A Hydrogen Chloride-Free *Pinner* Reaction Promoted by *Lewis* Acids

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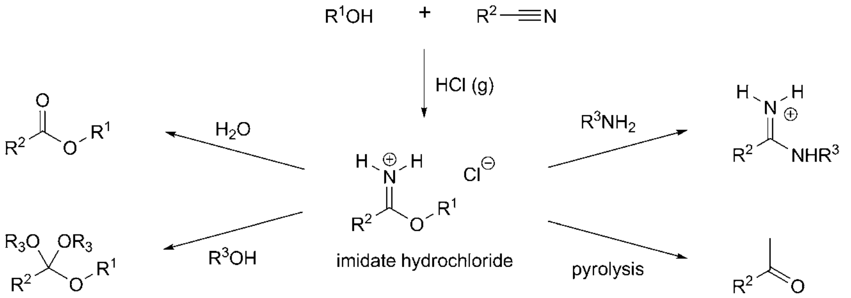
Dedicated to Prof. Dr. *Dieter Seebach* on the occasion of his 75th birthday

A hydrogen chloride-free variation of the *Pinner* reaction was developed, in which alcohols react with carbonitriles to furnish carboxylates. Best results were achieved with aliphatic alcohols, and aliphatic or benzylic nitriles in the presence of 2 equiv. of trimethylsilyl triflate (Me_3SiOTf). With these substrates, yields exceeding 80% were achieved. A strictly neutral variation of this protocol is possible, when 1 equiv. of Et_3N is added to the reaction mixture.

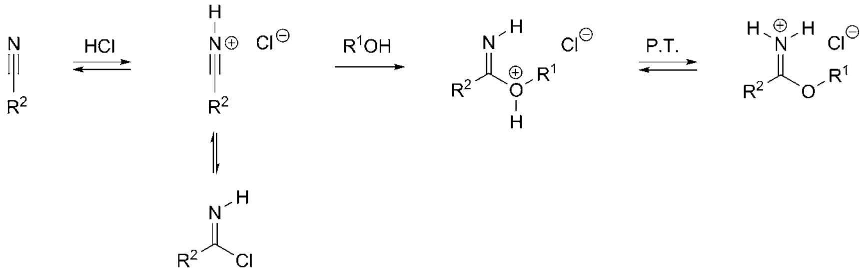
Introduction. – The *Pinner* imidate formation was first published in 1877 by *Pinner* and *Klein* [1][2]. Carbonitriles and alcohols react in the presence of gaseous HCl to form imidate hydrochlorides. Aliphatic and aromatic nitriles can be used (if steric hindrance is not too strong), and the second component is usually an aliphatic primary or secondary alcohol. Phenols can be used similarly, while electron-rich phenols (*e.g.*, dihydroxybenzenes) are substrates of a *Houben–Hoesch* reaction (electrophilic aromatic acylation), which is possible under these reaction conditions [3][4]. The imidate hydrochlorides can subsequently be transformed with H_2O to carboxylates, with alcohols into ortho esters, and with amines into amidines or amidine hydrochlorides. A less frequently used pyrolysis (above 0°) leads to carboxamides.

Scheme 1. Pinner *Reaction with Some Variations*



The mechanism of this reaction involves protonation of the nitrile N-atom leading to an activated nitrilium chloride, which is then attacked by the alcohol (*Scheme 2*). Proton transfer yields the imido-ester hydrochloride. A possible intermediate equilibrium formation of a carbonimidoyl chloride has no significant influence on the reaction outcome [2c].

Scheme 2. *Mechanism of the* Pinner *Reaction*. P.T., Proton transfer.

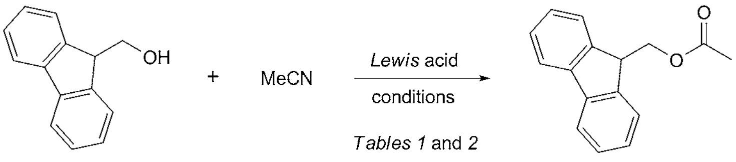


The rather drastic reaction conditions of the original *Pinner* reaction do not allow its broad application, especially not for the transformation of acid-sensitive substrates. Occasionally, milder conditions for the *Pinner* reaction have been reported. *Jiang et al.* reported on a variation, in which HCl was replaced with an ionic liquid based on a sulfonate. Nevertheless, these are similarly *Brønsted*-acidic conditions, and this methods has only been applied to aliphatic nitriles [5]. A significantly milder variation uses dihydridotetrakis(triphenylphosphano)ruthenium ($[RuH_2(PPh_3)_4]$) as a catalyst, where its catalytic activity is most probably due to its *Lewis* acidity [6]. Only poor yields have been reported with various Rh, Pd, Cu, and Mo catalysts. Primary aliphatic nitriles and alcohols were reacted by this method, and intramolecular variations (with formation of five-membered rings) were possible. This intramolecular variations furthermore allowed the utilization of secondary alcohols with good yields [6]. Reactions between electron-deficient nitriles (F- or Cl-substituted) and hydroxides with increased nucleophilicity (NH_2OH, oximes, or hydroxamic acids) are possible at elevated temperatures without further activation [7]. Formation of imidates from nitriles and alcohols is furthermore possible with base catalysis. Setting of an equilibrium usually results in slow reactions with poor yields, rendering this variation significantly less useful [8]. Nevertheless, a similar reaction is used in the most prominent trichloroacetimidate activation of sugars as glycosyl donors, developed by *Schmidt et al.* [9]. Furthermore, *Luo* and *Jeevanandam* reported on a variation in which HCl was generated *in situ* by reaction of Me_3SiCl with EtOH (both in excess) [10].

During elaboration of a total synthesis, we incidentally found that OH groups react with the solvent MeCN in the presence of 2 equiv. of hafnium triflate (= hafnium trifluoromethanesulfonate; $Hf(OTf)_4$). We considered this *Lewis* acid too expensive to be useful in a broadly applied method and started to work on a comprehensive optimization, which is reported below.

Results and Discussion. – We considered the reaction of (9*H*-fluoren-9-yl)methanol with MeCN to be a representative example, which was used for the optimization of the reaction conditions. With this substrate, a simple UV detection in thin layer chromatography was warranted, and its molecular weight prevents losses during evaporation procedures (*Scheme 3*). All given yields refer to isolated and purified substrates. Contrary to the originally proposed *Pinner* reaction, after aqueous workup we always observed formation of the ester instead of the imidate.

Scheme 3. *Reaction Used for Optimizations*



This reaction proceeded with good yield (72%), when 2 equiv. of $Hf(OTf)_4$ were used as *Lewis* acid in neat MeCN as the solvent (*Table 1*); presence of an inert-gas atmosphere was not necessary. Utilization of catalytic amounts of this *Lewis* acid led to significantly reduced yields.

Table 1. *Optimization of Reaction Conditions with* $Hf(OTf)_4$ (*cf.* *Scheme 3*)

Entry	*Lewis* acid (equiv.)	Conditions	Yield (s.m.)[a]) [%]
1	$Hf(OTf)_4$ (2)	MeCN, r.t., 48 h	72 (15)
2	$Hf(OTf)_4$ (0.2)	MeCN, r.t., 65 h	25 (69)
3	$Hf(OTf)_4$ (0.2)	$MeCN/H_2O$ 3 : 1, r.t., 65 h	9 (79)
4	$Hf(OTf)_4$ (0.2)	$MeCN/H_2O$ 1 : 1, r.t., 65 h	4 (87)
5	$Hf(OTf)_4$ (0.2)	$MeCN/H_2O$ 5 : 1, r.t., 65 h	17 (71)
6	$Hf(OTf)_4$ (0.2)	$MeCN/H_2O$ 10 : 1, r.t., 65 h	3 (81)

[a]) Yields of recovered starting material (s.m.) given in parentheses. All yields refer to isolated and purified substrates.

Various *Lewis* acids were tested (*Table 2*). Addition of $AlBr_3$ gave quite similar yields (50%) as have been achieved with $Hf(OTf)_4$. Since the former *Lewis* acid is significantly cheaper than the latter, we tested whether over-stoichiometric amounts of $AlBr_3$ together with $Hf(OTf)_4$ as catalyst leads to higher yields. Nevertheless, the reaction outcome could not be improved with this variation. Best results were achieved with 2 equiv. of Me_3SiOTf at room temperature (83%). Neither higher nor lower reaction temperatures led to an improvement. Replacement of this *Lewis* acid with the cheaper Me_3SiCl resulted in non-satisfactory yields (33%).

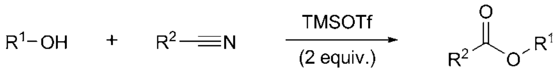
The optimized conditions have been applied to the reaction of four primary aliphatic alcohols and a selection of commonly used nitriles (*Table 3*). We combined (9*H*-fluoren-9-yl)methanol, decan-1-ol, 6-chlorohexan-1-ol, and diethylene glycol monoethyl ether with MeCN, acrylonitrile, benzonitrile, and benzyl cyanide (BnCN). Best results were obtained in the reactions of MeCN and BnCN, *i.e.*, in the reaction of aliphatic nitriles. Yields from 75 to 90% were obtained with these substrates. The yields were not satisfactory with acrylonitrile and benzonitrile. Nevertheless, a previously published alternative synthesis of (9*H*-fluoren-9-yl)methyl acrylate starting with (9*H*-fluoren-9-yl)methanol and the moisture-sensitive acryl chloride (in the presence of Et_3N) was conducted at 0° under a N_2 atmosphere and gave a yield of only 33% after 31 h [11]. The here presented protocol provides higher yields (52%, *Entry 2*) and allows the utilization of a less-sensitive substrate. The identity and purity of all products were determined by NMR spectroscopy.

Table 2. *Optimization of the* Lewis *Acid* (*cf. Scheme 3*)

Entry	*Lewis* acid (equiv.)	Conditions[a]	Yield (s.m.)[b] [%]
1	$Hf(OTf)_4$ (2)	r.t., 48 h	72 (15)
2	$LaCl_3$ (2)	r.t., 65 h	2 (83)
3	$ZnCl_2$ (2)	r.t., 65 h	4 (87)
4	$ZnBr_2$ (2)	r.t., 65 h	1 (87)
5	$FeCl_3$ (2)	r.t., 65 h	3 (82)
6	$CuBr_2$ (2)	r.t., 90 h	5 (68)
7	$CeCl_3 \cdot 6\,H_2O$ (2)	r.t., 90 h	1 (87)
8	$AlCl_3$ (2)	r.t., 65 h	7 (83)
9	$AlBr_3$ (2)	r.t., 65 h	50 (39)
10	$AlBr_3$ (2)	50°, 90 h	65 (20)
11	$AlCl_3$ (2), $Hf(OTf)_4$ (0.1)	r.t., 65 h	9 (82)
12	$AlBr_3$ (2), $Hf(OTf)_4$ (0.1)	r.t., 65 h	64 (24)
13	**TMSOTf (2)**	**r.t., 65 h**	**83 (9)**
14	TMSOTf (2)	50°, 65 h	78 (5)
15	TMSOTf (2)	0°, 65 h	60 (27)
16	TMSOTf (1)	50°, 65 h	77 (5)
17	TMSOTf (0.5)	50°, 65 h	41 (49)
18	TMSCl (2)	r.t., 65 h	33 (59)
19	TMSCl (2)	50°, 65 h	26 (64)
20	TMSOTf (2)	Et_3N, r.t., 65 h[c]	80 (10)

[a] Reactions performed in MeCN without inert-gas atmosphere. [b] Yields of recovered starting material (s.m.) given in parentheses. All yields refer to isolated and purified substrates. [c] TMSOTf was added to a solution of (9*H*-fluoren-9-yl)methanol and Et_3N (1 equiv.) in MeCN.

Table 3. *Variation of Some Alcohols and Carbonitriles*[a]

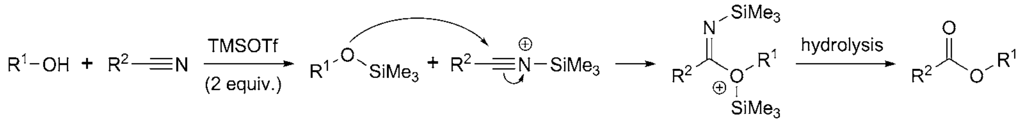


Entry	R^1	R^2	Yield [%][b]
1	(9*H*-Fluoren-9-yl)methyl	Me	83
2	(9*H*-Fluoren-9-yl)methyl	Vinyl	52
3	(9*H*-Fluoren-9-yl)methyl	Ph	44
4	(9*H*-Fluoren-9-yl)methyl	Bn	86
5	$Me(CH_2)_9$	Me	80
6	$Me(CH_2)_9$	Vinyl	29
7	$Me(CH_2)_9$	Ph	23
8	$Me(CH_2)_9$	Bn	85
9	$Cl(CH_2)_6$	Me	84
10	$Cl(CH_2)_6$	Vinyl	38
11	$Cl(CH_2)_6$	Ph	27
12	$Cl(CH_2)_6$	Bn	90
13	$EtO(CH_2)_2O(CH_2)_2$	Me	75
14	$EtO(CH_2)_2O(CH_2)_2$	Vinyl	23
15	$EtO(CH_2)_2O(CH_2)_2$	Ph	26
16	$EtO(CH_2)_2O(CH_2)_2$	Bn	85

[a] Reactions performed in the respective nitrile as solvent at room temperature for 65 h. [b] All yields refer to isolated and purified substrates.

A proposal of a plausible reaction mechanism includes formation of an *N*-silylnitrilium ion [12] (*Scheme 4*), which is thus activated for a nucleophilic attack. The nucleophilicity of an intermediate silyl ether should be higher compared to the nucleophilicity of the corresponding alcohol (albeit its steric hindrance is increased). Formation of the *Brønsted* acid TfOH is likely under these reaction conditions, but it seems to have no influence on the reaction outcome, since a similar reaction with addition of 1 equiv. of Et_3N leads to comparable yields (*Table 2*, *Entries 13* and *20*). Further experiments to gain a more detailed insight in the mechanism of this reaction are currently under investigation in our laboratories.

Scheme 4. *Proposal for a Reaction Mechanism*



Conclusions. – The here presented variation of the *Pinner* reaction with mild reaction conditions should be of significant use for the transformation of nitriles to carboxylates, for the acylation of alcohols, and thus for the protection of alcohols. Currently, we are trying to broaden the scope of this reaction.

This work was supported by the *Landesgraduiertenförderung Baden-Württemberg* (grant to *G. N.*).

Experimental Part

General Procedure for Reactions with MeCN and Acrylonitrile. Me_3SiOTf (336 mg, 1.51 mmol, 2.00 equiv.) was added to a soln. of the alcohol (0.76 mmol, 1.00 equiv.) in the nitrile (3 ml), and the mixture was stirred at r.t. for 65 h. H_2O (25 ml) and brine (25 ml) were added, and the mixture was extracted with AcOEt (3 × 30 ml). The combined org. layers were dried (Na_2SO_4) and concentrated. The crude product was purified by chromatography (silica gel).

General Procedure for Reactions with BnCN and PhCN. Me_3SiOTf (336 mg, 1.51 mmol, 2.00 equiv.) was added to a soln. of the alcohol (0.76 mmol, 1.00 equiv.) in the nitrile (3 ml), and the mixture was stirred at r.t. for 65 h. H_2O (25 ml) and brine (25 ml) were added, and the mixture was extracted with AcOEt (3 × 30 ml). The combined org. layers were dried (Na_2SO_4) and concentrated, and excess nitrile was distilled off at reduced pressure (90°, 0.1 mbar). The crude product was purified by chromatography (silica gel).

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Received August 9, 2012