Radical addition of ketones and cyanide to olefins via acid catalyzed formation of intermediate alkenyl peroxides†

Wen Shao,†a Marcel Lux,a Martin Breugstb and Martin Klussmann* a

A Brønsted acid catalyzed method was developed for the synthesis of \( \gamma \)-cyanoketones from sulfonyl cyanides, olefins and ketones. The reaction is believed to proceed via intermediate formation of alkenyl peroxides by condensation of ketones with tert-butylhydroperoxide. These unstable compounds decompose by homolytic O–O bond cleavage, generating ketone-derived radicals which add to the olefins and generate the final products after reaction with the sulfonyl cyanide, thereby forming two new C–C bonds. A range of different ketones and olefins can be used, including steroidal ketones and simple alky1 olefins. The products can be further transformed to substituted lactones and piperidines, including a tetracyclic one. This reaction can thus be utilized to gain access to complex molecules from simple starting materials in only a few synthetic steps.

**Introduction**

Radical addition reactions enable the double functionalization of olefins with heteroatom- and carbon-residues, thus much effort is put into their development.¹ We have recently developed a method for the acid-catalyzed generation of radicals from ketones and hydroperoxides via the intermediate formation of alkenyl peroxides 1 (Scheme 1a).² Alkenyl peroxides are highly unstable and can generally not be isolated at ambient temperature.³ Using this strategy, simple ketones can be utilized in radical reactions, for example towards the synthesis of \( \gamma \)-peroxyketones 2 and heterocycles.⁴

The generation of radicals in the \( \alpha \)-position of ketones can be achieved by alternative means,⁵ but often it is only effective with 1,3-dicarbonyl compounds,⁶ at temperatures above 100 °C,⁷ with \( \alpha \)-bromo-ketones as substrates⁸ and larger amounts of metal reagents,⁹ respectively. Their formation via alkenyl peroxides (1) by condensation with hydroperoxides, on the other hand, is particularly effective with plain ketones and only requires simple acids as catalysts. We were thus interested to extend the radical addition of ketones via this mechanism to the twofold addition of carbon-radicals instead of the carboperoxidation as in the synthesis of 2. Here, we report our results of the addition of ketones and cyanide to olefins (Scheme 1b).

We tested a variety of additional reagents to introduce a carbon residue instead of the peroxide group, but the peroxycarbon-dicarbonyl ketones 2 were always formed as major products. Overriding this preference was finally possible by employing sulfonyl cyanides which led to formation of cyanoketones 4. Sulfonyl cyanides are well-known reagents for the transfer of a cyano group to carbon-radicals.¹⁰ For example, the Landais group used para-toluenesulfonic cyanide (pTsCN, 3a) in the radical

![Scheme 1](image-url)

**Scheme 1.** Radical addition reactions via intermediate alkenyl peroxides (1) formed by acid catalysis.
addition of ester, thioester or amide residues to olefins, requiring
the use of stoichiometric organometallic reagents and pre-
functionalized substrates, respectively.\textsuperscript{10a–c} Radical trifluoro-
methylation with hypervalent iodine reagents together with cy-
anation has been reported by several groups.\textsuperscript{11} The groups of
Liu and Zhu reported an intramolecular CN-transfer after ra-
dical addition, requiring special olefin substrates.\textsuperscript{12} The
strategy of an intramolecular CN-transfer had previously been
employed by the groups of Kalvoda, Watt and Nikishin to syn-
thize \( \gamma \)-cyanoketones.\textsuperscript{13} However, the yield in those rea-
cctions was typically rather low. Zhu \textit{et al.} also described such pro-
ducts \textit{via} a radical ring-opening reaction of cyclobutanols in the
presence of \( p \)-TsCN.\textsuperscript{14f}

\( \gamma \)-Cyanoketones can also be prepared in a single step by
conjugate addition reactions of ketones to vinyl nitriles and of
nitriles to enones, respectively, generally requiring strong
bases or complex catalysts.\textsuperscript{14} Applying chiral catalysts, this can
allow the synthesis of \( \gamma \)-cyanoketones not easily accessible by
the aforementioned methods.

\section*{Results and discussion}

During the optimization of the method, we screened many
different conditions, \textit{e.g.} solvents, acids, cyanide reagents
and concentrations. Full details can be found in the ESI,\textsuperscript{†}
and exemplary results are shown in Table 1. The desired product
4aa was formed in good yields from \( p \)-TsCN (3a), styrene (5a)
and acetone (6a) in polar aprotic solvents (entries 1–3). Slightly
better results were achieved when using ethyl- or methyl-
sulfonyl cyanides 3b and 3c (entries 4 and 5),\textsuperscript{§} which can
easily be synthesized by oxidation of the thiocyanates.\textsuperscript{10b} We
achieved the best results with 3e in dichloromethane (entry 5).

In those reactions, two byproducts could be characterized
(Fig. 1). Peroxyketone 2aa – the product formed in the absence
of sulfonyl cyanides\textsuperscript{2a} – was found in low amounts of up to
10\% only. Peroxy-sulfone\textsuperscript{16} 7ac was formed in comparable, but
generally lower yields than cyanoketone 4aa. In order to
achieve good yields of the desired products, the olefin there-
fore has to be used in excess. Generally, sulfones 7 can easily be
separated from nitriles 4 by column chromatography.

Using the conditions as of Table 1, entry 5, we investigated
this method in the reactions of different ketones with styrene
(Scheme 2). Simple open-chain and cyclic alkyl ketones gave
the expected products 4aa–4ag. With methyl isopropyl ketone,
the new bond was exclusively formed at the methyl group
(4ab). Methyl aryl ketones afforded products 4ah–4al in similar
yields. The successful utilization of phenolic ketone 6i in the
synthesis of 4ai is interesting, as many phenols are known as
radical inhibitors. Two steroids, epiandrosterone 6m and preg-
nenolone 6n could be used as ketone component, giving the
products 4an and 4am. The presence of a free hydroxyl group
and an olefin in the ketone 6n did not hamper the yield sig-
nificantly, as 4an was formed in a relatively good yield of 43%.

With pinacolone (6c) as a model ketone, we also tested the
reaction with a variety of different aryl olefins (Scheme 3).
A range of products 4bc–4nc with different aryl-substituents
were formed in mostly good yields above 50\%, with the excep-
tion of the strongly electron-withdrawing and donating sub-
stituents CF\( _3 \), CN and OMe (4fc–4hc). A methyl substituent in the
ortho-position also gave a good yield of 60\% of 4ic, but the
ortho-bromide product 4ic gave a lower yield. Using indene
(5q) as olefin gave the products 4qc and 4qe (using cyclohexa-
one) in good yields, which are remarkable for their high
\textit{trans}-selectivity. For 4qc, a diastereomeric ratio of \( \sim 19 : 1 \) was
determined in the crude reaction mixture, but after purifi-
cation, we received the pure \textit{trans}-product. In the case of 4qe,
two diastereomers were isolated which differ in the configu-
ration at the \( \alpha \)-position of the cyclohexanone residue.

We also investigated the reaction between acetone or pinaco-
lone and non-aryl olefins which on average gave lower yields
than with styrene derivatives (Scheme 4). This is possibly due to
the nature of the ketone-derived radicals, as this had also been
observed during the synthesis of \( \gamma \)-peroxycarbonates.\textsuperscript{2a} Note-
worthy exceptions were the use of 1-octene (8b) and 6-cyano-1-hexene
(8c), providing yields above 50\%. A natural product, limonene

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Entry & R (3) & Solvent & Yield\textsuperscript{b}/\\
\hline
1 & \( \eta \)Tol (3a) & EtOAc & 60\\
2 & \( \eta \)Tol (3a) & CHCl\( _3 \) & 48\\
3 & \( \eta \)Tol (3a) & CH\( _2 \)Cl\( _2 \) & 61\\
4 & Et (3b) & CH\( _2 \)Cl\( _2 \) & 64\\
5 & Me (3c) & CH\( _2 \)Cl\( _2 \) & 69 (63)\textsuperscript{c}\\
\hline
\end{tabular}
\caption{Effect of reagents on the reaction outcome\textsuperscript{a}}
\end{table}

\textsuperscript{a} Screening reactions were typically performed with 0.5 mmol 5a,
1.25 mmol 6a, 0.25 mmol 3, 1.0 mmol BuOOH and 0.025 mmol acid in 0.2–1.0 ml
solvent under an argon atmosphere at 50 °C.\textsuperscript{c} Determined by \( ^1 \)H-NMR.
\textsuperscript{b} Isolated yield, reaction at a scale of 0.5 mmol 3, 1.5 mmol 6a, 1.5 mmol
BuOOH and 1.0 ml of CH\( _2 \)Cl\( _2 \).

\textsuperscript{§} The superiority of MeSCN (3e) over \( p \)-TsCN (3a) had already been noted before,
see ref. 10c.
(8g) could be used as olefin component, albeit with only a rather low yield of 22% of product 9gc. Interestingly, in the reactions with these olefins, the sulfonyl peroxide byproducts 7 were observed in traces only and could not be isolated.

Cyanoketones have previously been utilized as valuable synthetic intermediates that can be converted to lactones and piperidines, respectively, by reduction and subsequent cyclization.\(^{14}\)–\(^{17}\) We have also applied these strategies to selected products, without purification after the first step (Scheme 5). A substituted δ-valerolactone 10 was formed from product 4aa in a 1 : 1 mixture of diastereomers. Reduction of the nitrile group by hydrogenation in the presence of RANEY® Nickel and subsequent protection with a Boc-group gave piperidines 11 and 12 from cyanoketones 4ai and 4qe, respectively.

Interestingly, the major diastereomer of 11 was found to obtain a solution conformation with both aryl groups in axial position, as shown in Scheme 5 (determined by NMR coupling constants and an NOESY experiment, see the ESI‡ for details). This at first surprising result was supported by DFT calculations:\(^{18}\) this conformation was indeed found to be more stable than the one with both aryl groups in equatorial position by 3.3 kJ mol\(^{-1}\) and also more stable than alternative boat conformations. This results presumably from the avoidance of steric repulsion between the \(p\)-methoxyphenyl and the Boc group\(^{19}\) and from a favorable orbital interaction between the nitrogen lone pair and the \(\sigma^*\)-bond of the C–aryl bond (see the ESI‡ for further details).
Tetracyclic piperidine 12 was formed with a high preference for one diastereomer, as depicted in Scheme 5. The structure of the major one was confirmed by NMR spectroscopy and X-ray crystallography of the corresponding ammonium salt 13, which was isolated diastereomerically pure after recrystallization (see the ESI† for further details).

In accordance with our earlier mechanistic studies of alkenyl peroxide formation2 and based on the observation of byproducts 2 and 7, a radical mechanism appears reasonable (Scheme 6).

Alkenyl peroxides 1 are formed by acid-catalyzed condensation of ketones and tBuOOH. Rapid homolytic O–O cleavage generates a tert-butyl oxide radical and resonance-stabilized radical 14, which adds to an olefin, forming the intermediate C-radical 15. Reaction with MeSO_2CN generates the cyanoketones 4 and a sulfonyl radical 16. Rapid H-atom transfer from tBuOOH to the oxyl radical generates the tert-butyl peroxy radical,20 which can attack 15, forming peroxyketone 2 as minor byproduct. Major byproduct 7 is formed by subsequent attack of a sulfonyl and peroxy radical on an alkene.16,21

Conclusions

In summary, we have developed a Brønsted-acid catalyzed synthetic method for the radical addition of ketones and cyanide to olefins, achieving the formation of two new C–C bonds. A variety of ketones can be added to styrene derivatives but also to various alkyl olefins, giving a range of structurally diverse γ-cyanoketones. Selected products were further converted to a lactone and two piperidines, including the case of a tetracyclic piperidine that was thus synthesized in three steps only from simple starting materials.

Conflicts of interest

There are no conflicts to declare.

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Notes and references
