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Full Paper

Co-Catalysis | *Very Important Paper* |

VIP Vitamin B_{12} Enables Consecutive Generation of Acyl and Alkyl Radicals from One Reagent

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Abstract: Co complex – $Cby(OMe)_7$ - enables consecutive generation of alkyl and acyl radicals from adequately designed carboxylic acids possessing a halogen atom in theirs structures. Mechanistic studies reveal that alkyl corrins forms at much higher rate than the respective acyl derivatives enabling selective reactions with activated olefins.

Introduction

The formation of carbon–carbon bonds via free-radical-mediated reactions is a powerful tool for constructing molecules that are inaccessible by other means or for functionalization of complex molecules under mild conditions.[1–7] In recent years, transition metal complexes (Co, Fe, Ni, Mn) became a viable tool for achieving selective radical reactions.[8–14] Of particular importance are Co complexes that mimic native reactivity of vitamin B_{12} (**1**, cobalamin) (Figure 1, Scheme 1).[15–18] These are represented by cobaloxime (**2**)[19] and heptamethyl cobyrinate ($(CN)(H_2O)Cby(OMe)_7$, **3**) which is a derivative of vitamin B_{12} that have been already successfully applied to radical-processes.[15,20]

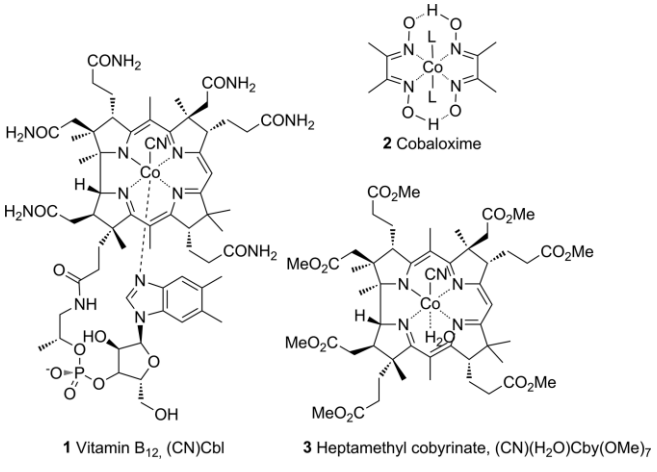
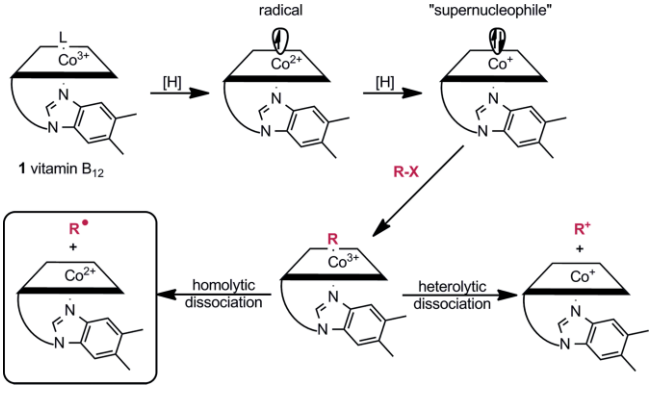


Figure 1. Vitamin B_{12} and heptamethyl cobyrinate structures.

Catalytic activity of these compounds is inherently connected with the central Co(III) ion and its ability to access +1 and +2 oxidation states (Scheme 1). In particular, heptamethyl ccobyrinate (**3**) can be reduced chemically (Zn/NH_4Cl, $NaBH_4$, etc.)[21] or electrochemically[22] generating either radical Co(II) (–0.4 V vs. SCE) or nucleophilic Co(I) (-–0.6 V vs. SCE) species, which when reacted respectively with radicals or electrophiles give alkyl cobalamins.[15,16,23–28] The weak Co–C bond is susceptible to cleavage upon thermolytic, electrolytic or photolytic conditions providing *C*-centered radicals.[29] In fact, most of the vitamin B_{12}-catalysed reactions proceed via a radical mechanism and various chemical processes utilizing this unique catalyst have been developed up to date.[15] These include coupling,[26,30,31] isomerization,[32,33] dehalogenation,[34–41] cyclopropanation[42] or transmethylation[43–48] etc. However, the area of vitamin B_{12} catalysis has so far been mainly dominated by only one type of species being formed during the reactions, namely alkyl radicals. One of the latest advancements in this area was the discovery regarding generation of acyl radicals from 2-*S*-pyridyl thioesters in the presence of vitamin B_{12} derivative **3**.[49]



Scheme 1. Catalytic modes of action of vitamin B_{12}.

We wondered whether it would be possible to generate both alkyl and acyl radicals at the same time from one starting material and achieve selective reactions. High reactivity of radicals is often associated with low selectivity due to many side reactions that can occur including homo-coupling of free radicals. This

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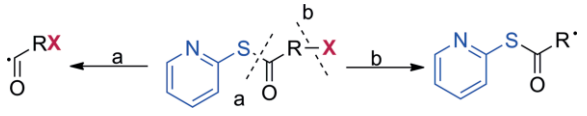
seems even more problematic for processes when two different radicals are formed at the same time. However alkyl and acyl radicals are generated via different mechanisms and they differ in their nucleophilic character, thus we assumed that these should permit their selective reactions with electrophilic olefins.

Herein, we demonstrate that both acyl and alkyl radicals can be generated by means of vitamin B_{12} catalysis from one molecule and their reaction with an electrophile proceed in a selective manner.

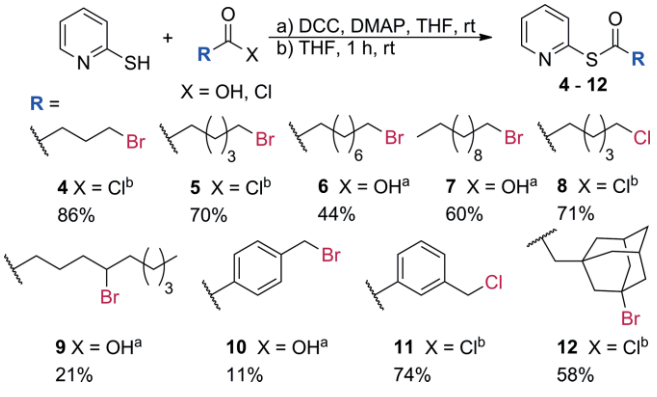
Results and Discussion

Our studies commenced with the design and synthesis of specifically substituted thioesters as a source of acyl radicals possessing halide moiety at the distant alkyl chain as a precursor of alkyl radicals (Scheme 2).



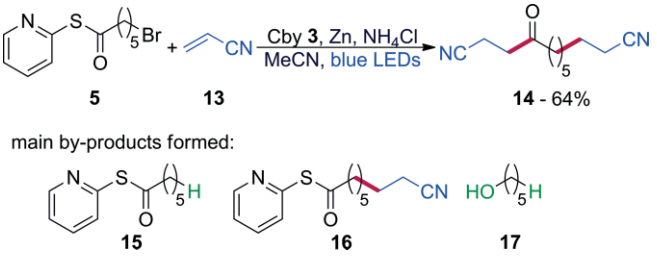
Scheme 2. Adequately designed precursor of alkyl and acyl radicals.

These starting materials are synthesized from commercially available either carboxylic acids or acid chlorides bearing halide substituent (Scheme 3).



Scheme 3. Synthesis of thioesters **4–12**. Conditions for: a) acids, X = OH, b) acid chlorides, X = Cl.

In order to verify the hypothesis of the consecutive generation of alkyl/acyl radicals from 2-*S*-pyridyl thioesters we engaged the Giese type reaction. The initial set of conditions for the model reaction of *S*-pyridin-2-yl 6-bromohexanethioate (**5**) with acrylonitrile (**13**) relied on our previous work on vitamin B_{12}-catalysed acylation of activated olefins – Zn/NH_4Cl system was applied as a reductant and MeCN was used as a solvent (Scheme 4).[49] To provide sufficient solubility hydrophobic vitamin B_{12} derivative $(CN)(H_2O)Cby(OMe)_7$ (**3**) was selected as a catalyst. The formation of desired product **14** in only 30 % yield and the presence of by-products indicated a number of competing reactions, including: dehalogenation (**15**), generation of only alkyl radical (**16**), reduction (**17**), all common for B_{12} catalysis.



Scheme 4. Model reaction of *S*-pyridin-2-yl 6-bromohexanethioate (**5**) with acrylonitrile (**13**).

Interestingly, the structure of products **15** and **16**, the lack of halide and the presence of thioester moiety respectively, suggests that alkyl radicals generate faster than acyl ones.

In the next step we optimized the reaction conditions (for details see SI). The yield substantially increased when the substrates (**5**/**13**) were used in 1:2.2 ratio. For vitamin B_{12}-catalysed reactions Zn/NH_4Cl system usually furnishes superior results but the amount and ratio of these components is often a crucial issue for effective catalyst reduction (Table 1).

Table 1. Optimization of the Zn/NH_4Cl system.[a]

Entry	Zn [equiv.]	NH_4Cl [equiv.]	Ratio Zn/NH_4Cl	Yield **14** [%][b]
1	1.5	1.5	1:1	traces
2	3	1	3:1	traces
3	3	3.4	1:1.1	51
4	6	1.5	4:1	29
5	**3**	**4.5**	**1:1.5**	**64**
6	3	6	1:2	55

[a] Conditions: $(CN)(H_2O)Cby(OMe)_7$ (**3**, 5 mol%), acrylonitrile (**13**, 0.55 mmol), thioester (**5**, 0.45 equiv.), MeCN (2.5 mL). [b] Isolated yield.

Indeed, once the amount of NH_4Cl was changed from 1.5 to 3.4 equiv. the yield increased to 51 % (entries 1 and 3). This result further improved upon fine tuning of the Zn/NH_4Cl ratio, being 64 % for 1:1.5 (entry 5). The use of other solvents as reaction medium or the addition of a base, an acid, or H_2O had only detrimental effect on the yield of product **14**.

With the optimized conditions in hand, we explored the scope of the developed transformation by subjecting to the reaction a set of structurally different thioesters differing in the chain length, position and a halogen as well as various olefins. The designed 2-*S*-pyridyl thioesters possess primary, secondary, tertiary, benzylic bromide and chloride in their structure (Scheme 3). Homologous bromoalkyl carboxylic acid derivatives **4–7** and **9** reacted equally well with acrylonitrile (**13**) giving products **14**, **18–20** in decent yield while for thioester (**9**) with secondary bromide attached product **21** formed in 35 % yield (Figure 2).

Dechlorination is one of the biomimetic reactions catalysed by vitamin B_{12} thus utilizing halogenated derivatives in B_{12}-catalyzed reactions is often plagued by the formation of a significant amount of dehalogenated products.[34–41,50] In accordance, the reaction with thioester **8** possessing the chlorine substituent afforded desired product **14** in only 23 % yield in contrast to 64 % for the respective bromide. For substrates with more reactive benzyl substituents the competing dehalogenation predominated under optimized conditions, for thioester *S*-pyridin-

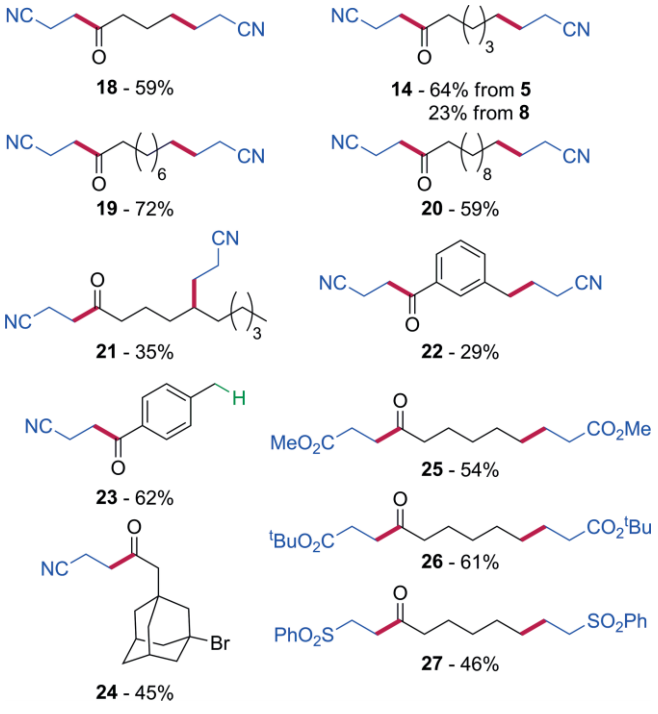
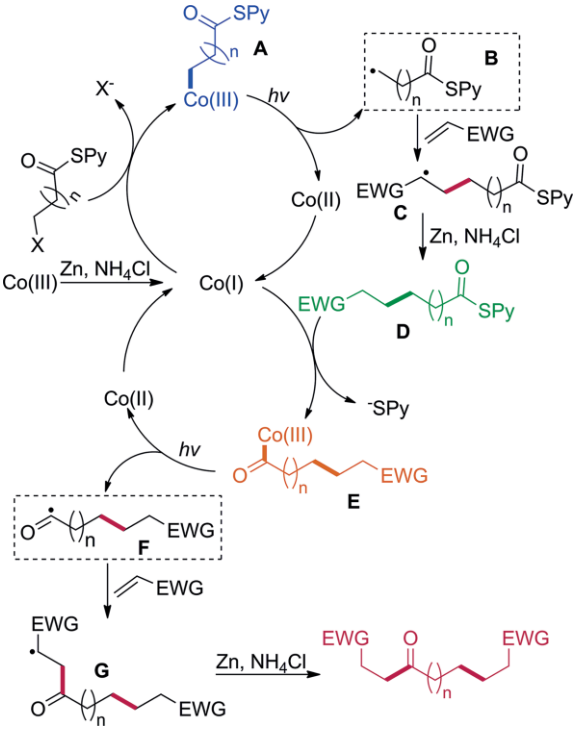


Figure 2. Scope and limitations of double functionalization of carboxylic acid derivatives.



Scheme 5. Plausible reaction mechanism.

2-yl-3-(chloromethyl)benzothioate (**11**) product **22** formed in only 29 % yield, while substrate (**10**) with benzyl bromide moiety was entirely dehalogenated affording product **23**. In contrast, tertiary bromide remained intact allowing for selective generation of acyl radical leading to nitrile **24**. For activated olefins, their reactivity depended on the nature of the electron-withdrawing group. Methyl and *tert*-butyl acrylates gave a desired product **25** and **26** in 54 % and 61 % yield, for vinyl sulfone the yield slightly decreased. We found that under optimized conditions acryl amides, styrenes, and internal olefins are unreactive while for vinyl ketones side reactions predominate.

Scheme 5 outlines the proposed mechanism. Based on the literature data and our experience, we assumed that after reduction of the central Co(III) ion with Zn, formed supernucleophilic Co(I) should react with halide and thioester moieties. Taking into consideration the structure of side-products **15** and **16**, the halide moiety reacts faster with cobalamin derivative giving alkyl-cobalt complex **A** (confirmed by ESI MS (*m/z* = 1244.5 $[M+H]^+$, see SI section 4.4). Upon light irradiation it decomposes to give alkyl radical **B** that is quickly trapped by an electron-deficient olefin. After reduction intermediate **D** is formed as detected by ESI MS (*m/z* = 263.0 $[M+H]^+$). Cobalt at the first oxidation state enters the second cycle and immediately reacts with **D** to form acyl-cobalt complex **E** (detected by ESI MS, *m/z* = 1188.0 $[M+H]^+$). Upon light irradiation another homolytic cleavage liberate nucleophilic acyl radical **F** which reacts with the second molecule of the olefin while the Co(II)-catalyst is reduced back to its Co(I)-form by Zn to maintain the catalytic cycle.

To confirm the aforementioned mechanism several experiments were performed. First, the control reaction in the absence of light, the catalyst, or the reducing agent did not afford desired product thus confirming the catalytic process (see SI for full optimization studies, section 3). The addition of a radical trap (TEMPO) stopped the reaction completely proving its radical character (see SI, section 4.3).

ESI MS analysis of the reaction mixture showed signals at *m/z* 1244.5 and 1188.0 corresponding to alkyl and acyl-Co complexes **A** and **E** respectively. Kinetic studies confirmed that cobalt-alkyl complex **A** generates almost immediately and at much faster rate as compared with cobalt-acyl species **E** (Figure 3). Over time, the concentration of complex **A** decreases

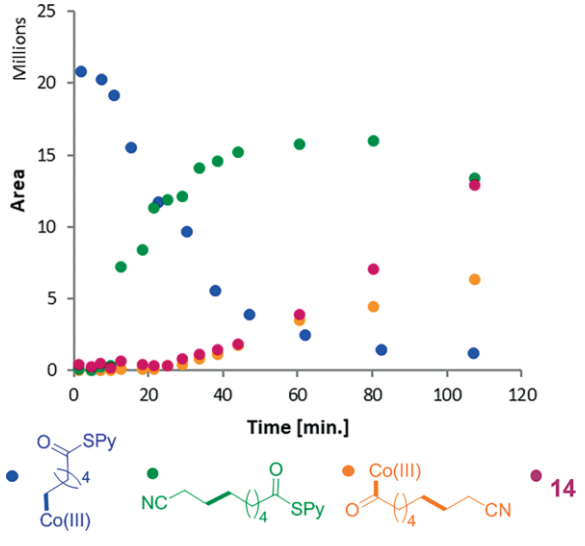
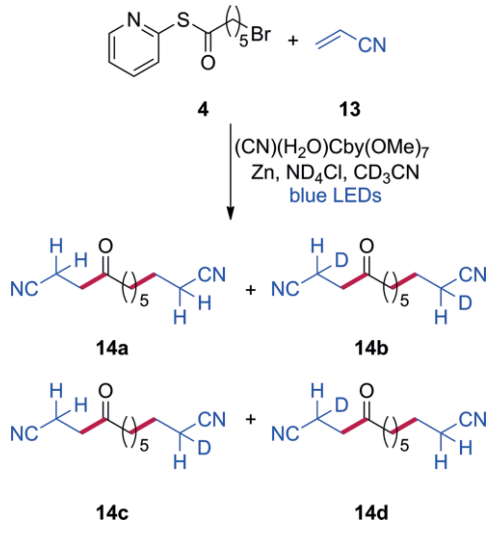


Figure 3. Kinetic studies.

indicating the cleavage of the Co–C bond, while the concentration of cobalt-acyl derivative **E** increases.

Moreover, once radical **B** is formed, it has to be immediately trapped by the olefin because we were not able to detect a species with two molecules of the catalyst attached.

When the reaction was performed with the addition of ND_4Cl in CD_3CN, the deuterium incorporation occurred only at the α positions to the electron withdrawing groups originating from the olefin thus indicating the formation of anions at these positions resulted from reduced radicals **C** and **G** (Scheme 6).



Scheme 6. Experiment with deuterated reagent.

Conclusions

In summary, under light irradiation vitamin B_{12}-mediated reaction of adequately substituted thioesters with electron-deficient olefins yields products resulting from the addition of two molecules of olefin to the alkyl and acyl radical respectively. Interestingly, dehalogenation, a reaction common for B_{12}-catalysis is competing with the developed transformation only in the case of alkyl chlorides and benzyl halides. Inactivity of tertiary alkyl bromides enables selective acylation of carboxylic acid bearing this type of substituents.

Mechanistic studies revealed that alkyl bromides react with the Co complex instantly and at much higher rate as compared to thioesters. Both alkyl and acyl radicals selectively react with electron deficient olefins via the Giese-type alkylation and acylation giving access to highly functionalized molecules in just one step.

Experimental Section

General Synthetic Procedure: A glass tube (inner diameter = 18 mm) equipped with a magnetic stirrer was charged with heptamethyl cobyrinate (14 mg, 5.0 mol%), activated Zn (48 mg, 0.75 mmol, 3 equiv.), and NH_4Cl (60 mg, 1.1 mmol, 4.5 equiv.) and sealed with a septum. Then MeCN (2.5 mL) was added and the reaction mixture was degassed by purging the solution with argon with simultaneous sonication in an ultrasonic bath (solution turned from red to dark green) for 15 min. Subsequently, an olefin (0.55 mmol, 1.0 equiv.) followed by a thioester (0.25 mmol, 0.45 equiv.) were added via syringe and the reaction mixture was irradiated with blue LED light (λ = 460 nm) for 16 h at room temperature. It was then diluted with Et_2O, filtered through the cotton wool and concentrated in vacuo. A crude product was purified by column chromatography.

Acknowledgments

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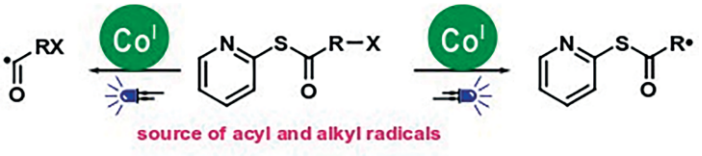
Co-Catalysis



Under light-irradiation the Co-corrin complex enables generation of alkyl and acyl radicals from adequately designed carboxylic acid derivatives and their reaction with activated olefins.

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