DOI: 10.1002/adsc.202100214

Advanced Synthesis & Catalysis

Oxidative Cleavage of Indoles Mediated by Urea Hydrogen Peroxide or H_2O_2 in Polar Solvents

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Manuscript received: February 16, 2021; Revised manuscript received: May 24, 2021;
Version of record online: ■■, ■■

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202100214

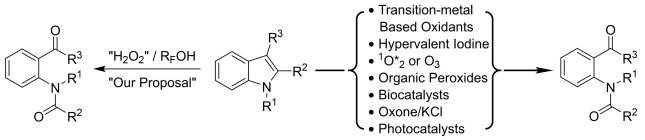
Abstract: The oxidative cleavage of indoles (Witkop oxidation) involving the use of H_2O_2 or urea hydrogen peroxide in combination with a polar solvent has been described. Among these solvents, 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) stands out as the one affording the corresponding 2-ketoacetanilides generally in higher yields The protocol described has also enabled the oxidation of different pyrroles and furans derivatives. Furthermore, the procedure was implemented in a larger-scale and HFIP was distilled from the reaction mixture and reused (up to 4 cycles) without a significant detriment in the reaction outcome, which remarks its sustainability and applicability.

Keywords: Oxidation; Indoles; HFIP; Hydrogen Peroxide; Witkop oxidation

Compounds bearing indole moieties are widely present in many naturally occurring compounds, mainly alkaloids, with most of them possessing biological activity.[1] Therefore, it is not surprising that several different strategies have been developed for their further elaboration and transformation.[2] Among them, the oxidative cleavage of C2–C3 double bond of indoles, known as Witkop oxidation,[3,4] gives access to a variety of 2-ketoacetanilide derivatives, which are key intermediates in the synthesis of quinolones and related bioactive compounds. Traditionally the main strategies for this reaction involve using transition-metal based oxidants, hypervalent iodine compounds, singlet oxygen or ozone and organic peroxides (Scheme 1).[4] In the last decades, concerns about the safety, sustainability and environment impact of chemical protocols have prompted the development of operationally simple, atom-economy and greener oxidation methodologies.[5] In this sense, the use of biocatalysts together with H_2O_2 as oxidant[6] or the recent findings about the use of photocatalysts[7] or KCl (cat.)/Oxone system[8,9] (Scheme 1) for the oxidative cleavage of indoles represent a great achievement in this direction.

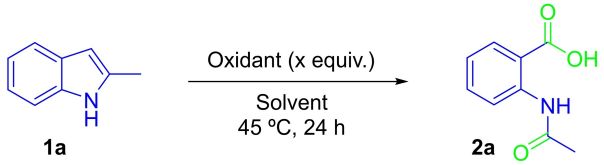
On the other hand, our research group has been working for some years on the use of fluorinated alcohols as solvents and promoters in different organic transformations.[10,11] More concretely, in the last years, we became interested in the use of the combination of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and H_2O_2, or its most stable form UHP (urea-hydrogen peroxide adduct), as a green alternative for the oxidation of organic compounds.[12,13] In this regard, we envisioned the possibility of testing this system to carry out this synthetic transformation in a catalyst-free reaction. The results of this study are herein disclosed.

Initially, the search for the optimal reaction conditions was conducted using 2-methylindole (**1a**) as model substrate and H_2O_2 or UHP indistinctly as oxidants in different solvents (Table 1). As can be observed, regardless of the oxidant, the employment of



Scheme 1. Witkop oxidation.

Table 1. Reaction conditions optimization.[a]

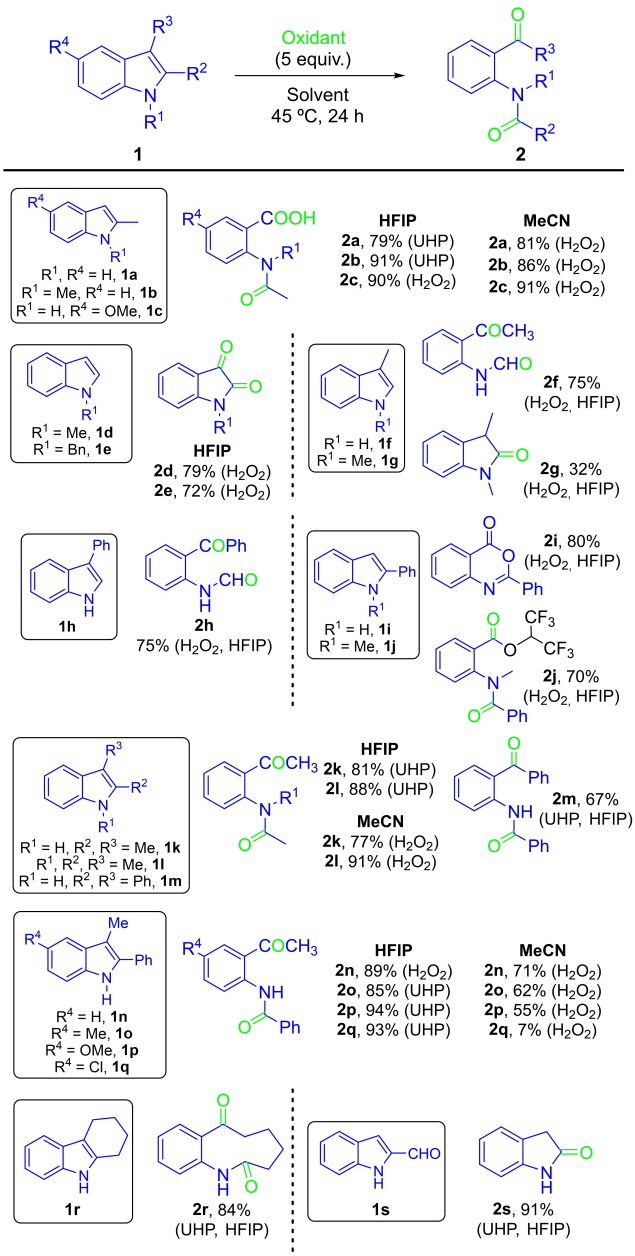


Entry	Oxidant (equiv.)	Solvent	Conv (%)[b]
1	H_2O_2 (2.5)	H_2O	<5
2	H_2O_2 (2.5)	*i*-PrOH	<5
3	H_2O_2 (2.5)	MeOH	35
4	H_2O_2 (2.5)	TFE	72
5	H_2O_2 (2.5)	HFIP	84
6	H_2O_2 (2.5)	MeCN	85
7	H_2O_2 (2.5)	DMSO	81
8	***H_2O_2 (5)***	***MeCN***	***91 (81)***[c]
9	***H_2O_2 (5)***	***HFIP***	***89 (77)***[c]
10	UHP (2.5)	H_2O	<5
11	UHP (2.5)	*i*-PrOH	<5
12	UHP (2.5)	MeOH	30
13	UHP (2.5)	TFE	80
14	UHP (2.5)	HFIP	85
15	UHP (2.5)	MeCN	70
16	UHP (2.5)	DMSO	77
17	***UHP (5)***	***HFIP***	***92 (79)***[c]

[a] Reaction conditions: indole (0.15 mmol), oxidant and solvent (150 µL), 45 °C, 24 h. [b] Conversion toward the formation of **2a** determined by GC-MS. [c] Yield of the isolated product after preparative TLC.

H_2O or *i*-PrOH as solvents did not produce any reaction (entries 1, 2, 10 and 11). However, the formation of some desired product was detected when MeOH was used instead (entries 3 and 12). A significant change was observed when fluorinated alcohols, 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) were used as solvents. The oxidation reaction took place obtaining high conversion towards the formation of compound **2a** with both oxidants (entries 4, 5, 13 and 14). Since HFIP produced better conversions, a further refinement of the reaction conditions was conducted with this solvent. Thus, increasing both oxidant equivalents (from 2.5 up to 5 equiv.) resulted in an amelioration of the conversion (Table 1, entries 9 and 17). However, a further increase in the oxidant turned out to be negative for the formation of the desired product. For the sake of comparison, other polar solvents were also studied such as MeCN and DMSO. To our surprise, the reaction worked with both oxidants, being especially successful using H_2O_2 (Table 1, entries 6, 7, 15 and 16). Due to its ease of work-up, purification and cleaner reaction crude, we selected the reaction performed with MeCN and H_2O_2 for a further refinement. Thus, as in the previous case, increasing the amount of oxidant produced a better yield for **2a** (Table 1, entry 8). It is worth mentioning that lowering the temperature produced a substantial decrease in the conversion of **2a** in all the cases.

As depicted in Table 1, the optimization study revealed that there was not a significant difference in the results achieved when using H_2O_2 or UHP (5 equiv.) as oxidants and HFIP as solvent in the model reaction (Table 1, entries 9 and 17). This situation led us to evaluate the reaction scope under both conditions. Additionally, the good results achieved when MeCN in combination with H_2O_2 (Table 1, entry 8) prompted us to explore the reaction under these conditions too. The best results obtained for each substrate with the different conditions essayed are shown in Scheme 2. As already mentioned, good yield was observed for *N*-acetylanthranilic acid (**2a**). The yield was even better for the *N*-methylated analogue **2b**, with UHP being the oxidant that provided the best results in HFIP. As somewhat expected, 5-methoxy-2-methylindole (**1c**) produced acid **2c** in excellent yield. Similar or slightly superior results for these substrates were obtained when the reaction was performed in MeCN. Next, free *N*–H indoles (indole, 5-methoxyindole, 5-fluoroindole and 8-ethylindole) lacking a substituent in position 2 or 3 were tested without success. The reaction did not work or if so, led to the formation of a complex mixture of oxidation products (isatins among them). Meanwhile, the *N*-alkylated analogues, such as *N*-methylindole (**1d**) and *N*-benzylindole (**1e**) clearly reacted toward the formation of the corresponding isatins (**2d** and **2e**). These were obtained in good yields, being H_2O_2 in HFIP the conditions of choice. Next, skatole (**1f**) was essayed providing the corresponding formamide derivative **2f** in good yield when H_2O_2 and HFIP were employed. Contrariwise, the reaction with 1,3-dimethyl-1*H*-indole (**1g**) sluggishly produced, at best, the corresponding oxindole **2g** in a poor 32% yield. This was the major isolated product amongst other oxidation products (Witkop oxidation among them) regardless of the reaction condition employed. 2-Benzoylacetanilide (**2h**) was isolated in 75% yield, starting from 3-phenyl-1*H*-indole (**1h**) and using H_2O_2 in HFIP. To our delight, the use of 2-phenyl-1*H*-indole (**1i**) gave the pesticide Dianthalexin B (**2i**)[14] in high yield in a one-step operation procedure when UHP in HFIP was employed. Under the same conditions, to our surprise, ester **2j** was obtained in good yield when the corresponding *N*-methyl-2-phenyl-1*H*-indole (**1j**) was used. Next, 2,3-dimethyl-1*H*-indole (**1k**) and the *N*-methylated analogue (**1l**) were reacted obtaining high yields for acetamides **2k** and **2l** in both solvents, being UHP the oxidant of choice for HFIP. However, lower yields were achieved when 2,3-diphenyl-1*H*-indole (**1m**) was tested under the same conditions with the better of results being reached with HFIP as solvent. Disubstituted 3-methyl-2-phenyl-1*H*-indoles (**1n**–**1q**) bearing different sub-

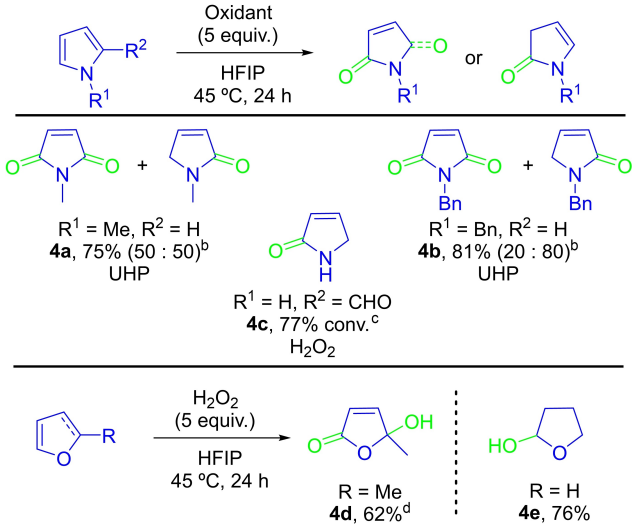


Scheme 2. Scope of the oxidative cleavage of indoles. [a] Reaction conditions: indole (0.15 mmol), oxidant (5 equiv.) and solvent (150 µL), 45 °C, 24 h. Yield of the isolated product after preparative TLC.

stituents at position 5 were also analyzed. As somehow expected, better yields were obtained when electron-donating group were present. It is also remarkable that the higher performance of HFIP in comparison to MeCN, with the results of the latter being notably lower. 1,2,3,4-Tetrahydrocarbazole (**1r**) was next submitted to the optimized conditions giving rise to benzocondensed macrocyclic amide **2r** in high yields, especially with the combination UHP/HFIP. Formylindoles were also assayed and whereas indole-2-carboxaldehyde (**1s**) produced oxindole (**2s**) as sole product in high yields with both oxidants, the regioisomer 3-formylindole produced a complex mixture of unidentified oxidation products. This was due to as a consequential Dakin oxidation.[12b] Finally is worth mentioning that the reaction with indole-3-carboxylic acid and ethyl indole-2-carboxylate was also attempted without success.

With the aim to expand the applicability of the procedure described, the oxidation of pyrrole and furan derivatives was also taken into account (Scheme 3). In this regard, *N*-methyl and *N*-benzylpyrrole (**3a** and **3b**) were essayed under the optimized reaction conditions using HFIP as solvent. In both cases good yields were obtained for a mixture of *N*-benzyl and *N*-methyl-1,5-dihydro-2*H*-pyrrol-2-one along with the corresponding *N*-alkylmaleimide respectively (**4a** and **4b**), using UHP as oxidant. In contrast, 1*H*-pyrrole produced a complex mixture of oxidation products. Next, 1*H*-pyrrole-2-carbaldehyde (**3c**) was also tested, affording, 3-pyrrolin-2-one (**4c**) as major oxidation product in good conversion as a consequence of a Dakin oxidation and a double bond isomerization.[12b,15] Furans were eventually evaluated, in which furan produced an unidentified complex mixture of oxidation products. 2-Methylfuran (**3d**) gave rise in moderate yield to the formation of lactone (**4d**), and finally, 2,3-dihydrofuran (**3e**) produced cyclic hemiacetal **4e** in good yield.

Additionally, it is important to mention that benzofurans were also considered as substrates for the



Scheme 3. Evaluation of pyrroles and furan derivatives. [a] Reaction conditions: substrate (0.15 mmol), oxidant (5 equiv.) and HFIP (150 µL), 45 °C, 24 h. Yield of the isolated product after preparative TLC. [b] Products ratio determined by GC-MS and ^{1}H NMR. [c] Not purely isolated, conversion determined by GC-MS. [d] Product decomposed during purification, estimated yield by ^{1}H NMR.

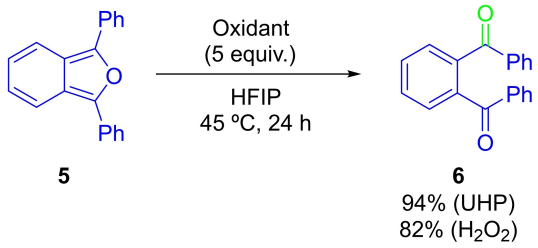
oxidation protocol described. However, the reaction barely worked even when more forcing conditions (higher temperatures and oxidant amount as well as longer reaction time) were employed. On the contrary, 1,3-diphenylisobenzofuran (**5**) smoothly reacted to afford o-dibenzoylbenzene (**6**) in excellent yields especially when UHP was the oxidant of choice (Scheme 4).

Finally, the methodology herein described was implemented in a larger scale experiment (Figure 1). 2-methylindole (**1a**) (5.0 mmol) was submitted to the optimal reaction conditions using H_2O_2, with UHP being implemented as the selected oxidant because it allows an easier purification by recrystallization. As a result, the corresponding *N*-acetylanthranilic acid (**2a**) was obtained in 67% yield after recrystallization (*n*-pentane/CH_2Cl_2 3/1). The high efficiency and low environmental impact of the whole process was clearly demonstrated by the fact that the *E*-factor calculated turned out to be 22.4 which is within the rank for fine chemical industry and below the lowest limit for the pharmaceutical industry.[16]

In addition, to further demonstrate the sustainability of the methodology, the recycling of the solvent was considered in this larger scale reaction. Thus, as depicted in Figure 1, HFIP could be recovered and reused up to four times observing only a slight erosion on the conversion after each cycle.

In order to gain some insight into the possible reaction mechanism, a couple of control experiments were carried out. Accordingly, oxindoles **2o** and **7** were submitted to the optimized reaction conditions with both oxidants and after 24 hours no reaction was observed (Scheme 5). This result suggest that the oxidative cleavage does not proceed *via* the formation of the corresponding oxindole and that once such compound is formed the reaction does not evolve further. Additionally, a radical-based mechanism was relinquished since the reaction carried out using TEMPO as radical scavenger worked practically the same in both solvents (HFIP and MeCN). Based on the results, previous experience and the literature precedents[6,17] a possible reaction mechanism has been proposed (Scheme 5). As depicted, indole would attack H_2O_2 which can act as electrophile thanks to the activation carried out by HFIP,[18] rendering the hydroperoxide **A** as an intermediate. This can evolve toward the formation of dioxetane **B** after an intramolecular cyclization reaction. This unstable compound would rearrange to afford the desired product. Other mechanisms proposals leading to the formation of other products described in the article can be found in the supporting information file.

In summary, we have disclosed herein the development of an alternative strategy for the oxidative cleavage of indoles (Witkop oxidation) using UHP or H_2O_2 as oxidants. From the results obtained, the reaction seems to work well in the presence of highly polar solvents when indoles bearing a substituent on position 2 and/or 3 were employed. However, among all of solvent tested, HFIP usually showed a higher performance and wider substrate scope, acting as solvent and reaction promoter. The products were obtained generally in good yields under smooth reaction conditions. Additionally, other heteroaromatic compounds were also conveniently oxidized. The success of this protocol relies on the electrophilic



Scheme 4. Oxidative cleavage of isobenzofuran (**5**).

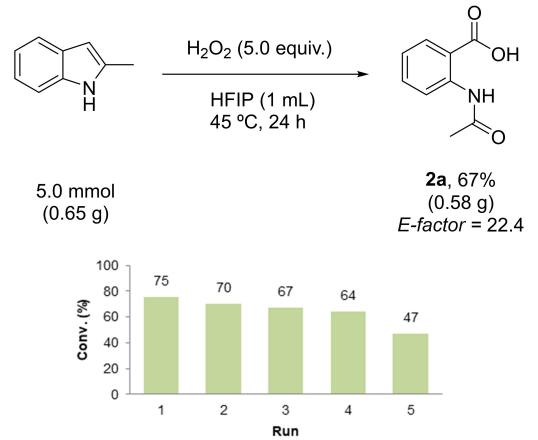
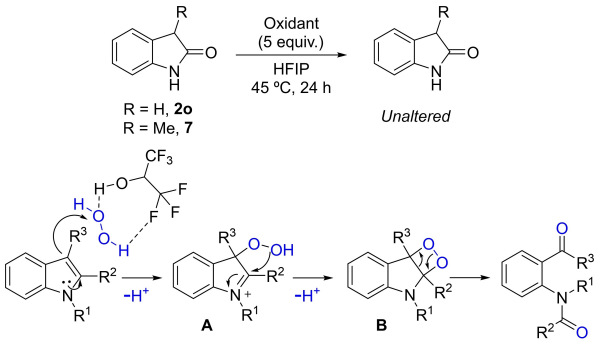


Figure 1. Large-scale reaction, *E*-factor and recycling of solvent.



Scheme 5. Control experiments and proposed reaction mechanism.

activation of H_2O_2 by the fluorinated alcohol. Finally, the applicability of the procedure was clearly accomplished by the implementation of a large-scale experiment and recycling of the HFIP.

Experimental Section

General Procedure for the Oxidative Cleavage of Indoles

In a capped tube, the corresponding indole derivative (0.15 mmol), HFIP (150 μL) and oxidant (5 equiv.) were added sequentially in one portion and the mixture was subjected to conventional heating (sand bath) for 24 hours at 45 °C. After cooling down the reaction mixture, it was filtered through Celite® plug using ethyl acetate as eluent. Then, the solvent was evaporated under reduced pressure. The corresponding pure products were obtained after purification by preparative TLC, using mixtures of hexane and ethyl acetate as eluent.

Following the general procedure described, the reaction was carried out at large scale employing 2-methylindole (5.0 mmol, 0.65 g), HFIP (3 mL) and H_2O_2 (5 equiv., 1 mL), which were added sequentially in a round-bottom flask. The reaction was stirred at 45 °C (sand bath) for 24 hours. After this time, the reaction mixture was evaporated under reduced pressure. The corresponding product was purified by recrystallization in CH_2Cl_2/*n*-pentane (1/3) and filtered, yielding the *N*-acetylanthranilic acid (**2 a**) in 67% (0.58 g).

Acknowledgements

We would like to thank the Spanish Ministerio de Economía, Industria y Competitividad (CTQ2017-88171-P) and Spanish Ministerio de Ciencia, Innovación y Universidades (PGC2018-096616-B-I00) and the University of Alicante (VIGROB-316/19, UADIF19-106) for the financial support. S.-J. Burlingham is acknowledged for the English correction of the manuscript.

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COMMUNICATIONS

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Adv. Synth. Catal. **2021**, *363*, 1 – 6

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