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An efficient conversion of nitriles to amides: application in the synthesis of *N*,*N*-diethyl-*m*-toluamide (DEET™)

Apurba Bhattacharya,[a,*] Robert Erik Plata,[a] Victor Villarreal,[a]
Savitha Muramulla[a] and Jiejun Wu[b]

[a] *Department of Chemistry, Texas A&M University–Kingsville, Kingsville, TX 78363, USA*
[b] *J&J Pharmaceutical Research and Development, LLC, 3210 Merryfield Row, San Diego, CA 92121, USA*

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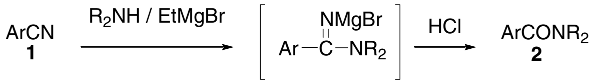
Abstract—Arylnitriles react with magnesium amides to produce carboxamides in excellent yield. The method was applied for the preparation of the insect repellent DEET™.

As part of our ongoing industry—university collaborative research program directed toward developing efficient pharmaceutical processes, we wish to report an efficient, one-step conversion of arylnitriles to the corresponding amides, a desirable transformation for which few mild and practical methods exist.[1,2] Increasing the

Table 1. Preparation of arylamides from nitriles and magnesium amide[6]



Entry	Aromatic nitrile	Amide	Yield (%)
1	Benzonitrile	*N*,*N*-Dipropylbenzamide	88
2	4-Bromo benzonitrile	4-Bromo-*N*,*N*-dipropylbenzamide	86
3	Naphthalene-1-carbonitrile	Naphthalene-1-carboxylic acid dipropylamide	89
4	3-Methoxy benzonitrile	3-Methoxy-*N*,*N*-dipropylbenzamide	87
5	4-Methyl benzonitrile	4-Methyl-*N*,*N*-dipropylbenzamide	86
6	3-Chloro benzonitrile	3-Chloro-*N*,*N*-dipropylbenzamide	87
7	3-Cyano pyridine	*N*,*N*-Dipropyl-nicotinamide	85
8	2,6, Dimethyl benzonitrile	2,6-Dimethyl-*N*,*N*-dipropylbenzamide	85
9	2,3 Dichloro benzonitrile	2,3-Dichloro-*N*,*N*-dipropylbenzamide	86
10	2-Cyano pyridine	Pyridine-2-carboxylic acid dipropylamide	84
11	2-Methyl benzonitrile	2-Methyl-*N*,*N*-dipropylbenzamide	85
12	4-Methoxy benzonitrile	4-Methoxy-*N*,*N*-dipropylbenzamide	86
13	4-(Methylthio) benzonitrile	4-(Methylthio)-*N*,*N*-dipropylbenzamide	84
14	2-Chloro benzonitrile	2-Chloro-*N*,*N*-dipropylbenzamide	85
15	3-Methyl benzonitrile	3-Methyl-*N*,*N*-dipropylbenzamide	86
16	3-Methyl benzonitrile	*N*,*N*-Diethyl-*m*-toluamide (DEET™)	90
17	4-Methoxy benzonitrile	*N*,*N*-Diethyl-4-methoxy-benzamide	81
18	Benzonitrile	*N*-Butyl-benzamide	83
19	3-Methyl benzonitrile	*N*-Butyl-3-methyl-benzamide	90
20	Benzonitrile	*N*-Cyclohexyl-benzamide	76

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* Corresponding author. Tel.: +1 361 593 2664; fax: +1 361 593 3597; e-mail: kfab002@tamuk.edu

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nucleophilicity of the amine via the aminomagnesium bromide derivative and its utility in the conversion of acylimidazolides to amides was reported earlier.[3] Herein, we further demonstrate the application of this methodology to a convenient synthesis of arylamides from the corresponding arylnitriles. The enhanced reactivity of these magnesium reagents could be attributed to a 'push–pull' mechanism, originating from the nucleophilicity of the magnesium amide coupled with the Lewis acid activation of the $MgBr_2$ produced from potential disproportionation of the aminomagnesium bromide moiety.[4] The aminomagnesium bromides, which are conveniently generated from equimolar amounts of alkylamine and ethylmagnesium bromide in THF with evolution of ethane, efficiently add to nitriles and afford the desired amides in good to excellent yields after aqueous work-up. Interestingly, the corresponding lithium amides were ineffective and the presence of a large excess of amine stops the reaction. This methodology was successfully utilized to prepare the insect repellant *N*,*N*-diethyl-*m*-toluamide (DEET™) in 90% yield.[5] Representative examples are summarized in Table 1.[7] A typical experimental procedure is as follows: *n*-butylaminomagnesium bromide was prepared by dropwise addition of *n*-butylamine (3.12 g, 42.7 mmol) in 5 mL THF to a stirred solution of ethylmagnesium bromide (5.17 g, 38.8 mmol, 12.8 mL of 3 M solution in ether) under nitrogen. The mixture was stirred for 1 h at 30 °C. The resulting magnesium amide solution was added to a stirred solution of benzonitrile (1 g, 9.7 mmol) dissolved in THF (2 mL) and the mixture was stirred for 1 h at 30 °C. The reaction was quenched by adding to a stirred mixture of dichloromethane (20 mL) and aqueous HCl (10 mL of 2 M solution) at 22 °C. The organic layer containing the product was washed with brine (2 × 10 mL), dried over sodium sulfate, and evaporation of the solvent in vacuo produced 1.53 g of *n*-butylbenzamide (89% yield).

In summary, we have developed a simple, conceptually distinct amidation of arylnitriles which complements the existing technologies in terms of practicality, and demonstrates yet another facet of the utility of aminomagnesium derivatives in organic synthesis.[8]

Acknowledgements

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References and notes

1. *Chem. Eng. News*; Education Concentrate, **2001**, *July 23*, 41.
2. For nitriles to amidines by aluminum amide addition, see: Gargipati, R. S. *Tetrahedron Lett.* **1990**, *31*, 1969.
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4. The stoichiometry is based on assumed metathesis without considering complexation, aggregation, etc.
5. DEET, In *Merck Index*; 12th ed. Budavari, S., Ed.; Merck, 1996; Vol. 2912, p 483.
6. All products exhibited satisfactory spectral properties (Bruker 600 MHz ^1H NMR and ^{13}C NMR) fully in accord with known or expected values and GC–MS analysis (Shimadzu QP5050A) in the EI mode provided similarity index match of >90% compared to the authentic samples in the NIST-98 database.
7. The product amides were pure as evidenced by NMR and no un-substituted benzamide was detected in the reaction as evidenced by both NMR and HPLC.
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