A Lewis acid-promoted Pinner reaction

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Abstract
Carbonitriles and alcohols react in a Lewis acid-promoted Pinner reaction to carboxylic esters. Best results are obtained with two equivalents of trimethylsilyl triflate as Lewis acid. Good yields are achieved with primary alcohols and aliphatic or benzylic carbonitriles, but the straightforward synthesis of acrylates and benzoates starting with acrylonitrile and benzonitrile, respectively, is similarly possible. Phenols are not acylated under these reaction conditions. The method has been used for the first total synthesis of the natural product monaspilosin. In the reaction of benzyl alcohols variable amounts of amides are formed in a Ritter-type side reaction.

Introduction
In 1877 Pinner and Klein discovered the proton-induced imidate syntheses [1,2]. They passed anhydrous gaseous hydrogen chloride through a mixture of isobutyl alcohol and benzonitrile. A crystalline product precipitated, which they identified as an imidate hydrochloride (Scheme 1). Best results in the Pinner reaction are obtained with primary or secondary alcohols and aliphatic or benzylic carbonitriles, but the straightforward synthesis of acrylates and benzoates starting with acrylonitrile and benzonitrile, respectively, is similarly possible. Phenols are not acylated under these reaction conditions. The method has been used for the first total synthesis of the natural product monaspilosin. In the reaction of benzyl alcohols variable amounts of amides are formed in a Ritter-type side reaction.
Scheme 2: Mechanism of the Pinner reaction.

A less frequently used pyrolysis leads to carboxamides (Scheme 3) [3-5].

Scheme 3: Transformations of imidate hydrochlorides.

The harsh reaction conditions preclude a broad application of the Pinner reaction. The high toxicity and the laborious handling of gaseous hydrogen chloride are further drawbacks of this reaction. Nevertheless, milder protocols have developed over the decades: Luo and Jeevanandam used trimethylsilyl chloride (TMSCl) and ethanol for an in situ generation of hydrogen chloride [6]. Watanabe et al. reported on a Pinner reaction with a 4 N hydrogen chloride solution in cyclopentyl methyl ether (CPME) [7]. An ionic liquid based on a sulfonic acid was used by Jiang et al. [8], where this method has only been applied to aliphatic nitriles. A transition metal-catalyzed Pinner reaction using dihydridotetrakis(triphenylphosphane) ruthenium ([RuH₂(PPh₃)₄]) as catalyst has been applied to aliphatic nitriles and alcohols and was similarly used for intramolecular reactions [9]. Schaefer et al. reported a base-catalyzed Pinner reaction, which gave only poor yields because of the setting of an equilibrium [10].

While developing a total synthesis of altenuic acid II [11], we observed the reaction of an aliphatic hydroxy group with acetonitrile in the presence of two equivalents of hafnium triflate [Hf(OTf)₄] yielding the respective acetate. A detailed investigation on this reaction is reported in this article [12].

Results and Discussion

The Lewis acid-mediated Pinner reaction of aliphatic alcohols with nitriles was first observed by us, when hafnium triflate was present in the reaction mixture. We first aimed to replace this rather expensive Lewis acid with a more favorable substitute. As a test reaction for optimization we used the acylation of 9H-fluoren-9-ylmethanol (1) with acetonitrile as the nitrile component and solvent (Scheme 4). This substrate and the respective ester 2 are simply detected by thin-layer chromatography (TLC) and their molecular weights prevent losses during evaporation procedures.

Scheme 4: Reaction used for optimizations.

A 72% yield was achieved, when two equivalents of hafnium(IV) triflate were used and when the nitrile was used as the solvent (Table 1, entry 1). Catalytic amounts of this Lewis acid led to unsatisfactory yields, when the reaction was performed in acetonitrile or in mixtures of acetonitrile with water (Table 1, entries 2 and 3). The 3% yield in acetonitrile/water (10:1) suggests that water is detrimental in the Pinner reaction. Among various tested Lewis acids, the best results were obtained with aluminium tribromide at 50 °C (65%, Table 1, entry 5) and with trimethylsilyl triflate at room temperature (83%, Table 1, entry 7). The less expensive trimethylsilyl chloride turned out to be an unsuitable alternative (Table 1, entry 8). The yield could not be improved, when two equivalents of aluminium bromide were used together with catalytic amounts of hafnium triflate (Table 1, entry 6).

Since two equivalents of a Lewis acid are necessary for optimum results, we presume activation of both the alcohol and the nitrile. A plausible mechanism includes formation of a silyl ether and an \( N \)-nitrilium cation. The former should be more nucleophilic than an alcohol and the latter should be an efficient electrophile (Scheme 5). Reaction of silyl ether and nitrilium cation leads to a cationic \( N,O \)-bis(trimethylsilyl)imino ester, which is hydrolyzed to a carboxylic ester. Formation of
Table 1: Selection of optimization experiments.

| #  | Lewis acid (equiv) | Conditions                     | Yield (s. m.)<sup>a</sup> [%] |
|----|-------------------|--------------------------------|--------------------------------|
| 1  | Hf(OTf)<sub>4</sub> (2.0) | MeCN, rt, 48 h               | 72 (15)                        |
| 2  | Hf(OTf)<sub>4</sub> (0.2) | MeCN, rt, 65 h               | 25 (69)                        |
| 3  | Hf(OTf)<sub>4</sub> (0.2) | MeCN/H<sub>2</sub>O 10:1, rt, 65 h | 3 (81)                         |
| 4  | AlBr<sub>3</sub> (2.0) | MeCN, rt, 65 h               | 50 (39)                        |
| 5  | AlBr<sub>3</sub> (2.0) | MeCN, 50 °C, 90 h             | 65 (20)                        |
| 6  | AlBr<sub>3</sub> (2.0), Hf(OTf)<sub>4</sub> (0.1) | MeCN, rt, 65 h | 64 (24) |
| 7  | TMSOTf (2.0) | MeCN, rt, 65 h               | 83 (9)                         |
| 8  | TMSCl (2.0) | MeCN, rt, 65 h               | 33 (59)                        |
| 9  | TMSOTf (2.0) | MeCN, Et<sub>3</sub>N, rt, 65 h | 80 (10)                        |

<sup>a</sup>Yields of recovered starting material (s. m.) given in parentheses. <sup>b</sup>Et<sub>3</sub>N (1 equiv) was added.

Scheme 5: Plausible mechanism of the Lewis acid-promoted Pinner reaction.

The high yields observed in the reactions of para-nitrobenzyl alcohol (21) and especially in its reaction with acrylonitrile brought us to the speculation that the nitro group has a special beneficial effect on this reaction, possibly as radical scavenger. It turned out that the addition of nitrobenzene [16] in the reactions with acrylonitrile led to increased yields in some cases. Other radical scavengers like hydroquinone had a similar effect.

The Lewis acid promoted Pinner reaction is highly chemoselective; phenols were not acylated by these conditions and were re-isolated with high yields (Table 2, entries 12–14). In this context we tested 4-(2-hydroxyethyl)phenol (53) containing an aliphatic and a phenolic hydroxy function in the reaction
with acetonitrile and benzyl cyanide, respectively (Scheme 6).
The respective esters 54 and 55 were obtained with good yields: no esterification of the phenolic hydroxy group was observed.
The reaction of 4-(2-hydroxyethyl)phenol (53) with benzyl cyanide yielded monaspilosin (55), an aromatic ester isolated from the mould fungus Monascus pilosus by Cheng et al. [18]. This compound was reported to have radical scavenger properties. The first total synthesis of this natural product was here-achieved with 73% yield in only one step.

Good yields were observed, when benzyl alcohols with electron withdrawing (−M) substituents such as 4-nitrobenzyl alcohol (21, Table 2, entry 5) and 4-hydroxymethylbenzoic acid (26, Table 2, entry 6) were reacted with benzyl cyanide or acetonitrile and even with acrylonitrile. A protection of the carboxylic acid turned out to be not necessary. In contrast, a 4-methoxy-substituted benzyl alcohol 52, i.e., an electron-rich benzyl alcohol, furnished no carboxylic ester at all (Table 2, entry 15). Rather poor yields of the respective carboxylic esters were achieved, when unsubstituted benzyl alcohol (56) or 4-fluorobenzyl alcohol (64) were reacted with one of the carbonitriles (Table 3). Instead we isolated significant amounts of carboxamides. These amides result from a Ritter-type reaction [19-21], where a carbenium ion (or a substrate with significant positive partial charge) reacts at the nitrogen atom of a nitrile. This transformation is a competition to the Pinner reaction, when benzyl alcohols are used. A possible mechanism of this reaction is given in Scheme 7. Double silylation leads to the formation of a good leaving group and the highly electrophilic benzylic carbon is attacked by the nitrile yielding a nitrilium cation. The reaction is finalized by hydrolysis furnishing the

Table 2: Variation of nitriles and alcohols. a

| # | R1-CN + R2-OH | TMSOTf (2 equiv) | Product, Yield [%] |
|---|---|---|---|
| 1 | Fluorenylmethanol (1) | | 2.83 |
| 2 | Me(CH2)2OH (6) | | 7.80 |
| 3 | Cl(CH2)6OH (31) | | 32.32 (33, 19c) |
| 4 | HO(CH2)6OH (31) | | 32, 32 (33, 19b) |
| 5 | PhOH (49) | | 0 |
| 6 | p-NO2C6H4OH (50) | | 0 |
| 7 | 3,4,5-Trimethoxyphenol (51) | | 0 |
| 8 | p-MeOC6H4OH (52) | | 0 |

a Alcohol (1 equiv), TMSOTf (2 equiv) dissolved in the nitrile (4 mL:mmol alcohol), rt, 65 h. b TMSOTf (2 equiv) and nitrobenzene (1 equiv) were added. c TMSOTf (4 equiv) was added. Yield of the monoacylated by-products 33 and 35, respectively, in parentheses.
Table 3: Carboxamide formation in a Pinner-type reaction.a

| # | R₁ | R₂ | Yield [%] (Product) |
|---|----|----|---------------------|
| 1 | Me | Bn (56) | 41 (57) | 18 (58) |
| 2 | Bn | Bn (56) | 18 (59) | 59 (60) |
| 3 | Ph | Bn (56) | 0 (62) | 66 (61) |
| 4 | Vinyl | Bn (56) | 4 (62) | 90 (63) |
| 5 | Me | p-FC₆H₄CH₂ (64) | 29 (65) | 66 (61) |
| 6 | Bn | p-FC₆H₄CH₂ (64) | 0 (62) | 79 (67) |
| 7 | Ph | p-FC₆H₄CH₂ (64) | 0 (62) | 70 (68) |
| 8 | Vinyl | p-FC₆H₄CH₂ (64) | 0 (62) | 89 (69) |

aAlcohol (1 equiv), TMSOTf (2 equiv) dissolved in the nitrile (4 mL/mmol alcohol), rt, 65 h.

Conclusion
The Lewis acid-promoted Pinner reaction is a mild and chemo-selective alternative for the synthesis of carboxylic esters starting with alcohols and nitriles. The esterification of primary aliphatic alcohols is possible even in the presence of unprotected carboxylic acids or phenolic hydroxy groups.

Supporting Information
Supporting Information File 1
Experimental section and NMR spectra of all synthesized compounds.
[http://www.beilstein-journals.org/bjoc/content/support/1860-5397-9-179-S1.pdf]

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