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Arylnitration of alkenes by nitration/C–H functionalization cascade using $AgNO_3$ and HOAc

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ABSTRACT

A novel arylnitration of alkenes by nitration and C–H functionalization cascade process has been developed. This methodology provides an efficient way to construct a variety of nitro-containing oxindoles and dihydroquinolin-2(1*H*)-ones. In addition, the process exhibits significant functional group tolerance. Moreover, the use of inexpensive and readily available starting materials makes this practical and atom-economical approach particularly attractive.

Introduction

Oxindoles are ubiquitous heterocycles found in a wide range of natural products, pharmaceuticals, and biologically active compounds.[1] In the past few years, a number of traditional processes for the synthesis of these motifs have been established.[2] Among these methods, the transition-metal-catalyzed cyclization functionalization of *ortho*-nonfunctionalized aniline derivatives has received special attention due to the high atom economy. Buchwald and co-workers first used *ortho*-nonfunctionalized anilines (α-chloroacetanilides) in the formation of oxindole through palladium-catalyzed C–H functionalization.[2c] Subsequently, the groups of Kündig[2e] and Taylor[2f] reported the copper-mediated direct $C(sp^2)$–H/$C(sp^3)$–H functionalization of anilide to form a variety of oxindoles through a radical process. Very recently, metal-mediated and metal-free intramolecular difunctionalization of alkenes, including aryloxygenation, arylalkylation, aryltrifluoromethylation, arylphosphination, and azidoarylation also provides an elegant method for the construction of the oxindole skeleton.[3]

On the other hand, nitro compounds are widely used in various fields such as medicine, industry, and fuels. Such compounds are also valuable synthetic intermediates in organic chemistry.[4] Classical nitration of aromatics and alkenes by electrophilic substitution using nitronium cation (NO_2^+) is well-known.[5a-f] As a method for synthesis of aliphatic nitro compounds, nucleophilic substitution reaction of an alkyl halide with nitrite anion (NO_2^-) has been used.[5g,h] Moreover, addition of nitrogen dioxide to a C–C multiple bond also affords corresponding aliphatic nitro compounds.[5i-n] In addition, transition-metal-catalyzed synthesis of aromatic nitro compounds from aryl chlorides, triflates, and nonaflates has also been developed.[5o-q] However, despite progress in this area, examples of preparation of nitro compounds via alkene difunctionalization strategy are quite rare. Taniguchi et al. have reported the halonitration and hydroxylnitration of alkenes to give a variety of substituted aliphatic nitro compounds.[6] Very recently, we reported a novel metal-free oxidative arylnitration of alkenes via nitration and C–H functionalization cascade process.[3q] This methodology provides an efficient way to construct nitro-containing oxindoles and dihydroquinolin-2(1*H*)-ones. However, the efficiency for the arylnitration of unactivated alkenes is low, and the yields of corresponding dihydroquinolin-2(1*H*)-ones are not satisfactory. After great efforts, we discovered that transformation could also occur smoothly in the presence of $AgNO_3$ and HOAc, and afford corresponding products in good yields. Herein, we disclose our findings (Scheme1).

Results and discussions

In an initial study, we chose the *N*-methyl-*N*-arylacrylamide **1a** as the model substrate to evaluate different nitrating source in the presence of 10 equiv AcOH in CH_3CN at 100 °C. To our delight, when 3 equiv nitrates, such as $Mg(NO_3)_2{\cdot}6H_2O$, $Cu(NO_3)_2{\cdot}3H_2O$,

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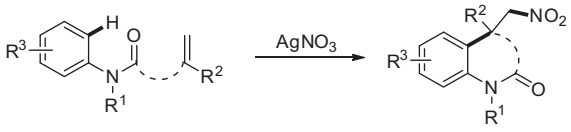
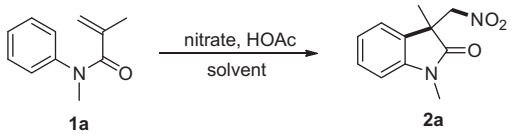


Scheme 1. Arylnitration of alkenes.

Table 1
Optimization of reaction conditions[a]



1a **2a**

Entry	Nitrate (equiv)	Solvent	*T* (°C)	Yield[b] (%)
1	$NaNO_3$ (3)	MeCN	100	0
2	KNO_3 (3)	MeCN	100	0
3	$Mg(NO_3)_2{\cdot}6H_2O$ (3)	MeCN	100	14
4	$Cu(NO_3)_2{\cdot}3H_2O$ (3)	MeCN	100	12
5	$Y(NO_3)_3{\cdot}6H_2O$ (3)	MeCN	100	19
6	$Co(NO_3)_2{\cdot}6H_2O$ (3)	MeCN	100	9
7	$Ce(NO_3)_3{\cdot}6H_2O$ (3)	MeCN	100	18
8	$AgNO_3$ (3)	MeCN	100	27
9	$AgNO_3$ (3)	DMF	100	13
10	$AgNO_3$ (3)	DMSO	100	18
11	$AgNO_3$ (3)	Toluene	100	0
12	$AgNO_3$ (3)	1,4-Dioxane	100	34
13	$AgNO_3$ (3)	1,4-Dioxane	120	44
14	$AgNO_3$ (3)	1,4-Dioxane	140	41
15[c]	$AgNO_3$ (3)	1,4-Dioxane	120	42
16[d]	$AgNO_3$ (3)	1,4-Dioxane	120	58
17[e]	$AgNO_3$ (3)	1,4-Dioxane	120	73
18[f]	$AgNO_3$ (3)	1,4-Dioxane	120	56
19[e]	$AgNO_3$ (4)	1,4-Dioxane	120	58
20[e]	$AgNO_3$ (2)	1,4-Dioxane	120	61
21[e,g]	$AgNO_3$ (3)	1,4-Dioxane	120	57
22[e,h]	$AgNO_3$ (3)	1,4-Dioxane	120	63

[a] Reaction conditions: **1a** (0.3 mmol) and nitrate, HOAc (10 equiv) in dry 1,4-dioxane (3 mL) with stirring at the given temperature for 24 h.
[b] Isolated yield.
[c] 1.5 mL dioxane was used.
[d] 6 mL dioxane was used.
[e] 9 mL dioxane was used.
[f] 12 mL dioxane was used.
[g] 5 equiv HOAc.
[h] 15 equiv HOAc.

$Y(NO_3)_3{\cdot}6H_2O$, $Co(NO_3)_2{\cdot}6H_2O$, $Ce(NO_3)_3{\cdot}6H_2O$, and $AgNO_3$ were used, oxindole **2a** was formed, and **2a** was obtained in 27% highest yield when $AgNO_3$ was employed. But no product **2a** could be observed in the absence of $NaNO_3$ or KNO_3 (Table 1, entries 1–8). Encouraged by the results, we then screened different solvents such as DMF, DMSO, toluene, and 1,4-dioxane, and 1,4-dioxane proved to be better than the others (entries 8–12). Among the reaction temperatures examined, it turned out that the reaction at 120 °C gave the best results (entries 12–14). Notably, the concentration of substrate **1a** was important. Screening showed that decreasing the concentration of **1a** from 0.1 M to 0.033 M, the yield of **2a** improved from 44% to 73%, further decreasing the substrate concentration resulted in a decrease in yield (entry 13 vs entries 15–18). The amount of nitrate and acid was also screened, the results show that 3 equiv $AgNO_3$ and 10 equiv AcOH was the best choice (entry 17 vs entries 19–22). Thus, entry 17 in Table 1 was identified as the optimized reaction conditions.

With the optimized conditions in hand, we then set out to explore the scope and limitations of the above method, and the results are summarized in Table 2. Substrates bearing methyl and benzyl protecting groups on the nitrogen were good for this transformation, but unprotected *N*–H acrylamide failed to give the desired product **2c**. It indicated that the nitrogen protecting group was essential under the reaction conditions. Tetrahydroisoquinoline structural motif is commonly encountered in many biologically active compounds. Acrylamides prepared from this amine provided the corresponding tricyclic oxindole derivative in excellent yield under the developed reaction conditions (**2d**). A variety of electron-donating and electron-withdrawing groups on the aniline moieties survived well in this transformation (**2e**–**2g**). However, amide with the methoxyl group at the *para* position of the aromatic ring failed to afford the desired product **2h**. Notably, the halo-substituted *N*-methyl-*N*-phenylmethacrylamides were tolerated and led to the corresponding halo-substituted nitro-containing oxindoles in good yields (**2i**–**2k**). Substrates having two substituents on the phenyl rings also reacted well with $AgNO_3$ (**2l**, **2m**). Satisfactorily, acrylamides bearing different functional groups such as benzyl, acetoxymethyl, phthalimide, and azidoethyl at the α-position also worked well, affording the products **2n**–**2q** in reasonable yields. It is noteworthy that the above reactions could be extended to unactivated alkenes as well. The arylnitration proceeded smoothly to give the corresponding dihydroquinolin-2(1*H*)-ones products in good to excellent yields (**2r**–**2x**). Moreover, this transformation also enjoys the tolerance of a wide variety of functional groups, including methyl, methoxyl, and halide, etc.

The detailed mechanism is still not clear, but this transformation might involve a free-radical process.[3q] Under the reaction conditions, the nitrogen dioxide radical might be formed.[6a,7] Addition of the nitrogen dioxide radical to alkene gives carbon-centered radical intermediate, followed by intramolecular cyclization to afford final product.

Conclusion

In summary, we have developed a novel and efficient arylnitration of alkenes by nitration and C–H functionalization cascade process with $AgNO_3$ and HOAc. In addition, the process exhibits significant functional group tolerance and allows the synthesis of structurally diverse nitro-containing oxindoles and dihydroquinolin-2(1*H*)-ones that are expected to be useful intermediates for the preparation of pharmaceutically and biologically active compounds as well as functional materials. Moreover, the use of inexpensive and readily available starting materials makes this practical and atom-economical approach particularly attractive. Further investigations toward the reaction scope, a detailed mechanism, and applications in organic synthesis are currently ongoing in our laboratory.

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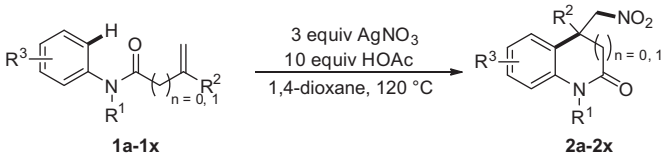
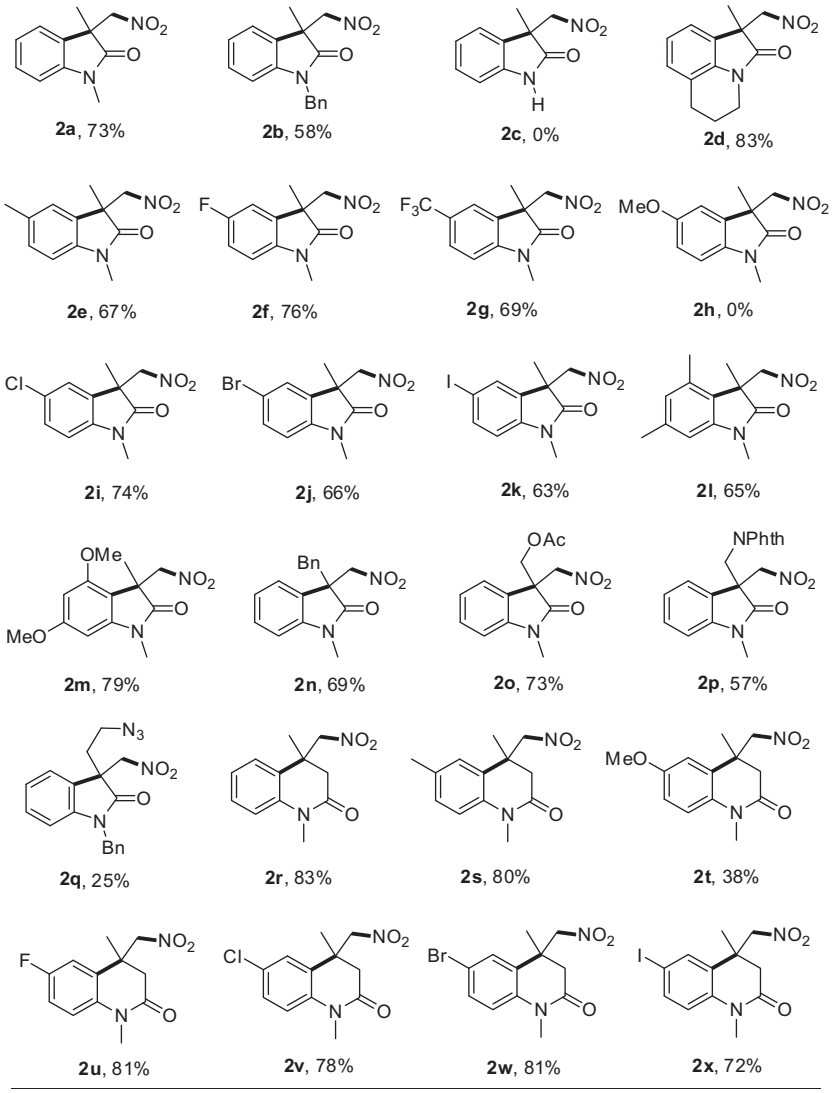
Supplementary data

Supplementary data (Copies of ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra of products. Experimental procedures and data for products.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.043.

Table 2
Scope of arylnitration[a,b]





[a] All the reactions were carried out in the presence of 0.3 mmol of **1a**–**1x**, $AgNO_3$ (3 equiv) and HOAc (10 equiv) in 9 mL 1,4-dioxane at 120 °C.
[b] Isolated yield.

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