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N-Heterocyclic carbene-catalyzed radical ringopening acylation of oxime esters with aldehydes†

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A cross-coupling of cycloketone oxime esters with aldehydes catalyzed by N-heterocyclic carbenes *via* a radical pathway was established. This modular protocol features easy operation, no external oxidants or reductants, and a broad functional group compatibility. The merit of this method was showcased by latestage modification of complicated aldehydes derived from the medical intermediate pregnenolone and natural product diacetone-p-glucose.

Introduction

Owing to their unique nucleophilicity and Lewis basicity, N-heterocyclic carbenes (NHCs) have arisen as prominent organocatalysts with wide applications in chemical synthesis. Commonly, NHC-catalyzed transformations proceed by the generation of Breslow, 2 π -extended Breslow or acyl azolium intermediates in electron-pair-transfer pathways. In contrast, the emerging realm of NHC catalyzed single-electron-transfer (SET) reactions still remains underdeveloped, but has opened new avenues for developing novel catalytic modes and promising synthetic strategies. Thus, the development of novel reaction types via radical NHC catalysis is highly desirable.

Since the pioneering disclosure of the reducing ability of the enolate form of the Breslow intermediate by the Fukuzumi group, ⁷ elegant radical transformations mediated by NHCs have been reported by Scheidt, ⁸ Studer, ⁹ Rovis, ¹⁰ Chi, ¹¹ Ye, ¹² Ohmiya, ¹³ and other groups. ¹⁴ Recently, we also developed a regioselective, intermolecular 1,2-cyanoalkylacylation of alkenes with oxime esters ¹⁵ and aldehydes by NHC organocatalysis (Scheme 1A). ¹⁶ A SET from the enolate form of the Breslow intermediate to a cyclobutanone oxime ester occurs to give a persistent aldehyde-derived ketyl radical and a transient

primary cyanoalkyl radical after radical transposition *via* C–C bond cleavage. Radical addition of the primary cyanoalkyl radical to styrene occurs preferentially to lead to the more stable benzyl radical, which then engages in radical–radical cross-coupling with the persistent ketyl radical to afford the three-component coupling product.

Enlightened by this finding, we surmised that if the cycloketone oxime esters themselves can form the more stable benzyl radicals, the direct radical cross-coupling of aldehydes with such cycloketone oxime esters might be realized. Herein, we report an NHC-catalyzed radical ring-opening acylation of oxime esters with aldehydes under transition-metalfree and redox-neutral conditions, granting a straightforward, flexible access to ketonitrile structures (Scheme 1B). It is noteworthy that the products are a class of versatile building blocks.

A. NHC-catalyzed 1,2-cyanoalkylacylation of alkenes (our previous work)

$$R^3$$
 + Ar + R^4 H R^4 R^4 R^4 R^3

B. NHC-catalyzed ring-opening acylation of oxime esters (this work)

Scheme 1 Synthetic strategy.

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Results and discussion

At the outset, 4-methylbenzaldehyde 1a and O-(tert-butoxycarbonyl) oxime 2a were chosen as model substrates to investigate the ring-opening acylation of oxime esters in the presence of the carbene precursor. Indeed, in our most recent work, 16 the two-component cross-coupling of an oxime and an aldehyde was observed;¹⁷ thus a brief optimization of the carbene catalyst, solvent, and base led to the identification of optimal conditions, which involved the use of the N-2,6-diisopropylphenylsubstituted cycloheptane-fused thiazolium precatalyst C1 (20 mol%), dichloromethane (DCM), and cesium carbonate to furnish the two-component coupling product ketonitrile 3aa in 95% yield (Table 1, entry 1).

It was found that both the backbone architecture and the N-aryl substituent of the thiazolium salts played a significant role in reaction efficiency (Table 1, entries 2-5). Employing 10 mol% carbene precursor C, such as the six-membered-ring thiazolium salt bearing N-2,6-diisopropylphenyl-substituent C2

Table 1 Optimization of the reaction conditions^a

Entry	Deviation from standard conditions	Yield ^b (3aa, %)
1	None	95
2	Using 10 mol% C1	66
3^c	C2 instead of C1	53
4^c	C3 instead of C1	40
5 ^c	C4 instead of C1	30
6 ^c	C5 instead of C1	1
7^c	C6 instead of C1	0
8 ^c	C7 instead of C1	0
9^c	C8 instead of C1	0
10	DCE instead of DCM	12
11	MeCN instead of DCM	1
12	THF instead of DCM	3
13	DMSO instead of DCM	0
14	Na ₂ CO ₃ instead of Cs ₂ CO ₃	6
15	K ₂ CO ₃ instead of Cs ₂ CO ₃	93
16	DBU instead of Cs ₂ CO ₃	10
17	TMG instead of Cs ₂ CO ₃	43
18	No NHC catalyst	0
19	No base	0

^a Reaction conditions: 1a (0.1 mmol), 2a (0.12 mmol), C1 (20 mol%), and Cs₂CO₃ (0.15 mmol) in DCM (1.0 mL) at 60 °C for 12 h under Ar. ^b Yield determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. ^c Using 10 mol% C. Boc = tert-butyloxycarbonyl, DBU = 1,8-diazabicyclo[5.4.0]-7-undecene, and TMG = 1,1,3,3tetramethylguanidine.

(entry 3), or the thiazolium salt with an acyclic backbone C3 (entry 4), or the seven-membered-ring thiazolium salt bearing an N-mesityl-substituent C4 (entry 5) resulted in reduced yields. The sterically demanding N-2,6-diisopropylphenyl group and a cycloheptane backbone were identified as the optimum structure (entry 2). Increasing the precatalyst C1 loading to 20 mol% further boosted the product yield (entry 1). On the other hand, the commercially available imidazolium- and thiazolium-type NHC precatalysts C5 and C6 were quite ineffective in this transformation (entries 6 and 7), as were non-heterocyclic-based carbenes derived from bis(amino) cyclopropenium salts¹⁸ C7 and C8 (entries 8 and 9).

The solvent had a profound effect on the reaction, as other solvents including 1,2-dichloroethane (DCE), acetonitrile (MeCN), tetrahydrofuran (THF), and dimethyl sulfoxide (DMSO) were found to be unsuitable for this ring-opening acylation transformation (Table 1, entries 10-13). The choice of the base also proved to be the key. K2CO3 gave 3aa in a comparable yield to Cs₂CO₃, whereas the use of other bases such as Na₂CO₃, DBU, or TMG instead of Cs₂CO₃ all led to a stark decrease in yield (entries 14-17). Control experiments revealed that the NHC catalyst and base were necessary for the success of this ring-opening acylation of oxime esters.

With the optimal reaction conditions in hand, the scope and limitations of this ring-opening acylation of oxime esters were investigated (Schemes 2 and 3). The initial focus was on assessing aldehyde diversity. As shown in Scheme 2, the C-C bond cleavage of benzocyclobutenone-derived oxime ester occurred with complete regioselectivity to form the more stable benzyl radical to engage in the reaction. When benzaldehyde 1b was subjected to the standard conditions, the ketonitrile 3ba was obtained in 86% yield. Benzaldehydes 1c-**1h** bearing a gamut of pendant functionalities at the *para* position, such as ether (3ca), halides (3da-3fa), cyano group (3ga), and ester (3ha), were well accommodated, giving access to the corresponding coupling products 3ca-3ha with yields ranging from 65% to 91%. Relatively lower reactivity was observed for 4-methoxybenzaldehyde 1c, indicating that the introduction of a strong electron-donating group onto the aryl ring of the aldehyde might be detrimental for the aldehyde-derived Breslow radical intermediate to undergo radical-radical coupling with the benzyl radical. Although a substituent at the para and meta positions of the aryl aldehyde was tolerated (3ea and 3ja), o-substituted benzaldehyde completely inhibited the reaction (data not shown). 2-Naphthaldehyde proved to be a viable coupling partner in this reaction manifold, affording the expected product 3ka in 83% yield. Furthermore, aldehydes containing electron-rich and electron-deficient heteroaromatic rings such as thiophene and pyridine can also be used, as exemplified by 3la and 3ma. As a current limitation, aliphatic aldehydes are not competent as acyl donors in this reaction. This may be attributed to the instability (short lifetime) of the aliphatic aldehyde-derived Breslow radical intermediate. Although cinnamaldehyde was also attempted, no products were observed. Finally, this organocatalytic approach was further applied to the late-stage modification of complex mole-

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Scheme 2 Scope with respect to aldehydes. Standard reaction conditions: 1 (0.1 mmol), 2a (0.12 mmol), C1 (20 mol%), and Cs_2CO_3 (0.15 mmol) in DCM (1.0 mL) at 60 °C for 12 h under Ar; isolated yields based on 1 are given. ^a Using 40 mol% C1. ^b Using 30 mol% C1.

Scheme 3 Scope of the NHC-catalyzed ring-opening acylation of oxime esters. Reaction conditions: 1 (0.1 mmol), 2 (0.11 mmol), C1 (20 mol%), and Cs_2CO_3 (0.15 mmol) in DCM (1.0 mL) at 60 °C for 12 h under Ar; isolated yields based on 1 are given. ^a 0.2 mmol scale.

cules. For example, complex aldehyde derivatives of pregnenolone and diacetone-p-glucose were apt to give serviceable yields of the coupling products **3na** and **3oa**. It is noteworthy that the thus obtained ketonitrile products **3** could be further converted to biologically active CWJ-a-5 analogues according to a reported procedure.¹⁹

Our attention then turned to evaluating the scope of cycloketone oxime esters. Gratifyingly, the range of cycloketone oxime esters was not restricted to the benzocyclobutenonederived oxime ester 2a, and could also encompass α-aryl-substituted cyclobutanone-derived oxime esters (Scheme 3). The cyclobutanone oxime esters 2 with substituents such as tertiary butyl (2b), bromide (2c), and phenyl (2d) groups at the paraposition of the aromatic ring reacted smoothly with 4-chlorobenzaldehyde 3e, affording the corresponding products δ -keto nitriles (3eb, 3ec, and 3ed) with yields ranging from 71% to 92%. On the downside, the reaction performed poorly with the α-methyl-substituted cyclobutanone-derived oxime ester 2e and non-substituted cyclobutanone-derived oxime ester 2f, presumably due to the instability of the generated secondary or primary radical in comparison with the benzyl radical. The less-strained, five-membered cycloketone oxime ester 2g was nonproductive under the present organocatalytic conditions. Only a trace amount of the target product 3eg was detected by HRMS.

To shed light on the tentative reaction mechanism, a preliminary mechanistic investigation was performed (Scheme 4). In the presence of 2.0 equivalents of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), the standard reaction of 4-methylbenzaldehyde 1a and *O-(tert-*butoxycarbonyl) oxime 2a was totally inhibited. Furthermore, 4-methylbenzaldehyde 1a was reacted with *O-(tert-*butoxycarbonyl) oxime 2a under standard conditions in the presence of 2.0 equivalents of the radical scavenger 2,6-*di-tert-*butyl-4-methylphenol (BHT), affording the two-component coupling product 3aa in only 28% yield. This result indicated the radical nature of this transformation.

On the basis of the above experimental results and the literature, ^{13a,16} a tentative mechanism for the NHC-catalyzed ring-opening acylation of oxime esters is illustrated in Scheme 5. First, NHC reacts with the aldehyde 1 to give the corresponding Breslow intermediate I. Next, the enolate form of the Breslow intermediate II would be generated by deprotonation in the presence of a base and induce the SET event

Scheme 4 Mechanistic investigations.

Scheme 5 Proposed mechanism for the NHC-catalyzed ring-opening acvlation of oxime esters.

between the enolate II and cyclobutanone oxime ester 2, affording a persistent ketyl radical III and an iminyl radical A, respectively. Subsequent regioselective ring-opening of A via C–C bond β-cleavage forms the benzyl radical **B**. Intermediates III and B would undergo radical-radical cross-coupling to furnish the intermediate IV (path a).20 Alternatively, another addition of the benzyl radical B to the enolate form of the Breslow intermediate II might occur, giving a plausible NHCbound radical intermediate V. SET from the intermediate V to oxime ester 2 would ensue to form the intermediate IV and a new iminyl radical A, respectively (path b). Currently, we cannot exclude either pathway. Ultimately, the species IV would undergo facile elimination to deliver the target product ketonitrile 3 and release the NHC, thereby closing this catalytic redox-neutral cycle.

Experimental

General procedure for ring-opening acylation of oxime esters

A flame-dried 10 mL resealable screw-cap Schlenk tube containing a magnetic stirring bar was charged with the aldehyde 1 (0.1 mmol, 1.0 equiv.), oxime ester 2 (0.12 mmol, 1.2 equiv.), NHC precursor C1 (8.3 mg, 0.02 mmol, 0.2 equiv.), Cs₂CO₃ (48.9 mg, 0.15 mmol, 1.5 equiv.), and anhydrous DCM (1.0 mL) under an argon atmosphere. The reaction mixture was stirred in a preheated 60 °C oil bath for 12 h. After that, the mixture was concentrated under reduced pressure. The resulting crude product was purified by silica gel flash column chromatography to give the corresponding products 3aa-3ef.

Conclusions

In summary, we have developed an emerging NHC-catalyzed radical cross-coupling of cycloketone oxime esters with readily

available aldehydes. By using an N-2,6-diisopropylphenyl-substituted cycloheptane-fused thiazolium salt as the NHC precatalyst, the cyanoalkyl or 2-cyanobenzyl from the cycloketone oxime esters and the acyl from the aldehydes were docked efficiently, giving access to ketonitriles in moderate to good vields. The aromatic nitriles can be used to construct a compound library of topoisomerase I inhibitor CWJ-a-5 analogues. This protocol features easy operation, with no need for external oxidants, reductants or transition-metal catalysts, and a good functional group tolerance. The compatibility of substrate scope covers benzocyclobutenone oxime esters, α-aryl-substituted cyclobutenone oxime esters, and aromatic aldehydes. Complicated aldehydes derived from the medical intermediate pregnenolone and natural product diacetone-D-glucose also proved to be viable coupling partners, affording the corresponding coupling products in synthetically useful yields. Mechanistic studies indicated that a radical pathway was involved. This work further enriches the types of radical reactions catalyzed by NHC.

Conflicts of interest

There are no conflicts to declare.

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