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Study of Radical Decarboxylation Toward Functionalization of Naphthoquinones

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Dedicated to the memory of Anne Chobelet

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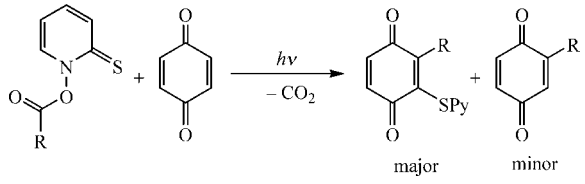
In order to obtain functionalized naphthoquinones, a systematic study of the Kochi–Anderson procedure for the alkylation of quinones is presented. While linear amino acids of different lengths were good substrates for this decarboxylation procedure, chiral α-amino acids were unsuccessful substrates. The best reaction conditions were evaluated with β-alanine and then applied to a series of carboxylic acids to obtain chemical diversity on the naphthoquinones. We observed that the substitution of the acids is critical for the alkylation, and that it was possible to realize a double alkylation with 1,4-naphthoquinone, even with different reactants. The Barton procedure was attempted on some substrates to compare with our results, but no reaction was observed, no matter which radical trap was used.

Introduction

Quinones are present in many natural products and have been widely used in medicinal chemistry due to their broad spectrum of biological activity including antimicrobial, antibiotic, antiviral, antimalarial, and anticancer activities.[1,2] In the course of our ongoing research in the field of anticancer drugs, we are interested in synthesizing simple naphthoquinone derivatives incorporating a chemical group that would allow further functionalization.

Examples of radical addition to quinones in the literature are numerous, either with organotellurium compounds[3] or mediated by metal ions like Mn^{III} or Ce^{IV} as a way to initiate a carbon radical.[4,5] To date, the most common procedure is the Barton method that uses esters as radical precursors.[6] While the alkylation of a variety of quinones gave good yields with this reaction,[7,8] it still suffers from serious drawbacks. The sensitive thiohydroxamic ester has to be prepared prior to the addition, which usually leads to a mixture of two quinone adducts (Scheme 1) under oxidative conditions (most commonly obtained by a quinone excess). Moreover, in the case of naphthoquinones, desulfurization of the major product proved to be difficult if not impossible.[7] Previous work in the field of naphthoquinone functionalization[7,9] led us to consider a radical decarboxylation method with Ag^{I} and ammonium persulfate as a radical initiator because of its reported ease of handling and its efficiency in synthesizing amine-functionalized quinones. This little-known procedure resembles earlier work by Kochi and Anderson,[10] which involved an excess of a suitable carboxylic acid mixed with a quinone in a homogeneous H_2O/CH_3CN mixture. Such a procedure, with variations in the quinone/acid ratio was shown to be successful in the preparation of natural products[11] and was sometimes reported as the Minisci reaction when performed in a two-phase solvent mixture.[12]



Scheme 1. Barton procedure adducts.

Results and Discussion

Preliminary Amino Acid Addition

Our first aim was to obtain a naphthoquinone moiety bearing a lateral chain terminated by an amine. Menadione (2-methyl-1,4-naphthoquinone, **M**) was chosen since only the carbon atom at position 3 could react. Boc-glycine was first allowed to react with **M** to lead to the corresponding functionalized quinone in a moderate yield under previously reported conditions. The homologous linear amino

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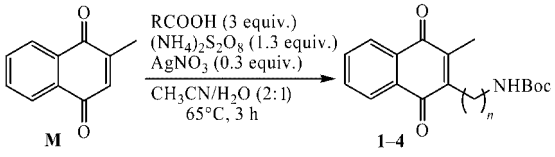
acids with 2–4 methylene groups, namely Boc-β-alanine, Boc-aminobutyric, and Boc-aminopentanoic acid, were also added under the same conditions in order to compare our results with the initial report (Scheme 2).[9] Our results differed slightly from the original study. The best compromise between reaction yield and **M** recycling was obtained with one methylene unit (**1**), while three methylene units led to the best alkylation yield (**3**). One might consider these yields as poor, but they correspond to the purified adducts and do not take into account the low conversion rate of the quinone, which was easily recovered by chromatography and recycled (yields based on conversions for **1** and **3** were 82% and 80%, respectively).

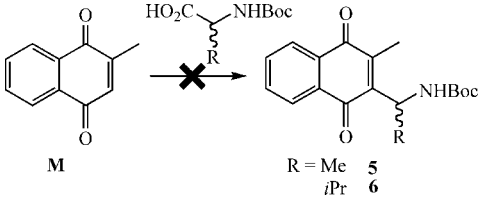


R	M[a] (%)	Yield[b] (%)	Compound
$BocNHCH_2$-	54	37	**1**
$BocNH(CH_2)_2$-	43	37	**2**
$BocNH(CH_2)_3$-	37	52	**3**
$BocNH(CH_2)_4$-	14	29	**4**

[a] Percentage of recovered **M** after workup and purification.
[b] Isolated yield.

Scheme 2. Radical addition of linear carboxylic acids.

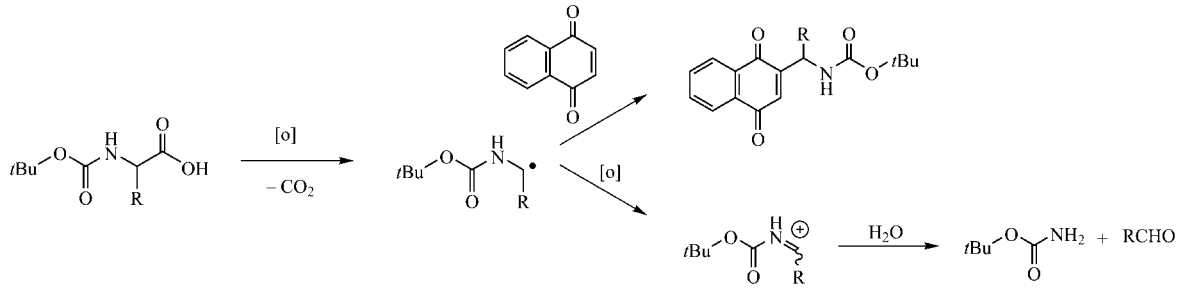
We then attempted to introduce chiral substituents into the naphthoquinone ring. This might be achieved by the same method, with a protected α-amino acid (Scheme 3). Surprisingly, neither Boc-alanine nor Boc-valine led to the desired adducts, while a substantial quantity of menadione was recycled after purification. No trace of the α-amino acids, neither decarboxylated nor unreacted, was recovered, which led us to suppose that rearranged substrates were removed during workup. These unsuccessful attempts could be the result of a lack of reactivity of the carbon radical bearing both an alkyl group and a carbamate-protected amino group. Indeed, the mild electron-donor effect of the menadione methyl group can decrease the reactivity of the intermediate radical, leading to side reactions or degradation.[13] Among the expected degradation pathways, the oxidation of the amidoalkyl radical has been reported for its synthetic usefulness, and should lead to a *tert*-butyl carbamate (Scheme 4).[14] However, this amine was not detected, and we suppose the carbamate protecting group was unstable under the reaction conditions.[15] The absence of an alkyl side-chain in Boc-glycine, while explaining its decreased inclination to oxidation and reactivity (Scheme 2) does not substantiate the stability of the amine protecting group. Another possibility could be that the alkyl substituent in a chiral α-amino acid could change the course of the reaction to favor a one-electron transfer to the quinone instead of a radical addition.[16]



Scheme 3. Radical addition of α-amino acids to **M**.

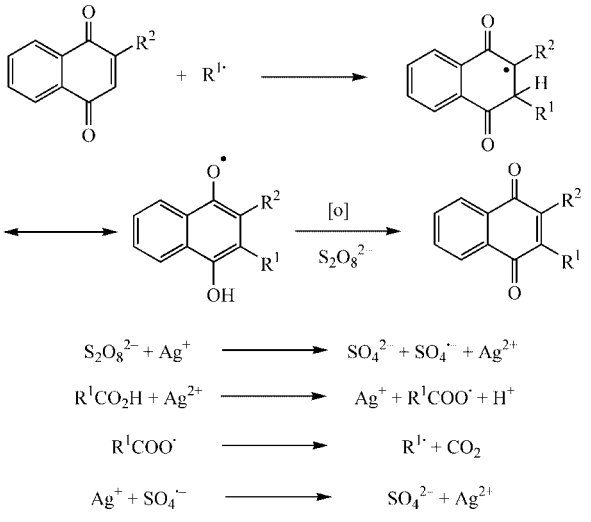
Assessment of the Reaction Parameters

The mechanism of the reaction involves the generation of the carbon radical through an Ag^{II}-assisted oxidative decarboxylation of the carboxylic acid. Nucleophilic addition of the radical to an electron-deficient naphthoquinone, followed by rearomatization can allow carbon alkylation (Scheme 5). To determine the validity of the procedure, we varied the parameters of the reaction of readily available Boc-β-alanine with **M**. The experimental procedure was realized in a homogeneous solvent mixture, which insured solubility of all reaction components (see Experimental Section). In the case of the Minisci reaction, either a two-phase mixture[12,17] or a strong acidic medium has been used.[15] While the latter conditions were unsuitable with a *tert*-butyl carbamate protecting group and led to unpredictable results in the case of α-amino acids, they also gave an unexpected (and in our case undesired) regioselectivity when **M** was used.[12] In all reports related to the Minisci procedure, the ammonium persulfate was initially present or quickly added to the reaction mixture. In our hands, the radical initiator had to be slowly added to the medium to ensure a correct balance between conversion of the quinone and addition yield (Table 1, Entries 1, 5, and 6). Changing the amount of carboxylic acid also diminished the reaction yield (Table 1, Entries 1–4). Concentration of the medium in order to increase the primary radical reactivity also led to a less satisfactory result (Table 1, Entry 7). Moreover, it appeared that these modifications were also accompanied by a decreased



Scheme 4. Behavior of carbon radicals derived from carboxylic acids.

recycling of the naphthoquinone (Table 1, Entries 3–7), whereas carboxylic acid recovery after workup was deceiving. Unexpectedly, the initial reaction conditions were the most suitable to functionalize the quinone. To the best of our knowledge, no previous study had considered the problem.



Scheme 5. Kochi–Anderson addition to naphthoquinones.

Table 1. Influence of addition parameters on Boc-β-alanine addition.

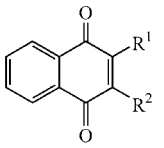
Entry	Acid [equiv.]	Addition time [h]	Yield of product [%]	Yield of **M** [%][a]	Yield of acid [%][a]
1	3	2	43	51	12
2	1.3	2	17	67	15
3	2	2	31	24	24
4	6	2	33	7	22
5	3	0.5	7	39	1
6	3	5	25	19	12
7[b]	3	2	25	40	15

[a] After workup and purification. [b] More concentrated than in Entry 1.

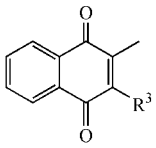
Reaction of Different Substrates with Naphthoquinones

Considering these results, we thought it could be important to determine the behavior of differently functionalized substrates toward the Kochi–Anderson procedure. Either a primary, secondary, or tertiary carbon-radical-containing acid was first allowed to react with **M** and 1,4-naphthoquinone (**NQ**, Table 2, Entries 1–6). Interestingly, reactions with acetic and isobutyric acids yielded the alkylated quinones, while pivaloic acid gave no conversion in the case of **M**. These results need to be compared with those obtained from a previous study in which no addition occurred when thiocarbonyl derivatives leading to the three types of radicals were used with **M** according to the Barton methodology.[8c] On the contrary, reaction of pivaloic acid with **NQ** led to the desired adduct (Table 2, Entry 6), which might be explained by a lack of steric hindrance from the methyl group present in **M**. The reaction between acetic or isobutyric acid and **NQ** led to **M** or **11** as expected but also yielded the double-addition compounds **9** (Table 2, Entry 4) and **12** (Table 2, Entry 5). This double addition was not observed with more highly substituted acids (Table 2, Entry 6), confirming the importance of steric hindrance on the reaction outcome.

Table 2. Addition of various carboxylic acids to **M** or **NQ**.



NQ $R^1 = R^2 = H$
11 $R^1 = H$, $R^2 = i$Pr
12 $R^1 = R^2 = i$Pr
13 $R^1 = H$, $R^2 = t$Bu
15 $R^1 = H$, $R^2 = (CH_2)_2CO_2Me$
16 $R^1 = H$, $R^2 = (CH_2)_2NHBoc$
17 $R^1 = R^2 = (CH_2)_2NHBoc$
18 $R^1 = H$, $R^2 = CH_2NHBoc$
19 $R^1 = CH_2NHBoc$, $R^2 = (CH_2)_2NHBoc$
20 $R^1 = R^2 = CH_2NHBoc$



M $R^3 = H$
7 $R^3 = CH(Me)CH_2CO_2H$
8 $R^3 = CH_2CH(Me)CO_2H$
9 $R^3 = Me$
10 $R^3 = i$Pr
14 $R^3 = (CH_2)_2CO_2Me$

Entry	Quinone	Carboxylic acid	Compound, Yield [%]
1	**M**	CH_3–COOH	**9**, 38
2	**M**	*i*Pr–COOH	**10**, 32
3	**M**	$(CH_3)_3C$–COOH	no addition
4[a]	**NQ**	CH_3–COOH	**M**, 36 **9**, 23
5[a]	**NQ**	*i*Pr–COOH	**11**, 42 **12**, 9
6	**NQ**	$(CH_3)_3C$–COOH	**13**, 25
7	**M**	$BrCH_2$–COOH	no addition
8	**M**	MeO–CH_2–COOH	no addition
9	**M**	MeOOC–CH_2–COOH	no addition
10	**M**	HO_2C–$CH(CH_3)$–CH_2–CO_2H	**7**, 10 **8**, 3
11	**M**	MeOOC–$(CH_2)_2$–COOH	**14**, 58
12	**NQ**	MeOOC–$(CH_2)_2$–COOH	**15**, 28
13[b]	**NQ**	Boc–β-Ala–OH	**16**, 27
14[c]	**NQ**	Boc–β-Ala–OH	**16**, 26 **17**, 12
15	**NQ**	Boc–NH–CH_2–CO_2H	**18**, 47
16	**18**	Boc–β-Ala–OH	**19**, 76
17	**16**	Boc–NH–CH_2–CO_2H	**19**, 45
18[d]	**NQ**	Boc–NH–CH_2–CO_2H and Boc–β-Ala–OH	**18**, 37 **20**, 19

[a] Yields were calculated from NMR spectra (see Experimental Section). [b] 3 equiv. of carboxylic acid, 1.3 equiv. of $(NH_4)_2S_2O_8$, and 0.3 equiv. of $AgNO_3$. [c] 6 equiv. of carboxylic acid, 2.6 equiv. of $(NH_4)_2S_2O_8$, and 0.6 equiv. of $AgNO_3$. [d] 3 equiv. of each carboxylic acid, 2.6 equiv. of $(NH_4)_2S_2O_8$, and 0.6 equiv. of $AgNO_3$.

Reactions of three carboxylic acids bearing electron-donating or electron-withdrawing groups only resulted in the recycling of the starting quinone (Table 2, Entries 7–9). Introduction of a second methylene unit in the starting material was more successful, as demonstrated by Table 2, Entries 10–13.

As expected, the reaction of **M** with racemic 2-methylsuccinic acid led to a regioisomeric mixture, albeit with a poor yield (Table 2, Entry 10), the major product **7** resulting from the formation of the secondary radical (Figure 1).

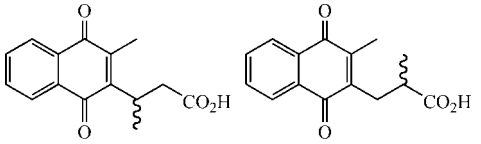


Figure 1. Products of 2-methylsuccinic acid addition to **M**.

Monomethylsuccinic acid led to a much better yield with **M** than with **NQ** (Table 2, Entries 11–12). This is fully in accordance with a greater stability of the intermediate semiquinone radical obtained in the case of the 2-methyl-substituted aromatic ring (Scheme 5). The reaction between Boc-β-alanine and **NQ** (Table 2, Entry 13) gave only monoalkylated adduct **16** but in a lower yield than that obtained with **M**, which confirms the previous observation. We surmised that a double addition on **NQ** might be possible if the amount of carboxylic acid was increased. By reaction of 6 equiv. of Boc-β-alanine, we obtained both mono- and disubstituted **NQ** in a 2:1 ratio (Table 2, Entry 14). In that case, the yield of isolated **16** (26%) was similar to that obtained when performing the reaction under the usual conditions (27%, Table 2, Entry 13), despite the excess of carboxylic acid. However, the yield obtained for the dialkylated adduct **17** (12%) was not consistent with a higher stability of the substituted quinone, which would then allow a second radical addition.

This latter experiment suggested the possibility of introducing some diversity on the **NQ** structure by successively treating different carboxylic acids. In order to test this hypothesis, Boc-glycine was added to **NQ** to yield the desired substrate **18** in a better yield (47%) than that obtained with **M** (37%, Scheme 2). A second substituent was then added (Table 2, Entry 16) by a reaction between Boc-β-alanine and **18** to yield the expected dialkylated adduct **19** in good yield. Reversing the order of the double addition by treating the protected glycine with **16** (Table 2, Entry 17) led to the desired doubly substituted naphthoquinone **19** but in a much lower yield. Finally, the simultaneous addition of 3 equiv. of Boc-glycine and 3 equiv. of Boc-β-alanine was attempted with **NQ** (Table 2, Entry 18) to yield only the mono- and dialkylated adducts of the former carboxylic acid. In this case, no addition of Boc-β-alanine was observed, which confirmed the better reactivity of the carbon radical formed from Boc-glycine.

The results presented in Table 2 demonstrate the dramatic influence of the substitution on the carbon atom bearing the carboxylic acid group. It was quite surprising to observe no reaction with Boc-protected α-amino acids (Scheme 3), while Boc-glycine led to the desired compound. Moreover, Table 2, Entries 7–9 suggest that a functionalized single methylene group was unsuitable for this reaction, Table 2, Entries 10–12 seem to confirm this hypothesis.

The Barton Procedure

The Barton decarboxylation procedure was then applied to some carboxylic acids in order to allow comparison with our results. Preparation of the thiopyridone derivatives of monoethyl malonate or monomethyl succinate led to unstable compounds (Figure 2, **21** and **22**). No purification was possible with either thiohydroxamic ester since a color shift was observed when silica filtration was attempted, and a complex decomposition mixture was eluted. Direct addition of the crude esters **21** and **22** to **M** under UV light led only to recovered quinone. Boc-alanine ester **23** proved more stable, but no reaction occurred under irradiation. Even when the well-known radical trap phenyl vinyl sulfone[18] was subjected to the same conditions, it was recovered unreacted. Neither addition products nor amino acid derivatives were detected after purification. The Boc-β-alanine ester **24** was also directly treated with **M** and led to a complex mixture, which probably contained the desired addition compound as a trace among unknown species.[19]

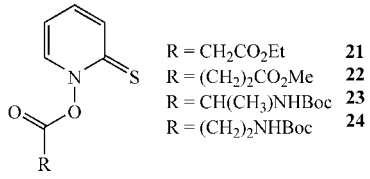


Figure 2. Thiohydroxamic esters used in the Barton procedure.

From these experiments, with the better known decarboxylation procedure, we observed either a lack of stability and reactivity toward the desired compounds or the formation of complex mixtures, which were difficult to purify.

Conclusions

We have described the reactivity of versatile carboxylic acids toward **NQ** and **M**, with the rarely reported Kochi–Anderson decarboxylation procedure. We have first assessed the best reaction conditions with an *N*-Boc-protected linear β-amino acid. While the addition of a chiral α-amino acid proved impossible with this method, we had no more success with the Barton procedure. Nevertheless, we were able to easily prepare new functionalized naphthoquinone derivatives in reasonable yields. Monosubstituted compounds resulted from the reaction of **M**, and both mono- and disubstituted analogs resulted from the reaction of **NQ**. Introduction of different moieties in the latter case was possible and opened the door to structural diversity. All new compounds reported herein allow for further variation through the introduced chemical functionality. We have noted the importance of the quinone substitution (**M** compared to **NQ**), as well as the carbon-radical stability on the reaction outcome (Table 2). So far, we believe that both parameters are equally important to alkylation with the Kochi–Anderson procedure. Further work is currently in progress to determine whether replacement of the *N*-Boc group could lead to the addition of chiral α-amino acids.

Experimental Section

General Techniques: All reagents were commercially obtained (Aldrich, Acros) at the highest commercial quality and used without further purification. Yields refer to spectroscopically (^{1}H NMR) homogeneous materials. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) with UV light for detection and *p*-anisaldehyde or ninhydrin solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash chromatography. NMR spectra were recorded with Bruker 300 MHz or 400 MHz instruments and calibrated with residual non-deuterated solvent as an internal reference. Chemical shifts are reported in ppm downfield from the internal reference. The following abbreviations are used for the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad. IR spectra were recorded with a Bruker Tensor 27 spectrophotometer with ATR (Attenuated Total Reflection). Absorbance frequencies are given at the maximum of intensity in cm^{-1}. High resolution mass spectra (HRMS) were recorded with a WATERS ESI-TOF LCT Premier spectrometer under electrospray (ESI) conditions.

Synthetic Procedures

General Procedure for Radical Decarboxylation: To a solution of quinone (1 equiv., 0.1 M) in CH_3CN/H_2O (2:1), the carboxylic acid (3 equiv.) was added, and the mixture was warmed to 65 °C. Silver nitrate (0.3 equiv.) was added to the stirred mixture. A homogeneous solution of ammonium persulfate (1.3 equiv., 0.3 M) in CH_3CN/H_2O (2:1) was added dropwise over 2 h. At the end of the addition, the reaction mixture was continually stirred at 65 °C for 1 h. The mixture was then cooled to room temperature, extracted with CH_2Cl_2, and washed with brine. The organic layer was dried with $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

***tert*-Butyl (3-Methyl-1,4-dioxo-1,4-dihydroaphthalen-2-ylmethyl)-carbamate (1):** This compound was prepared according to the general procedure starting from **M** (1000 mg, 5.80 mmol) and was purified by flash chromatography on silica gel with CH_2Cl_2 as the eluent. The pure compound was obtained as an orange solid (651 mg, 2.16 mmol, 37% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 [dd, J = 5.6 and 3.2 Hz, 2 H, C*H*CC(O)], 7.72 [dd, J = 5.6 and 3.2 Hz, 2 H, C*H*CHCC(O)], 5.18 (br. s, 1 H, N*H*), 4.31 (d, J = 6.4 Hz, 2 H, CH_2NH), 2.36 [s, 3 H, C(O)CCH_3], 1.41 [s, 9 H, OC(CH_3)$_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.5 and 185.4 [*C*(O)CCH$_2$ and *C*(O)CCH$_3$], 155.6 (NH*C*O), 145.1 (=*C*CH$_3$), 142.0 (=*C*CH$_2$), 133.7 and 133.6 [2 × *C*HCC(O)], 132.1 and 131.8 [2 × CH*C*C(O)], 126.5 and 126.1 [2 × *C*HCHCC(O)], 79.6 [*C*(CH$_3$)$_3$], 37.1 (*C*H$_2$NH), 28.3 [C(*C*H$_3$)$_3$], 12.6 (=C*C*H$_3$) ppm. IR (ATR): $\tilde{\nu}$ = 3385, 2924, 1691, 1650, 1592, 1520, 1281, 1248, 1155, 783, 715, 690, 613 cm^{-1}. HRMS: calcd. for $C_{17}H_{19}NNaO_4$ 324.1212; found 324.1211; Δ = 0.2 ppm.

***tert*-Butyl [2-(3-Methyl-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)ethyl]-carbamate (2):**[9] This compound was prepared according to the general procedure starting from **M** (260 mg, 1.51 mmol) and was purified by flash chromatography on silica gel with C_6H_{12}/AcOEt (9:1) as the eluent. The pure compound was obtained as an orange solid (205 mg, 0.65 mmol, 43% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 [dd, J = 5.7 and 3.6 Hz, 2 H, C*H*CC(O)], 7.67 [dd, J = 5.7 and 3.6 Hz, 2 H, C*H*CHCC(O)], 4.81 (br. s, 1 H, N*H*), 3.29 (pseudo q, J = 6.6 Hz, 2 H, CH_2NH), 2.86 (t, J = 6.6 Hz, 2 H, CH_2CH$_2$N), 2.22 [s, 3 H, C(O)CCH_3], 1.37 [s, 9 H, OC(CH_3)$_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.0 and 184.8 [*C*(O)CCH$_2$ and *C*(O)CCH$_3$], 155.9 (NH*C*O), 145.1 (=*C*CH$_3$), 143.9 (=*C*CH$_2$), 133.4 and 133.3 [2 × *C*HCC(O)], 132.1 and 132.0 [2 × CH*C*C(O)], 126.3 and 126.2 [2 × *C*HCHCC(O)], 79.3 [*C*(CH$_3$)$_3$], 39.4 (*C*H$_2$NH), 28.3 [C(*C*H$_3$)$_3$], 27.8 (*C*H$_2$CH$_2$NH), 12.9 (=C*C*H$_3$) ppm. IR (ATR): $\tilde{\nu}$ = 3378, 2971, 1686, 1659, 1594, 1520, 1336, 1251, 1162, 767, 683, 662 cm^{-1}. HRMS: calcd. for $C_{18}H_{21}NNaO_4$ 324.1368; found 338.1335; Δ = 3.9 ppm.

***tert*-Butyl [3-(3-Methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)propyl]carbamate (3):**[9] This compound was prepared according to the general procedure starting from **M** (1.050 mg, 6.10 mmol) and was purified by flash chromatography on silica gel with CH_2Cl_2 as the eluent to furnish the desired product as an orange solid (1.04 g, 3.16 mmol, 52% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 [m, 2 H, C*H*CC(O)], 7.69 [m, 2 H, C*H*CHCC(O)], 4.81 (br. s, 1 H, N*H*), 3.17 (m, 2 H, CH_2N), 2.68 (m, 2 H, CH_2C$_{Ar}$), 2.19 [s, 3 H, C(O)CCH_3], 1.68 (m, 2 H, CH_2CH$_2$N), 1.44 [s, 9 H, OC(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.9 [*C*(O)CCH$_2$], 184.6 [*C*(O)CCH$_3$], 155.9 (NH*C*O), 146.3 (=*C*CH$_3$), 143.6 (=*C*CH$_2$), 133.3 and 133.2 [2 × *C*HCC(O)], 131.9 and 131.8 [2 × CH*C*C(O)], 126.1 and 126.0 [2 × *C*HCHCC(O)], 78.9 [*C*(CH$_3$)$_3$], 40.1 (*C*H$_2$NH), 28.7 (*C*H$_2$CH$_2$N), 28.3 [C(*C*H$_3$)$_3$], 24.0 (*C*H$_2$C$_{Ar}$), 12.5 (=C*C*H$_3$) ppm. IR (ATR): $\tilde{\nu}$ = 3388, 2976, 1694, 1657, 1595, 1516, 1294, 1251, 1168, 787, 716 cm^{-1}. HRMS: calcd. for $C_{19}H_{23}NNaO_4$ 352.1525; found 352.1544; Δ = 5.5 ppm.

***tert*-Butyl [4-(3-Methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)butyl]-carbamate (4):**[9] This compound was prepared according to the general procedure starting from **M** (450 mg, 2.61 mmol), and its purification on silica gel with C_6H_{12}/AcOEt (7:3) led to the desired compound as an orange solid (262 mg, 0.76 mmol, 29% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 [dd, J = 5.4 and 3.3 Hz, 2 H, C*H*CC(O)], 7.67 [dd, J = 5.4 and 3.3 Hz, 2 H, C*H*CHCC(O)], 4.83 (br. s, 1 H, N*H*), 3.17 (m, 2 H, CH_2NH), 2.64 (t, J = 7.5 Hz, 2 H, CH_2C$_{Ar}$), 2.18 [s, 3 H, C(O)CCH_3], 1.64–1.48 (m, 4 H, CH_2CH_2CH$_2$N), 1.44 [s, 9 H, OC(CH_3)$_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.0 and 184.4 [*C*(O)CCH$_2$ and *C*(O)CCH$_3$], 155.9 (NH*C*O), 146.7 (=*C*CH$_3$), 143.2 (=*C*CH$_2$), 133.15 and 133.14 [2 × *C*HCC(O)], 131.92 and 131.91 [2 × CH*C*C(O)], 126.1 and 126.0 [2 × *C*HCHCC(O)], 78.8 [*C*(CH$_3$)$_3$], 40.0 (*C*H$_2$NH), 30.1 (*C*H$_2$CH$_2$N), 28.2 [C(*C*H$_3$)$_3$], 26.4 and 25.6 (*C*H$_2$*C*H$_2$CH$_2$CH$_2$NH), 12.4 (=C*C*H$_3$) ppm. HRMS: calcd. for $C_{20}H_{25}NNaO_4$ 366.1681; found 366.1699; Δ = 4.8 ppm.

3-Methyl-3-(3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)butyric Acid (7) and 2-Methyl-3-(3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)propionic Acid (8): These compounds were prepared according to the general procedure starting from **M** (300 mg, 1.74 mmol), and flash chromatography on silica gel with C_6H_{12}/AcOEt (1:1) as the eluent led to an inseparable 3:1 mixture (orange solid) of the two regioisomers **7** and **8** (60 mg, 0.23 mmol, 13% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 [m, 4 H, C*H*CC(O)], 7.67 [m, 4 H, C*H*CHCC(O)], 3.50 [m, 1 H, C*H*CH$_3$ (**7**)], 3.06 [m, 2 H, parts of CH_2 (**7**) and CH_2 (**8**)], 2.82 [m, 3 H, parts of CH_2 (**7**) and CH_2 (**8**), C*H*CH$_3$ (**8**)], 2.23 [s, 3 H, C(O)CCH_3 (**7**)], 2.19 [s, 3 H, C(O)CCH_3 (**8**)], 1.36 [d, J = 6.9 Hz, 3 H, CHCH_3 (**7**)], 1.22 [d, J = 6.3 Hz, 3 H, CHCH_3 (**8**)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$) of **7**: δ = 185.3 and 184.8 [*C*(O)CCH$_2$ and *C*(O)CCH$_3$], 178.6 (*C*OOH), 148.2 (=*C*CH$_3$), 144.2 (=*C*CH$_2$), 133.5 and 133.3 [2 × *C*HCC(O)], 132.5 and 131.8 [2 × CH*C*C(O)], 126.21 and 126.19 [2 × *C*HCHCC(O)], 38.9 (*C*H$_2$COOH), 31.6 (C*H*CH$_3$), 19.1 (CHCH_3), 12.4 (=C*C*H$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) of **8**: δ = 185.1 and 184.7 [*C*(O)CCH$_2$ and *C*(O)CCH$_3$], 181.6 (*C*OOH), 145.1 (=*C*CH$_3$), 144.1 (=*C*CH$_2$), 133.53 and 133.51 [2 × *C*HCC(O)], 132.1 and 132.0 [2 × CH*C*C(O)], 126.4 and 126.3 [2 × *C*HCHCC(O)], 38.8

(*C*HCH$_3$), 30.8 [C*H*$_2$CH(CH$_3$)], 17.0 (CHC*H*$_3$), 13.2 (=C*C*H$_3$) ppm. IR (ATR): $\tilde{\nu}$ = 2924, 1702, 1651, 1591, 1292, 1234, 922, 863, 716, 688 cm^{-1}. HRMS: calcd. for $C_{15}H_{14}NaO_4$ 281.0766; found 281.0774; Δ = 5.6 ppm. HRMS: calcd. for $C_{15}H_{13}Na_2O_4$ 303.0609; found 303.0611; Δ = 0.6 ppm.

2,3-Dimethyl-1,4-naphthoquinone (9).[20] **Method A:** This compound was prepared according to the general procedure starting from **M** (400 mg, 2.32 mmol) and was purified by flash chromatography on silica gel with C_6H_{12}/AcOEt (95:5) as the eluent. The pure compound was obtained as a yellow solid (165 mg, 0.89 mmol, 38% yield). **Method B:** This compound was prepared according to the general procedure starting from **NQ** (316 mg, 2.00 mmol) and was purified by flash chromatography on silica gel with C_6H_{12}/AcOEt (95:5) as the eluent. A mixture of **NQ**, **M**, and **9** was obtained as a yellow solid (240 mg) with **M/9** = 9:5 (see Supporting Information). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 [dd, J = 5.6 and 3.2 Hz, 2 H, C*H*CC(O)], 7.68 [dd, J = 5.6 and 3.2 Hz, 2 H, C*H*CHCC(O)], 2.18 [s, 6 H, C(O)CC*H*$_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.7 (2× *C*=O), 143.3 (2× =*C*CH$_3$), 133.2 [2× *C*HCC(O)], 132.0 [2× CH*C*C(O)], 126.1 [2× *C*HCHCC(O)], 12.8 (2× =C*C*H$_3$) ppm. IR (ATR): $\tilde{\nu}$ = 2924, 1656, 1620, 1592, 1458, 1371, 1334, 1293, 790, 695 cm^{-1}. HRMS: calcd. for $C_{12}H_{11}O_2$ 181.0759; found 181.0756; Δ = 1.6 ppm (the molecular ion peak is very weak).

2-Isopropyl-3-methyl-1,4-naphthoquinone (10):[3] This compound was prepared according to the general procedure starting from **M** (150 mg, 0.87 mmol) and was purified by flash chromatography on silica gel with C_6H_{12}/AcOEt (95:5) as the eluent. The pure compound was obtained as a yellow solid (60 mg, 0.28 mmol, 32% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 [dd, J = 5.6 and 3.2 Hz, 2 H, C*H*CC(O)], 7.66 [dd, J = 5.6 and 3.2 Hz, 2 H, C*H*CHCC(O)], 3.25 [sept, J = 6.8 Hz, 1 H, C*H*(CH$_3$)$_2$], 2.21 [s, 3 H, C(O)CC*H*$_3$] 1.35 [d, J = 6.8 Hz, 6 H, CH(C*H*$_3$)$_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.6 and 184.8 (2× *C*=O), 151.4 [=*C*CH(CH$_3$)$_2$], 142.7 (=*C*CH$_3$), 133.3 and 133.0 [2× *C*HCC(O)], 132.8 and 131.8 [2× CH*C*C(O)], 126.1 and 126.0 [2× *C*HCHCC(O)], 29.3 [*C*H(CH$_3$)$_2$], 20.4 [CH(*C*H$_3$)$_2$], 12.3 (=C*C*H$_3$) ppm. HRMS: calcd. for $C_{14}H_{15}O_2$ 215.1072; found 215.1072; Δ = 0.0 ppm (the molecular ion peak is very weak).

2-Isopropyl-1,4-naphthoquinone (11) and 2,3-Diisopropyl-1,4-naphthoquinone (12): These compounds were prepared according to the general procedure starting from **NQ** (316 mg, 2.00 mmol) and were purified by flash chromatography on silica gel with C_6H_{12}/AcOEt (95:5) as the eluent to lead to an inseparable 9:2 mixture (213 mg, orange solid) of **11** and **12** (see Supporting Information). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 [m, 4 H, C*H*CC(O) (**11** and **12**)], 7.62 [m, 4 H, C*H*CHCC(O) (**11** and **12**)], 6.71 [s, 1 H, *i*PrCC*H* (**11**)], 3.35 [sept, J = 6.9 Hz, 1 H, C*H*(CH$_3$)$_2$ (**12**)], 3.19 [sept, J = 6.9 Hz, 1 H, C*H*(CH$_3$)$_2$ (**11**)], 1.30 [d, J = 6.9 Hz, 12 H, CH(C*H*$_3$)$_2$ (**12**)], 1.15 [d, J = 6.9 Hz, 6 H, CH(C*H*$_3$)$_2$ (**11**)] ppm.

2-*tert*-Butyl-1,4-naphthoquinone (13):[21] This compound was prepared according to the general procedure starting from **NQ** (475 mg, 3.00 mmol) and was purified by flash chromatography on silica gel with CH_2Cl_2/CH_3OH (10:0 to 95:5) as the eluent. The pure compound was obtained as a yellow solid (165 mg, 0.77 mmol, 25%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 [m, 2 H, C*H*CC(O)], 7.68 [m, 2 H, C*H*CHCC(O)], 6.82 [s, 1 H, C(O)C*H*], 1.35 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.8 and 184.8 (2× *C*=O), 158.3 [=*C*C(CH$_3$)$_3$], 133.8 and 133.6 [2× *C*HCC(O)], 133.5 and 131.5 [2× CH*C*C(O)], 133.2 (=*C*H), 126.8 and 125.5 [2× *C*HCHCC(O)], 35.7 [*C*(CH$_3$)$_3$], 29.3 [C(*C*H$_3$)$_3$] ppm. IR (ATR): $\tilde{\nu}$ = 2958, 1654, 1593, 1483, 1459, 1361, 1330, 1306, 1248, 1201, 1125, 892, 785, 719, 670, 626 cm^{-1}. We were unable to detect the molecular ion peak by HRMS, as was the case for **9** and **10**.

Methyl 3-(3-Methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)propionate (14): This compound was prepared according to the general procedure starting from **M** (1 g, 5.81 mmol), and its purification on silica gel with CH_2Cl_2 as the eluent gave the pure compound as a yellow solid (875 mg, 3.39 mmol, 58% yield) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 [m, 2 H, C*H*CC(O)], 7.69 [m, 2 H, C*H*CHCC(O)], 3.68 (s, 3 H, CO$_2$C*H*$_3$), 2.97 (t, J = 8.0 Hz, 2 H, =CC*H*$_2$), 2.55 (t, J = 8.0 Hz, 2 H, C*H*$_2$CO$_2$Me), 2.22 (s, 3 H, =CC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.0 [*C*(O)CCH$_2$], 184.4 [*C*(O)CCH$_3$], 172.8 (*C*O$_2$CH$_3$), 145.1 (=*C*CH$_3$), 144.3 (=*C*CH$_2$), 133.45 and 133.44 [2× *C*HCC(O)], 132.10 and 132.06 [2× CH*C*C(O)], 126.30 and 126.28 [2× *C*HCHCC(O)], 51.8 (CO$_2$*C*H$_3$), 32.6 (*C*H$_2$CO$_2$CH$_3$), 22.8 (*C*H$_2$CH$_2$CO$_2$CH$_3$), 12.7 (=C*C*H$_3$) ppm. IR (ATR): $\tilde{\nu}$ = 2923, 1733, 1656, 1594, 1437, 1377, 1330, 1291, 1171, 790, 715 cm^{-1}. HRMS: calcd. for $C_{15}H_{14}NaO_4$ 281.0790; found 281.0781; Δ = 3.1 ppm.

Methyl 3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)propionate (15):[22] This compound was prepared according to the general procedure starting from **NQ** (97 mg, 0.61 mmol), and its purification on silica gel with C_6H_{12}/AcOEt (9:1) as the eluent gave the pure compound as a yellow solid (40 mg, 0.17 mmol, 28% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 [m, 2 H, C*H*CC(O)], 7.73 [m, 2 H, C*H*CHCC(O)], 6.82 (s, 1 H, C*H*=CCH$_2$), 3.69 (s, 3 H, CO$_2$C*H*$_3$), 2.91 (t, J = 7.2 Hz, 2 H, =CC*H*$_2$), 2.66 (t, J = 7.2 Hz, 2 H, C*H*$_2$CO$_2$Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.86 and 184.84 [2× *C*(O)], 172.5 (*C*O$_2$CH$_3$), 149.6 (=*C*CH$_2$), 135.3 (*C*H=CCH$_2$), 133.8 and 133.7 [2× *C*HCC(O)], 132.1 and 132.0 [2× CH*C*C(O)], 126.6 and 126.1 [2× *C*HCHCC(O)], 51.8 (CO$_2$*C*H$_3$), 32.0 (*C*H$_2$CO$_2$CH$_3$), 25.1 (*C*H$_2$CH$_2$CO$_2$CH$_3$) ppm. IR (ATR): $\tilde{\nu}$ = 2923, 2852, 1726, 1658, 1590, 1435, 1422, 1328, 1302, 1266, 1208, 1173, 1163, 893, 846, 785, 721, 708 cm^{-1}. HRMS: calcd. for $C_{14}H_{13}O_4$ 245.0814; found 245.0805; Δ = 3.6 ppm.

***tert*-Butyl [2-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)ethyl]carbamate (16). Method A:** This compound was prepared according to the general procedure starting from **NQ** (300 mg, 1.90 mmol) and was purified by flash chromatography on silica gel with C_6H_{12}/AcOEt (90:10) as the eluent. The pure compound was obtained as an orange solid (154 mg, 0.51 mmol, 27% yield). **Method B:** To a solution of **NQ** (300 mg, 1.90 mmol, 0.1 M) in CH_3CN/H_2O (2:1, 12 mL) was added Boc-β-alanine (2.14 g, 11.38 mmol, 6 equiv.), and the mixture was warmed to 65 °C. Silver nitrate (194 mg, 1.14 mmol, 0.6 equiv.) was added to the stirred mixture. A homogeneous solution of ammonium persulfate (1.13 g, 4.94 mmol, 2.6 equiv., 0.3 M) in CH_3CN/H_2O (2:1, 9 mL) was added dropwise over 2 h. At the end of the addition, the reaction mixture was stirred at 65 °C for 1 h. The mixture was then cooled to room temperature, extracted with CH_2Cl_2, and washed with brine. The organic layer was dried with $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. Purification by flash chromatography on silica gel with C_6H_{12}/AcOEt (8:2) as the eluent led to the desired product as an orange solid (146 mg, 0.49 mmol, 26% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 [m, 2 H, C*H*CC(O)], 7.73 [m, 2 H, C*H*CHCC(O)], 6.82 (s, 1 H, C*H*=CCH$_2$), 4.69 (br. s, 1 H, N*H*), 3.41 (pseudo q, J = 6.3 Hz, 2 H, C*H*$_2$NH), 2.76 (t, J = 6.3 Hz, 2 H, C*H*$_2$C$_{Ar}$), 1.37 [s, 9 H, OC(C*H*$_3$)$_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.0 and 184.8 [*C*(O)CCH$_2$ and *C*(O)CCH$_3$], 155.8 (NH*C*O), 148.5 (*C*H=CCH$_2$), 136.0 (=*C*CH$_2$), 133.66 and 133.61 [2× *C*HCC(O)], 132.1 and 132.0 [2× CH*C*C(O)], 126.6 and 126.0 [2× *C*HCHCC(O)], 79.4 [*C*(CH$_3$)$_3$], 39.1 (*C*H$_2$NH), 31.0 [C-

($CH_3)_3$], 28.2 (CH_2C_{Ar}) ppm. IR (ATR): $\tilde{\nu}$ = 3392, 2966, 2932, 1704, 1656, 1591, 1514, 1304, 1269, 1250, 1158, 981, 966, 854, 777, 735, 702 cm^{-1}. HRMS: calcd. for $C_{17}H_{19}NNaO_4$ 324.1212; found 324.1202; Δ = 3.0 ppm.

***tert*-Butyl {2-[3-(2-*tert*-Butoxycarbonylaminoethyl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]ethyl}carbamate (17):** This compound was obtained along with **16** (method B described above) as an orange solid (101 mg, 0.23 mmol, 12% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 [dd, J = 5.7 and 3.3 Hz, 2 H, C*H*CC(O)], 7.70 [dd, J = 5.7 and 3.3 Hz, 2 H, C*H*CHCC(O)], 5.01 (br. s, 2 H, N*H*), 3.35 (t, J = 6.6 Hz, 4 H, CH_2NH), 2.90 (t, J = 6.6 Hz, 4 H, CH_2C_{Ar}), 1.35 [s, 18 H, OC(C$H_3)_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.9 [2 × *C*(O)], 156.0 (2 × NH*C*O), 145.5 (2 × =*C*CH$_2$), 133.4 [2 × *C*HCC(O)], 132.1 [2 × CH*C*C(O)], 126.3 [2 × *C*HCHCC(O)], 79.3 [2 × *C*(CH$_3)_3$], 50.7 (2 × *C*H$_2$CH$_2$NH), 39.9 (2 × *C*H$_2$NH), 28.2 [2 × C(*C*H$_3)_3$] ppm. IR (ATR): $\tilde{\nu}$ = 3365, 2925, 2852, 1689, 1657, 1594, 1510, 1450, 1391, 1284, 1248, 1161, 971, 857, 780, 717 cm^{-1}. HRMS: calcd. for $C_{24}H_{32}N_2NaO_6$ 467.2158; found 467.2151; Δ = 1.5 ppm.

***tert*-Butyl (1,4-Dioxo-1,4-dihydronaphthalen-2-ylmethyl)carbamate (18):** This compound was prepared according to the general procedure starting from **NQ** (950 mg, 6.00 mmol) and was purified by flash chromatography on silica gel with CH_2Cl_2/CH_3OH (10:0 to 95:5) as the eluent. The pure compound was obtained as an orange solid (812 mg, 2.83 mmol, 47% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 [dd, J = 5.1 and 3.3 Hz, 2 H, CHCC(O)], 7.71 [dd, J = 5.1 and 3.3 Hz, 2 H, CHCHCC(O)], 5.06 (br. s, 1 H, N*H*), 4.24 (d, J = 5.7 Hz, 2 H, CH_2NH), 1.43 [s, 9 H, OC(C$H_3)_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.1 and 184.9 [*C*(O)CCH$_2$ and *C*(O)CCH$_3$], 155.6 (NH*C*O), 147.2 (*C*H=CCH$_2$), 133.98, 133.96 and 133.94 [=*C*CH$_2$ and 2 × *C*HCC(O)], 133.75 and 133.74 [2 × CH*C*C(O)], 126.3 and 126.2 [2 × *C*HCHCC(O)], 80.1 [*C*(CH$_3)_3$], 39.5 (*C*H$_2$NH), 28.3 [C(*C*H$_3)_3$] ppm. IR (ATR): $\tilde{\nu}$ = 3378, 2971, 1686, 1658, 1634, 1520, 1363, 1336, 1251, 1162, 1050, 890, 859, 767, 683, 662 cm^{-1}. HRMS: calcd. for $C_{16}H_{17}NNaO_4$ 310.1055; found 310.1069; Δ = 4.4 ppm.

***tert*-Butyl {2-[3-(*tert*-Butoxycarbonylaminomethyl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]ethyl}carbamate (19):** This compound was prepared according to the general procedure starting from **18** (290 mg, 1.01 mmol) and was purified on silica gel with C_6H_{12}/AcOEt (9:1 to 7:3) to yield the desired compound as an orange solid (330 mg, 0.77 mmol, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 [m, 2 H, C*H*CC(O)], 7.70 [t, J = 3.3 Hz, 2 H, C*H*CHCC(O)], 5.38 (br. s, 1 H, N*H*), 5.03 (br. s, 1 H, N*H*), 4.30 (d, J = 6.6 Hz, 2 H, =CCH_2NH), 3.37 (m, 2 H, CH$_2$CH_2NH), 3.06 (m, 2 H, CH_2CH$_2$NH), 1.41 [s, 9 H, OC(C$H_3)_3$], 1.23 [s, 9 H, OC(C$H_3)_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.7 and 185.0 [2 × *C*(O)], 156.1 and 156.0 (2 × NH*C*O), 145.8 [=*C*(CH$_2$)], 142.7 [=*C*(CH$_2)_2$], 133.8 and 133.7 [2 × C(O)*C*$_{Ar}$], 132.2 and 131.8 [2 × *C*HCC(O)], 126.6 and 126.0 [2 × *C*HCHCC(O)], 79.8 and 79.1 [2 × *C*(CH$_3)_3$], 43.4 (*C*H$_2$CH$_2$NH), 31.5 and 30.1 (2 × *C*H$_2$NH), 28.3 and 28.1 [2 × C(*C*H$_3)_3$] ppm. IR (ATR): $\tilde{\nu}$ = 3381, 2977, 2930, 1702, 1664, 1595, 1512, 1367, 1294, 1251, 1164, 859 cm^{-1}. HRMS: calcd. for $C_{23}H_{30}N_2NaO_6$ 453.2002; found 453.2019; Δ = 3.8 ppm.

***tert*-Butyl [3-(*tert*-Butoxycarbonylaminomethyl)-1,4-dioxo-1,4-dihydronaphthalen-2-ylmethyl]carbamate (20):** To a solution of **NQ** (475 mg, 3.00 mmol, 0.1 M) in CH_3CN/H_2O (2:1, 30 mL) was added Boc-glycine (1.58 g, 9 mmol, 3 equiv.) and Boc-β-alanine (1.7 g, 9 mmol, 3 equiv.), and the mixture was warmed to 65 °C. Silver nitrate (153 mg, 0.9 mmol, 0.6 equiv.) was added to the stirred mixture. A homogeneous solution of ammonium persulfate (890 mg, 3.9 mmol, 2.6 equiv., 0.3 M) in CH_3CN/H_2O (2:1, 15 mL) was added dropwise over 2 h. At the end of the addition, the reaction mixture was stirred at 65 °C for 1 h. The mixture was cooled to room temperature, extracted with CH_2Cl_2, and washed with brine. The organic layer was dried with $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. Purification by flash chromatography on silica gel with C_6H_{12}/AcOEt (10:0 to 9:1 and finally 7:3) as the eluent led to the desired product as an orange solid (240 mg, 0.58 mmol, 19% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 [dd, J = 5.7 and 3.3 Hz, 2 H, C*H*CC(O)], 7.72 [dd, J = 5.7 and 3.3 Hz, 2 H, C*H*CHCC(O)], 5.61 (br. s, 2 H, N*H*), 4.45 (d, J = 6.3 Hz, 4 H, CH_2NH), 1.40 [s, 18 H, OC(C$H_3)_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.5 [*C*(O)], 155.7 (NH*C*O), 142.8 (*C*$_{Ar}$CH$_2$), 133.9 [C(O)*C*$_{Ar}$], 131.8 [*C*HCC(O)], 126.4 [*C*HCHCC(O)], 79.7 [*C*(CH$_3)_3$], 36.3 (*C*H$_2$NH), 28.3 [C(*C*H$_3)_3$] ppm. IR (ATR): $\tilde{\nu}$ = 3354, 2975, 2927, 1690, 1661, 1594, 1507, 1366, 1248, 1155, 938, 857, 762, 719 cm^{-1}. HRMS: calcd. for $C_{22}H_{28}N_2NaO_6$ 439.1845; found 439.1844; Δ = 0.2 ppm.

2-Thioxo-2*H*-pyridin-1-yl 2-(*tert*-Butoxycarbonylamino)propionate (23): Boc-L-alanine (446 mg, 2.36 mmol, 1 equiv.) and 2-mercaptopyridine *N*-oxide (300 mg, 2.36 mmol, 1 equiv.) in CH_2Cl_2 (4 mL) were added to a flask, which was protected from light by aluminum foil at 0 °C in an ice bath. *N*-[3-(Dimethylamino)propyl]-*N*′-ethylcarbodiimide hydrochloride (452 mg, 2.36 mmol, 1 equiv.) was then added, and the mixture was stirred at room temperature for 10 h. After completion of the reaction, the organic phase was washed twice with saturated aqueous $NaHCO_3$ (10 mL) and then with brine (10 mL). The aqueous phases, still protected from light, were extracted CH_2Cl_2 (2 × 10 mL), and the organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was quickly filtered through a small pad of silica gel and washed with C_6H_{12}/AcOEt (1:1). The crude product was obtained as a yellow oil (703 mg, 2.36 mmol, quantitative yield) and used without further purification due to its instability. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (m, 1 H, C*H*CHC=S), 7.25 (m, 2 H, C*H*CHNO and C*H*C=S), 6.65 (m, 1 H, C*H*NO), 5.18 (br. s, 1 H, N*H*), 4.63 (q, J = 6.7 Hz, 1 H, C*H*CH$_3$), 1.73 (d, J = 6.7 Hz, 3 H, CHC*H*$_3$), 1.50 [s, 9 H, OC(C$H_3)_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9 (*C*=S), 169.4 (NO*C*=O), 155.2 (NH*C*OO), 137.7 (*C*HCHC=S), 137.0 (*C*HC=S), 133.4 (*C*HNO), 113.0 (*C*HCHNO), 80.4 [O*C*(CH$_3)_3$], 48.6 (*C*HCH$_3$), 28.1 [C(*C*H$_3)_3$], 17.7 [CH(*C*H$_3$)] ppm.

2-Thioxo-2*H*-pyridin-1-yl 3-(*tert*-Butoxycarbonylamino)propionate (24): This compound was prepared according to the procedure described for **23** starting from 2-mercaptopyridine *N*-oxide (150 mg, 1.18 mmol) and was obtained as a yellow oil (350 mg, 1.18 mmol, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (m, 1 H, C*H*CHC=S), 7.25 (m, 2 H, C*H*CHNO and C*H*C=S), 6.67 (m, 1 H, C*H*NO), 5.52 (br. s, 1 H, N*H*), 3.64 (m, 2 H, CH_2NH), 2.91 (m, 2 H, CH_2CO), 1.47 [s, 9 H, OC(C$H_3)_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.4 (*C*=S), 167.4 (NO*C*=O), 155.8 (NH*C*OO), 137.7 (*C*HCHC=S), 136.9 (*C*HC=S), 133.8 (*C*HNO), 112.7 (*C*HCHNO), 79.4 [O*C*(CH$_3)_3$], 36.0 (*C*H$_2$N), 33.1 (CH*C*H$_2$N), 28.2 [C(*C*H$_3)_3$] ppm.

Supporting Information (see footnote on the first page of this article): NMR spectra of all synthesized compounds are available.

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