1737, 1692, 1626, 1541 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 1.29 (m, 6H), 1.42 (t, $J$ = 7.2 Hz, 3H), 3.75 (q, $J$ = 7.2 Hz, 2H), 4.18 (q, $J$ = 7.2 Hz, 2H), 4.40 (q, $J$ = 7.2 Hz, 2H), 4.58 (s, 2H), 7.59 (m, 3H), 8.04 (m, 2H), 9.52 (s, 1H), 10.62 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 13.8, 14.14, 14.16, 33.1, 61.0, 62.0, 118.4, 127.0, 127.3, 129.0, 129.5, 129.7, 132.7, 133.2, 136.4, 138.5, 165.5, 165.6, 167.5, 169.4, 170.6 (1 signal hidden); MS (ES+) $m/z$ (%) = 453 (25) [$M + H]^+$, 475 (100) [$M + Na]^+$. Anal. Calcd for $C_{24}H_{24}N_2O_7$: C, 63.71; H, 5.21; N, 6.16. Found: C, 63.81; H, 5.21; N, 6.16.

***N*-(2-Ethyl-1,3-dioxo-7-phenyl-2,3-dihydro-1*H*-isoindol-4-yl)benzamide (9g).** Yield: 192 mg (52%) as a yellow solid; mp 201−203 °C (EtOH); IR (KBr) $\nu$ 1759, 1686, 1625, 1608, 1530 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 1.28 (t, $J$ = 7.2 Hz, 3H), 3.73 (q, $J$ = 7.2 Hz, 2H), 7.55 (m, 8H), 7.68 (d, $J$ = 8.7 Hz, 1H), 8.07 (m, 2H), 9.01 (d, $J$ = 8.7 Hz, 1H), 10.84 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 13.9, 32.9, 116.9, 124.9, 126.7, 127.4, 128.1, 128.6, 129.0, 129.3, 132.6, 133.5, 135.8, 135.9, 136.9, 138.0, 165.6, 167.1, 170.3; MS (EI) $m/z$ (%) = 370 (55) [$M^+$], 105 (100). Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.40; H, 4.84; N, 7.56.

***N*-[2-Ethyl-7-(2-furyl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]benzamide (9h).** Yield: 148 mg (41%) as an orange-green solid; mp 203−205 °C (EtOH); IR (KBr) $\nu$ 1745, 1694, 1682, 1625, 1531 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 1.32 (t, $J$ = 7.2 Hz, 3H), 3.78 (q, $J$ = 7.2 Hz, 2H), 6.58 (dd, $J$ = 3.5, 1.8 Hz, 1H), 7.56 (m, 4H), 7.88 (dd, $J$ = 3.5, 0.6 Hz, 1H), 8.05 (m, 2H), 8.22 (d, $J$ = 9.0 Hz, 1H), 9.00 (d, $J$ = 9.0 Hz, 1H), 10.92 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 13.9, 33.0, 112.3, 113.7, 116.6, 123.4, 124.1, 125.1, 127.3, 128.9, 132.5, 133.40, 133.42, 136.4, 143.0, 148.7, 165.4, 167.0, 170.0; MS (EI) $m/z$ (%) = 360 (36) [$M^+$], 105 (100). Anal. Calcd for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.48; N, 7.77. Found: C, 69.88; H, 4.58; N, 7.91.

***N*-[2-Ethyl-7−1,3-dioxo-(2-thienyl)-2,3-dihydro-1*H*-isoindol-4-yl]benzamide (9i).** Yield: 233 mg (62%) as an orange solid; mp 183−184 °C (acetone); IR (KBr) $\nu$ 3355, 1748, 1692, 1679, 1625, 1603, 1593, 1531, 1516, 1494 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 1.31 (t, $J$ = 7.2 Hz, 3H), 3.76 (q, $J$ = 7.2 Hz, 2H), 7.16 (m, 1H), 7.44 (m, 1H), 7.58 (m, 3H), 7.85 (m, 2H), 8.06 (m, 2H), 8.97 (d, $J$ = 9.0 Hz, 1H), 10.90 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 13.8, 33.0, 117.0, 125.1, 125.5, 127.2, 127.3, 127.8, 128.4, 129.0, 129.4, 132.5, 133.4, 136.8, 137.37, 137.40, 165.5, 167.0, 170.0; MS (ES+) $m/z$ (%) = 377 (100) [$M + H]^+$. Anal. Calcd for $C_{21}H_{16}N_2O_3S$: C, 67.00; H, 4.28; N, 7.44. Found: C, 67.07; H, 4.03; N, 7.44.

***N*-[2-Ethyl-5-methyl-1,3-dioxo-7-(2-pyridyl)-2,3-dihydro-1*H*-isoindol-4-yl]benzamide (9j).** Yield: 281 mg (73%) as a pale yellow solid; mp 204−205 °C (acetone); IR (KBr) $\nu$ 3414, 1764, 1725, 1700, 1686, 1644, 1600, 1578, 1531, 1511, 1486 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 1.24 (t, $J$ = 7.2 Hz, 3H), 2.51 (s, 3H), 3.68 (q, $J$ = 7.2 Hz, 2H), 7.35 (m, 1H), 7.58 (m, 3H), 7.80 (m, 1H), 7.88 (m, 1H), 7.97 (s, 1H), 8.07 (m, 2H), 8.75 (m, 1H), 9.48 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 13.8, 20.0, 32.9, 123.0, 123.2, 125.5, 127.1, 127.8, 128.9, 132.5, 133.6, 135.3, 135.8, 136.2, 139.1, 141.8, 149.6, 153.4, 165.9, 167.0, 169.1; MS (ES−) $m/z$ (%) = 384 (100) [$M - H]^-$. Anal. Calcd for $C_{23}H_{19}N_3O_3$: C, 71.68; H, 4.97; N, 10.90. Found: C, 71.53; H, 4.83; N, 10.91.

***N*-(6-Acetyl-2-methyl-7-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)benzamide (9k).** Yield: 255 mg (76%) as a pale yellow solid; mp 187−188.5 °C (acetone); IR (KBr) $\nu$ 3435, 1756, 1690, 1620, 1582, 1536, 1493 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 2.64 (s, 3H), 2.69 (s, 3H), 3.17 (s, 3H), 7.56 (m, 3H), 7.99 (m, 2H), 9.18 (s, 1H), 10.55 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 14.3, 23.8, 30.2, 117.7, 124.1, 127.2, 129.0, 129.1, 131.9, 132.7, 133.0, 135.3, 146.7, 165.5, 167.8, 169.5, 201.0; MS (ES+) $m/z$ (%) = 337 (100) [$M + H]^+$. Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33. Found: C, 67.81; H, 4.70; N, 8.29.

***N*-(6-Acetyl-2,7-dimethyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)benzamide (9l).** Yield: 318 mg (80%) as an off-white solid; mp 219−220 °C (acetone); IR (KBr) $\nu$ 3446, 1764, 1687, 1672, 1620, 1597, 1537, 1493 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 2.55 (s, 3H), 3.21 (s, 3H), 7.56 (m, 6H), 7.84 (m, 2H), 7.99 (m, 2H), 8.90 (s, 1H), 10.63 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 14.2, 23.8, 117.1, 123.5, 127.3, 128.8, 129.0, 130.1, 130.7, 132.6, 133.2, 134.2, 135.2, 136.1, 147.9, 165.5, 168.0, 169.9, 196.0 (1 signal hidden); MS (ES−) $m/z$ (%) = 397 (100) [$M - H]^-$. Anal. Calcd for


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$C_{24}H_{18}N_2O_4$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.03; H, 4.49; N, 7.03.

***N*-(2-Methyl-6-methoxycarbonyl-7-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)benzamide (9m).** Yield: 257 mg (73%) as a yellow solid; mp 211−213 °C (acetone); IR (KBr) $\nu$ 3445, 1764, 1731, 1701, 1677, 1617, 1580, 1534 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 2.85 (s, 3H), 3.19 (s, 3H), 3.96 (s, 3H), 7.58 (m, 3H), 8.03 (m, 2H), 9.37 (s, 1H), 10.58 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 14.5, 23.8, 52.6, 118.3, 126.3, 127.2, 128.8, 128.9, 132.6, 133.1, 134.0, 135.0, 138.4, 165.2, 166.3, 167.8, 169.4; MS (ES+) $m/z$ (%) = 353 (100) $[M + H]^+$. Anal. Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.50; H, 4.62; N, 7.93.

***N*-(2-Methyl-6-ethoxycarbonyl-7-ethoxycarbonylmethyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)benzamide (9n).** Yield: 289 mg (66%) as a very pale orange solid; mp 157−159 °C ($Me_2CO$); IR (KBr) $\nu$ 3451, 1770, 1727, 1697, 1626, 1541 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 1.28 (t, $J$ = 7.2 Hz, 3H), 1.42 (t, $J$ = 7.2 Hz, 3H), 3.19 (s, 3H), 4.18 (q, $J$ = 7.2 Hz, 2H), 4.41 (q, $J$ = 7.2 Hz, 2H), 4.57 (s, 2H), 7.59 (m, 3H), 8.04 (m, 2H), 9.52 (s, 1H), 10.59 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 14.11, 14.14, 23.9, 33.1, 61.0, 62.0, 118.4, 127.0, 127.3, 129.0, 129.5, 129.7, 132.7, 133.1, 136.3, 138.5, 165.5, 165.6, 167.7, 169.4, 170.5; MS (ES+) $m/z$ (%) = 439 (31) $[M + H]^+$. Anal. Calcd for $C_{23}H_{22}N_2O_7$: C, 63.01; H, 5.06; N, 6.39. Found: C, 62.83; H, 5.05; N, 6.40.

***N*-[2,5-Dimethyl-1,3-dioxo-7-(2-pyridyl)-2,3-dihydro-1*H*-isoindol-4-yl]benzamide (9o).** Yield: 260 mg (70%) as an off-white solid; mp 217−218 °C (acetone); IR (KBr) $\nu$ 3337, 1759, 1713, 1698, 1663, 1584, 1530, 1520, 1493 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ (ppm) 2.49 (s, 3H), 3.11 (s, 3H), 7.35 (m, 1H), 7.55 (m, 2H), 7.61 (m, 1H), 7.83 (m, 2H), 7.95 (s, 1H), 8.06 (m, 2H), 8.73 (m, 1H), 9.48 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 20.0, 23.8, 123.2, 123.3, 125.4, 127.7, 128.9, 132.4, 133.6, 135.3, 135.9, 136.2, 139.1, 141.9, 149.6, 153.4, 165.9, 167.2, 169.1 (1 signal hidden); MS (ES+) $m/z$ (%) = 372 $[M + H]^+$, 236 (100). Anal. Calcd for $C_{22}H_{17}N_3O_3$: C, 71.15; H, 4.61; N, 11.31. Found: C, 70.96; H, 4.42; N, 11.27.

***N*-(6-Acetyl-7-methyl-1,3-dioxo-2-phenyl-2,3-dihydro-1*H*-isoindol-4-yl)benzamide (9p).** Yield: 338 mg (85%) as a very pale yellow solid; mp 266−267 °C ($Me_2CO$); IR (KBr) $\nu$ 3441, 1758, 1692, 1618, 1597, 1536, 1493 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 2.69 (s, 3H), 2.78 (s, 3H), 7.55 (m, 8H), 8.03 (m, 2H), 9.31 (s, 1H), 10.74 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 14.4, 30.4, 117.2, 124.4, 126.6, 127.3, 128.6, 129.1, 129.3, 131.0, 132.3, 132.8, 133.1, 136.0, 147.6, 165.8, 166.8, 168.8, 201.2 (1 signal hidden); MS (ES−) $m/z$ (%) = 397 $[M - H]^-$. Anal. Calcd for $C_{24}H_{18}N_2O_4$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.20; H, 4.45; N, 6.94.

***N*-(6-Benzoyl-7-methyl-1,3-dioxo-2-phenyl-2,3-dihydro-1*H*-isoindol-4-yl)benzamide (9q).** Yield: 402 mg (87%) as an off-white solid; mp 254−255 °C (acetone); IR (KBr) $\nu$ 3433, 1763, 1703, 1676, 1620, 1597, 1535, 1502, 1493 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 2.60 (s, 3H), 7.55 (m, 11H), 7.87 (m, 2H), 8.00 (m, 2H), 9.00 (s, 1H), 10.76 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 14.3, 116.6, 123.8, 126.6, 127.3, 128.3, 128.5, 128.90, 128.99, 129.3, 130.1, 131.0, 131.2, 132.7, 133.1, 134.3, 135.8, 136.1, 148.5, 165.5, 166.8, 169.0, 195.9; MS (ES+) $m/z$ (%) = 461 (100) $[M + H]^+$. Anal. Calcd for $C_{29}H_{20}N_2O_4$: C, 75.64; H, 4.38; N, 6.08. Found: C, 75.34; H, 4.25; N, 6.00.

***N*-(6-Methoxycarbonyl-7-methyl-1,3-dioxo-2-phenyl-2,3-dihydro-1*H*-isoindol-4-yl)benzamide (9r).** Yield: 302 mg (73%) as a pale yellow-green solid; mp 226−228 °C (acetone); IR (KBr) $\nu$ 3453, 1767, 1729, 1699, 1681, 1626, 1599, 1539, 1504, 1494 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 2.85 (s, 3H), 3.94 (s, 3H), 7.50 (m, 8H), 7.99 (m, 2H), 9.41 (s, 1H), 10.65 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 14.6, 52.7, 117.9, 126.6, 126.7, 127.3, 128.3, 128.5, 129.0, 129.2, 130.9, 132.7, 133.0, 134.5, 135.6, 139.1, 165.4, 166.4, 166.7, 168.7; MS (ES+) $m/z$ (%) = 415 (100) $[M + H]^+$. Anal. Calcd for $C_{24}H_{18}N_2O_5$: C, 69.56; H, 4.38; N, 6.76. Found: C, 69.56; H, 4.27; N, 6.72.

***N*-(6-Ethoxycarbonyl-7-ethoxycarbonylmethyl-1,3-dioxo-2-phenyl-2,3-dihydro-1*H*-isoindol-4-yl)benzamide (9s).** Yield: 355 mg (71%) as a yellow solid; mp 194−196.5 °C (acetone); IR (KBr) $\nu$ 3459, 1765, 1732, 1721, 1704, 1682, 1622, 1599, 1536, 1502, 1493 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 1.28 (t, $J$ = 7.2 Hz, 3H), 1.44 (t, $J$ = 7.2 Hz, 3H), 4.18 (q, $J$ = 7.2 Hz, 2H), 4.43 (q, $J$ = 7.2 Hz, 2H), 4.63 (s, 2H), 7.53 (m, 8H), 8.04 (m, 2H), 9.61 (s, 1H), 10.72 (s, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ (ppm) 14.15, 14.17, 33.2, 61.1, 62.1, 117.9. 126.6, 127.4, 128.6, 129.0, 129.2, 129.3, 130.0, 130.8, 132.8, 133.1, 137.0, 139.1, 165.6, 166.6, 168.6, 170.5 (2 signals hidden); MS (ES+) $m/z$ (%) = 501 $[M + H]^+$, 286 (100). Anal. Calcd for $C_{28}H_{25}N_2O_7$: C, 67.19; H, 4.83; N, 5.60. Found: C, 67.23; H, 4.81; N, 5.62.

***N*-Ethylsuccinimide (11a).**[14a,b] Compound **11a** (which is also commercially available) was prepared by a modification of a procedure described by Johnson and co-workers.[14c] In a 250 mL hydrogenation vessel, the solution of *N*-ethylmaleimide (**2a**) (628 mg, 5.02 mmol) in methanol (25 mL) was flushed with argon. The Pd/C (240 mg) was added, the walls were washed with additional methanol (5 mL), and the reaction mixture was hydrogenated for 4 h at 55 psi hydrogen. Thereafter, the mixture was filtered, and the volatile components were removed under vacuum, yielding the product *N*-ethylsuccinimide (**11a**) as a colorless, viscous oil. Yield: 490 mg (77%); mp 24−25 °C; lit.[14a] mp 26 °C; IR (neat on a NaCl plate) $\nu$ 3455, 2982, 2943, 1770, 1697, 1443, 1405, 1379, 1348 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 1.17 (t, $J$ = 7.2 Hz, 3H), 2.70 (s, 4H), 3.56 (q, $J$ = 7.2 Hz, 2H).

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Copies of $^1H$ and $^{13}C$ NMR spectra for products **9a**−**s** are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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