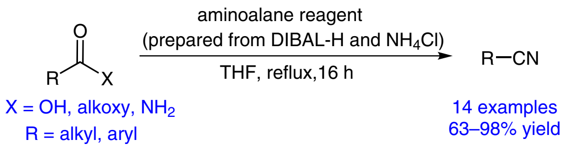
One-Step Synthesis of Nitriles from Acids, Esters and Amides Using DIBAL-H and Ammonium Chloride

Agnieszka Wojtkielewicz*
Zenon Łotowski
Jacek W. Morzycki

Institute of Chemistry, University of Białystok,
Ciołkowskiego 1K, 15-245 Białystok, Poland
jeremy@uwb.edu.pl



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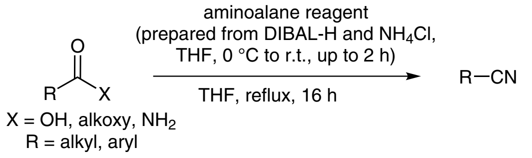
Abstract A convenient, one-step procedure is presented for the conversion of carboxylic acids or their derivatives (esters, lactones, amides) to nitriles with an aminoalane reagent prepared from diisobutylaluminum hydride (DIBAL-H) and ammonium chloride.

Key words nitrile, carboxylic acid, diisobutylaluminum hydride, aluminum amide, ammonium chloride

Nitriles constitute an important class of organic compounds. They can be easily converted to aldehydes, ketones, carboxylic acids, amines, amides, and nitrogen-containing heterocycles (e.g., oxazoles, thiazoles, tetrazoles).[1] Therefore, nitriles are used for the preparation of various products of commercial significance, e.g., polyamides, pharmaceuticals, agrochemicals, dyes, and fine chemicals.[2] Moreover, the cyano group itself is present in biologically active compounds, such as Letrazole (used in the treatment of breast cancer), Periciazine (an antipsychotic drug), Citalopram (an antidepressant drug), HIV protease inhibitors, and 5-lipoxygenase inhibitors.[3–5] So far, numerous methods of nitrile preparation have been developed. The most common synthetic strategies include nucleophilic substitution of halides by the CN ion,[6] oxidation of amines,[7] and dehydration of amides[6,8] or aldoximes.[9] Most of the described syntheses of nitriles involve the use of high temperatures (>150 °C), acidic dehydrating reagents, or toxic reagents (e.g., metal cyanides, ruthenium compounds, sodium azide, pyridine, liquid ammonia). Due to the great practical importance of nitriles, alternative methods for their preparation under mild, non-acidic conditions are still needed. Although many protocols for the preparation of nitriles from carboxylic acids and their derivatives can be found in the literature, most of them consist of two or more step procedures and often require the isolation of intermediates. Only a few examples of the direct conversion of carboxylic acids or inactivated esters into nitriles have been reported.[10] In 1979 Weinreb described one-step preparation of nitriles from esters.[11] In this procedure the ester substrate is treated with aluminum amide prepared from trimethylaluminum and anhydrous liquid ammonia in a refluxing xylene to afford nitrile. The other method of nitrile synthesis from carboxylic acids is based on the use of diphosphorus tetraiodide and ammonium carbonate in anhydrous carbon disulfide.[12] Carboxylic acids and esters can also be transformed into nitriles in multistep but one-pot synthesis by treatment with ethyl iodide, K_2CO_3, 18-crown-6 and, subsequently, with sodium diisobutyl-*tert*-butoxyaluminum hydride (SDBBA-H) and, finally, with iodine and aqueous ammonia in the case of carboxylic acid substrates or by using SDBBA-H followed by treatment with iodine and aqueous ammonia in the case of ester substrates.[13,14] The analogous strategy may be employed to convert amides to nitriles, however, the reaction with ammonia and iodine must be preceded by amide reduction with diisobutylaluminum hydride (DIBAL-H).[15]

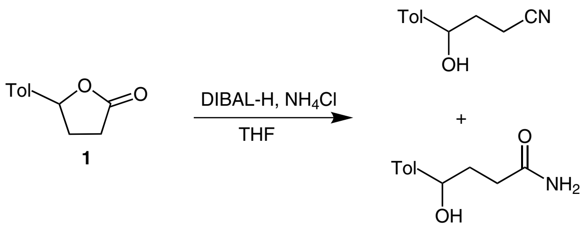
Herein we report an alternative facile transformation of carboxylic acids or their derivatives (esters, lactones, and amides) into nitriles using aminoalane reagent prepared from DIBAL-H and ammonium chloride (Scheme 1). Previously, scientists from China employed aluminum N-substituted amides obtained from DIBAL-H and an appropriate amine or its hydrochloride for amide synthesis from esters and lactones.[16] To the best of our knowledge, this way of preparing N-unsubstituted diisobutylaluminum amide as well as the direct synthesis of nitriles using DIBAL-H and NH_4Cl has not been reported.



Scheme 1 Synthesis of nitriles from carboxylic acids, esters, and amides using DIBAL-H and NH_4Cl

Our study was inspired by the observation made during attempts to prepare a primary amide from lactone **1** using aminoalane reagent (Table 1). Based on a report[16] from Chinese researchers and the fact that the Al–C bond is stronger than the Al–H bond, we prepared the desired aluminum amide from DIBAL-H instead of trimethylaluminum that is used in the Weinreb method.[11] Additionally, this procedure seems to be more convenient from a practical point of view in comparison to the Weinreb method, which requires the use of trimethylaluminum and anhydrous liquid ammonia. The desired aminoalane was synthesized in a reaction of DIBAL-H with ammonium chloride under mild reaction conditions (0 °C to r.t., THF, up to 2 h).[17] The reaction of lactone **1** with 20 equivalents of the prepared aluminum amide at room temperature led to the formation of the primary amide in 59% yield (Table 1, entry 1).

Table 1 Reaction of Lactone **1** with Aminoalane Prepared from DIBAL-H and NH_4Cl under Various Reaction Conditions



Entry	Aluminum amide	Temp	Product yield	
			Nitrile	Amide
1	20 equiv	r.t.	0%	59%
2	20 equiv	66 °C	98%	0%
3	10 equiv	66 °C	75%	21%
4	5 equiv	66 °C	64%	35%
5	2 equiv	66 °C	<2%	12%

When the reaction temperature was increased to 66 °C (refluxing THF), nitrile was obtained as the only product in 98% yield (Table 1, entry 2). Nitrile was also the major product in the reaction with lower excess of reagent (10 or 5 equiv) in refluxing THF (Table 1, entries 3 and 4). With only two equivalents of aluminum reagent, conversion of the reaction was poor (Table 1, entry 5). The results of these experiments prompted us to investigate the DIBAL-H–NH_4Cl system as a novel, efficient reagent for nitrile preparation from carboxylic acids and their derivatives. To prove the usefulness of the proposed method, we examined reactions of various carboxylic acids, esters, and amides with aluminum amide obtained in situ from DIBAL-H and NH_4Cl (Table 2).[18]

The results clearly indicate that various carboxylic acids (aliphatic, unsaturated, aromatic) as well as their derivatives (lactones, esters, and amides) can be conveniently converted to corresponding nitriles in good yields (Table 2). However, in most cases amide was obtained as a by-product. Its formation was dependent on the amount of aluminum amide. An increase in the aminoalane amount resulted in higher nitrile yields (Table 2, entries 1 vs. 2 or 9 vs. 10). The reactions of carboxylic acids or their esters with a carboxyl group bound to the tertiary carbon atom were stopped at the amide stage. Nitriles were not formed from these substrates (Table 2, entries 7, 8, and 14). Esters of various alcohols appear to have a similar reactivity (Table 2, entries 9 and 11). Almost no racemization was observed in the case of chiral acids or esters having a stereogenic center at the α position (Table 2, entries 6 and 13) under reaction conditions.

It seems that the reagent formed from DIBAL-H and ammonium chloride exhibits greater reactivity than that generated from Me_3Al and liquid NH_3. First of all, the present reagent appeared to be effective not only for the conversion of esters and lactones, but also of carboxylic acids to nitriles. The corresponding nitriles were obtained from all substrate types in good yields (Table 2). The reaction conditions applied here (boiling THF) were much milder than those previously used for the synthesis of nitriles, with Me_2AlNH_2 prepared from Me_3Al (boiling xylene). This reactivity difference may result from replacing the methyl groups by isobutyl ones in the dialkylaluminum amide. However, it is also possible that a species of a different structure [e.g. $(i\text{-Bu})_2AlNH_2xHCl$ or $(i\text{-Bu})ClAl\text{-}NH_2$], other than the expected aminoalane [$(i\text{-Bu})_2AlNH_2$], is formed. Unfortunately, the structure has not been determined yet.

In subsequent experiments we investigated the influence of ammonium salt on the reactivity of the obtained reagent. The aluminum amides obtained from DIBAL-H with various ammonium salts, chloride, nitrate, and carbonate were examined in the model reaction (Table 3). All synthesized aluminum complexes were reactive and led to the nitrile formation. The best product yield was obtained for the reagent prepared from ammonium chloride, albeit only slight differences were observed (Table 3).

The use of another aluminum hydride, i.e. $LiAlH(t\text{-BuO})_3$, to prepare the aluminum amides was also studied. The reagent obtained from this aluminum hydride appeared to be less reactive and less stable. It did not react with carboxylic acids, but it did promote limited conversion (less than 20%) of lactone **1** to amide. The nitriles were not formed with this reagent.

Table 2 Synthesis of Nitriles from Carboxylic Acids, Esters, and Amides with Aluminum Amide Obtained from DIBAL-H and NH_4Cl^a

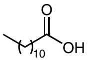
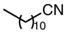
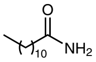
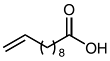
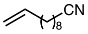
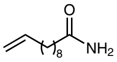
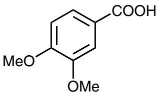
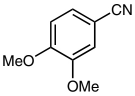
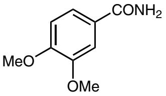
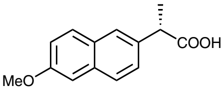
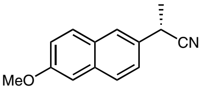
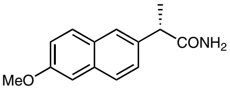
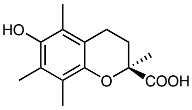
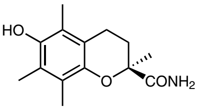
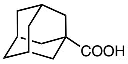
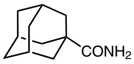
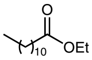
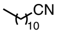
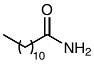
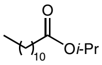
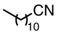
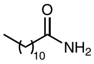
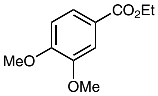
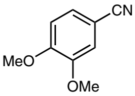
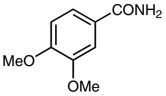
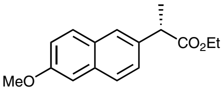
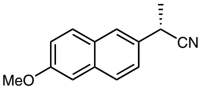
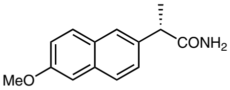
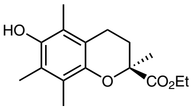
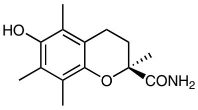
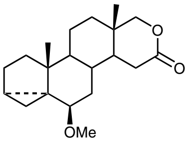
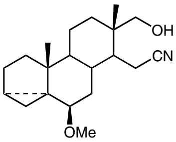
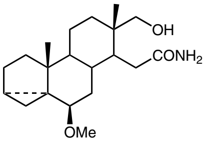
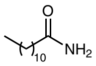
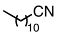
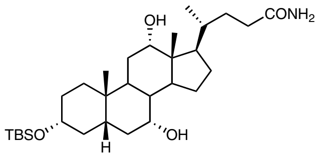
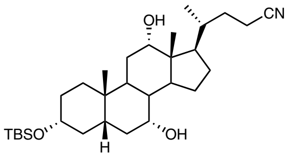
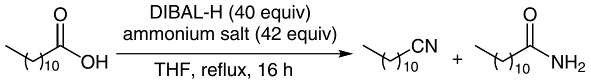
Entry	Substrate	DIBAL-H (equiv)	NH_4Cl (equiv)	Product (yield)			
1		20	21		(37%)		(60%)
2		40	42		(75%)		(<2%)
3[b]		20	21		(0%)		(0%)
4		40	42		(67%)		(15%)
5		40	42		(67%)		(30%)
6	 (ee > 98%)	40	42		(52%, ee 88%)		(40%, ee 95%)
7		40	42		(90%)		
8		40	42		(64%)		
9		20	21		(59%)		(41%)
10		40	42		(78%)		(12%)
11		20	21		(63%)		(30%)
12		20	21		(77%)		(23%)
13	 (ee 98%)	20	21		(68%, ee 88%)		(23%, ee 94%)
14		20	21		(96%)		
15		20	21		(70%)		(<1%)

Table 2 (continued)

Entry	Substrate	DIBAL-H (equiv)	NH_4Cl (equiv)	Product (yield)
16		40	42	 (70%)
17		40	42	 (98%)
18		20	21	(48%)

[a] Reaction temperature: 66 °C; reaction time: 16 h.
[b] Reaction was carried out at r.t.

Table 3 Reactivity of Aminoalane Prepared from Various Ammonium Salts



Entry	Ammonium salt	Product yield	
		Nitrile	Amide
1	NH_4Cl	75%	<2%
2	NH_4NO_3	56%	15%
3	$(NH_4)_2CO_3$	61%	25%

In summary, a simple one-step protocol was developed for the synthesis of nitriles from carboxylic acids or their derivatives (lactones, esters, amides). A new aminoalane reagent was prepared in situ from DIBAL-H and ammonium salt. By employing this method, various substrates, e.g., aliphatic, unsaturated, aromatic acids (or their esters and amides), excluding those with a carboxyl group at the tertiary carbon atom, were transformed in good yields into the corresponding nitriles under relatively mild conditions.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1381060.

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(17) **Experimental Procedure for the Preparation of Aminoalane Reagent**: A solution of DIBAL-H in toluene (1 M, 1 equiv) was added to a cooled (0–5 °C) suspension of NH_4Cl (1.05 equiv) in anhyd THF under argon. The reaction was stirred for 15 min in an ice bath and then for 1.5 h at r.t. After this time, the obtained complex solution was used directly for nitrile synthesis.

(18) **Experimental Procedure for the Synthesis of Nitrile from Carboxylic Acid, Ester, Lactone or Amide**: The solution of aminoalane reagent (prepared from 20 equiv of DIBAL-H in case of ester and lactone substrates or from 40 equiv in case of carboxylic acid and amide substrates) was added to a solution of carboxylic acid (1 equiv) or its derivative (lactone, ester or amide, 1 equiv) in anhyd THF at r.t. Stirring was continued for 16 h at 66 °C. After this time, the reaction mixture was cooled, quenched with aqueous solution of $KHSO_4$ and the product was extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhyd Na_2SO_4, and the solvent was evaporated. The crude product was purified by silica gel chromatography with hexane–EtOAc elution.