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Light-Driven Vitamin B_{12}-Catalysed Generation of Acyl Radicals from 2-*S*-Pyridyl Thioesters

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Abstract. Acyl radicals are invaluable intermediates in organic synthesis, however their generation remains challenging. Herein, we present an unprecedented light-driven, cobalt-catalysed method for generation of acyl radicals from readily available 2-*S*-pyridyl thioesters. The synthetic potential of this methodology was demonstrated in the Giese-type acylation of activated olefins in the presence of heptamethyl cobyrrinate. This vitamin B_{12} derivative proved the most efficient catalysts in the studied process. The developed method features broad substrate scope (38 examples), good functional group tolerance, and mild reaction conditions. Moreover, it is easily scalable (illustrated on 20-fold scale-up procedure), enabling its preparative use.
Mechanistic studies revealed that the reaction proceeds via a radical pathway with the key steps involving the formation of acyl-vitamin B_{12} complex and subsequent photolysis of the Co-C bond.

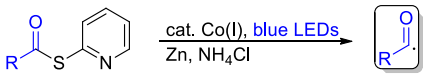
Keywords: cobalt • catalysis • acyl radicals • cobalamin• Giese-type acylation

Introduction

In the past few decades, transition-metal catalysis has emerged as a powerful tool for C-C bond forming reactions. Although, 4d and 5d transition metals have been mainly used, cobalt-catalysis provides an environmentally benign and inexpensive alternative to numerous noble metal catalysed transformations.[1] In addition to its wide application in C-H activation[2] and cross-coupling[3] reactions, it also gives a practical access to alkyl radicals via homolytic cleavage of weak Co-C bonds.[4] On the other hand, generation of acyl radicals via cobalt-catalysis remains challenging since the requirement for reductive conditions (i.e. $NaBH_4$, Zn, to generate supernucleophilic Co(I)) precludes the use of common acyl precursors (acyl chlorides, carboxylic acid anhydrides).

Acyl radicals are of particular interest as their nucleophilic character renders them exceptional acyl anion equivalents.[5] Their significance is emphasized by many applications in Giese-type additions to activated olefins[6] and Minisci-type acylations of heterocycles.[7] These reactive species are mainly formed via: a) homolytic rupture of a RCO-(X) bond,[8] b) carbonylation of carbon-centered radicals with CO,[9] and c) decarboxylation of α-ketocarbonyl compounds.[10] Recently, photocatalytic methods attracted a lot of attention.[8,10] Such processes enable to generate radical species via single-electron transfer, while Co(I)-porphyrinoids react with acyl surrogates as nucleophiles.[11,12] This unique reactivity allows to access acyl radicals from electrophilic derivatives with redox potentials beyond the scope of commonly used photoredox catalysts. In this line, light-driven cobalt catalysis may provide an alternative to current photocatalytic methods.

There are only few reports on cobalt-promoted generation of acyl radicals. Under light irradiation acyl-cobalt salophen complexes obtained from acyl chlorides react with olefins furnishing ketones.[11] Scheffold developed the electrochemical method for the acylation of double bonds with acid anhydrides involving acylcobalamin as an intermediate.[12] Notwithstanding, catalytic method for cobalt-mediated generation of acyl radicals remains unexplored.



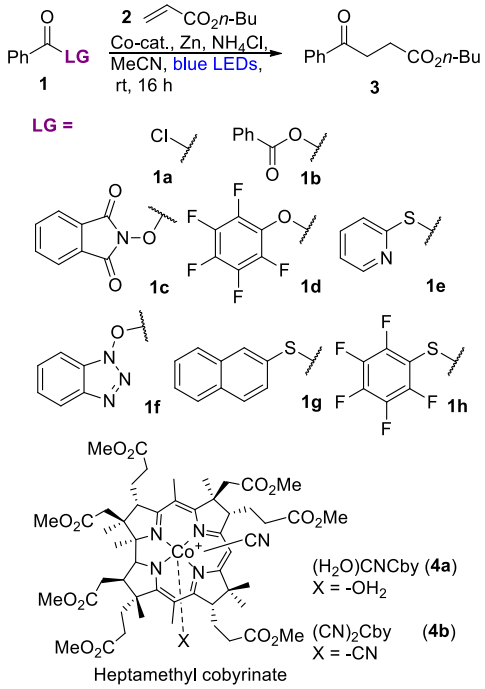
Scheme 1. Co(I)-catalysed generation of acyl radicals from 2-*S*-pyridyl thioesters.

Herein, we demonstrate an unprecedented application of 2-S-pyridyl thioesters as acyl-radicals precursors in Co- catalysis (Scheme 1). To the best of our knowledge this is also the first report featuring the use of thioesters to generate acyl-cobalt complexes.

Results and Discussion

Model studies

Our and others previous studies proved that vitamin B_{12} - a natural Co-complex can serve as an environmentally benign, efficient catalyst for many types of reactions.[4b,13,14] In its Co(I)-form it reacts with various electrophiles. Therefore, we anticipated that nucleophilic Co(I) complexes would react with acyl derivatives via the addition-elimination mechanism giving acyl-cobalt derivatives, hence providing a straightforward access to acyl radicals via subsequent photolytic cleavage of the Co-C bond. To this end the replacement of commonly used acyl chlorides with their reduction stable surrogates should facilitate an efficient, cobalt-catalysed access to acyl radicals. Our choice of acyl derivatives was inspired by a number of stable acylating agents routinely used in the amide bond formation, easily prepared from carboxylic acid, including active esters and thioesters.[15]



Scheme 2. Investigation of acyl derivatives and catalysts.

Due to their nucleophilic character, acyl radicals react with electrophiles, hence electron deficient alkenes were chosen as coupling partners.[5,16] Initially, a series of acyl derivatives (**1a**-**1h**) and cobalt catalysts (**4a**-**4e**) were tested in the acylation of *n*-butyl acrylate (**2**) (Scheme 2, Table 1). The reactions with thioesters **1e** and **1h** furnished desired product **3** in satisfactory yields in the presence of porphyrin-type Co catalysts (**4a**, **4b**, **4c**, Table 1, entries 5-8). Unsurprisingly, acyl chloride **1a** and anhydride **1b** did not facilitated the formation of the product **3**.

Higher efficiency of porphyrinoid-type complexes can be ascribed to their ability to stabilize radicals via persistent radical effect.[4a,17] The higher reactivity of thioesters (**1e**, **1h)** compared with active esters (**1c**, **1d** and **1f**) resulted from the stronger electrophilic character of the carbonyl group. On the basis of background studies (for detailed optimization studies see SI) all reaction components (catalyst, light and reducing agent) were identified as essential.

The potential of 2-*S*-pyridyl thioesters as an acyl chloride surrogates had been explored before in Grignard reactions,[18] Ni-catalysis,[19] or SmI_2 mediated generation of acyl radical anions.[20] Nevertheless, to the best of our knowledge, this is the first report on their use to generate acyl-cobalt complexes and acyl radicals. The presented procedure utilizing 2-*S*-pyridyl thioesters, easily accessible form carboxylic acids, and the abundant metal-based catalyst provides viable alternative to the previously published Ru- and Ir-catalysed methods for the generation of acyl radicals from α-oxocarboxylic acids.[10] Moreover, this mode of acyl-group activation in the Giese-type acylation is superior to the homolytic cleavage of the C-S bond, as it circumvents the lingering problems of competing couplings with sulfur-centered radicals.[5,21]

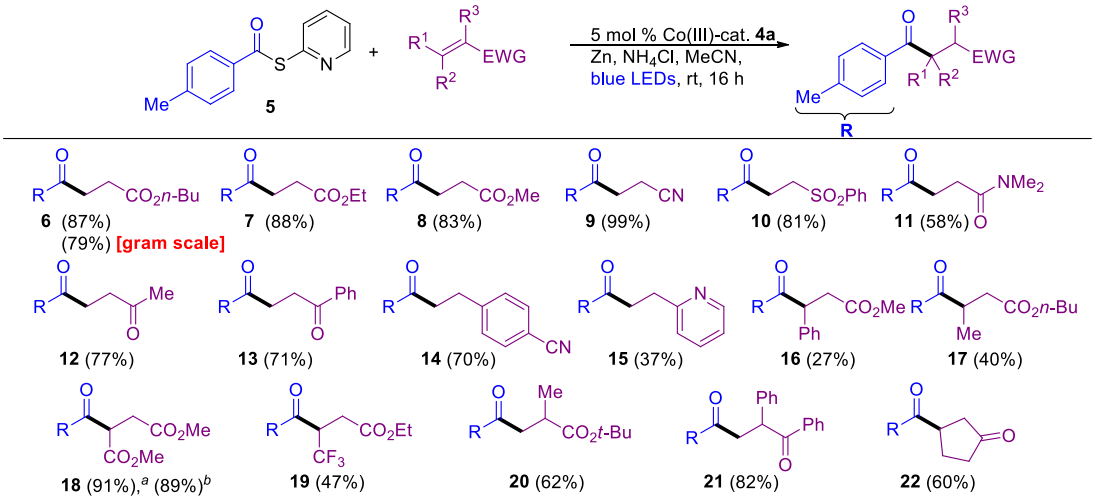
Table 1. Co-catalysed reactions of acrylate **2** with various precursors of acyl radicals.[a)]

Entry	Acyl reagent	Catalyst		Yield of 3 [%][b)]
1	**1a**	$(H_2O)Cby^+ClO_4^-$	(**4a**)	0
2	**1b**	$(H_2O)Cby^+ClO_4^-$	(**4a**)	0
3	**1c**	$(H_2O)Cby^+ClO_4^-$	(**4a**)	5
4	**1d**	$(H_2O)Cby^+ClO_4^-$	(**4a**)	0
5	**1e**	$(H_2O)Cby^+ClO_4^-$	(**4a**)	**73**
6	**1f**	$(H_2O)Cby^+ClO_4^-$	(**4a**)	7
7	**1g**	$(H_2O)Cby^+ClO_4^-$	(**4a**)	11
8	**1h**	$(H_2O)Cby^+ClO_4^-$	(**4a**)	57
9	**1e**	(CN)Cby	(**4b**)	45
10	**1e**	Co(II)(TPP)	(**4c**)	37
11	**1e**	$Co(dmgH)_2(py)Cl$	(**4d**)	9
12	**1e**	$Co(acac)_3$	(**4e**)	0

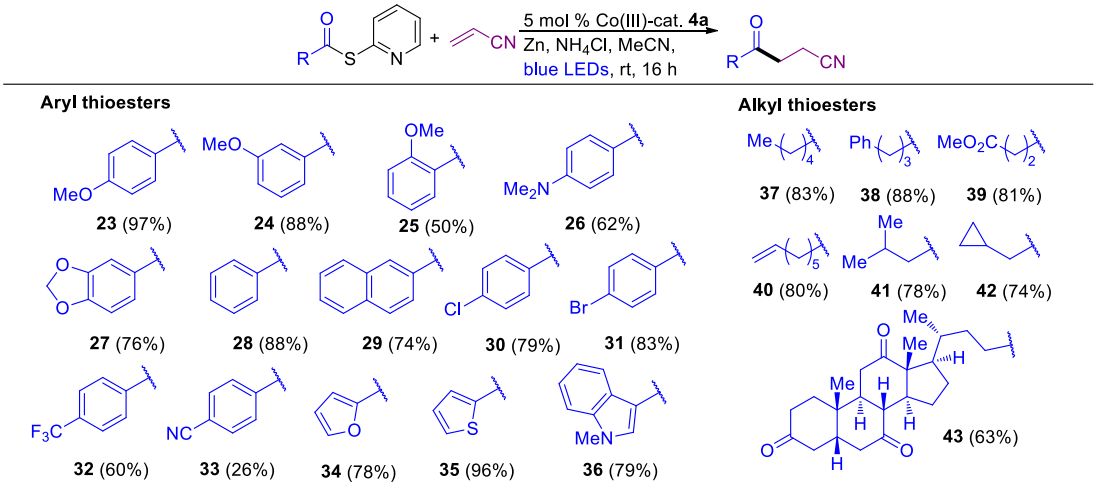
[a)] Reaction conditions: alkene **2** (0.25 mmol), acyl derivative (1.4 equiv), catalyst (5 mol %), Zn (3 equiv), NH_4Cl (1.5 equiv), MeCN (2.5 mL), light source: blue LEDs tape, 16 h at room temperature (19-25 ˚C) under argon atmosphere (for more details see SI).[b)] Isolated yields. TPP – tetraphenylporphyrin, dmgH – dimethylglyoxime, acac – acetylacetonate.

Scope and Limitations

Using our optimized conditions, the scope and limitations of the studied reaction were investigated. Alkenes bearing various electron-withdrawing groups such as esters, nitriles, sulfones, amides, and ketones provided products (**6**-**13**) in good to excellent yields (Scheme 3). Gratifyingly, even the electron-deficient styrenes were reactive enough to furnish β-aryl



Scheme 3. Scope of the Co(I)-catalysed radical acylation of electron-deficient olefins. Reaction conditions: alkene (0.25 mmol), thioester **5** (1.4 equiv.), catalyst **4a** (5 mol %), Zn (3 equiv.), NH_4Cl (1.5 equiv.), MeCN (2.5 mL, *c* = 0.1 M), light source: blue LEDs tape, rt (19-25 ˚C), 16 h, under argon atmosphere. All reported yield values are mean value of isolated yields from at least two independent experiments. [a] From dimethyl fumarate. [b] From dimethyl maleate.



Scheme 4. Scope of thioesters. Reaction conditions: acrylonitrile (0.25 mmol), thioester (1.4 equiv.), catalyst **4a** (5 mol %), Zn (3 equiv.), NH_4Cl (1.5 equiv.), MeCN (2.5 mL, *c* = 0.1 M), light source: blue LEDs tape, rt (19-25 ˚C), 16 h, under argon atmosphere. All reported yield values are mean value of isolated yields from at least two independent experiments.

ketones (**14**, **15**). Although the reaction is unencumbered by the presence of substituents at the α-position to the electron withdrawing group (**20**, **21**), substitution by an alkyl or aryl group at the β-position (**16**, **17**) led to a decrease in the product yield. This effect is not only of steric origins as the reaction with dimethyl fumarate afforded desired product **18** in excellent yields. The geometry of the double bond did not influence the outcome of the reaction, since both dimethyl fumarate (isomer *E*) and maleate (isomer *Z*) provided product **18** in comparable yields.

To examine the scope of thioesters, several thioesters were prepared from the corresponding acyl chlorides via an operationally simple, chromatography-free method developed by Lindsey[18b] or directly from acids using coupling reagents.[22] Aryl, heteroaryl, and alkyl derivatives reacted equally well, affording acylated products (Scheme 4). Aryl thioesters with a range of electron-donating (**23**-**27**) as well as mildly electron-withdrawing substituents (**30**, **31**) generated acyl radical efficiently. While those with electron-withdrawing furnished products **32**, **33** but with diminished yield, presumably due to their higher susceptibility to reduction (for -Me E_{pc} = -1.77 V, -CF_3 E_{pc} = -1.49 V, -CN E_{pc} = -1.36 V *vs.* Ag/AgCl, see SI). Additionally, substitution at the *ortho*-position of the aryl ring led to a significant decrease in the product yield (compare products **23** and **25**), presumably because of a steric hindrance imposed by catalyst **4a**. Interestingly, even notoriously challenging electron rich heterocycles performed

remarkably well, providing desired products in very good yields (**34**-**36**).

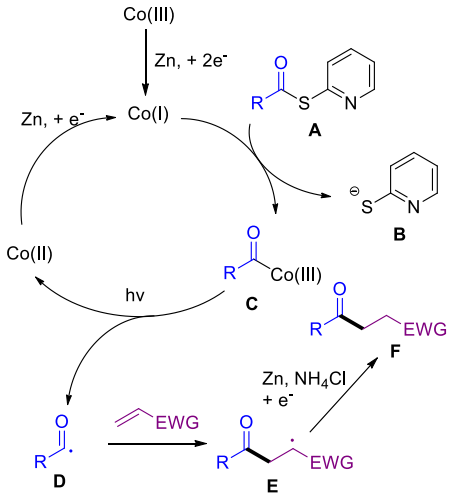
It is well documented that vitamin B_{12} derivatives (such as complex **4a**) exhibit exquisite reactivity in dehalogenation reactions,[4b,13] thus utilizing halogenated derivatives in B_{12}-catalyzed reactions is often plagued by the formation of a significant amount of dehalogenated products. Notwithstanding, in the studied reaction products bearing both bromo- and chloro- substituents (**30**, **31**) were obtained selectively. To the best of our knowledge this is the first example of such selective vitamin B_{12} derivative-catalysed reaction with no dehalogenation being observed.

Furthermore, primary alkyl thioesters regardless of the substituent tethered to the alkyl chain reacted equally well with acrylonitrile (**37**-**42**). Even complex molecules such as a dehydrocholic acid derivative afforded compound **43** in good yield.

During our study we encountered examples of substrates being beyond the reach of the developed method. The use of reductive conditions precludes the use of compounds bearing reduction-sensitive groups [-CHO, $-SO_2F$, $-P(O)(OMe)_2$]. Moreover, sterically demanding substrates were found to be unreactive under the developed conditions. Due to the competing decarbonylation of acyl radicals,[5] thioesters with highly electron-deficient aromatic rings or those derived from secondary or tertiary carboxylic acids did not give desired products.

The reaction was easily scalable and could be run on a preparative scale (5 mmol), giving product **6** in 79% yield (Scheme 3). A 20-fold increase in the scale of the model reaction required only prolongation of the reaction time (40 h).

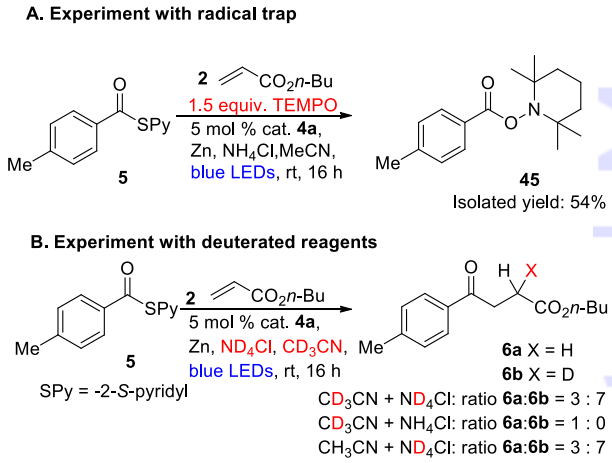
Mechanistic considerations



Scheme 5. Proposed mechanism of the Co(I)-catalysed acylation of olefins.

Scheme 5 outlines the proposed mechanism of the investigated reaction. Based on experimental evidences, Pattenden's[11] and Scheffold's[12] studies, we assume that the acylation occurs via complex **C** generated in the reaction of supernucleophilic Co(I)-complex with thioester **A**, which upon light irradiation undergoes homolytic cleavage, furnishing acyl radical **D** and Co(II)-complex. Subsequently, nucleophilic radical **D** reacts with electron-deficient olefin, providing radical **E**, while the Co(II)-catalyst is reduced back to its Co(I)-form by Zn to maintain the catalytic cycle.

To corroborate the aforementioned mechanism several experiments were performed. Firstly, Co(III)- and Co(II)-forms of catalyst **4a** were tested in the absence of the reducing agent, and in both cases formation of product **6** was not observed. Secondly, the presence of acyl-cobalt complex **C** in the reaction mixture was confirmed by ESI(+) LR-MS (*m/z* = 1155.7). Furthermore, the experiment with the addition of a radical trap, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, **44**), led to the formation of acylated TEMPO derivative **45** along with traces of product **6** (Scheme 6A). Finally, when the reaction was performed with the addition of ND_4Cl, the deuterium incorporation occurred only at the α position to the electron withdrawing group originating from compound **2**, despite the presence of two enolizable positions in the product **3** (Scheme 6B).



Scheme 6. Mechanistic studies.

The Co-C bond in alkyl and acyl vitamin B_{12} derivatives undergoes homolytic cleavage under photolytic, electrolytic, or thermolytic conditions.[13] To assess if in the studied reaction acyl radicals are generated via the photolytic pathway, the light ON/OFF experiment was performed (Figure 1). The generation of product **6** only during periods of constant irradiation supports our mechanism. The reaction conducted in darkness for seven days afforded product **6** in only 21% yield, suggesting some contribution from the thermolytic pathway. Nevertheless, all attempts to perform the reaction at elevated temperatures with no light irradiation (40 and 60 °C) gave only traces of the acylated olefin, mainly due to the accelerated reduction of the thioester (see SI).

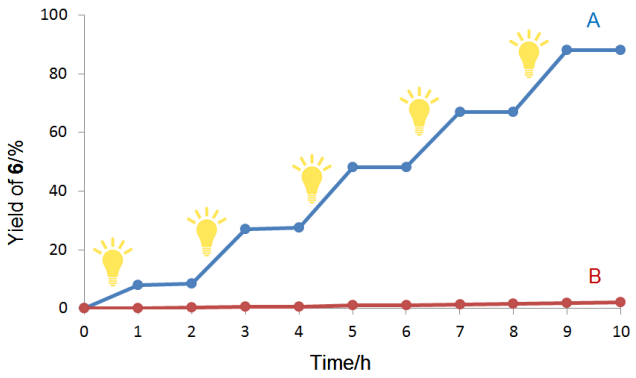


Figure 1. Light ON/OFF experiment. (A) The yield of the product **6** in the reaction of thioester **5** with *n*-butyl acrylate (**2**) monitored by GC-FID (0.1 mmol scale). (B) Control reaction maintained in darkness.

Conclusion

In summary, light-driven vitamin B_{12}-mediated reaction enabled to generate acyl radicals from thioesters. Their stability under reductive conditions renders them suitable electrophilic partners for the catalytically active, supernucleophilic Co(I)-corrin. Under light irradiation the obtained acylated Co-complex furnishes acyl radicals that react with electron deficient olefins via the Giese-type acylation. Hence, vitamin B_{12} and its derivatives can be considered 'reversible carriers' for acyl groups. Accordingly, we hope that this research will serve as an inspiration for further developments in vitamin B_{12}-catalysis.

Experimental Section

General procedure for the Co(I)-catalysed acylation of electron-deficient alkenes

A glass reaction tube equipped with a magnetic element and sealed with septum was charged with activated zinc (50 mg, 0.75 mmol, 3 equiv.), NH_4Cl (20 mg, 0.38 mmol, 1.5 equiv.) and catalyst **4a** (14.5 mg, 0.0125 mmol, 5 mol%). MeCN (2.5 mL) was added and the resulting mixture was degassed by purging the solution with argon for 15 min with simultaneous sonication using ultrasonic bath (solution turned from red to dark green/brown). Subsequently, an alkene (0.25 mmol, 1.0 equiv.) and a thioester (0.35 mmol, 1.4 equiv.) were added and the reaction vessel was placed in a photoreactor and irradiated with blue LED light (see SI) for 16 h under argon atmosphere. After that time, the mixture was quenched with Et_2O, filtered through a cotton pad, and concentrated *in vacuo*. A crude product was purified using column chromatography.

Acknowledgements

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