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Cyano-Acylation And Cyano-Esterification Of Unsaturated Hydrocarbons

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Abstract: This review aims to summarize the current literature on the direct vicinal cyano-acylation and cyano-esterification of unsaturated hydrocarbons, with a particular focus on the mechanistic features of these reactions. This review is structured into four main sections. The first section covers the cyano-acylation of alkenes, followed by a discussion of cyano-esterification of alkenes in the second section. The third section consists of an overview of cyano-acylation of alkynes, while the final section focuses on the cyano-esterification of alkynes.

Keywords: Alkenes, Alkynes, Cyanoacylation, Cyanoesterification β-cyano carbonyl compounds.

INTRODUCTION:

The nitrile group (−CN) is a crucial functional group in medicinal chemistry, as it is found in over 60 smallmolecule drugs available on the market, which are used to treat a wide range of diseases, ranging from viral infections to different types of cancer (Scheme 1). Nitrile- containing molecules are also abundant in nature and can be found in both prokaryotic and eukaryotic organisms . Moreover, nitriles are versatile intermediates in organic synthesis and are easily diversified into various important functional groups such as amines, amides, imines, oximes, carboxylic acids, aldehydes, esters and various nitrogen-containing heterocycles. Therefore, the development of new strategies for incorporating a nitrile group into organic compounds has always been an important topic in organic synthesis. The direct difunctionalization of unsaturated hydrocarbons is a highly effective synthetic strategy enabling the conversion of readily accessible alkenes and alkynes into complex molecular structures by introducing two functional groups into the π system in a single step. In this context, cyanative difunctionalization reactions have recently emerged as a highly powerful strategy for synthesizing β-substituted nitriles from alkene/alkyne feedstocks in a one-pot manner, without the need to isolation of intermediates. Within this class of reactions, the carbonylative cyanation. This review aims to summarize the current literature on the direct vicinal cyanoacylation and cyano-esterification of unsaturated hydrocarbons, with a particular focus on the mechanistic features of these reactions. This review is structured into four main sections. The first section covers the cyano-acylation of alkenes, followed by a discussion of cyano-esterification of alkenes in the second section. The third section consists of an overview of cyano-acylation of alkynes, while the final section focuses on the cyano-esterification of alkynes. Despite considerable progress in this field over the past decades, no comprehensive review has yet been found in the literature covering this emerging area of research. In order to fill this gap, herein, we provide a detailed overview of recent advancements on the direct vicinal cyano-acylation/-esterification of unsaturated hydrocarbons, with a particular emphasis on the mechanistic aspects of the reactions. Cyanoacylation of alkenes the possibility of synthesis of β-cyano ketones through the direct cyanoacylation of alkenes. By employing styrene as the model substrate, along with benzaldehyde and trimethylsilyl cyanide (TMSCN) as the acyl and cyano sources, respectively, various reaction parameters such as catalysts, ligands, and solvents were carefully screened. The results demonstrated that the combination of 2.5

mol% of CuCl with 3.5 mol% of 4,4'-dibromo-2,2'-bipyridine and 2.5 equiv. of tert-butyl hydroperoxide (TBHP) constituted the most effective catalytic system for this transformation and among the various solvents tested (e.g., DCM, DCE, MTBE, MeCN, dioxane, toluene); MTBE was identified as the most suitable. Under the optimized conditions, βcyano ketone derivatives 3 were obtained in moderate to high yields by reaction of terminal (hetero)aromatic alkenes 1 with various aldehydes (aromatic, heteroaromatic, and aliphatic) and TMSCN. The protocol was also applied to the efficient late-stage modification of estrone, a natural product derivative. Other substrates such as α-substituted styrene derivatives, α,β-unsaturated carbonyl compounds, and conjugated dienes were also found to be compatible with the reaction conditions, albeit affording only modest yields at best. Unfortunately, the applicability of unactivated alkenes as starting materials was not examined in this study. Several theoretical and experimental studies, such as radical trapping, radical clock, isotope-labeling, DFT calculation and others manifest that the mechanism of this difunctionalization reaction involves the initial formation of Cu(II) species A and $tBuO^{\cdot}$ through an inner-sphere single electron transfer (SET) process between LCuII and tBuOOH. Subsequently, the $tBuO^{\cdot}$ radical abstracts a hydrogen atom from the aldehyde 2 to propagate an acyl radical B and a molecule of tBuOH. Next, the addition of radical B to the styrene 1 affords a more stable benzyl radical C, which after reaction with in situ generated cyanocopper (II) complex D delivers the observed acylcyanation product 3 via an outer-sphere cyano group transfer pathway through an outer-sphere electron transfer crossing point E. Selected examples of marketed drugs with a nitrile moiety. Chen's group developed an efficient photoactivation strategy for asymmetric cyanoacylation of alkenes by merging a metallaphotoredox catalysis with a copper catalyst employing oxime esters as the acyl source and TMSCN as the cyano source. Thus, in the presence of 0.8 mol% of fac-Ir(ppy)3, as a photocatalyst and 1.5 mol% of Cu(MeCN)4PF6 as a transition-metal catalyst, in combination with 2.25 mol% of Box-type ligand L1 in DMA under irradiation of purple LEDs, the reaction of various (hetero)aromatic alkenes 4 bearing either electron-donating (e.g., Me, tBu, and Ph) or electronwithdrawing (e.g., F, Cl, Br, OAc, and Bpin) functional groups with different aryl/alkyl ketone-derived oxime esters 5 and TMSCN furnished the corresponding βcyano ketones 6 in good to high yields and excellent enantioselectivity Remarkably, the protocol was also successfully extended to pharmaceutically relevant compounds, including estrone, febuxostat-, and amino acid-derived alkenes. Unfortunately, the current catalytic system is not applicable to simple unactivated or electron-deficient alkenes, as well as cyclic oxime esters. Mechanistically, as stated by the authors, the reaction proceeds through two intertwined catalytic cycles as illustrated in Scheme 5. At first, the ground state photocatalyst (PC) undergoes photoexcitation under visible-light irradiation to produce the excited state (PC*), which subsequently reduces oxime ester 5 by a SET process to give iminyl radical A, with release of carboxylic anion. Then, radical A undergoes C–C bond β-cleavage to form acyl radical B that after addition to styrene 4 forms relatively more stable benzylic radical C. On the other hand, the initially formed carboxylic anion facilitates the ligand exchange between L1/CuI complex and TMSCN to form L1CuICN species. Subsequently, oxidation of newly generated complex by the oxidizing photocatalyst via a SET process, followed by another ligand exchange with TMSCN affords L1CuII(CN)2 complex with concomitant regeneration of ground-state photocatalyst. Finally, L1CuII(CN)2 traps the prochiral benzylic radical C to form a chiral highvalent CuIII complex D, which undergoes the reductive elimination to afford the target β-cyano ketone 6, with regeneration of L1CuICN species. In a closely related study, Dong, Guan, and He disclosed that fac-Ir(ppy)3 combined with CuOAc and pybox ligand L2 was highly effective catalytic system for the direct cyanoacylation of styrene derivatives 7 with aroyl chlorides 8 and TMSCN under blue LEDs irradiation at room temperature. By this protocol, thirty-two β-cyano ketones 9 were synthesized in fair to high yields. However, when aliphatic acyl chlorides were used as acyl donors under the optimal reaction conditions, no desired products were detected and most starting materials remained unchanged. The authors explained this observation by low reduction potential of aliphatic acyl chlorides. In order to expand the scope of this methodology, in this study, the reactivity of various sulfonyl chlorides was also examined. Interestingly, both aromatic and aliphatic sulfonyl chlorides reacted smoothly under the reaction conditions, providing a series of β-sulfonyl nitriles in satisfactory yields (8 examples, 62–76%). Mechanistic investigations revealed that the reaction proceeds via a SET pathway. Thus, the authors proposed a mechanism analogous to that of Chen's group depicted in Scheme 5. In an attractive contribution in this field, Kong et al. disclosed an interesting electrocatalytic vicinal cyanoacylation of terminal alkynes 10 employing α-keto acids 11 and cyanobenziodoxolone 12 as radical sources of acyl and cyano groups, respectively. The reactions were

conducted in an undivided cell assembled with a 3. Cyanoesterification of alkenes One of the earliest protocols for the direct vicinal cyanoesterification of olefinic double bonds has been reported by Nishihara and co-workers in 2005. They disclosed that the treatment of norbornene derivatives 14 with commercially available cyanoformates 15 as both cyanation and esterification agents in the presence of a catalytic amount of Pd(PPh3)4 in refluxing toluene, resulted in the formation of the corresponding β-cyano esters 16 in poor to excellent yields and outstanding 2- exo,3-exo stereoselectively . Various alkyl and benzyl cyanoformates worked well under optimized conditions, but extension of the reaction to aryl cyanoformates was failed. According to author's proposed mechanistic cycle, this reaction may proceed through an oxidative addition/ alkoxycarbonylpalladation/reductive elimination sequence. A decade later, the authors investigated the detailed mechanism of this cyanoesterification reaction with the aid of density functional theory (DFT) calculations to elucidate the origin of the observed exoselectivity. The results suggested that this strong selectivity originates from the steric and agostic hydrogen interactions between the methylene and the ethylene bridges of the norbornene and the adjacent cis-ligands at the PdII center.

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