Hydroperoxides and aryl diazonium salts as reagents for the functionalization of non-activated olefins

Olga Blank [a], Nicole Raschke [a], Markus R. Heinrich [a,b,*]

[a] *Organische Chemie 1, Technische Universität München, Lichtenbergstraße 4, 85747 Garching b. München, Germany*
[b] *Pharmazeutische Chemie, Friedrich-Alexander-Universität Erlangen-Nürnberg, Schuhstraße 19, 91052 Erlangen, Germany*

ABSTRACT

Hydroperoxides, olefins, and arenediazonium salts selectively combine to give azo compounds via an iron(II)-mediated three-component reaction. Starting with a fragmentation liberating acetic acid, the hydroperoxides act as radical source and the diazonium ions as nitrogen-centered radical scavengers.

© 2010 Elsevier Ltd. All rights reserved.

While aryl diazonium salts have been widely employed as sources of aryl radicals in Meerwein,[1] Gomberg–Bachmann,[2] Pschorr,[3] and Sandmeyer[4] type reactions, their use and applicability as nitrogen-centered radical scavengers has so far only been marginally explored.[5,6] Among the other known nitrogen-centered radical scavengers, sulfonyl azides especially have proved to be versatile and useful reagents in recent years.[7]

Our activities in the field of aryl radicals and aryl diazonium salts began with the development of carbodiazenylation reactions for the functionalization of non-activated olefins.[8] By employing aryl diazonium salts as aryl radical sources[9] and nitrogen-centered radical scavengers simultaneously, a broad range of olefinic substrates can be converted into β-aryl azo compounds. The products easily accessible by the previously developed procedures can serve as valuable starting materials for ketones, hydrazones, amino acids, and a broad range of heterocycles.

In this Letter, we present a new type of olefin functionalization which is based on aryl diazonium salts acting as nitrogen-centered radical scavengers only. For this purpose, the reaction conditions had to be found, under which electrophilic radicals can be generated in the presence of olefinic substrates and diazonium ions.[10] The electrophilic character of the initially formed radical is necessary to ensure fast addition to non-activated olefins and to avoid direct trapping of the radical by the diazonium ion.[11] Due to the pH-dependent reduction potential of iron(II) ions, most diazonium ions are no longer reduced to aryldiazenyl radicals when the pH

value of the solution is slightly acidic, for example, by using acetic acid as co-solvent. Despite the decreased reductive power, iron(II) remains capable of cleaving hydroperoxides under the same conditions.[12] To explore the applicability of this principle, we investigated the reaction shown in Scheme 1.

In the first step, hydroperoxide **2** was prepared by treatment of ethyl 3-oxobutanoate (**1**) with hydrogen peroxide.[13,14] The resulting solution was then added slowly to a mixture of diazonium salt **3**, olefin **4** and iron(II)-sulfate in acetic acid, and water. The formation of product **5** can be rationalized by an iron(II)-induced cleavage of **2** and subsequent fragmentation of the oxyl radical **6** to give
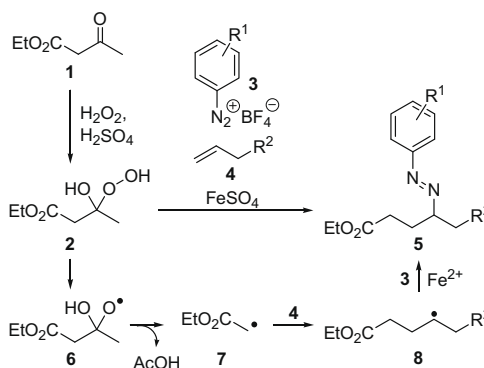
Scheme 1. Iron(II)-mediated olefin functionalization with hydroperoxides and aryl diazonium salts.

* Corresponding author. Tel.: +49 9131 85 24115; fax: +49 9131 85 22585.
E-mail address: Markus.Heinrich@medchem.uni-erlangen.de (M.R. Heinrich).

Table 1
Hydroperoxide **2** formation from ethyl-3-oxo-butanoate (**1**)
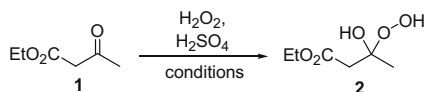
Temperature	Reaction time (min)	H_2O_2 (equiv)	Yield[a] (**2**) (%)
0 °C	120	1.5	10
rt	10	1.0	5
rt	10	4.0	9
rt	60	1.0	13
rt	60	2.0	18
rt	60	3.0	23
rt	120	1.5	32
rt	120	4.0	39
rt	**120**	**8.0**	**40**
rt	120	16.0	37
50 °C	30	2.0	40[b]

[a] Formation of hydroperoxide **2** from ketoester **1** determined by ^{1}H NMR after extraction with CDCl$_3$.
[b] Numerous by-products observed.

Table 2
Extraction of hydroperoxide **2** with different solvents for the synthesis of azo compound **5a**
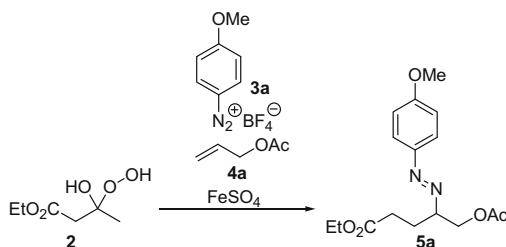
Extraction with	Ketoester **1**[a] (equiv)	Olefin **4a**[a] (equiv)	Yield (%) A[b]/B[c]
(neat)	0.6	1.0	>90/26
EtOAc	0.6	6.4	>90/25
CH$_2$Cl$_2$	1.2	6.4	58/28
CH$_2$Cl$_2$	**2.0**	**3.2**	**50/40**

[a] Equivalents related to diazonium salt **3a**.
[b] Yield A based on hydroperoxide **2** (40% conversion from **1**).
[c] Yield B based on diazonium salt **3a**.

acetic acid and **7**. Addition of the electrophilic radical **7** to the olefinic substrate **4** and trapping of the nucleophilic adduct **8** by a diazonium ion **3** lead to the desired product **5** via a final reductive step.

The following series of experiments was carried out to investigate the hydroperoxide formation from ethyl 3-oxobutanoate (**1**) (Table 1).

The best ratio in favor of the desired hydroperoxide **2** with no by-products observable by ^{1}H NMR spectroscopy was obtained within 2 h reaction time using 8.0 equiv of aqueous hydrogen peroxide at room temperature. In the next step, the hydroperoxide **2** was added to a mixture of the olefin, the diazonium salt, and iron(II)-sulfate in aqueous acetic acid. Preliminary experiments with 4-methoxyphenyldiazonium tetrafluoroborate (**3a**) and allyl acetate (**4a**) revealed that the best results are obtained by intermediate extraction of the hydroperoxide **2** from its acidic aqueous solution with dichloromethane (Table 2).

The optimized conditions[15] were then applied to a range of olefins and diazonium salts (Table 3).

With most substrate combinations, synthetically useful yields of the products **5** were obtained. An adjustment of conditions—as

Table 3
Application to various substrates
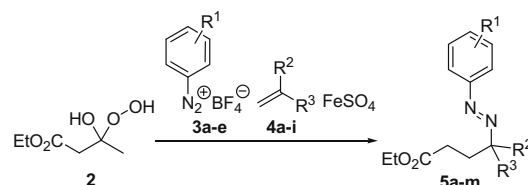
| Diazonium salt **3** R^1 =		Olefin **4** R^2 =	R^3 =		Product **5**	Yield[a] (%)
p-OMe	**3a**	CH$_2$OAc	H	**4a**	**5a**	50
p-COOMe	**3b**[b]	CH$_2$OAc	H	**4a**	**5b**	41
p-OMe	**3a**	CH$_2$OH	H	**4b**	**5c**	61
o-COOMe	**3c**	CH$_2$OH	H	**4b**	**5d**	55
p-OMe	**3a**	(CH$_2$)$_2$OH	H	**4c**	**5e**	67
H	**3d**	(CH$_2$)$_2$OH	H	**4c**	**5f**	35
p-OMe	**3a**	CH$_2$OH	Me	**4d**	**5g**	58
p-OMe	**3a**	OAc	Me	**4e**	**5h**	22
p-OMe	**3a**	OAc	H	**4f**	**5i**	71
p-OMe	**3a**	(CH$_2$)$_4$OH	H	**4g**	**5j**	62
p-OMe	**3a**	(CH$_2$)$_2$COMe	H	**4h**	**5k**	76
p-F	**3e**	(CH$_2$)$_2$COMe	H	**4h**	**5l**	47
p-OMe	**3a**	2,5-Norbornadiene		**4i**	**5m**	56

[a] Reaction carried out under the conditions described in the general procedure[15] (1.25 equiv of diazonium salt **3a**, **c**–**e** and 4 equiv of olefin **4a**–**i** per hydroperoxide **2**); yield based on hydroperoxide **2**.
[b] Diazonium salt **3b** was used as sulfate without intermediate isolation. For a detailed protocol, see Supplementary data.

it is often required in Sandmeyer or Meerwein protocols—was not necessary when shifting from donor—to acceptor-substituted diazonium salts. Sufficient polarity of the diazonium salt or aryl radical appears to be beneficial, as is indicated by the comparatively low yield of product **5f** (35%) obtained from unsubstituted phenyldiazonium tetrafluoroborate. The formation of the tricyclic azo compound **5m** from 2,5-norbornadiene (**4i**) in 56% yield shows that lipophilic olefins are well tolerated (Fig. 1).[16]

The synthesis of azo compound **5h** is complicated by an undesired single-electron transfer step (Fig. 1, Scheme 2).[17] While the intermediate radical **9**, arising from the addition of radical **7** to the isopropenyl acetate (**4e**), is usually trapped by diazonium ions (to give **5h**), **9** is oxidized by diazonium ion **3a** to give cation **10** and the aryldiazenyl radical **11**. As a consequence, ethyl levulinate (**12**) and azo compound **13** (formation via the carbodiazenylation sequence)[8] were isolated from the reaction mixture (yields over 60%) along with only minor amounts of **5h** (22%). The structural modification from isoprenyl acetate (**4e**) to vinyl acetate (**4f**) renders the radical intermediate less reducible (compared to **9**) and leads to a good yield of the desired product **5i** (71%).

In conclusion, we have shown that α-acetic acid ester radicals can be generated from ethyl 3-oxobutanoate via hydroperoxides under slightly reductive conditions which do not lead to the decomposition
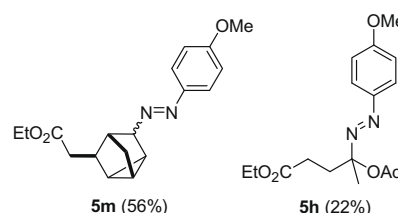
Figure 1. Azo compounds **5h** and **5m**.
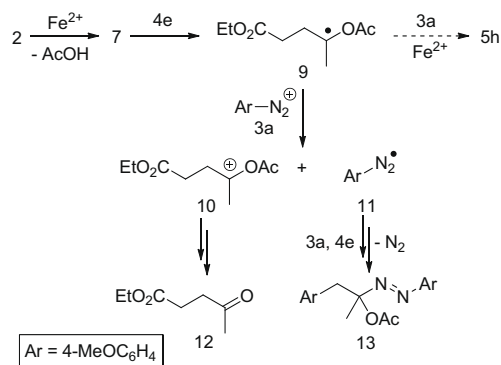
Scheme 2. Formation of ethyl levulinate (**12**) and azo compounds **5h** and **13**.

of radical aryldiazonium ions. In this way, a new type of multicomponent olefin functionalization was developed, in which diazonium ions serve as highly effective and selective nitrogen-centered radical scavengers.[7h] Compared with our previously reported procedure, which was based on iodine transfer,[18a,19] the new protocol does not rely on diazonium ions as radical sources and does not therefore produce iodobenzenes as by-products. Only non-toxic reagents were used and the excess olefin and ketoester—the latter resulting from the hydroperoxide equilibrium—were recovered by distillation in vacuo. The method has been shown to be applicable to a range of non-activated olefins and not to be sensitive to electron-donating or electron-withdrawing substituents on the aromatic core of the diazonium ions. The structurally diverse azo compounds, which are accessible from this simple sequence, can serve as precursors of γ-amino acids (by reductive N–N bond cleavage), numerous heterocycles (including pyrroles and indoles) and functionalized tricyclanes.[8,18b]

Acknowledgments

Supplementary data

Supplementary data (experimental procedures, analytical data and NMR spectra are available for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.098.

References and notes

1. For a first report, see: (a) Meerwein, H.; Büchner, E.; Emster, K. V. *J. Prakt. Chem.* **1939**, *152*, 237–266; For a recent review, see: (b) Heinrich, M. R. *Chem. Eur. J.* **2009**, *15*, 820–833.
2. (a) Gomberg, M.; Bachmann, W. E. *J. Am. Chem. Soc.* **1924**, *46*, 2339–2343; (b) Beadle, J. R.; Korzeniowski, S. H.; Rosenberg, D. E.; Garcia-Slanga, B. J.; Gokel, G. W. *J. Org. Chem.* **1984**, *49*, 1594–1603.
3. For a first report, see: Pschorr, R. *Chem. Ber.* **1896**, *29*, 496–501.
4. For a review on Sandmeyer reactions, see: (a) Minisci, F.; Fontana, F.; Vismara, E. *Gazz. Chim. Ital.* **1993**, *123*, 9–18; (b) Merkushev, E. B. *Synthesis* **1988**, 923–937.
5. For a first report, see Al Adel, I.; Salami, B. A.; Levisalles, J.; Rudler, H. *Bull. Soc. Chim. Fr.* **1976**, 934–938.
6. (a) Citterio, A.; Minisci, F.; Albinati, A.; Bruckner, S. *Tetrahedron Lett.* **1980**, *21*, 2909–2910; (b) Packer, J. E.; Heighway, C. J.; Muller, H. M.; Dobson, B. C. *Aust. J. Chem.* **1980**, *13*, 965–977; (c) Citterio, A.; Minisci, F. *J. Org. Chem.* **1982**, *47*, 1759–1761.
7. (a) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2000**, *122*, 6496–6497; (b) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2001**, *123*, 4717–4727; (c) Panchaud, P.; Renaud, P. *J. Org. Chem.* **2004**, *69*, 3205–3207; (d) Panchaud, P.; Ollivier, C.; Renaud, P.; Zigmantas, S. *J. Org. Chem.* **2004**, *69*, 2755–2759; (e) Chabaud, L.; Landais, Y.; Renaud, P. *Org. Lett.* **2005**, *7*, 2587–2590; (f) Nyfeler, E.; Renaud, P. *Org. Lett.* **2008**, *10*, 985–988; (g) Chabaud, L.; Landais, Y.; Renaud, P.; Robert, F.; Castet, F.; Lucarini, M.; Schenk, K. *Chem. Eur. J.* **2008**, *14*, 2744–2756; (h) Godineau, E.; Landais, Y. *Chem. Eur. J.* **2009**, *15*, 3044–3055.
8. (a) Heinrich, M. R.; Blank, O.; Wölfel, S. *Org. Lett.* **2006**, *8*, 3323–3325; (b) Heinrich, M. R.; Blank, O.; Wetzel, A. *J. Org. Chem.* **2007**, *72*, 476–484.
9. Cao, L.; Li, C. *Tetrahedron Lett.* **2008**, *49*, 7380–7382.
10. Elofson, R. M.; Gadallah, F. F. *J. Org. Chem.* **1969**, *34*, 854–857.
11. For polarity effects in radical diazonium trapping reactions, see: (a) Citterio, A.; Minisci, F.; Vismara, E. *J. Org. Chem.* **1982**, *47*, 81–88; (b) See also Ref. 6c.
12. (a) Walling, C. *Acc. Chem. Res.* **1975**, *8*, 125–131; (b) Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6163–6165; (c) Dichtl, A.; Seyfried, M.; Schoening, K.-U. *Synlett* **2008**, *12*, 1877–1881.
13. (a) Minisci, F.; Galli, R.; Cecere, M.; Malatesta, V.; Caronna, T. *Tetrahedron Lett.* **1968**, *54*, 5609–5612; (b) See also Ref. 6c.
14. For a synthesis of hydroperoxides from ozonides, see: Schreiber, S. L.; Liew, W.-F. *J. Am. Chem. Soc.* **1985**, *107*, 2980–2982.
15. *Representative procedure for the preparation of compounds* **5a,c–m**: Preparation of the hydroperoxide **2**. To a mixture of ethyl 3-oxobutanoate (0.63 mL, 0.65 g, 5.0 mmol) and aqueous hydrogen peroxide (35% solution, 3.4 mL, 40 mmol) was added one drop of 50% sulfuric acid. After stirring at room temperature for 2 h, satd aqueous sodium chloride (2 mL) was added and the resulting mixture was extracted twice with dichloromethane (2 × 5 mL). The combined organic phases were concentrated under reduced pressure to a volume of 2 mL containing ca. 2 mmol of hydroperoxide **2**. ^{1}H NMR analysis of several samples extracted with CDCl$_3$ had shown a 3:2 ratio of hydroperoxide **2** to ethyl 3-oxobutanoate (**1**) which corresponds to a 40% conversion of **1**. Hydroperoxide **2**: ^{1}H NMR (CDCl$_3$, 360 MHz) δ 1.29 (t, J = 7.1 Hz, 3H), 1.54 (s, 3H), 2.86 (s, 2H), 4.21 (q, J = 7.1 Hz, 2H). Since organic peroxides are flammable and potentially explosive materials they should not be prepared in large quantities. *Olefin functionalization*. To a mixture of diazonium salt **3**[20] (2.5 mmol) and olefin **4** (8.0 mmol) in water (6 mL) and acetic acid (2 mL) was added FeSO$_4$·7H$_2$O (4.17 g, 20.0 mmol). The previously prepared hydroperoxide solution (2 mmol in 2 mL CH$_2$Cl$_2$) was added dropwise by a syringe over 10 min. After stirring for 15 min, water (50 mL) was added and the mixture was extracted with CH$_2$Cl$_2$ (3 × 75 mL). The combined organic phases were washed with satd aqueous sodium chloride and dried over sodium sulfate. Excess olefin and ethyl 3-oxobutanoate (**1**) were removed in vacuo and the product **5** was purified by flash chromatography on silica gel. *Analytical data for compound* **5a**: R_f 0.60 (pentane/EtOAc 2:1); IR: $\nu\sim$ = 2978 (w), 2836 (w), 1732 (vs), 1603 (m), 1587 (w), 1513 (s), 1443 (w), 1420 (w), 1367 (w), 1247 (vs), 1179 (s), 1146 (s), 1104 (w), 1031 (s), 840 (s) cm^{-1}; ^{1}H NMR (C$_6$D$_6$, 250 MHz): δ 0.90 (t, J = 7.1 Hz, 3H), 1.55 (s, 3H), 1.92-2.06 (m, 1H), 2.09-2.27 (m, 1H), 3.17 (s, 3H), 3.88 (q, J = 7.1 Hz, 2H), 3.99 (m, 1H), 4.34 (dd, J = 4.2 Hz, J = 11.4 Hz, 1H), 4.58 (dd, J = 8.0 Hz, J = 11.4 Hz, 1H), 6.67 (d, J = 9.0 Hz, 2H), 7.81 (d, J = 9.0 Hz, 2H); ^{13}C NMR (C$_6$D$_6$, 62.9 MHz) δ 14.2 (CH$_3$), 20.2 (CH$_3$), 25.6 (CH$_2$), 30.6 (CH$_2$), 54.9 (CH$_3$), 60.2 (CH$_2$), 65.2 (CH$_2$), 75.1 (CH), 114.3 (2 × CH), 124.8 (2 × CH), 146.6 (C$_q$), 162.3 (C$_q$), 169.9 (CO), 172.2 (CO); MS (ESI) [M$^+$+H] 323; HRMS (ESI) C$_{16}$H$_{23}$N$_2$O$_5$ [M$^+$+H] calcd: 323.1602, found: 323.1591.
16. (a) Giese, B.; Jay, K. *Chem. Ber.* **1977**, *110*, 1364–1376; (b) Giese, B.; Jay, K. *Chem. Ber.* **1979**, *112*, 298–303.
17. (a) Minisci, F.; Coppa, F.; Fontana, F.; Pianese, G.; Zhao, L. *J. Org. Chem.* **1992**, *57*, 3929–3933; (b) Molinaro, C.; Mowat, J.; Gosselin, F.; O'Shea, P. D.; Marcoux, J.-F.; Angelaud, R.; Davies, I. W. *J. Org. Chem.* **2007**, *72*, 1856–1858.
18. (a) Blank, O.; Heinrich, M. R. *Eur. J. Org. Chem.* **2006**, 4331–4334; (b) Blank, O.; Wetzel, A.; Ullrich, D.; Heinrich, M. R. *Eur. J. Org. Chem.* **2008**, 3179–3189.
19. For a review on radical atom and group transfer reactions, see: Byers, J., first ed.. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; vol. 1, pp 72–89.
20. For the preparation of aryl diazonium salts, see Ref. 8b.