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# A DIRECT CONVERSION OF ESTERS TO NITRILES

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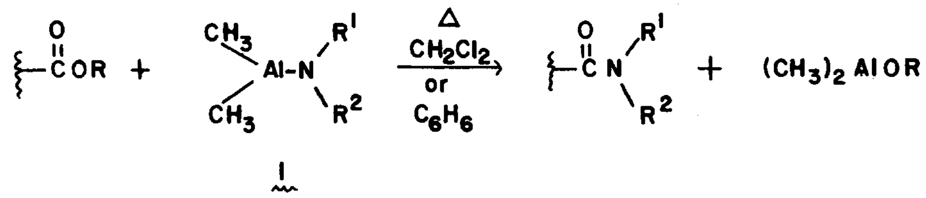
Summary: Treatment of an ester with dimethylaluminum amide (2) in refluxing xylene produces a nitrile in good yield.

We recently reported[2] a simple and general procedure for converting carboxylate esters to carboxamides using easily generated dimethylaluminum amide reagents of type 1 [equation (1)].

(1)

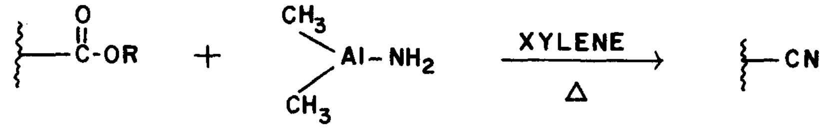


$R^1, R^2$ = H, alkyl, aryl

This transformation has proven successful with a wide variety of esters using both N-substituted and unsubstituted aluminum amide reagents in either refluxing methylene chloride or benzene.

We once noticed that upon heating an ester with dimethylaluminum amide (2) in benzene for a long period of time, small amounts of the corresponding nitrile began to appear. This observation has led us to develop a useful and apparently general synthetic procedure for a "one-pot" transformation of esters to nitriles. Thus, if an ester is heated with two equivalents of dimethylaluminum amide (2) in refluxing xylene for 0.5-19 hr, it is converted into the corresponding nitrile in good yield [equation (2)].[3] To our knowledge, no other one-step conversion of esters to nitriles has been reported previously.

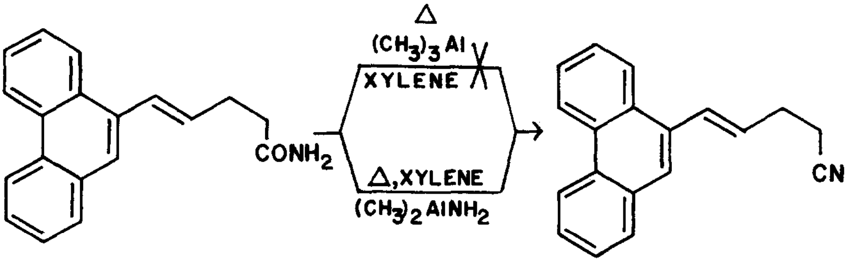
(2)



2

We have tested this method on a number of functionalized esters and isolated yields of the nitriles prepared are listed in the Table. As noted earlier,[2] aluminum amide reagents are compatible with a wide variety of functional groups.

It is not clear as to exactly how this transformation is occurring, but we believe a carboxamide or an aluminum derivative of a carboxamide must undoubtedly be an intermediate. Interestingly, treatment of amide 3 with trimethyl aluminum in refluxing xylene very slowly produced nitrile 4.[4] On the other hand, treatment of 3 with aluminum reagent 2 gave nitrile 4 in good yield on heating in xylene for 45 minutes.[5]



3 4

Preparation of a Stock Solution of Dimethylaluminum Amide (2):

A solution of 22% trimethyl aluminum in hexane (35 mL) in 25 mL of dry methylene chloride was placed in a 100 mL 3-necked flask equipped with a dry ice condenser and a nitrogen inlet and was cooled in a dry ice-acetone bath. Excess anhydrous ammonia (7-8 mL) was slowly distilled from sodium into the flask. After about half of the addition was completed, the external cooling bath was removed. When the addition of ammonia was complete, the dry ice condenser was removed and the solution was stirred at room temperature until gas was no longer evolved. This solution, estimated to be approximately 1.2 M, could be stored in the freezer for up to two weeks.[6] It was allowed to come to room temperature before use.

General Procedure for Conversion of Esters to Nitriles:

A solution of the ester (2 mmol) in 40 mL of dry xylene (distilled from $P_2O_5$) was treated with 3.3 mL (∼4 mmol) of dimethylaluminum amide (2) in $CH_2Cl_2$. The mixture was heated at reflux for 0.5-19 hr until TLC indicated that complete reaction had occurred. The mixture was cooled and water was added. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was generally purified by chromatography on silica gel. Isolated yields of some representative test cases are listed in the Table.

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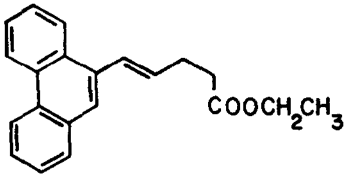
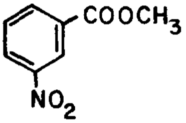
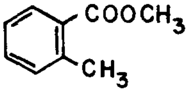
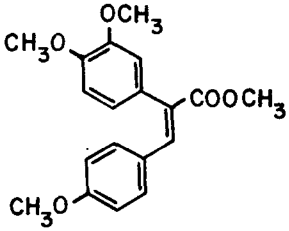
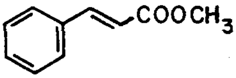
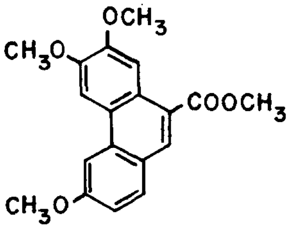
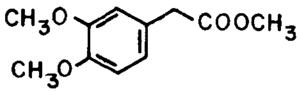
## References and Notes

1. Fellow of the A. P. Sloan Foundation, 1975-79; Recipient of a Research Career Development Award from the National Institutes of Health (HL-00176), 1975-80.
2. (a) A. Basha, M. Lipton and S. M. Weinreb, *Tetrahedron Lett.*, 4171 (1977); (b) M. F. Lipton, A. Basha and S. M. Weinreb, *Org. Syn.*, 59, 00 (1979).
3. Addition of dimethylaluminum N,N-dimethylamide to nitriles has been reported: T. Hirabayashi, K. Itoh, S. Sakai and Y. Ishii, *J. Organomet. Chem.*, 21, 273 (1970). We see no products resulting from this sort of addition to our product nitriles.
4. See: H. Tani, T. Araki and H. Yasuda, *J. Polymer Sci., B*, 4, 727 (1966); J. R. Jennings, K. Wade and B. K. Wyatt, *J. Chem. Soc., A*, 2535 (1968); Y. Kai, N. Yasuoka, N. Kasai, M. Kakudo, H. Yasuda and H. Tani, *J. Chem. Soc., Chem. Commun.*, 1332 (1968) for aluminum complexes of carboxamides.
5. I. T. Harrison and S. Harrison, "Compendium of Organic Synthetic Methods," Wiley-Interscience, New York, vol. 1, 1971, p. 464-5, for a listing of ways to convert amides into nitriles. We see no particular advantage in developing reagent 2 for use in converting amides to nitriles considering the plethora of good methods which now exist.
6. Best results were obtained with freshly prepared reagent.

Table. Conversion of esters to nitriles with dimethylaluminum amide (2) in refluxing xylene

| Ester | Reaction time (hr) | Isolated yield of nitrile |
|---|---|---|
|  | 0.5 | 80 |
|  | 1 | 91 |
|  | 1 | 77 |
|  | 4 | 71 |
|  | 13 | 75 |
|  | 4.75 | 73 |
|  | 19 | 50 |

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