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Cobalt-catalyzed acylation-reactions of (hetero)arylzinc pivalates with thiopyridyl ester derivatives†

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A cobalt-catalyzed acylation reaction of various primary, secondary and tertiary alkyl, benzyl and (hetero)aryl *S*-pyridyl thioesters with (hetero)arylzinc pivalates is reported. The thioesters were prepared directly from the corresponding carboxylic acids under mild conditions, thus tolerating sensitive functional groups. Acylations of α -chiral *S*-pyridyl esters proceeded with very high stereoretention leading to optically enriched α -chiral ketones.

Introduction

The carbonyl group is a central functionality in organic chemistry and the performance of acylation reactions employing organometallic reagents represents a general access to various ketones.¹ A major drawback of these reactions is the moderate chemoselectivity or the use of expensive catalysts.¹ Acid chlorides are the most common acylation reagents.^{1,2} However, their preparation requires harsh conditions, thus lowering the functional group tolerance. In contrast, the use of thioesters is a valuable alternative since Fukuyama showed in pioneering work that these acylating reagents react readily with organozinc halides in the presence of a palladium catalyst.³ Additionally, Seki,⁴ Rovis,⁵ Fleischer,⁶ and others⁷ showed that these reactions can be performed using various transition metal catalysts. Recently, we have shown that organozinc pivalates (RZnOPiv) are an attractive class of zinc organometallics due to their enhanced air- and moisture stability and their excellent compatibility with various transition metal-catalyzed transformations.⁸ Especially, cobalt-catalyzed reactions have proven to be advantageous.⁹

Herein, we wish to report a new cobalt-catalyzed acylation reaction of various saturated and unsaturated thioesters of type R¹C(O)SPy (1) with aryl- and heteroarylzinc pivalates of type R²ZnOPiv (2), leading to a broad range of polyfunctional ketones of type 3. Although thioesters are readily available from the corresponding acid chlorides and thiols,¹⁰ the pyridyl thioesters 1 were prepared under exceedingly mild and neutral conditions from the corresponding carboxylic acid of type 4 using Mukaiyama's method (Scheme 1).¹¹

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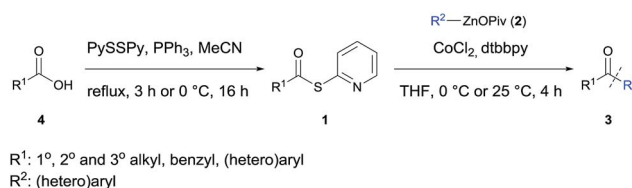
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Results and discussion


In preliminary experiments, *S*-(pyridin-2-yl)-cyclohexanecarboxithioate (1a) was treated with 4-(methoxyphenyl)zinc pivalate (2a) under various conditions (Table 1). In the absence of a catalyst, ketone 3a was obtained in only 9% yield (Table 1, entry 1). Although palladium and nickel are well-known metal catalysts for the Fukuyama acylation, the use of cheaper¹² and more abundant catalysts is highly desirable. Whereas, MnCl₂, CrCl₂, FeCl₂ or CuCl₂ gave unsatisfying results (entries 2–5), CoCl₂ proved to be an excellent catalyst for this transformation (entry 6). Its catalytic efficiency could be further improved by the addition of various ligands. After a short screening it became clear that 4,4'-di-*tert*-butyl-2,2'-dipyridyl (dtbbpy) gave the best results leading to the ketone 3a in 88% isolated yield (entry 11). At this point, we verified that no other metal contaminations are responsible for this catalysis. Thus, using CoCl₂ (99.99% purity)¹³ led to 3a in 86% yield (entry 12). Furthermore, a screening showed that RC(O)SPy thioesters are superior to thioesters of type RC(O)SEt or RC(O)SPh.¹⁴

In a typical experiment palmitic acid (4b) was treated with 2,2'-dipyridyl disulfide (1.1 equiv.) and PPh₃ (1.5 equiv.) in acetonitrile (0.3 M) under reflux for 3 h. Short purification using flash column chromatography afforded 1b in 98% yield. The required zinc pivalate 2b was prepared by treating 1-bromo-3,4-



Scheme 1 Preparation of thiopyridyl esters of type 1 from carboxylic acids 4 and cobalt-catalyzed acylation with organozinc pivalates 2, affording ketones of type 3. Py = 2-pyridyl.



Table 1 Optimization of the reaction conditions for the acylation of thioester **1a** with arylzinc pivalate **2a**


| Entry | Catalyst | Ligand | Yield of 3a ^a [%] |
|-------|--------------------------------|-------------------------------|--|
| 1 | — | — | 9 |
| 2 | MnCl ₂ | — | Traces |
| 3 | CrCl ₂ | — | Traces |
| 4 | FeCl ₂ | — | 50 |
| 5 | CuCl ₂ | — | 29 |
| 6 | CoCl ₂ | — | 67 |
| 7 | CoCl ₂ | PPh ₃ ^b | 63 |
| 8 | CoCl ₂ | TMEDA | 64 |
| 9 | CoCl ₂ | Neocuproine | 49 |
| 10 | CoCl ₂ | bipy ^c | 71 |
| 11 | CoCl ₂ | dtbbpy ^d | 90 (88) ^e (87) ^f |
| 12 | CoCl ₂ ^g | dtbbpy ^d | 86 |

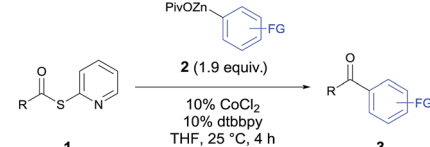
^a Reactions were performed on a 0.5 mmol scale. Determined by GC-analysis. Tetradecane (C₁₄H₃₀) was used as internal standard. ^b 20% of the ligand was used. ^c 2,2'-Bipyridine. ^d 4,4'-Di-*tert*-butyl-2,2'-dipyridyl. ^e Isolated yield. ^f Reaction was performed on a 5 mmol scale. ^g CoCl₂ (99.99% purity) was used.

(methylene-dioxy)benzene (**5b**) with Mg (1.2 equiv.) and anhydrous LiCl (1.2 equiv.) for 2 h at 0 °C leading to the corresponding arylmagnesium derivative (91% yield).¹⁵ Transmetalation with Zn(OPiv)₂ (1.0 equiv.) afforded the zinc organometallic **2b** in 93% yield.¹⁵ The thioester **1b** reacted with 3,4-(methylene-dioxy)-1-phenylzinc pivalate (**2b**) in the presence of 10% CoCl₂ and 10% dtbbpy in THF (25 °C, 4 h) furnishing after standard workup and chromatographic purification the ketone **3b** in 90% yield (Table 2, entry 1).

According to this procedure various ketones of type **3** were prepared. Hence, the heterocyclic indolylzinc pivalate (**2c**) was acylated with palmitic *S*-pyridyl thioate (**1b**) furnishing ketone **3c** in 74% yield (entry 2). Additionally, secondary thioesters derived from cyclobutane- (**4c**) and cyclohexanecarboxylic acid (**4a**) were employed to this acylation procedure leading to the corresponding ketones (**3d–3g**) in 60–95% yield (entries 3–6). Tertiary *S*-pyridyl thioesters **1d** and **1e** derived from 1-adamantanecarboxylic acid (**4d**) and the lipid regulating drug gemfibrozil¹⁶ (**4e**) reacted smoothly with various functionalized arylzinc pivalates affording acylation products (**3h–3k**) in 61–81% yield (entries 7–10).

Furthermore, the acylation reaction was extended to aryl- and heteroaryl-*S*-pyridyl thioesters (Table 3). Thus, (4-(ethoxycarbonyl)-phenyl)-zinc pivalate (**2k**) prepared *via* I/Mg-exchange using *i*PrMgCl·LiCl followed by transmetalation with Zn(OPiv)₂^{8d} was readily acylated with *S*-pyridyl thioester **1f** affording the benzophenone **3l** in 71% yield (entry 1).

Also, 2-benzothiophenylzinc pivalate **2l** generated *via* directed metalation of benzothiophene using TMPMgCl·LiCl and subsequent transmetalation with Zn(OPiv)₂^{8d} underwent a cobalt

Table 2 Ketones **3** obtained by the acylation of various alkylthiopyridyl esters **1** with (hetero)arylzinc pivalates **2**^a


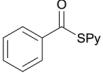
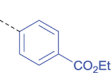
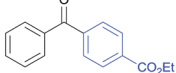
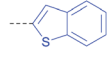
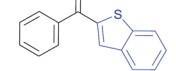
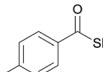
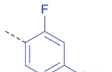
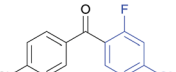
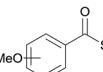
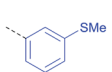
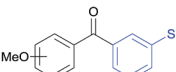

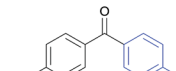
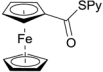
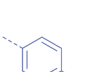
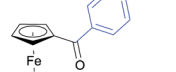

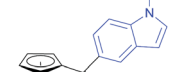
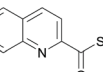

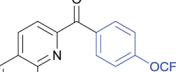
| Entry | Thiopyridyl ester 1 (yield) ^b | Zinc reagent PivOZn-R 2 | Product 3 : yield ^c |
|-------|---|--------------------------------|---------------------------------------|
| 1 | 1b (98%) | 2b | 3b : 90% |
| 2 | 1b | 2c | 3c : 74% |
| 3 | 1c (79%) | 2d | 3d : 84% |
| 4 | 1c | 2e | 3e : 95% |
| 5 | 1a (76%) | 2f | 3f : 60% |
| 6 | 1a | 2g ^d | 3g : 79% |
| 7 | 1d (85%) | 2h | 3h : 61% |
| 8 | 1d | 2g | 3i : 81% |
| 9 | 1e (98%) | 2i | 3j : 72% |
| 10 | 1e | 2j | 3k : 78% |

^a The reactions were performed on a 0.5 mmol scale. ^b Isolated yield of the *S*-pyridyl thioester prepared from the corresponding carboxylic acid, PySSPy (1.1 equiv.), PPh₃ (1.5 equiv.), MeCN, reflux, 3 h. ^c Isolated yield. ^d Prepared using *i*PrMgCl·LiCl (1.1 equiv.), THF, −20 °C, 2 h.

catalyzed acylation reaction with **1f** leading to the ketone **3m** in 68% yield (entry 2). Various substituted aryl thioesters and ferrocenyl derivatives reacted successfully with functionalized



Table 3 Ketones **3** obtained by the acylation of (hetero)aryl thiopyridyl esters **1** with (hetero)arylzinc pivalates **2^a**

| Entry | Thiopyridyl ester 1 (yield) ^b | Zinc reagent PivOZn-R 2 | Product 3 : yield ^c |
|-------|---|--|---|
| 1 |  1f (84%) |  2k^d |  3l : 71% |
| 2 | 1f |  2l^e |  3m : 68% ^f |
| 3 |  1g (66%) |  2m |  3n : 92% |
| 4 |  <i>para</i> : 1h (69%) <i>ortho</i> : 1h' (96%) |  2n |  <i>para</i> : 3o : 96% <i>ortho</i> : 3o' : 71% |
| 5 | 1h |  2f |  3p : 86% |
| 6 |  1i (91%) |  2o |  3q : 81% |
| 7 | 1i |  2b |  3r : 84% |
| 8 |  1j (75%) |  2o |  3s : 68% |

^a The reactions were performed on a 0.5 mmol scale. ^b Isolated yield of the *S*-pyridyl thioester prepared from the corresponding carboxylic acid, PySSPy (1.1 equiv.), PPh₃ (1.5 equiv.), MeCN, reflux, 3 h. ^c Isolated yield. ^d Prepared using *i*PrMgCl·LiCl (1.1 equiv.), THF, -40 °C, 2 h. ^e Prepared using TMPMgCl·LiCl (1.0 equiv.), THF, 0 °C, 3 h. ^f TMEDA was used instead of dtbbpy.

(hetero)arylzinc pivalates affording the diaryl ketones **3n–3r** in 81–96% yield (entries 3–7). Additionally, 4-trifluoromethoxyphenylzinc pivalate (**2o**) was acylated using quinoline thioester **1j** furnishing ketone **3s** in 68% yield (entry 8).¹⁷

The synthesis of α -chiral ketones is of great interest^{3,5,7c,7f,18} but often challenging under basic conditions due to


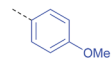
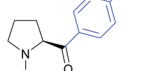
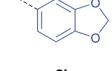
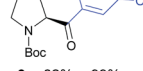
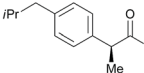
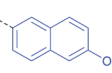
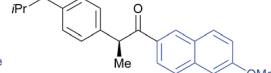
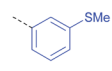
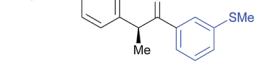

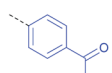
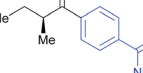
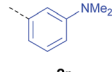
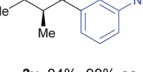
epimerization. Also, reactions under pH-neutral conditions have been reported by Liebeskind *et al.* for the synthesis of highly enantiopure peptidyl ketones.¹⁹

We also tested the applicability of this cobalt-catalyzed acylation to the synthesis of optically enriched α -chiral ketones. Using α -chiral *S*-pyridyl thioesters at 0 °C afforded several α -chiral ketones with high stereoretention (Table 4). Thus, *S*-pyridyl thioester **1k** prepared from *N*-Boc protected (*S*)-proline was treated with arylzinc reagents **2a** and **2b** leading to the corresponding α -chiral ketones in 72–82% yield and >99% ee (entries 1 and 2).

Furthermore, thioester **1l** derived from enantiopure (*S*)-ibuprofen reacted smoothly with the functionalized arylzinc pivalates **2p** and **2n** in 71–89% yield and 94–97% ee (entries 3 and 4).

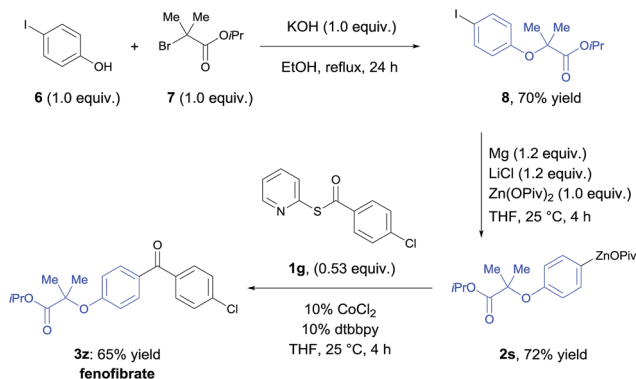
Also, arylzinc pivalates **2q** and **2r** bearing an amide or dimethylamino functionality were acylated using optically pure *S*-(pyridin-2-yl)-(*S*)-2-methylbutanethioate (**1m**) furnishing the α -chiral ketones **3x** and **3y** in 69–84% yield and 95–98% ee (entries 5 and 6).

Table 4 Preparation of α -chiral ketones **3** by acylation of thiopyridyl esters **1** with (hetero)arylzinc pivalates **2^a**

| Entry | Thiopyridyl ester 1 (yield) ^b | Zinc reagent PivOZn-R 2 | Product 3 : yield ^c |
|-------|---|--|---|
| 1 |  1k , (73%; >99% ee) |  2a |  3t , 72%, >99% ee |
| 2 | 1k |  2b |  3u , 82%, >99% ee |
| 3 |  1l , (96%; 98% ee) |  2p |  3v , 89%, 97% ee |
| 4 | 1l |  2n |  3w , 71%, 94% ee |
| 5 |  1m , (97%; 98% ee) |  2q^d |  3x , 69%, >95% ee |
| 6 | 1m |  2r |  3y , 84%, 98% ee |

^a The reactions were performed on a 0.5 mmol scale and at 0 °C instead of 25 °C. ^b Isolated yield of the *S*-pyridyl thioester prepared from the corresponding carboxylic acid, PySSPy (1.0 equiv.), PPh₃ (1.0 equiv.), MeCN, 0 °C to 25 °C, 16 h. ^c Isolated yield. ^d Prepared using *i*PrMgCl·LiCl (1.1 equiv.), THF, 0 °C, 2 h.





Scheme 2 Synthesis of fenofibrate (**3z**) using the Co-catalyzed acylation.

To gain insights into the reaction mechanism, radical trapping experiments were carried out. Thus, to a standard acylation setup of the developed protocol using *S*-pyridyl thioester **1a** and organozinc pivalate **2a**, various amounts of the radical trapping agent 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) were added. With 10% of the trapping reagent a decrease of the yield by 19% was observed for the acylation product **3a**. However, using 1.5 equiv. of TEMPO the product formation is almost completely suppressed. This may indicate the involvement of radical intermediates within this acylation reaction.¹⁴

The utility of this acylation was demonstrated in the synthesis of the antilipidemic drug fenofibrate²⁰ (**3z**, Scheme 2). Alkylation of 4-iodophenol (**6**) with isopropyl 2-bromo-2-methylpropanoate (**7**) affords the corresponding iodo-aryl ether **8** in 70% yield. **8** was treated with Mg, LiCl and Zn(OPiv)₂ generating the arylzinc pivalate **2s** in 72% yield.^{8a} Using the new cobalt-catalyzed acylation procedure, fenofibrate (**3z**) was obtained in 65% yield.

Conclusion

In conclusion, we have reported a cobalt-catalyzed acylation procedure of a variety of functionalized (hetero)arylzinc pivalates utilizing primary, secondary and tertiary alkyl, benzyl and (hetero)aryl *S*-pyridyl thioesters as mild acylating agents. These thioesters were readily prepared under neutral conditions from the corresponding carboxylic acid thus allowing their synthesis in the presence of various sensitive functional groups. Several α -chiral ketones were prepared with high stereoretention (94% to >99% ee). Further investigations are currently underway in our laboratories.

Conflicts of interest

There are no conflicts to declare.

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Germany) for the generous gift of chemicals. We also thank Vanessa Braun, Constantin Nuber, and Arne Stolpmann for the preparation of starting materials.

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