One-pot, solvent-free synthesis of α-aminonitriles under catalysis by magnesium bromide ethyl etherate

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Abstract: A three-component, efficient, and facile procedure has been developed for the synthesis of α-aminonitriles from aldehydes, amines, and trimethylsilyl cyanide using a catalytic amount of magnesium bromide ethyl etherate in the absence of solvent. Rapid formation of products is observed at room temperature in a one-pot procedure under very mild conditions giving excellent yields of the title compounds.

Key words: catalyzed Strecker's reaction, α-aminonitriles, magnesium bromide, solvent-free.

Résumé : On a développé une méthode simple et efficace pour réaliser la synthèse de α-aminonitriles par réaction monotope d'aldéhydes, d'amines et de cyanure de triméthylsilyle, en présence d'une quantité catalytique du complexe bromure de magnésium/éthérate d'éthyle, en l'absence de solvant. La formation rapide de produits se produit à la température ambiante, dans des conditions très douces et conduit aux composés mentionnés dans le titre avec d'excellents rendements.

Mots clés : réaction de Strecker catalysée, α-aminonitriles, bromure de magnésium, sans solvant.

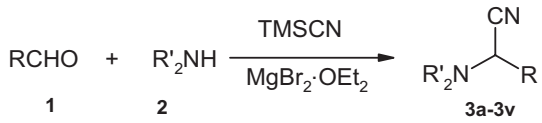
[Traduit par la Rédaction]

Introduction

A three-component combination of aldehydes, amines, and "cyanide", known as Strecker's reaction (1), facilitates the formation of α-aminonitriles (2), which are equivalent synthones to imminium moieties (3) and acyl anions (4). These compounds are very versatile intermediates for the synthesis of α-amino acids (5, 4*b*), 1,2-diamines (6), amides (7), and various nitrogen-containing heterocycles such as thiadiazoles and imidazoles (8). Recent progress such as the development of one-pot procedures for aminative cyanation of carbonyl compounds (9), use of Lewis acidic conditions (10), and employment of new cyanating reagents, especially trimethylsilyl cyanide (TMSCN) (11, 1*a*), have contributed outstanding elaborations (12) to the classical version of the Strecker's reaction (13). However, use of expensive reagents and strong acidic conditions, long reaction times, deactivation and decomposition of the catalytic systems under the reaction circumstances, and production of toxic disposals are still among the deficiencies of many of these methods. Thus, development of efficient, clean, and catalytic reactions for the synthesis of the title structures are still in demand.

In recent years, magnesium bromide ethyl etherate ($MgBr_2{\cdot}OEt_2$) has found many applications as a mild Lewis acid (14) because of its ease of preparation, oxophilic nature, and coordinating ability for bidentate chelation (15) that makes various chelation-controlled organic transformations easier. Our experiences with the use of such reaction conditions (16) prompted us to look for a mild medium for the synthesis of the title compounds. We would like to introduce here an efficient, three-component combination of aldehydes with various amines and TMSCN at room temperature for the synthesis of α-aminonitriles using a catalytic amount of $MgBr_2{\cdot}OEt_2$ (Scheme 1).

Scheme 1.



Results and discussion

Initial experiments were carried out by subjecting a benzaldehyde, pyrrolidine (piperidine), and $MgBr_2{\cdot}OEt_2$ mixture to reaction with TMSCN at room temperature in the absence of solvent (Table 1). Complete disappearance of the aldehyde and rapid formation of the product were monitored by TLC. Various amounts of the Lewis acid were used to optimize the reaction conditions. A catalytic quantity of $MgBr_2{\cdot}OEt_2$ (5 mol%) proved to be effective for the complete conversion of starting materials to the desired product (**3a** or **3b**) in 5 min (Table 1, entry 1). Use of smaller amounts of the catalyst down to 1 mol% only prolonged the reaction time up to 45 min, leading to nearly quantitative formation of **3a** (or **3b**). Similar reactions using various aromatic aldehydes bearing electron-withdrawing and electron-releasing groups with cyclic amines were conducted under the same conditions. Consequently, more than 90% yields of

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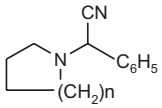
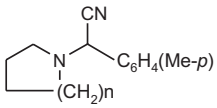
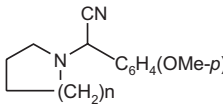
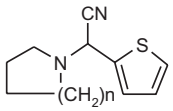
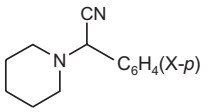
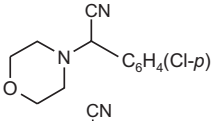
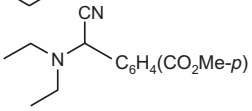
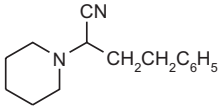
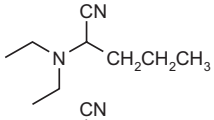
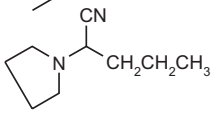
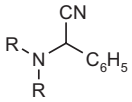
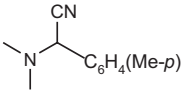
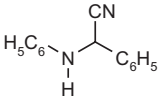
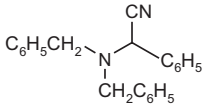
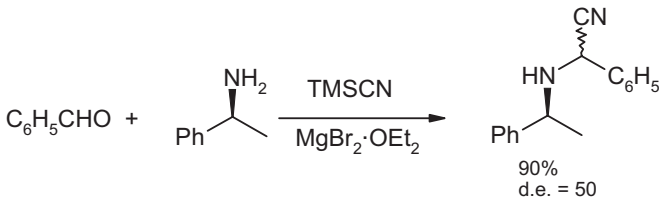
Table 1. Room-temperature $MgBr_2 \cdot OEt_2$-catalyzed synthesis of α-aminonitriles.

Entry	Aldehyde	Amine	Product		Yield (%)[a]
1	C_6H_5CHO	Pyrrolidine Piperidine		**3a**: *n* = 1 **3b**: *n* = 2	94 93
2	(*p*-Me)C_6H_4CHO	Pyrrolidine Piperidine		**3c**: *n* = 1 **3d**: *n* = 2	94 94
3	(*p*-OMe)C_6H_4CHO	Pyrrolidine Piperidine		**3e**: *n* = 2 **3f**: *n* = 2	93 96
4	2-Thiophen-CHO	Pyrrolidine Piperidine		**3g**: *n* = 2 **3h**: *n* = 2	91 93
5	(*p*-X)C_6H_4CHO	Piperidine		**3i**: X = F **3j**: X = Cl	98 93
6	(*p*-Cl)C_6H_4CHO	Morpholine		**3k**	94
7	(*p*-CO_2Me)C_6H_4CHO	$HNEt_2$		**3l**	96
8	$C_6H_5CH_2CH_2CHO$	Piperidine		**3m**	92
9	$CH_3CH_2CH_2CHO$	$HNEt_2$		**3n**	88
10	$CH_3CH_2CH_2CHO$	Pyrrolidine		**3o**	91
11	C_6H_5CHO	$TMSNMe_2$ $HNEt_2$ $HNBu_2$		**3p**: R = Me **3q**: R = Et **3r**: R = Bu	97 88 94
12	(*p*-Me)C_6H_4 CHO	$TMSNMe_2$		**3s**	91
13	C_6H_5CHO	Aniline		**3t**	88
14	C_6H_5CHO	$HN(CH_2C_6H_5)_2$		**3u**	90

[a]Isolated yields.

products **3c**–**3l** were all easily obtained in less than 10 min (Table 1, entries 2–7). The methodology proved to be equally effective for the smooth conversion of aliphatic aldehydes into α-aminonitriles when 3-phenyl-propionaldehyde or butyraldehyde were subjected to the reaction conditions (Table 1, entries 8–10).

Scheme 2.



The procedure was further explored using acyclic amines. Reactions between *N*-trimethylsilyldimethylamine ($TMSNMe_2$), diethylamine ($HNEt_2$), or dibuthylamine ($HNBu_2$) with benzaldehyde (Table 1, entry 11) and $TMSNMe_2$ with *p*-methylbenzaldehyde (Table 1, entry 12) resulted in rapid formation of products **3p** (97%), **3q** (88%), **3r** (94%), and **3s** (91%), respectively. Use of aromatic amines was successfully examined by a reaction between benzaldehyde and aniline leading to 88% formation of **3t** (Table 1, entry 13). Due to the synthetic importance of *N*,*N*-dibenzyl protected α-aminonitriles (17), the present procedure was employed to attempt the preparation of these compounds. As an example, the reaction between benzaldehyde and dibenzylamine in the presence of TMSCN and $MgBr_2{\cdot}OEt_2$ facilitated 90% formation of **3u** (Table 1, entry 14).

To test the diastereoselectivity of the process, a test reaction between (*S*)-1-phenylethylamine and benzaldehyde was conducted under the same sets of conditions leading to formation of **3v** in 90% yield within a few minutes. NMR spectroscopy of the reaction mixture revealed the formation of both possible products with a moderate diastereoselectivity of 3:1 (Scheme 2).

In summary, we have demonstrated a highly efficient, three-component conversion of aldehydes, amines, and TMSCN to α-aminonitriles at room temperature using a catalytic amount of $MgBr_2{\cdot}OEt_2$ in the absence of any solvent. The procedure is applicable to various aromatic and aliphatic aldehydes and amines. The versatility of the reaction, production of pure single compounds, easy procedure and work up, and no use of solvent or extra additives are among other benefits of the present method.

Experimental

General procedure

A mixture of aldehyde (2 mmol), amine (4 mmol), and $MgBr_2{\cdot}OEt_2$ (5 mol% in respect to aldehyde) was stirred at room temperature for 5 min. TMSCN (2.4 mmol) was added to this mixture and stirring continued for an appropriate length of time until TLC showed completion of the reaction. The product was extracted three times by 10 mL portions of diethyl ether and the combined etheral phases were washed with brine and dried over sodium sulphate. The solvent was removed under reduced pressure and the product was purified by column chromatography over silica gel using an EtOAc–hexane eluant, if necessary. The isolated yields of the products were 88%–98%. All products were identified by ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopic methods and the results were compared with those available in the literature.[2]

Selected spectral data

(4-Methoxy-phenyl)-piperidin-1-yl-acetonitrile (3f)

IR (neat, cm^{-1}) ν: 2219, 1513, 1250. ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.22–1.50 (m, 6H), 2.25–2.50 (m, 4H), 3.65 (s, 3H), 4.61 (s, 1H), 6.77 (d, J = 8 Hz, 2H), 7.27 (d, J = 8 Hz, 2H). ^{13}C NMR (20 MHz, $CDCl_3$) δ: 23.7, 25.5, 50.4, 54.9, 61.9, 113.7, 115.5, 125.3, 128.7, 159.5. MS *m*/*z*: 230 (M^+), 204, 146, 121, 84.

Piperidin-1-yl-thiophen-2-yl-acetonitrile (3h)

IR (neat, cm^{-1}) ν: 3107, 2937, 2368, 1442. ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.30–1.75 (m, 6H), 2.25–2.70 (m, 4H), 4.85 (s, 1H), 6.80–7.32 (m, 3H). ^{13}C NMR (20 MHz, $CDCl_3$) δ: 23.7, 25.5, 50.7, 58.5, 114.7, 126.2, 126.5, 126.7, 137.8. MS *m*/*z*: 206 (M^+), 122, 97, 84.

(4-Fluoro-phenyl)-piperidin-1-yl-acetonitrile (3i)

IR (neat, cm^{-1}) ν: 2928, 2808, 2224, 1608. ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.30–1.75 (m, 6H), 2.38–2.45 (m, 4H), 4.72 (s, 1H), 6.89–7.54 (m, 4H). ^{13}C NMR (20 MHz, $CDCl_3$) δ: 23.6, 25.5, 50.6, 63.4, 115.3, 116.4, 129.1, 129.5, 214.8. MS *m*/*z*: 218 (M^+), 217, 134, 123, 107.

4-Phenyl-2-piperidin-1-yl-butyronitrile (3m)

IR (neat, cm^{-1}) ν: 3027, 2937, 2222, 1684. ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.32–1.80 (m, 6H), 2.03 (t, J = 7 Hz, 2H), 2.20–2.82 (m, 6H), 3.40 (t, J = 8 Hz, 1H), 7.14–7.19 (m, 5H). ^{13}C NMR (20 MHz, $CDCl_3$) δ: 23.9, 25.6, 31.5, 32.2, 50.8, 57.1, 115.6, 126.1, 128.3, 139.8, 215.0. MS *m*/*z*: 228 (M^+), 201, 123, 110.

Acknowledgments

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[2] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5013.

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