Hydrogen Peroxide and Arenediazonium Salts as Reagents for a Radical Beckmann-Type Rearrangement

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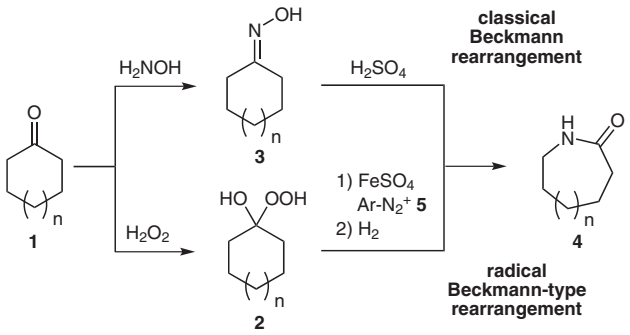
Abstract: The reductive ring-opening of hydroperoxides derived from cyclic ketones leads to alkyl radicals which can effectively be trapped by arenediazonium salts. This synthetic transformation yielding azo carboxylic acids or lactams, after a reductive step, can be classified as a radical version of the well-known Beckmann rearrangement. In this article, we present results on the scope, the limitations and possible applications of this new reaction type.

Key words: radical reaction, rearrangement, ketones, carboxylic acids, azo compounds

The acid-catalyzed rearrangement of ketoximes, accessible from the corresponding ketones by standard procedures,[1] to amides is widely known as the Beckmann rearrangement (Scheme 1). The reaction, named after Ernst Otto Beckmann, was first described by its inventor in 1886 and has since then become a well-known and widely applied method in organic chemistry.[2,3] The most prominent example of its industrial use is probably the large-scale production of the Nylon 6 precursor ε-caprolactam from cyclohexanone oxime.[4]

Most commonly, the Beckmann rearrangement is carried out in strongly acidic and dehydrating media such as phosphorus pentachloride, concentrated sulfuric acid, or the so-called 'Beckmann's mixture' which contains acetic acid, acetic anhydride, and hydrogen chloride.[3a] Since these reagents are not suitable for a large number of sensitive substrates, several attempts have been made to achieve the Beckmann rearrangement under significantly milder conditions. In these studies, thionyl chloride,[5] silica gel,[6] molybdenum trioxide on silica gel,[7] montmorillonite KSF,[8] ruthenium(III) chloride,[9] yttrium(III) triflate,[10] bismuth(III) chloride,[11] 2,4,6-trichloro-1,3,5-triazine,[12] and gallium(III) triflate[13] have been evaluated as substitutes for the traditionally employed reagents. Recently, several lanthanide-containing catalysts [with Ce(III), La(III), and Sm(III) among others] have also been found to effect the rearrangement.[14,15] The reaction could be performed in the vapor phase,[16] a process which has been shown to be applicable even on an industrial scale with the use of a high-silica MFI zeolite as catalyst.[16c] It is also possible to initiate the Beckmann rearrangement in supercritical water[17] or ionic liquids.[18] However, limited substrate tolerance, expensive reagents, or demanding conditions are potentially remaining drawbacks of the classical Beckmann rearrangement in spite of the newly reported methodologies. For this reason, we turned our interest to alternative reaction types that would lead to comparable overall transformations, but could be conducted under significantly milder conditions. In this article we present a conceptual study in which radical chemistry has been employed for this purpose.



Scheme 1 Classical and radical version of the Beckmann rearrangement

Inspired by current research in the field of nitrogen-centered radical scavengers,[19] which comprises reagents such as sulfonyl azides,[20] nitroso compounds,[21] imines,[22] azo compounds,[23] and diazirines,[24] we focused on a possible application of arenediazonium ions[25] in a radical Beckmann-type rearrangement (Scheme 1). Instead of employing cyclic ketoximes **3**, which traditionally lead to ring enlargement and the formation of lactams **4**, we planned to replace the cyclic oximes **3** by hydroperoxides **2** which would also be readily accessible from ketones **1**,[26] and which could be reacted with arenediazonium salts **5** under reductive conditions (Scheme 1).[27] Comparable to the ionic reaction, lactams **4** would be accessible by a further reductive step such as hydrogenation.[28] In addition, the radical pathway from hydroperoxide **2** could open up several further synthetic routes since it passes through an acyclic azo carboxylic acid intermediate.

The designated reaction course is presented in detail in Scheme 2. Pioneering work on the generation of oxygen-centered radicals from hydroperoxides has been published by Walling[29a,b] and Schreiber.[29c,d] Recent advances in the field of oxyl radicals[30] have been reported by the groups of Suarez[31a,b] and Schoening.[31c] In our case, very well-

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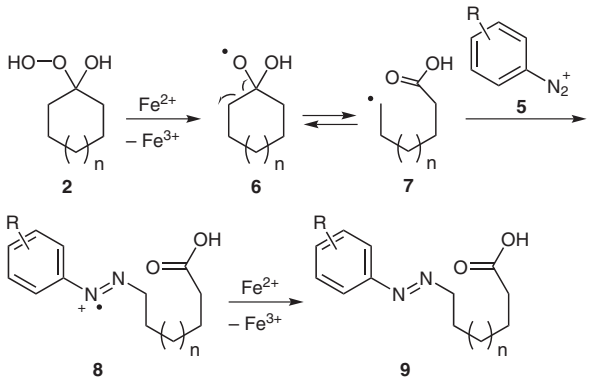
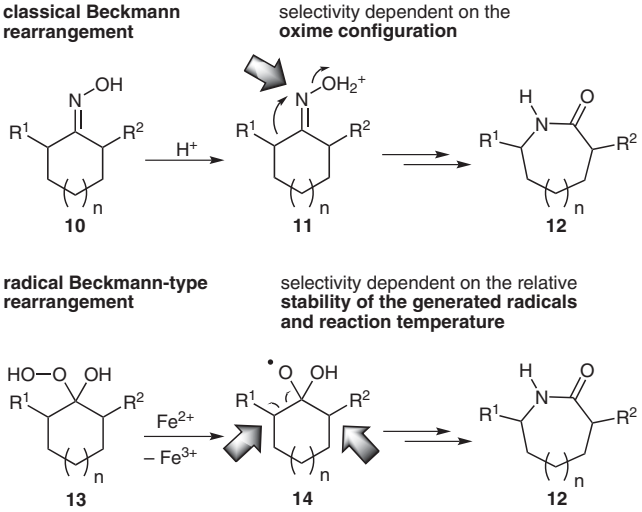
defined reductive conditions are required to induce the formation of oxyl radicals **6** by cleavage of the O–O bond in hydroperoxide **2**, since the diazonium ions **5** need to remain stable.[32] Reversible ring-opening of oxyl radical **6** and trapping of the newly formed alkyl radicals **7** by diazonium ions **5** leads to radical cations **8**.[27,33] These are quickly further reduced by iron(II) to azo carboxylic acids **9**, which represent the key intermediates of the reaction pathway.



Scheme 2 Formation of azo carboxylic acids **9** as key intermediates

The typical feature of the Beckmann rearrangement is the migration of a substituent from carbon to nitrogen (Scheme 3, upper pathway). Regarding the regioselectivity of the classical reaction, the migrating substituent is generally in the *E* position to the leaving group (**11**, R^1 in *E* position to H_2O), so that the structure of the lactam **12** depends on the configuration of the oxime **10** rather than on the nature of the substituents R^1 and R^2. Given that there is no simplification due to symmetry ($R^1 = R^2$), care has to be taken that the oxime **10** can be prepared with the correct configuration which will later lead to the desired product.[3c] Under certain reaction conditions isomerization of the oxime has been observed prior to the migration step, which can occasionally be either helpful or complicating with respect to predictable reaction outcomes.[3d] The selectivity of the radical reaction (Scheme 3, lower pathway), in contrast, is controlled by the relative stability of the alkyl radicals arising from the fragmentation of oxyl radical **14** as well as thermochemical aspects. Given that R^1 is a better radical-stabilizing substituent or group than R^2, the ring opening will preferably occur towards the R^1 side,[34] as long as an increase in temperature does not displace the equilibrium towards the less stable radical.[35,36] Since the configuration of the hydroperoxide **13** is unimportant (compared to that of oxime **10**), the product of the radical reaction will in most cases be well predictable. On the other hand, there is only a small possibility of opening the oxyl radical **14** towards the less radical-stabilizing substituent.



Scheme 3 Comparison of the regioselectivity of the classical Beckmann rearrangement and its radical version

Biographical Sketches

Agnes Prechter (born 1985) studied pharmacy at the Friedrich-Alexander-Universität Erlangen-Nürnberg. After receiving her approbation in 2009 she became a Ph.D. student in the group of Markus Heinrich. In the same year she was awarded a fellowship of the 'Bayerische Eliteförderung'. Her current research is centered on the development of new synthetic methods for the preparation of chiral azo compounds and amines.

Prof. Dr. Markus Heinrich (born 1975) studied chemistry at the Ludwig-Maximilians-Universität München and received his Ph.D. under the supervision of Prof. Dr. Wolfgang Steglich in 2003. After a postdoctoral stay with Prof. Dr. Samir Zard at the Ecole Polytechnique in Palaiseau/France he returned to Germany in 2005, where started independent research at the TU München associated to Prof. Dr. Thorsten Bach. He finished his habilitation on new radical reactions for industrial, medicinal, and radiopharmaceutical purposes in 2009. In the same year, Markus Heinrich was appointed as an associate professor for pharmaceutical chemistry at the Friedrich-Alexander-Universität Erlangen-Nürnberg.

Although the synthesis of hydroperoxides **2** from cyclic ketones **1** has been reported in the literature and quite different conditions can be found to effect this conversion,[37] almost no practically useful data on equilibria or reaction rates were available.[38] Even more disturbingly, several of the synthetic studies revealed the formation of complex product mixtures, in which the desired 1-hydroxycycloalkyl hydroperoxides **2** only occurred as minor constituents.[37] Radical reactions using these not clearly defined intermediates as starting materials led to varying yields of the respective products.[39]

We, therefore, first reinvestigated the formation of hydroperoxide **2a** from ketone **1a**. With respect to the further transformation planned, the conditions were chosen in a way to allow a simple separation of the hydroperoxide **1a** from the reaction mixture by extraction with an organic solvent.[27b] Selected results from this study are summarized in Table 1.

Table 1 Hydroperoxide Formation from Cyclohexanone (**1a**)[a]

1a **2a**

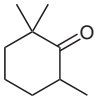
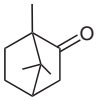
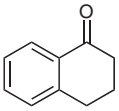
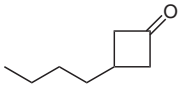
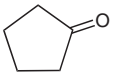
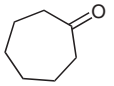
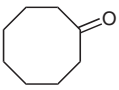
Entry	Ratio **1a**/H_2O_2	Time (min)	Ratio[b] **2a/1a**
1	1:3	30	0.7:1
2	1:5	30	0.9:1
3	1:3	60	0.8:1
4	1:3	150	1.6:1
5	1:3	225	2.6:1
6	1:3[c]	5	7.3:1

[a] Reaction conditions: **1a**, 30% H_2O_2, r.t.
[b] Determined by ^{1}H NMR after extraction with $CDCl_3$.
[c] HCl (0.06 equiv) was added.

A virtually clean formation of hydroperoxide **2a**, with only minor quantities of **1a** remaining, could be achieved in the presence of catalytic amounts of hydrochloric acid (entry 6) (see ^{13}C NMR spectra in the Supporting Information). Without the use of acid (entries 1–5), the reactions also showed no major detectable byproducts, but significantly longer reaction times were required. Under the optimized conditions, we attempted the synthesis of various hydroperoxides **2** as potential intermediates for the Beckmann-type rearrangement (Table 2). The ketones **1** were selected to allow an investigation of the effects of ring size and substitution in α-positions.

As evidenced by entries 1 to 5, further substituents on the cyclohexanone moiety were only tolerated to a moderate extent. While the less hindered reactants **1a**, **1b**, and **1d** gave the hydroperoxides in good reactant to product ratios (entries 1, 2, and 4), no conversion was observed for the sterically more demanding ketones 2,2,6-trimethylcyclohexanone (**1c**) and camphor (**1e**) (entries 3 and 5). The fact that tetralone (**1f**) could not be converted into its hydroperoxide is probably due to the conjugation of the ketone and the, therefore, increased stability of the reactant (entry 6). This assumption was further supported by an also unsuccessful experiment with 2-cyclohexen-1-one. From the attempt with 3-butylcyclobutanone (**1g**) (entry 7), the

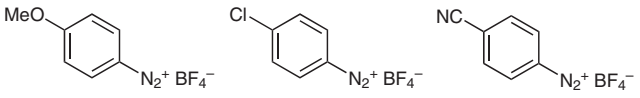
Table 2 Formation of Hydroperoxides **2** from Cyclic Ketones **1**[a]

Entry	Cyclic ketone **1**	Time (h)	Hydroperoxide **2**	Ratio[b] **2/1**
1	 **1a**	0.1	**2a**	7.3:1
2	 **1b**	16	**2b**	2.3:1[c]
3	 **1c**	24	–	–[d]
4	 **1d**	24	**2d**	12:1[e]
5	 **1e**	16	–	–[d]
6	 **1f**	24	–	–[d]
7	 **1g**	–	–	lactone[e]
8	 **1h**	20	**2h**	3.3:1
9	 **1i**	16	**2i**	2.5:1
10	 **1j**	16	**2j**	0.6:1

[a] Reaction conditions: **1**, 30% H_2O_2 (3 equiv), HCl (0.06 equiv), r.t.
[b] Determined by ^{1}H NMR after extraction with $CDCl_3$.
[c] A mixture of two stereoisomers of **2b** was formed in a ratio of 1:0.4.
[d] No conversion.
[e] Formation of lactones by Baeyer–Villiger reaction of **1d** or **1g**: 2-oxabicyclo[3.2.1]octan-3-one (13% from **1d**), 4-butyldihydrofuran-2-one (quant. from **1g**).

rearranged γ-lactone[40] was isolated instead of the desired hydroperoxide. Several variations of the reaction conditions failed to prevent formation of the undesired lactone.[38] Five-, seven-, and eight-membered cyclic ketones **1h–j** again yielded the desired 1-hydroxycycloalkyl hydroperoxides **2** with reasonable product/reactant ratios (entries 8–10). No evidence for cyclic peroxides could be found by inspection of the ^{13}C NMR spectra. Prior to the following series of experiments, the hydroperoxides **2** were prepared as described above and separated from excess aqueous hydrogen peroxide by extraction with dichloromethane. In contrast to some of the previously reported procedures, the cyclic hydroperoxyacetals **2** can further be used in solution and no concentration or isolation of these potentially explosive substances is necessary.[37a–c] We, therefore, consider the danger of handling as very limited. Furthermore, the preliminary determination of the hydroperoxide **2**/ketone **1** ratios by NMR (Table 2) allowed us to circumvent a titration step. The equilibrium data now available might also be useful for future preparative studies using cyclic hydroperoxyacetals.

The organic solution containing the hydroperoxide **2** and unreacted ketone **1** was then added to a mixture of iron(II) sulfate and a diazonium salt **5** in aqueous acetic acid and dimethyl sulfoxide. To explore the scope and limitations of the reaction, the six previously investigated hydroperoxides **2a**, **2b**, **2d** and **2h–j** were reacted with three arenediazonium salts **5a–c** (Figure 1), which were prepared by previously reported procedures.[41] To allow a comparison of substituent effects, the three salts **5a–c** were chosen in a way that either an electron-donating (R = OMe, **5a**), a more or less neutral (R = Cl, **5b**), or an electron-withdrawing substituent (R = CN, **5c**) was present on the aromatic core. In the case that arenediazonium salts take a role as nitrogen-centered radical scavengers, as it is true for this study, substituents effects have not yet been determined. When the salts are otherwise employed as sources for aryl radicals, radical generation by reduction is easier with electron-withdrawing groups on the aromatic core.[42]



5a **5b** **5c**

Figure 1 Diazonium tetrafluoroborates **5a–c**

The results of the synthetic study are summarized in Table 3.

From the first row of experiments using cyclohexanone (**1a**) as the starting material (entries 1–3), we obtained the azo carboxylic acids **9aa–ac** in high purity and moderate yields. Unexpectedly, the new samples of this practically unknown compound class showed a remarkable tendency to isomerize to the corresponding hydrazones upon standing at room temperature (Scheme 4).[43–45] Attempts to separate the nonisomerized azo compounds from the hydrazones by column chromatography were not fully successful since partial decomposition of the azo compounds was observed (entries 1, 2, and 5, Table 3). As an example, NMR spectra of azo compound **9aa** before and after column chromatography are included in the Supporting Information. Due to the excess of iron(II) sulfate used in the reactions, no unreacted peroxides were found along with the desired products.

Table 3 Synthesis of Azo Carboxylic Acids **9** from Hydroperoxides **2** and Arenediazonium Salts **5**[a]

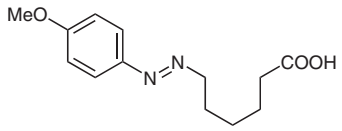
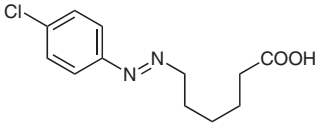
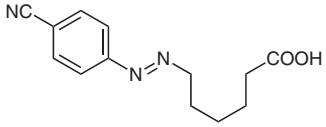
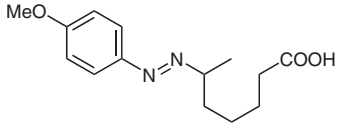
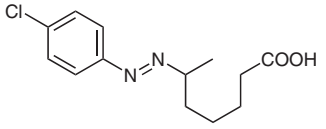
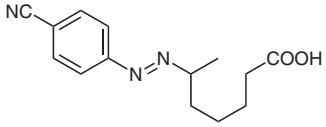
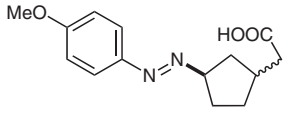
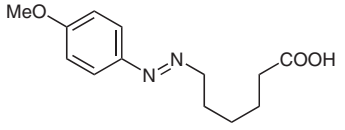
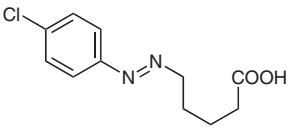
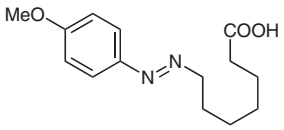
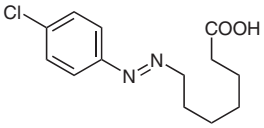
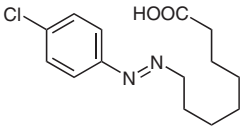
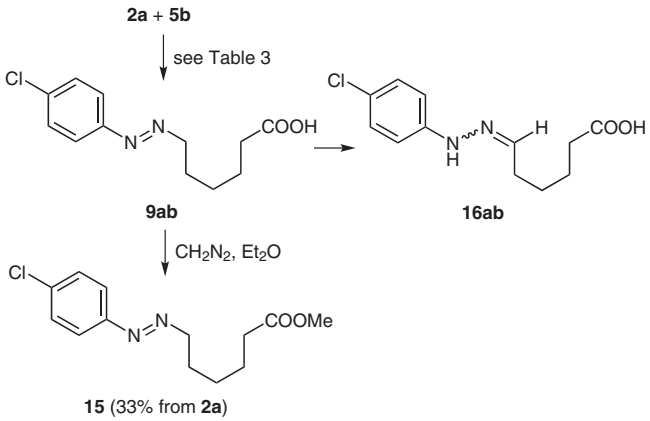
Entry	2	5	Azo carboxylic acid 9	Yield[b] (%)
1	**2a**	**5a**	 **9aa**	42 (32)
2	**2a**	**5b**	 **9ab**	68 (46)
3	**2a**	**5c**	 **9ac**	53[c]
4	**2b**	**5a**	 **9ba**	79[d]
5	**2b**	**5b**	 **9bb**	89[d] (60)
6	**2b**	**5c**	 **9bc**	74[d]
7	**2d**	**5a**	 **9da**	49[c]
8	**2h**	**5a**	 **9ha**	48[c]

Table 3 Synthesis of Azo Carboxylic Acids **9** from Hydroperoxides **2** and Arenediazonium Salts **5**[a] (continued)

Entry	2	5	Azo carboxylic acid **9**	Yield[b] (%)
9	**2h**	**5b**	 **9hb**	86
10	**2i**	**5a**	 **9ia**	78
11	**2i**	**5b**	 **9ib**	63
12	**2j**	**5b**	 **9jb**	56

[a] Reaction conditions: **2**, **5** (1.2 equiv), $FeSO_4 \cdot 7\ H_2O$ (3 equiv), H_2O–DMSO–AcOH (4:3:3), r.t., 15 min.
[b] Yields are based on the hydroperoxide/ketone ratios previously determined (Table 2); yields in brackets refer to products submitted to column chromatography.
[c] Products **9** were isolated without side products except for the following examples: products **9ac**, **9da**, and **9ha** accompanied by hydrazone; **9**/hydrazone, 2:1, 3:1, and 2:1, respectively.
[d] Products **9ba**–**bc** contained minor amounts of the isomers resulting from ring opening towards the primary alkyl radical: **9ba** and **9bb**: regioselectivity ≥ 10:1, **9bc**: regioselectivity ≥ 14:1.



Scheme 4 Conversion of carboxylic acid **9ab** into methyl ester **15** or hydrazone **16ab**

Our suspicion that the instability of **9aa**–**ac** might be enhanced by the free carboxylic acid functionality present in the molecules could not be confirmed, since the corresponding methyl ester **15** of **9ab** showed comparable reactivity.

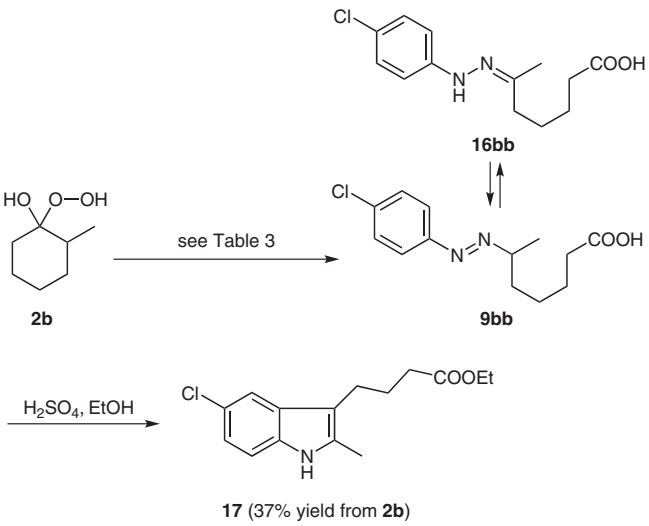
Since we have so far not observed this difficulty with secondary alkyl groups attached to the N=N moiety, we currently assign this special behavior to the primary alkyl chain, which probably facilitates the isomerization of the azo compounds to hydrazones **16**. Among the three diazonium salts, **5a** and **5b** appear to be better suited for the radical Beckmann-type rearrangement than **5c** since the methoxyphenyl- and chlorophenyl-substituted products **9aa** and **9ab** showed superior properties with respect to stability and handling.

With 2-methylcyclohexanone (**1b**) as reactant, the ring-opening of the corresponding cyclic hydroperoxide **2b** (step **6** → **7**, Scheme 2) occurs with clear preference (regioselectivity ≥ 10:1) towards the secondary alkyl radical. Only small amounts of regioisomers were, therefore, found along with the desired products (Table 3). The Beckmann rearrangement of 2-methylcyclohexanone oxime under classical conditions, for comparison, does not necessarily lead to a comparable preference for one of the two possible lactams.[46,47] Moreover, the products **9ba**–**bc** (entries 4–6) appeared more stable than those bearing primary alkyl chains on the N=N moiety.[44,45] As evidenced by the following entries 7–12, the methodology can be well extended to bicyclic as well as five-, seven-, and eight-membered monocyclic ketones.

Nearly all azo compounds shown in Table 3 were obtained from the two-step sequence without remarkable impurities other than the unreacted cyclic ketones remaining from the hydroperoxidation step.[48] In the case of sufficiently low boiling points, these could easily be removed under reduced pressure, leading to virtually pure azo carboxylic acids (see Supporting Information). Given the sensitivity of the azo carboxylic acids, we consider a further direct conversion of products **9** as the most practical procedure.

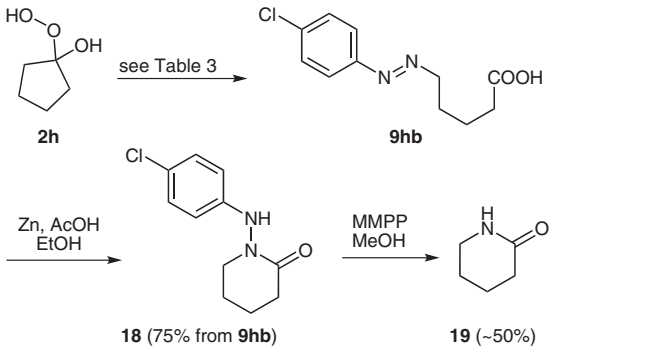
With regard to the known abilities of arenediazonium salts as nitrogen-centered radical scavengers, it is interesting to note that good results were obtained even from those reactions featuring the trapping of primary alkyl radicals (Scheme 2, step **7** → **8**).[19,27a] Due to their lower nucleophilicity,[49] this radical type has so far been considered as less well suited for additions to the N≡N moiety of diazonium ions. In our case, a relatively low excess of diazonium ions (1.2 equiv per hydroperoxide, initially 0.2 mol/L) was sufficient to achieve good to high efficiency of alkyl radical trapping.

As a primary application for the azo carboxylic acids **9**, we envisaged the synthesis of indoles via a Fischer-type cyclization.[50] We considered this potential transformation as especially appropriate, since the more or less pronounced tendency of the azo compounds to form hydrazones would be a part of the desired reaction course. An example employing the previously prepared azo carboxylic acid **9bb** is depicted in Scheme 5.



Scheme 5 Synthesis of indole **17** using azo carboxylic acid **9bb** as an intermediate

A product comparable to those available from the classical Beckmann rearrangement was prepared by reductive cyclization of azo carboxylic acid **9hb** (Scheme 6).[51] Regarding the transformation of **18** to lactam **19** by reductive cleavage of the N–N bond, several potentially useful reaction conditions have already been reported.[52] To obtain piperidin-2-one (**19**), we evaluated different methods including reductions with Raney nickel/hydrogen,[52a] zinc in hydrochloric acid, and borane–tetrahydrofuran.[52e] The best results were observed with magnesium monoperoxyphthalate hexahydrate (MMPP·6 H_2O).[52d,53] The volatility of compound **19** made its isolation on a small scale somewhat inconvenient.



Scheme 6 Synthesis of lactams **18** and **19** from azo carboxylic acid **9hb**

Starting from cyclic ketones, hydrogen peroxide and arenediazonium salts have been shown to be useful reagents to achieve a transformation comparable to the well-known Beckmann rearrangement. The radical reaction leading to azo carboxylic acids proceeds under mild conditions and, in contrast to the classical version, its regioselectivity is governed by radical stability and not oxime configuration. Azo carboxylic acids, which have so far been a compound class practically unknown in organic synthesis, can serve as valuable intermediates for a large number of products including long-chain amino acids, lactams, and heterocycles.

Solvents and reagents were used as received. ^{1}H NMR were recorded on 360 and 600 MHz spectrometers using $CDCl_3$ and C_6D_6 as solvents referenced to TMS (δ = 0 ppm), $CHCl_3$ (δ = 7.26 ppm), or C_6HD_5 (δ = 7.15 ppm). ^{13}C NMR were recorded at 90.6 or 151 MHz in $CDCl_3$ or C_6D_6 using $CDCl_3$ (δ = 77.0 ppm) or C_6D_6 (δ = 128.0 ppm) as standard. Mass spectra were recorded using electron impact (EI). Analytical TLC was carried out on Merck silica gel plates using short wave (254 nm) UV light or a $KMnO_4$ color reagent [$KMnO_4$ (3.00 g), K_2CO_3 (20.0 g), aq NaOH (5% w/w, 5.00 mL), H_2O (300 mL)] to visualize components. Silica gel (Kieselgel 60, 40–63 μm, Merck) was used for flash column chromatography. Reactions were performed at r.t. unless otherwise indicated. Diazonium tetrafluoroborates **5a–c** were prepared by previously reported procedures.[41]

4-Methoxybenzenediazonium Tetrafluoroborate (5a)

^{1}H NMR (360 MHz, CD_3CN): δ = 4.06 (s, 3 H), 7.35 (d, *J* = 9.5 Hz, 2 H), 8.40 (d, *J* = 9.5 Hz, 2 H).

Analytical data was in accordance with literature data.[41]

4-Chlorobenzenediazonium Tetrafluoroborate (5b)

^{1}H NMR (600 MHz, CD_3CN): δ = 7.94 (d, *J* = 9.2 Hz, 2 H), 8.46 (d, *J* = 9.2 Hz, 2 H).

^{13}C NMR (151 MHz, CD_3CN): δ = 113.9 (C_q), 133.2 (2 CH), 134.8 (2 CH), 150.0 (C_q).

Analytical data was in accordance with literature data.[54]

4-Cyanobenzenediazonium Tetrafluoroborate (5c)

^{1}H NMR (600 MHz, CD_3CN): δ = 8.25 (d, *J* = 9.2 Hz, 2 H), 8.63 (d, *J* = 9.2 Hz, 2 H).

^{13}C NMR (90.6 MHz, CD_3CN): δ = 116.6 (C_q), 120.3 (C_q), 124.9 (C_q), 133.8 (2 CH), 136.3 (2 CH).

Analytical data was in accordance with literature data.[54a]

Hydroperoxides 2 from Cyclic Ketones 1; General Procedure

The ketone **1** was introduced into a pear-shaped flask and 3 M HCl (0.06 equiv) and 30% aq H_2O_2 (3 equiv) were added. The mixture was left to stir for the time indicated in Table 2 and was then extracted with CH_2Cl_2 (2 × 2 mL).

The conversions reported in Table 2 were determined from test reactions on a 0.30–5.00 mmol scale. Extraction of the aqueous phase was performed with $CDCl_3$ (1–2 mL) and an aliquot of the organic phase was analyzed by ^{1}H NMR. The equilibrium data obtained from these test reactions was used to calculate the amounts of starting materials for the experiments on the preparative scale. In the case of less favorable equilibria (hydroperoxide **2**/ketone **1**), the preceding hydroperoxyacetal formation was simply conducted on a larger scale. In this way, constant amounts of all hydroperoxides were available for the radical rearrangements.

1-Hydroperoxycyclohexanol (2a)

Prepared according to the general procedure from cyclohexanone (**1a**, 491 mg, 0.52 mL, 5.00 mmol) and 30% aq H_2O_2 (1.53 mL, 15.0 mmol).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.40–1.52 (m, 2 H), 1.54–1.65 (m, 4 H), 1.79–1.96 (m, 4 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 22.5 (2 CH_2), 25.3 (CH_2), 29.8 (2 CH_2), 111.1 (C_q).

1-Hydroperoxy-2-methylcyclohexanol (2b)
Prepared according to the general procedure from 2-methylcyclohexanone (**1b**, 561 mg, 0.60 mL, 5.00 mmol) and 30% aq H_2O_2 (1.53 mL, 15.0 mmol). A mixture of two stereoisomers (ratio 1:0.4) was observed after stirring for 16 h.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 7.2 Hz, 3 H, major), 1.10 (d, *J* = 7.2 Hz, 3 H, minor), 1.33–2.48 (m, 9 H, major + minor).

2-Hydroperoxybicyclo[2.2.1]heptan-2-ol (2d)
Prepared according to the general procedure from norcamphor (**1d**, 110 mg, 1.00 mmol) and 30% aq H_2O_2 (0.31 mL, 3.00 mmol). ^{1}H NMR indicated the formation of 2-oxabicyclo[3.2.l]octan-3-one (ca. 13%) as side-product from a Baeyer–Villiger reaction.[55]

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.26–2.21 (m, 8 H), 2.31–2.38 (m, 1 H), 2.53–2.59 (m, 1 H).

1-Hydroperoxycyclopentanol (2h)
Prepared according to the general procedure from cyclopentanone (**1h**, 421 mg, 0.44 mL, 5.00 mmol) and 30% aq H_2O_2 (1.53 mL, 15.0 mmol).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.70–1.82 (m, 4 H), 1.92–2.12 (m, 4 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 24.6 (2 CH_2), 33.3 (2 CH_2), 122.5 (C_q).

1-Hydroperoxycycloheptanol (2i)
Prepared according to the general procedure from cycloheptanone (**1i**, 561 mg, 0.59 mL, 5.00 mmol) and 30% aq H_2O_2 (1.53 mL, 15.0 mmol).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.53–1.79 (m, 8 H), 1.89–2.07 (m, 4 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 22.8 (2 CH_2), 29.8 (2 CH_2), 33.0 (2 CH_2), 116.3 (C_q).

1-Hydroperoxycyclooctanol (2j)
Prepared according to the general procedure from cyclooctanone (**1j**, 126 mg, 1.00 mmol) and 30% aq H_2O_2 (0.31 mL, 3.00 mmol).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.50–1.71 (m, 10 H), 1.80–2.06 (m, 4 H).

Carboxylic Acids 9aa–ja; General Procedure
Unless otherwise indicated, the amount of cyclic ketone **1** necessary to yield approximately 5 mmol of hydroperoxide **2** (calculated from the reactant/product ratios given in Table 2) was mixed with 3 M HCl (0.06 equiv) and 30% aq H_2O_2 (3 equiv) and left to stir for the time given in Table 2. The mixture was then extracted with CH_2Cl_2 (2 × 2 mL) and immediately used for the consecutive step.

To a mixture of H_2O–DMSO–AcOH (4:3:3, 30 mL) were added $FeSO_4$·7 H_2O (4.17 g, 15.0 mmol) and diazonium tetrafluoroborate **5** (6.00 mmol). The previously prepared soln containing hydroperoxide **2** and unreacted ketone **1** in CH_2Cl_2 (see above) was added dropwise over 5 min. Stirring was continued for 15 min and the mixture was diluted with H_2O (30 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (1 × 100 mL) and brine (1 × 100 mL) and dried (Na_2SO_4). The solvent was removed in vacuo, yielding orange to dark red thick oils as products. In the case of sufficiently low boiling points [e.g. for cyclopentanone (**1h**)], the ketones remaining from the hydroperoxide formation could be removed in vacuo.

6-(4-Methoxyphenylazo)hexanoic Acid (9aa)
Prepared according to the general procedure from cyclohexanone (**1a**, 560 mg, 0.59 mL, 5.71 mmol), 30% aq H_2O_2 (1.75 mL, 17.1 mmol), and 4-methoxybenzenediazonium tetrafluoroborate (**5a**, 1.33 g, 6.00 mmol); R_f = 0.40 (hexane–EtOAc, 3:1, 1% AcOH) [UV].

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.45–1.55 (m, 2 H), 1.63–1.78 (m, 2 H), 1.87–1.98 (m, 2 H), 2.38 (t, *J* = 7.5 Hz, 2 H), 3.85 (s, 3 H), 4.00 (t, *J* = 7.1 Hz, 2 H), 6.95 (d, *J* = 9.1 Hz, 2 H), 7.66 (d, *J* = 9.1 Hz, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 24.5 (CH_2), 26.9 (CH_2), 27.6 (CH_2), 33.8 (CH_2), 55.5 (CH_3), 68.8 (CH_2), 114.0 (2 CH), 123.9 (2 CH), 146.2 (C_q), 161.5 (C_q), 179.2 (C_q).

MS (EI): *m*/*z* (%) = 250 (10) [M$^+$], 160 (46), 123 (42), 122 (87), 108 (60), 85 (60), 83 (100), 80 (41), 45 (49), 37 (89).

HRMS (EI): *m*/*z* calcd [M$^+$] for $C_{13}H_{18}N_2O_3$: 250.1317; found: 250.1317.

6-(4-Chlorophenylazo)hexanoic Acid (9ab)
Prepared according to the general procedure from cyclohexanone (**1a**, 560 mg, 0.59 mL, 5.71 mmol), 30% aq H_2O_2 (1.75 mL, 17.1 mmol), and 4-chlorobenzenediazonium tetrafluoroborate (**5b**, 1.36 g, 6.00 mmol); R_f = 0.45 (hexane–EtOAc, 3:1, 1% AcOH) [UV].

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.46–1.54 (m, 2 H), 1.69–1.76 (m, 2 H), 1.91–1.98 (m, 2 H), 2.39 (t, *J* = 7.5 Hz, 2 H), 4.05 (t, *J* = 7.1 Hz, 2 H), 7.42 (d, *J* = 8.7 Hz, 2 H), 7.61 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 24.4 (CH_2), 26.9 (CH_2), 27.5 (CH_2), 33.8 (CH_2), 69.2 (CH_2), 123.5 (2 CH), 129.2 (2 CH), 136.3 (C_q), 150.3 (C_q), 179.6 (C_q).

MS (EI): *m*/*z* (%) = 256 (26) [^{37}Cl-M$^+$], 254 (77) [^{35}Cl-M$^+$], 168 (29), 140 (39), 129 (40), 128 (50), 127 (100), 126 (100), 111 (55), 99 (65).

HRMS (EI): *m*/*z* calcd [M$^+$] for $C_{12}H_{15}ClN_2O_2$: 254.0822; found: 254.0821.

6-(4-Cyanophenylazo)hexanoic Acid (9ac)
Prepared according to the general procedure from cyclohexanone (**1a**, 560 mg, 0.59 mL, 5.71 mmol), 30% aq H_2O_2 (1.75 mL, 17.1 mmol), and 4-cyanobenzenediazonium tetrafluoroborate (**5c**, 1.30 g, 6.00 mmol); R_f = 0.45 (hexane–EtOAc, 2:1, 1% AcOH) [UV].

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.48–1.55 (m, 2 H), 1.70–1.77 (m, 2 H), 1.94–2.01 (m, 2 H), 2.40 (t, *J* = 7.4 Hz, 2 H), 4.12 (t, *J* = 7.1 Hz, 2 H), 7.72 (d, *J* = 8.7 Hz, 2 H), 7.76 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 24.4 (CH_2), 26.8 (CH_2), 27.4 (CH_2), 33.7 (CH_2), 69.8 (CH_2), 113.7 (C_q), 118.3 (C_q), 122.8 (2 CH), 133.2 (2 CH), 153.9 (C_q), 179.2 (C_q).

MS (EI): *m*/*z* (%) = 245 (10) [M$^+$], 145 (25), 130 (80), 118 (49), 103 (19), 102 (100), 69 (31), 57 (24), 55 (32), 41 (23).

HRMS (EI): *m*/*z* calcd [M$^+$] for $C_{13}H_{15}N_3O_2$: 245.1164; found: 245.1164.

6-(4-Methoxyphenylazo)heptanoic Acid (9ba)
Prepared according to the general procedure from 2-methylcyclohexanone (**1b**, 804 mg, 0.86 mL, 7.17 mmol), 30% aq H_2O_2 (2.20 mL, 21.5 mmol), and 4-methoxybenzenediazonium tetrafluoroborate (**5a**, 1.33 g, 6.00 mmol); R_f = 0.65 (hexane–EtOAc, 2:1, 1% AcOH) [UV].

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.27–1.43 (m, 5 H), 1.60–1.76 (m, 3 H), 1.88–1.98 (m, 1 H), 2.34 (t, *J* = 7.5 Hz, 2 H), 3.65–3.72 (m, 1 H), 3.85 (s, 3 H), 6.95 (d, *J* = 9.0 Hz, 2 H), 7.66 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.0 (CH_3), 24.6 (CH_2), 25.7 (CH_2), 33.9 (CH_2), 34.9 (CH_2), 55.5 (CH_3), 72.5 (CH), 114.0 (2 CH), 123.9 (2 CH), 146.2 (C_q), 161.4 (C_q), 179.3 (C_q).

MS (EI): *m/z* (%) = 264 (4) [M$^+$], 135 (94), 108 (25), 107 (100), 92 (25), 83 (23), 77 (51), 69 (18), 55 (19), 42 (23).

HRMS (EI): *m/z* calcd [M$^+$] for $C_{14}H_{20}N_2O_3$: 264.1474; found: 264.1478.

6-(4-Chlorophenylazo)heptanoic Acid (9bb)

Prepared according to the general procedure from 2-methylcyclohexanone (**1b**, 804 mg, 0.86 mL, 7.17 mmol), 30% aq H_2O_2 (2.20 mL, 21.5 mmol), and 4-chlorobenzenediazonium tetrafluoroborate (**5b**, 1.36 g, 6.00 mmol); R_f = 0.30 (hexane–EtOAc, 3:1, 1% AcOH) [UV].

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.29–1.41 (m, 5 H), 1.60–1.77 (m, 3 H), 1.91–1.99 (m, 1 H), 2.34 (t, *J* = 7.5 Hz, 2 H), 3.70–3.78 (m, 1 H), 7.41 (d, *J* = 8.8 Hz, 2 H), 7.61 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 18.8 (CH_3), 24.6 (CH_2), 25.6 (CH_2), 33.7 (CH_2), 34.8 (CH_2), 73.0 (CH), 123.5 (2 CH), 129.1 (2 CH), 136.2 (C_q), 150.4 (C_q), 178.9 (C_q).

MS (EI): *m/z* (%) = 270 (1) [^{37}Cl-M$^+$], 268 (4) [^{35}Cl-M$^+$], 141 (31), 139 (92), 113 (44), 111 (100), 85 (26), 83 (53), 69 (57), 55 (53), 42 (44).

HRMS (EI): *m/z* calcd [M$^+$] for $C_{13}H_{17}ClN_2O_2$: 268.0979; found: 268.0979.

6-(4-Cyanophenylazo)heptanoic Acid (9bc)

Prepared according to the general procedure from 2-methylcyclohexanone (**1b**, 804 mg, 0.86 mL, 7.17 mmol), 30% aq H_2O_2 (2.20 mL, 21.5 mmol), and 4-cyanobenzenediazonium tetrafluoroborate (**5c**, 1.30 g, 6.00 mmol); R_f = 0.45 (hexane–EtOAc, 2:1, 1% AcOH) [UV].

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.27–1.42 (m, 5 H), 1.60–1.72 (m, 2 H), 1.73–1.81 (m, 1 H), 1.94–2.02 (m, 1 H), 2.35 (t, *J* = 7.4 Hz, 2 H), 3.78–3.85 (m, 1 H), 7.72 (d, *J* = 8.8 Hz, 2 H), 7.76 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 18.8 (CH_3), 24.5 (CH_2), 25.6 (CH_2), 33.8 (CH_2), 34.7 (CH_2), 73.6 (CH), 113.6 (C_q), 118.4 (C_q), 122.8 (2 CH), 133.2 (2 CH), 154.0 (C_q), 179.1 (C_q).

MS (EI): *m/z* (%) = 259 (2) [M$^+$], 130 (32), 129 (53), 111 (62), 102 (85), 83 (100), 69 (92), 55 (67), 45 (20), 41 (50).

HRMS (EI): *m/z* calcd [M$^+$] for $C_{14}H_{17}N_3O_2$: 259.1321; found: 259.1320.

[3-(4-Methoxyphenylazo)cyclopentyl]acetic Acid (Mixture of Diastereoisomers) (9da)

Prepared according to the general procedure from norcamphor (**1d**, 596 mg, 5.41 mmol), 30% aq H_2O_2 (1.65 mL, 16.2 mmol), and 4-methoxybenzenediazonium tetrafluoroborate (**5a**, 1.33 g, 6.00 mmol). In this case, the hydroperoxide soln contained small amounts (ca. 13%) of 2-oxabicyclo[3.2.1]octan-3-one. The product was obtained as a mixture of diastereoisomers; R_f = 0.40 (hexane–EtOAc, 2:1, 1% AcOH) [UV].

^{1}H NMR (600 MHz, $CDCl_3$,): δ = 1.40–2.60 (m, 8 H, major + minor), 2.69–2.78 (m, 1 H, major), 2.84–2.92 (m, 1 H, minor), 3.85 (s, 3 H, major), 3.86 (s, 3 H, minor), 4.00–4.05 (m, 1 H, minor), 4.15–4.23 (m, 1 H, major), 6.92–6.97 (m, 2 H, major + minor), 7.64–7.68 (m, 2 H, major + minor).

^{13}C NMR: (151 MHz, $CDCl_3$): δ = 28.8, 29.2, 30.2, 30.8, 31.0, 31.7, 32.1, 32.4, 33.2, 34.7, 34.9, 35.1, 35.5, 36.0, 37.7, 38.0, 38.3, 39.2, 39.3, 39.8, 39.9, 43.4, 44.5, 55.1, 55.5, 55.7, 73.6, 77.1, 77.6, 113.99 (2 C), 114.02 (2 C), 114.7 (2 C), 123.90 (2 C), 123.91 (2 C), 123.93 (2 C), 146.05, 146.07, 146.3, 161.4, 161.5, 178.5 (a third isomer which could not be detected by ^{1}H NMR was formed upon standing in $CDCl_3$).

MS (EI): *m/z* (%) = 262 (4) [M$^+$], 135 (90), 108 (21), 107 (100), 92 (19), 85 (15), 83 (24), 77 (46), 67 (33), 41 (17).

HRMS (EI): *m/z* calcd [M$^+$] for $C_{14}H_{18}N_2O_3$: 262.1318; found: 262.1316.

5-(4-Methoxyphenylazo)pentanoic Acid (9ha)

Prepared according to the general procedure from cyclopentanone (**1h**, 701 mg, 0.74 mL, 8.33 mmol), 30% aq H_2O_2 (2.56 mL, 25.0 mmol), and 4-methoxybenzenediazonium tetrafluoroborate (**5a**, 1.33 g, 6.00 mmol). This experiment was conducted with an unusual ratio of hydrogen peroxide/ketone, which led to a mixture of hydroperoxide/ketone (1.5:1) after 4 h; R_f = 0.25 (hexane–EtOAc, 4:1, 1% AcOH) [UV].

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.76–1.84 (m, 2 H), 1.93–2.00 (m, 2 H), 2.44 (t, *J* = 7.5 Hz, 2 H), 3.86 (s, 3 H), 4.01 (t, *J* = 7.0 Hz, 2 H), 6.95 (d, *J* = 9.0 Hz, 2 H), 7.66 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 22.7 (CH_2), 27.4 (CH_2), 33.6 (CH_2), 55.5 (CH_3), 68.4 (CH_2), 114.0 (2 CH), 123.9 (2 CH), 146.2 (C_q), 161.5 (C_q), 178.2 (C_q).

MS (EI): *m/z* (%) = 236 (18) [M$^+$], 160 (23), 135 (23), 123 (33), 122 (100), 108 (40), 107 (21), 85 (40), 83 (56), 37 (62).

HRMS (EI): *m/z* calcd [M$^+$] for $C_{12}H_{16}N_2O_3$: 236.1161; found: 236.1173.

5-(4-Chlorophenylazo)pentanoic Acid (9hb)

Prepared according to the general procedure from cyclopentanone (**1h**, 548 mg, 0.58 mL, 6.52 mmol), 30% aq H_2O_2 (2.00 mL, 19.6 mmol), and 4-chlorobenzenediazonium tetrafluoroborate (**5b**, 1.36 g, 6.00 mmol); R_f = 0.45 (hexane–EtOAc, 3:1, 1% AcOH) [UV].

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.73–2.05 (m, 4 H), 2.44 (t, *J* = 7.4 Hz, 2 H), 4.06 (t, *J* = 7.0 Hz, 2 H), 7.42 (d, *J* = 8.9 Hz, 2 H), 7.61 (d, *J* = 8.9 Hz, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 22.5 (CH_2), 27.2 (CH_2), 33.7 (CH_2), 68.9 (CH_2), 123.5 (2 CH), 129.2 (2 CH), 136.4 (C_q), 150.3 (C_q), 179.6 (C_q).

MS (EI): *m/z* (%) = 242 (24) [^{37}Cl-M$^+$], 240 (76) [^{35}Cl-M$^+$], 139 (40), 128 (46), 127 (92), 126 (100), 113 (28), 111 (81), 99 (67), 83 (34).

HRMS (EI): *m/z* calcd [M$^+$] for $C_{11}H_{13}ClN_2O_2$: 240.0666; found: 240.0665.

7-(4-Methoxyphenylazo)heptanoic Acid (9ia)

Prepared according to the general procedure from cycloheptanone (**1i**, 785 mg, 0.83 mL, 7.00 mmol), 30% aq H_2O_2 (2.14 mL, 21.0 mmol), and 4-methoxybenzenediazonium tetrafluoroborate (**5a**, 1.33 g, 6.00 mmol); R_f = 0.25 (hexane–EtOAc, 3:1, 1% AcOH) [UV].

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.39–1.80 (m, 6 H), 1.85–1.97 (m, 2 H), 2.35 (t, *J* = 7.4 Hz, 2 H), 3.85 (s, 3 H), 3.96–4.03 (m, 2 H), 6.95 (d, *J* = 9.1 Hz, 2 H), 7.66 (d, *J* = 9.1 Hz, 2 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 24.6 (CH_2), 27.1 (CH_2), 27.8 (CH_2), 28.9 (CH_2), 34.0 (CH_2), 55.5 (CH_3), 69.0 (CH_2), 114.0 (2 CH), 123.8 (2 CH), 146.3 (C_q), 161.4 (C_q), 179.1 (C_q).

MS (EI): *m/z* (%) = 264 (8) [M$^+$], 135 (91), 122 (24), 108 (28), 107 (100), 92 (33), 85 (18), 83 (27), 77 (63), 42 (20).

HRMS (EI): *m/z* calcd [M$^+$] for $C_{14}H_{20}N_2O_3$: 264.1474; found: 264.1474.

7-(4-Chlorophenylazo)heptanoic Acid (9ib)

Prepared according to the general procedure from cycloheptanone (**1i**, 785 mg, 0.83 mL, 7.00 mmol), 30% aq H_2O_2 (2.14 mL,

21.0 mmol), and 4-chlorobenzenediazonium tetrafluoroborate (**5b**, 1.36 g, 6.00 mmol); R_f = 0.40 (hexane–EtOAc, 3:1, 1% AcOH) [UV].

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.22–1.77 (m, 6 H), 1.86–1.98 (m, 2 H), 2.36 (t, *J* = 7.5 Hz, 2 H), 4.01–4.08 (m, 2 H), 7.42 (d, *J* = 8.9 Hz, 2 H), 7.61 (d, *J* = 8.9 Hz, 2 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 24.5 (CH_2), 27.1 (CH_2), 27.6 (CH_2), 28.8 (CH_2), 33.9 (CH_2), 69.4 (CH_2), 123.4 (2 CH), 129.2 (2 CH), 136.3 (C_q), 150.4 (C_q), 179.3 (C_q).

MS (EI): *m*/*z* (%) = 270 (1) [^{37}Cl-M$^+$], 268 (3) [^{35}Cl-M$^+$], 139 (48), 113 (26), 111 (79), 85 (65), 83 (100), 55 (18), 47 (24), 42 (21).

HRMS (EI): *m*/*z* calcd [M$^+$] for $C_{13}H_{17}ClN_2O_2$: 268.0979; found: 268.0979.

8-(4-Chlorophenylazo)octanoic Acid (9jb)

Prepared according to the general procedure from cyclooctanone (**1j**, 1.68 g, 13.3 mmol), 30% aq H_2O_2 (4.09 mL, 40.0 mmol), and 4-chlorobenzenediazonium tetrafluoroborate (**5b**, 1.36 g, 6.00 mmol); R_f = 0.65 (hexane–EtOAc, 2:1, 1% AcOH) [UV].

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.35–1.48 (m, 6 H), 1.61–1.68 (m, 2 H), 1.85–1.93 (m, 2 H), 2.35 (t, *J* = 7.5 Hz, 2 H), 4.02–4.06 (m, 2 H), 7.42 (d, *J* = 8.8 Hz, 2 H), 7.61 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 24.6 (CH_2), 27.2 (CH_2), 27.8 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 34.0 (CH_2), 69.6 (CH_2), 123.5 (2 CH), 129.2 (2 CH), 136.3 (C_q), 150.4 (C_q), 179.9 (C_q).

MS (EI): *m*/*z* (%) = 284 (2) [^{37}Cl-M$^+$], 282 (5) [^{35}Cl-M$^+$], 241 (23), 239 (72), 113 (31), 111 (100), 85 (17), 83 (26), 55 (21), 41 (17).

HRMS (EI): *m*/*z* calcd [M$^+$] for $C_{14}H_{19}ClN_2O_2$: 282.1135; found: 282.1134.

Methyl 6-(4-Chlorophenylazo)hexanoate (15)[56]

For the preparation of *N*-methyl-*N*-nitrosourea,[57] *N*-methylurea (14.8 g, 200 mmol) was dissolved in H_2O (120 mL). $NaNO_2$ (15.2 g, 220 mmol) was added and the mixture cooled to 0 °C in an ice bath. Concd aq HCl (26.7 mL, 0.26 mol) was added dropwise over a period of 1 h. The mixture was left to stir for 30 min at 0 °C. The precipitate that had formed was filtered off, washed with H_2O (ca. 20 mL), and dried in vacuo. *N*-Methyl-*N*-nitrosourea was obtained as a light beige powder (16.4 g, 159 mmol, 79%) and was found to be sufficiently pure for further reactions. It was stored at –28 °C.

N-Methyl-*N*-nitrosourea (850 mg, 8.25 mmol) was introduced into an Erlenmeyer flask containing Et_2O (20 mL) and 40% aq KOH (6 mL) previously cooled to 0 °C in an ice bath. The mixture was left to stand for 30 min at this temperature, carefully shaking it several times. The organic phase containing the generated diazomethane was decanted and dried (KOH pellets) at 0 °C for 3 h. Carboxylic acid **9ab** (300 mg of the crude product, ca. 0.85 mmol) was dissolved in a mixture of Et_2O (15 mL) and MeOH (10 mL) and cooled to 0 °C. The soln of diazomethane in Et_2O was added dropwise. After stirring for 15 min at 0 °C, AcOH (2.50 mL, 43.7 mmol) was added to quench unreacted diazomethane. After stirring for another 15 min, the soln was washed with sat. aq $NaHCO_3$ (1 × 50 mL) and brine (1 × 50 mL), and the solvent was removed in vacuo. Column chromatography (hexane–EtOAc, 4:1) gave the product as a red oil (111 mg, 0.41 mmol, 33% overall yield); R_f = 0.55 (hexane–EtOAc, 4:1) [UV].

^{1}H NMR (360 MHz, C_6D_6): δ = 1.15–1.25 (m, 2 H), 1.45–1.56 (m, 2 H), 1.63–1.73 (m, 2 H), 2.04 (t, *J* = 7.4 Hz, 2 H), 3.34 (s, 3 H), 3.86 (t, *J* = 7.1 Hz, 2 H), 7.07 (d, *J* = 8.8 Hz, 2 H), 7.55 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 24.7 (CH_2), 27.0 (CH_2), 27.5 (CH_2), 33.9 (CH_2), 51.5 (CH_3), 69.3 (CH_2), 123.5 (2 CH), 129.2 (2 CH), 136.3 (C_q), 150.4 (C_q), 174.0 (C_q).

MS (EI): *m*/*z* (%) = 270 (3) [^{37}Cl-M$^+$], 268 (8) [^{35}Cl-M$^+$], 141 (27), 139 (84), 113 (47), 111 (100), 75 (21), 69 (18), 55 (14), 41 (16).

HRMS (EI): *m*/*z* calcd [M$^+$] for $C_{13}H_{17}ClN_2O_2$: 268.0979; found: 268.0979.

6-[(4-Chlorophenyl)hydrazono]hexanoic Acid (16ab)

The carboxylic acid **9ab** (10.0 mg, 0.04 mmol) isomerized to the hydrazone upon standing in $CDCl_3$ (0.70 mL) overnight. Compound **16ab** was obtained as a mixture of *E*/*Z* isomers (ratio 3:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.55–1.89 (m, 4 H, major + minor), 2.20–2.45 (m, 4 H, major + minor), 6.51 (t, *J* = 5.1 Hz, 1 H, minor), 6.90 (d, *J* = 8.9 Hz, 2 H, major), 6.97 (d, *J* = 8.9 Hz, 2 H, minor), 7.06 (t, *J* = 5.3 Hz, 1 H, major), 7.17 (d, *J* = 8.9 Hz, 2 H, major), 7.19 (d, *J* = 8.9 Hz, 2 H, minor).

The identity of the hydrazone is supported by data reported the literature.[58]

Ethyl 4-(5-Chloro-2-methyl-1*H*-indol-3-yl)butyrate (17)[59]

Carboxylic acid **9bb** (150 mg of the crude product, ca. 0.50 mmol) was dissolved in a mixture of EtOH (2.5 mL) and concd H_2SO_4 (0.30 mL, 5.40 mmol). The mixture was refluxed for 3.5 h under N_2. After cooling to r.t. H_2O (10 mL) was added and the aqueous soln was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with H_2O (1 × 30 mL) and brine (1 × 30 mL) and dried (Na_2SO_4). The solvent was removed in vacuo. Column chromatography (100% $CHCl_3$) gave **17** as a brown oil (58.0 mg, 0.21 mmol, 37% overall yield); R_f = 0.40 (100% $CHCl_3$) [UV].

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.2 Hz, 3 H), 1.93 (quint, *J* = 7.4 Hz, 2 H), 2.31 (t, *J* = 7.4 Hz, 2 H), 2.33 (s, 3 H), 2.69 (t, *J* = 7.4 Hz, 2 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 7.03 (dd, *J* = 2.0 Hz, *J* = 8.5 Hz, 1 H), 7.14 (dd, *J* = 0.5 Hz, *J* = 8.5 Hz, 1 H), 7.43 (d, *J* = 2.0 Hz, 1 H), 7.82 (br, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 11.7 (CH_3), 14.2 (CH_3), 23.2 (CH_2), 25.6 (CH_2), 33.7 (CH_2), 60.3 (CH_2), 110.9 (C_q), 111.0 (CH), 117.5 (CH), 121.0 (CH), 124.8 (C_q), 129.9 (C_q), 132.8 (C_q), 133.6 (C_q), 173.7 (C_q).

MS (EI): *m*/*z* (%) = 281 (13) [^{37}Cl-M$^+$], 279 (42) [^{35}Cl-M$^+$], 234 (17), 191 (25), 180 (64), 179 (29), 178 (100), 143 (21), 85 (21), 83 (32).

HRMS (EI): *m*/*z* calcd [M$^+$] for $C_{15}H_{18}ClNO_2$: 279.1026; found: 279.1025.

1-(4-Chlorophenylamino)piperidin-2-one (18)[51]

Carboxylic acid **9hb** (125 mg, 0.52 mmol) was dissolved in EtOH (10 mL) under an argon atmosphere and Zn dust (600 mg, 9.17 mmol) and AcOH (5 mL) were added. The mixture was stirred for 5 min (until it had become nearly colorless) and the remaining Zn powder was filtered off. The soln was refluxed under an argon atmosphere for 5 h. After cooling to r.t. the solvent was removed in vacuo. The pure product was obtained after column chromatography (100% EtOAc) as a brownish powder (88.4 mg, 0.39 mmol, 75%); R_f = 0.25 (EtOAc) [UV].

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.84–1.94 (m, 2 H), 1.94–2.04 (m, 2 H), 2.53 (t, *J* = 6.6 Hz, 2 H), 3.57 (t, *J* = 6.0 Hz, 2 H), 6.69 (d, *J* = 8.8 Hz, 2 H), 6.76 (br, 1 H), 7.18 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 21.3 (CH_2), 23.6 (CH_2), 32.5 (CH_2), 51.3 (CH_2), 115.3 (2 CH), 126.3 (C_q), 129.2 (2 CH), 145.3 (C_q), 169.9 (C_q).

MS (EI): *m/z* (%) = 226 (34) [^{37}Cl-M$^+$], 224 (100) [^{35}Cl-M$^+$], 139 (61), 127 (55), 126 (71), 113 (30), 111 (92), 99 (44), 70 (42), 42 (42).

HRMS (EI): *m/z* calcd [M$^+$] for $C_{11}H_{13}ClN_2O$: 224.0716; found: 224.0716.

Piperidin-2-one (19)

Compound **19** was prepared from lactam **18** according to literature procedures.[52d,53]

R_f = 0.15 (EtOAc, 5% MeOH) [$KMnO_4$].

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.72–1.89 (m, 4 H), 2.38 (t, *J* = 6.4 Hz, 2 H), 3.30–3.36 (m, 2 H).

Analytical data was in accordance with literature.[60]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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