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Synthesis of Oxindoles by Brønsted Acid Catalyzed Radical Cascade Addition of Ketones

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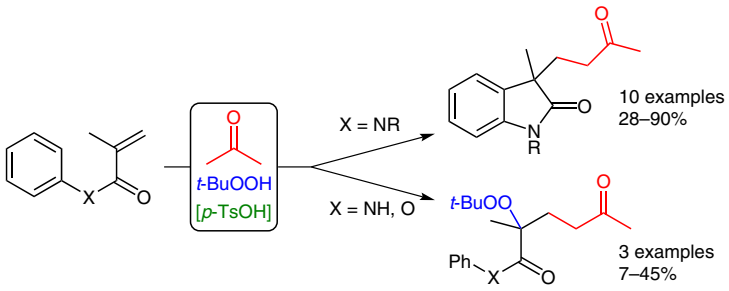

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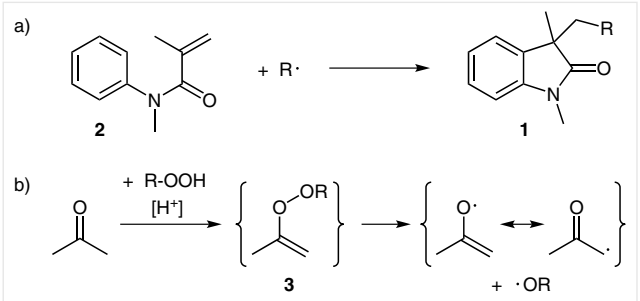
Abstract Oxindoles bearing ketone side chains in the 3-position can be synthesized by Brønsted acid catalysis from *N*-aryl methacrylamides, ketones, and hydroperoxides. The cyclized products are presumably formed in a radical cascade reaction, initiated by decay of intermediate alkenyl peroxides. In the case of acrylic substrates that do not undergo cyclization, γ-peroxyketones were isolated instead, indicating that the final cyclization step of the cascade does not take place in these cases.

Key words Brønsted acid catalysis, radicals, cyclization, heterocycles, peroxides



Scheme 1 Synthesis of oxindoles **1** by radical cascade addition using *N*-aryl methacrylamides **2**

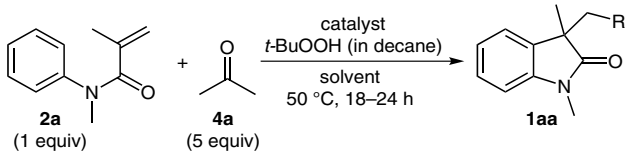
Oxindoles **1** are synthetically interesting compounds as they appear in natural products and pharmaceutically active compounds or are used as building blocks for their synthesis.[3] Recently, the formation of oxindoles by radical cascade reactions with *N*-aryl methacrylamides **2** has received some attention.[4–6] A variety of radicals formed in different ways have been found to react with acrylamides **2** to give substituted oxindole products **1** (Scheme 1, a). The reactions are believed to proceed via a radical cascade reaction, first by addition of the radicals to the acrylamide C–C double bond, followed by intramolecular addition to the arene ring and subsequent rearomatization.

Our group has recently discovered that ketone radicals can be generated from the combination of ketones and *tert*-butylhydroperoxide or hydrogen peroxide under acid catalysis.[7] The reaction is believed to proceed via alkenyl peroxides **3** that are formed in situ, which decompose rapidly by homolytic O–O bond cleavage, forming α-carbonyl and oxyl radicals (Scheme 1, b).[7b] This mixture of radicals could be applied to the addition of ketones to styrenes, forming γ-peroxyketones,[7b] or to facilitate oxidative C–H cross-coupling reactions.[7a] Herein, we show that the acid-catalyzed formation of ketone radicals can also be applied to cascade radical reactions forming oxindoles.

We investigated the feasibility of this reaction by reacting *N*-phenyl, *N*-methyl methacrylamide **2a**, and acetone with *tert*-butylhydroperoxide (as a solution in decane) and catalytic amounts of *p*-toluenesulfonic acid (*p*-TsOH) in acetonitrile under argon, conditions similar to those that we had developed for the addition of ketones to styrenes. The oxindole **1aa** was indeed formed in 55% yield (Table 1, entry 1).

Further variation of the solvent (Table 1, entries 2–4) showed that chloroform gave an improved yield of 66%, while performing the reaction neat resulted in very poor yields (see the Supporting Information for additional details of this optimization study). Alternative acid catalysts can be used (Table 1, entries 5–7), but *p*-TsOH remained the best catalyst amongst those that we studied. In agreement with our previous results,[7] trifluoroacetic acid appears to be the least active as a catalyst, while sulfonic acids are most suitable. Without acid, at best traces of the product could be detected (Table 1, entry 8). Increasing the acid

Table 1 Investigation of Reaction Conditions[a]

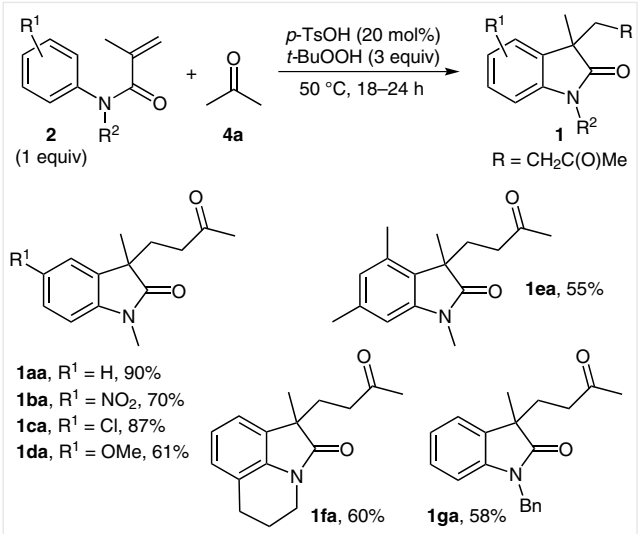


Entry	Catalyst (mol%)	*t*-BuOOH (equiv)	Solvent	Yield (%)[b]
1	*p*-TsOH (10)	2	MeCN	55
2	*p*-TsOH (10)	2	EtOAc	59
3	*p*-TsOH (10)	2	$CHCl_3$	66
4	*p*-TsOH (10)	2	–	18
5	TFA (10)	2	$CHCl_3$	16
6	H_2SO_4 (10)	2	$CHCl_3$	50
7	MsOH (10)	2	$CHCl_3$	53
8	–	2	$CHCl_3$	traces
9	*p*-TsOH (20)	2	$CHCl_3$	76
10	*p*-TsOH (10)	3	$CHCl_3$	74
11	*p*-TsOH (10)	2	$CHCl_3$	48[c]
12	*p*-TsOH (10)	2	acetone	80[d]
13	*p*-TsOH (20)	3	acetone	90[e]

[a] General conditions: **2a** (0.2 mmol), acetone (1.0 mmol), *t*-BuOOH (0.4 mmol, 5.5 M in decane), catalyst (0.02 mmol), solvent (1.0 mL), degassed by freeze-pump-thaw, 50 °C, under an atmosphere of argon, 18–24 h.
[b] Yields determined by ^{1}H NMR analysis using an internal standard.
[c] 0.2 mmol acetone.
[d] Not degassed.
[e] Isolated yield.

loading to 20 mol% (Table 1, entry 9) and the peroxide loading to three equivalents (Table 1, entry 10) further improved the yield. Interestingly, employing equimolar amounts of acetone still resulted in a relatively good yield of 48% (Table 1, entry 11). Using acetone in solvent amounts instead of chloroform improved the yields further (Table 1, entry 12), even if the reaction was performed without degasing the acetone (the presence of oxygen most likely lowers the yield by trapping intermediate radicals). Applying the findings of the reaction in chloroform, that is, performing the reaction in the absence of oxygen with 20 mol% catalyst loading and three equivalents of *t*-BuOOH, resulted in 90% isolated yield of **1a** (Table 1, entry 13). Thus, for reactions with acetone as the ketone component, the conditions of Table 1, entry 13 were taken; while the conditions of Table 1, entry 9 were chosen for reactions with other ketones.[8–10]

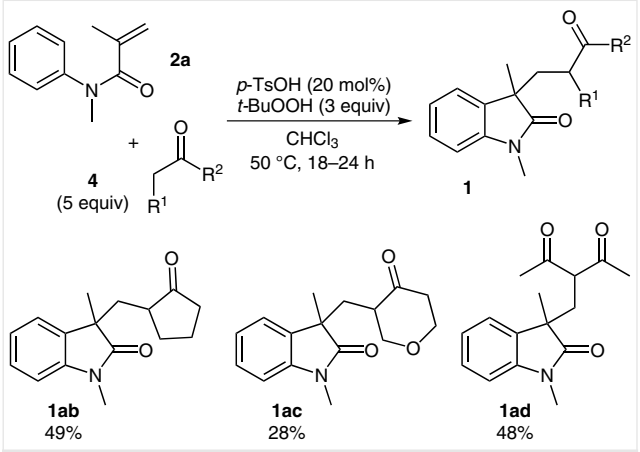
The reaction of other *N*-aryl acrylamide derivatives **2** with acetone led to the formation of the corresponding oxindoles **1** in good yields (Scheme 2).[8] Electron-withdrawing as well as electron-donating substituents on the arene ring led to similarly good yields (**1aa**–**ea**),[11,12] as did other alkyl groups on the nitrogen (**1fa**,**ga**).



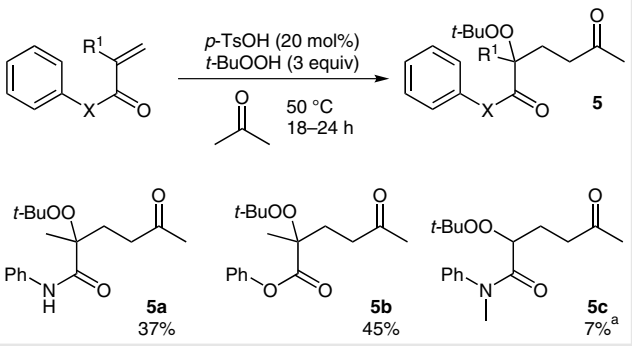
Scheme 2 Synthesis of oxindoles **1** by radical cascade addition of acetone to *N*-aryl methacrylamides **2**

Oxindoles with different side chains could be synthesized from other ketones in generally slightly lower yields compared with the use of acetone (Scheme 3),[9] as shown in examplars using cyclopentanone and tetrahydropyran-4-one (products **1ab** and **1ac**), and acetylacetone (**1ad**). Compounds **1ab** and **1ac** were obtained as diastereomeric mixtures in ratios of approximately 60:40. Cyclohexanone and methyl acetoacetate also reacted well, but we did not manage to purify the products sufficiently. In the case of cyclohexanone, the product could not be separated from residual **2a**.

As has been observed before in nearly all related radical cascade reactions, certain acrylic substrates do not give the desired cyclized products.[5] Likewise, we also failed to ob-



Scheme 3 Synthesis of oxindoles **1** by radical cascade addition of ketones using *N*-aryl methacrylamides **2**



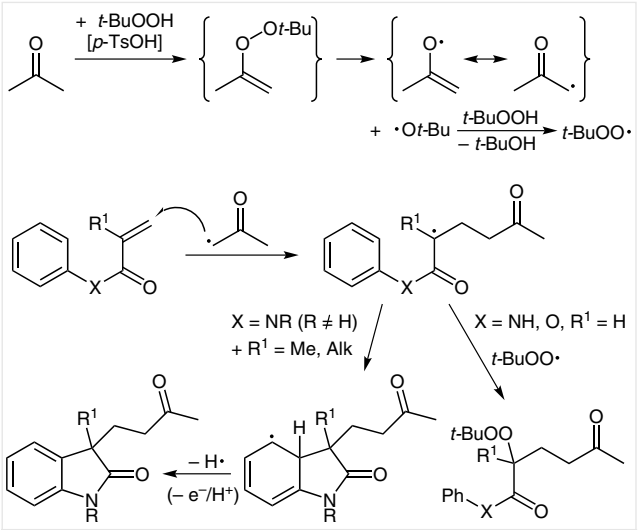
Scheme 4 Isolation of γ-peroxyketones **5** from reactions with acrylic substrates that failed to cyclize. [a] In $CHCl_3$ as solvent, 10 mol% catalyst.

tain oxindoles from secondary amides, from acrylamides lacking the 2-methyl group or from phenyl methacrylate. However, we could isolate γ-peroxyketones **5** in all these cases (Scheme 4).[13]

These products indicate that radical formation on the ketone and addition to the acrylic olefin had indeed taken place, but this was followed by an intermolecular reaction (forming the peroxides **5**), instead of the desired intramolecular attack onto the arene ring. Potentially, this is a general explanation for the failure of these substrates in all related radical cascade reactions. While we could not find conditions to form the desired cyclized compounds, even under microwave irradiation at 100 °C, these results at least indicate a focus for future mechanistic studies. Finding the reasons behind the failure of intramolecular radical attack could reveal strategies to overcome this substrate limitation. Moreover, compounds **5** could also be of synthetic value, as it has been shown before that γ-peroxyketones can be converted into furans, carbazoles, 1,4-diketones, homoaldol products, and alkyl ketones in a single step.[7b,14]

Based on previous suggestions for related reactions, the above observations thus add a further detail to the reaction mechanism (Scheme 5).

In summary, we have shown that acid-catalyzed radical formation from ketones and *tert*-butyl hydroperoxide can be applied to a radical cascade addition to *N*-aryl, *N*-alkylmethacrylamides, forming oxindoles bearing ketone side chains. In the case of acrylic substrates not leading to the desired cyclized products, γ-peroxyketones were isolated instead, indicating that the initial radical attack on the olefin is occurring but not the subsequent intramolecular reaction.



Scheme 5 Suggested reaction mechanism

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1381052.

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(8) **General Procedure for Reactions with Acetone**
In an oven-dried Schlenk flask, **2a** (1.5 mmol, 1 equiv) and *t*-BuOOH (5.5 M solution in decane, 4.5 mmol, 3 equiv) were dissolved in acetone (7.5 mL). The resulting mixture was freeze-pump-thaw degassed and allowed to warm to r.t. Then, *p*-TsOH (0.30 mmol, 0.2 equiv) was added under a stream of argon, and the reaction mixture was allowed to react overnight at 50 °C. It was then diluted with acetone, a small amount of silica was added and solvent removed. The residue was purified by column chromatography on silica gel using mixtures of hexanes and EtOAc to afford the pure products.

(9) **General Procedure for Reactions with Other Ketones**
In an oven-dried Schlenk flask, **2a** (1.5 mmol, 1 equiv), ketone (7.5 mmol, 5 equiv), and *t*-BuOOH (5.5 M solution in decane, 4.5 mmol, 3 equiv) were dissolved in dry $CHCl_3$ (7.5 mL). The resulting mixture was freeze–pump–thaw degassed and allowed to warm to r.t. Then, *p*-TsOH (0.30 mmol, 0.2 equiv) was added under a stream of argon and after closing the flask, the reaction mixture was allowed to react overnight at 50 °C. The reaction mixture was then diluted with $CHCl_3$, a small amount of silica was added and solvent removed. The resulting powder was purified by column chromatography on silica gel using mixtures of hexanes and EtOAc to afford the pure products.

(10) **Warning:** Although we never experienced any problem in working with or handling the compounds described in this work, precautions against explosions should be taken when working with peroxides. In particular, neat peroxides should not be heated or brought into contact with metals or metal salts. Explosive triacetone triperoxide should not be formed under the reaction conditions described here, as *tert*-butyl hydroperoxide and not hydrogen peroxide is used. In addition, the reaction conditions described here lead to the consumption of hydroperoxides (as confirmed for hydrogen peroxide, see ref. 7a).

(11) **Characterization Data of Compound 1da**
Yellow oil. ^{1}H NMR (500 MHz, DMSO): δ = 6.98 (d, *J* = 2.5 Hz, 1 H), 6.93 (d, *J* = 8.5 Hz, 1 H), 6.83 (dd, *J* = 2.5, 8.5 Hz, 1 H), 3.73 (s, 3 H), 3.10 (s, 3 H), 2.10–1.85 (m, 4 H), 1.93 (s, 3 H), 1.24 (s, 3 H). ^{13}C NMR (125 MHz, DMSO): δ = 207.4, 178.8, 155.6, 136.4, 134.3, 112.0, 110.3, 108.7, 55.5, 47.1, 37.9, 31.3, 29.7, 26.0, 23.3. HRMS (ESI$^+$): *m/z* [M$^+$] calcd for $C_{15}H_{19}N_1O_3Na$: 284.125712; found: 284.125640.

(12) **Characterization Data of Compound 1ea**
Yellow oil. ^{1}H NMR (500 MHz, DMSO): δ = 6.69 (s, 1 H), 6.64 (s, 1 H), 3.10 (s, 3 H), 2.28 (s, 3 H), 2.24 (s, 3 H), 2.15–2.08 (m, 1 H), 1.99–1.87 (m, 2 H), 1.88 (s, 3 H), 1.82–1.74 (m, 1 H), 1.29 (s, 3 H). ^{13}C NMR (125 MHz, DMSO): δ = 207.3, 179.3, 143.4, 137.2, 133.5, 126.3, 125.2, 107.1, 47.4, 38.2, 29.7, 29.6, 26.0, 22.0, 21.1, 17.6. HRMS (ESI$^+$): *m/z* [M$^+$] calcd for $C_{16}H_{21}N_1O_2Na$: 282.146448; found: 282.146440.

(13) **Characterization Data of Compound 5b**
Clear oil. ^{1}H NMR (500 MHz, DMSO): δ = 7.48–7.43 (m, 2 H), 7.31–7.27 (m, 1 H), 7.14–7.10 (m, 2 H), 2.60 (app t, *J* = 7.8 Hz, 2 H), 2.17–2.10 (m, 1 H), 2.14 (s, 3 H), 2.05–1.99 (m, 1 H), 1.47 (s, 3 H), 1.23 (s, 9 H). ^{13}C NMR (125 MHz, DMSO): δ = 207.3, 171.1, 150.5, 129.6, 125.9, 121.5, 82.7, 79.6, 36.7, 29.7, 28.8, 26.2, 19.9. HRMS (ESI$^+$): *m/z* [M$^+$] calcd for $C_{17}H_{24}O_5Na$: 331.151594; found: 331.151520.

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