Synthesis of Nitroolefins via the Direct Nitration of Alkenes

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Nitroolefins are highly versatile building blocks for organic synthesis.[1] Their strongly electron-withdrawing nitro group renders the alkene highly electron deficient. Indeed, nitroalkenes are powerful electrophiles and undergo addition reactions with various different nucleophiles. Furthermore, the nitro group can be readily converted into various other functionalities such as amines, ketones, carboxylic acids, nitrile oxides, oximes, or hydroxylamines.[2] In addition, the nitroolefin moiety forms the key functionality in nitro fatty acids (NFAs), a class of potent endogenous lipid signaling mediators, which mainly act by posttranslational protein modification via nucleophilic addition of thiol residues to the electrophilic nitroalkene.[3] Consequently, the synthesis of nitroolefins has received considerable attention.[4] A two-step Henry reaction–condensation sequence is arguably the most common approach for the preparation of nitroolefins.[5] However, the direct nitration of alkenes provides a powerful and straightforward synthetic approach to the nitroolefin scaffold. Indeed, naturally occurring nitro fatty acids are formed by the reaction of reactive nitrogen species, such as nitric oxide, with the corresponding unsaturated acids.[6] Also the direct chemical nitration of alkenes has been reported already 60 years ago.[7] Since then, various new procedures for the direct nitration of alkenes have been reported.[4]

Herein, we want to highlight some of the most recent advances in the synthesis of nitroolefins via a direct nitration of their parent alkenes (Table 1). Despite all recent advances, one should be aware that the stereo- and regioselective nitration of di- or trisubstituted olefins stills remains a considerable challenge. Whereas the direct nitration of terminal alkenes usually proceeds with almost excellent regio- and stereoselectivities, reactions starting from unsymmetrical internal alkenes usually afford an almost equimolar mixture of both possible regioisomers. Therefore, many studies solely focus on examples with terminal alkenes or symmetrical cycloalkenes.

Table 1 Synthesis of Nitroolefins via Direct Nitration

(A) Maiti (2013); Begari (2014) TEMPO-mediated nitration using AgNO$_2$, Fe(NO$_3$)$_3$, or clay-supported Cu(NO$_3$)$_2$ (*claycop*) affords nitroolefins with exclusive *E*-selectivity. Particularly well suited for the nitration of terminal alkenes, also with complex scaffolds.	AgNO$_2$, Fe(NO$_3$)$_3$ or Cu(NO$_3$)$_2$ / TEMPO (20 mol%) solvent, 70–80 °C - ≥50% yield - *E*-only - high FG compatibility
(B) Maiti (2013); Guo (2015) TEMPO-mediated nitration using NaNO$_2$, or *t*BuONO affords nitroolefin with high *E*-selectivities.	*t*BuONO and air or NaNO$_2$ + K$_2$S$_2$O$_8$ / TEMPO (0.4 or 1.2 equiv) solvent, 90–100 °C - ≥40% yield - high *E*-selectivities
(C) Kuhakarn (2014); Singh (2019) Room-temperature nitration with NaNO$_2$, mediated by Oxone/KI or K$_2$S$_2$O$_8$/TFA. Studies are almost exclusively limited to terminal alkenes.	NaNO$_2$ / Oxone + KI or K$_2$S$_2$O$_8$ + TFA solvent, 25 °C - ≥20% yield - high *E*-selectivities
(D) Corey (2021) Nitration with in situ generated triflyl nitrate. Amendable to the nitration of complex structures. Formation of allylic nitroolefins or rearrangement can occur.	Tf$_2$O + Bu$_4$N$^+$NO$_3^-$ / CH$_2$Cl$_2$, 30 °C - ≥70% yield - complex scaffolds - rearrangement can occur
(E) Nacci (2020) Catalyst- and additive-free nitration with NaNO$_2$, limited to styrenes.	NaNO$_2$ / [Bmim]Cl 80 °C - ≥40 yield - no catalyst or additive - limited to styrenes
(F) Katayev (2019) Photoredox-catalyzed nitration using a novel nitrating agent. Photochemically induced switching of the nitroolefin configuration for β-nitrostyrenes (R^1 = Ar).	N-NO$_2$ / [Ru(bpy)$_3$](PF$_6$)$_2$ (2.5 mol%) blue LED, MeCN - ≥40% yield - high *E*-selectivities - *E*-to-*Z* switching

The group of Maiti disclosed two closely related methods for an efficient and predictable nitration of alkenes using either AgNO$_2$ or Fe(NO$_3$)$_3$ in combination with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as catalyst (entry A).[8] Both methods give access to various nitroolefins in high yields with a good tolerance towards functional groups with excellent *E*-selectivity. Although some examples with internal alkenes are reported, both reactions seem to be particularly well suited for terminal alkenes. The utility of these methods was demonstrated in the nitration of natural product derived alkenes. Later, Begari and co-workers reported a similar method using clay-supported Cu(NO$_3$)$_2$ (*claycop*) as mild nitrating agent.[9] Recently, Maiti and Guo described analogous, TEMPO-mediated nitrations of alkenes using either *tert*-butyl nitrite (*t*BuONO) or NaNO$_2$ (entry B).[10] Although both methods do not utilize (transition) metals, additional oxidants (air or K$_2$S$_2$O$_8$) and (sub)stoichiometric amounts of TEMPO are necessary. Two attractive alternatives for the direct nitration of alkenes using NaNO$_2$ were described by Kuhakarn and Singh (entry C).[11] Both reactions proceed readily at ambient temperature, mediated either by a combination of Oxone and KI or K$_2$S$_2$O$_8$ and trifluoroacetic acid (TFA). Unfortunately, the scope of these methods seems limited and both processes proceed efficiently only with styrenes or monosubstituted

alkenes. A closely related reaction with *t*BuONO and K$_2$S$_2$O$_8$ by the group of Patel gives access to different product types, depending on the starting material structure, and is therefore of limited use for a general preparation of nitroolefins.[12] A recently reported process from Corey based on in situ generated triflyl nitrate provides a useful process for the direct conversion of olefins into nitroolefins (entry D).[13] This procedure was successfully employed for the nitration of more complex substrates. However, in several cases, the reaction conditions led to the formation of the allylic nitroolefins or a rearrangement product instead. Nacci and co-workers reported a straightforward ionic liquid controlled nitration of alkenes with NaNO$_2$ (entry E).[14] Employing the imidazolium-based ionic liquid [Bmim]Cl (1-butyl-3-methylimidazolium chloride) styrenes were efficiently converted into the corresponding nitroolefins in the absence of any additional catalyst or mediator. Unfortunately, this process seems solely limited to monosubstituted styrenes. The group of Katayev introduced *N*-nitrosuccinimide as a versatile and inexpensive nitrating agent (entry F).[15] This reagent was successfully employed for a visible-light-mediated, photoredox-catalyzed nitration of alkenes, affording *E*-nitroolefins in good yields and high stereoselectivities. As before, the reported substrate scope mostly includes terminal alkenes, but also some more complex,

druglike scaffolds. Interestingly, the authors could induce a photoisomerization of the *E*- to the *Z*-nitroolefin upon prolonged irradiation. Thereby, this method offers a so far very rare access to the thermodynamically unfavored nitroalkene, albeit limited to β-nitrostyrenes.

In conclusion, the direct nitration of alkenes has become a versatile synthetic tool for the construction of the nitroolefin scaffold from simple alkenes. Current methods are particularly well suited for the regio- and stereoselective nitration of terminal alkenes. On the other hand, the regioselective nitration of unsymmetrical internal alkenes remains a challenge yet to be solved.

Conflict of Interest

The authors declare no conflict of interest.

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