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Strecker reaction and α-amino nitriles: Recent advances in their chemistry, synthesis, and biological properties

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Dedicated to the memory of Professor José M. Barluenga (1940–2016).

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ABSTRACT

α-Amino nitrile compounds have a profound impact on bio-chemical sciences, as they have been prepared from inexpensive starting materials and have become valuable intermediates in the chemical synthesis of vitally important heterocyclic and carbocyclic molecules, which serve as suitable models in pharmacological and biological research. The α-amino nitrile moiety has been found in the structure of different alkaloids, while the α-amidoacetonitrile group is an essential fragment of new anti-hyperglycemic drugs and promising pharmacological and agrochemical agents. Due to their synthetic, biological and practical importance, this review highlights the recent information about the preparation of α-amino nitriles through the Strecker-type and α-cyanation reactions, their chemical and biological properties, as well as their synthetic application, paying attention on the wonderful capacity for generating novel molecular diversity for pharmacological, biological and agrochemical researches, which ends with the total synthesis of complex alkaloids, preparation of new *N*-heterocycles and α-amino-nitrile-containing drugs. Analyzing modern synthetic protocols for the Strecker-type reactions and cyanation reactions based on cross-dehydrogenative coupling (CDD) process, the advantages and disadvantages of new catalysts and green reaction conditions are also discussed. In addition, remarkable biological properties of α-amidoacetonitrile derivatives as potent and selective protease inhibitors as well as promising pesticidal agents were briefly reviewed. The bibliography includes 461 references.

Contents

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1. Introduction

Regarded as possible prebiotic precursors to nicotinic acids, porphyrins, corrins, and nucleic acids,[1–5] α-amino nitriles are specific and interesting bifunctional compounds possessing an amino and a nitrile group, located at the same carbon atom. Depending on the molecular structure, they could be grouped into conventional (**A**) and cyclic (**B**) α-amino nitriles (Fig. 1). These amino nitrile compounds have a profound impact on bio-chemical sciences, serving as suitable models in pharmacological and biological research, prepared from inexpensive starting materials and giving valuable intermediates for the chemical synthesis of vitally, important and more complex heterocyclic and carbocyclic molecules. The α-amino nitrile moiety (the cyanomethyleneamino [CH(CN)NH] group) has been found in structurally different alkaloids such as tetrahydroisoquinoline anti-tumor antibiotic saframycin A, which was isolated from a culture broth of *Streptomyces lavendulae* No. 314,[6–9] phthalascidin 650,[10,11] a synthetic analogue of ecteinascidin 743 (now is trabectedin, yondelis®), extracted from the marine tunicate *Ecteinascidia* turbinate,[12–18] or the simple cyanogenic piperidine molecule without glucoside moiety, the alkaloid girgensohnine, found in the green petals of the shrub *Girgensohnia oppositiflora*.[19–21] As may be seen from Fig. 1, the latter alkaloid has a 2-(4-hydroxyphenyl)-2-(piperidin-1-yl)acetonitrile substructure, representing a simple and conventional α-amino nitrile type **A**, while tetrahydroisoquinoline alkaloids possessing the piperidine-2-carbonitrile skeleton, belongs to the cyclic α-amino nitrile type **B**. New dipeptidyl peptidase-4 (DPP-4) inhibitor class of anti-hyperglycemic drugs anagliptin, vildagliptin and saxagliptin, called gliptins, have the pyrrolidine-2-carbonitrile skeleton as well as the cyclic α-amino nitrile moiety.[22,23] These DPP-4 inhibitors have gain an important interest among the armamentarium drugs used for the management of hyperglycemia, offering a new opportunities for the a personalized treatment of patients with type 2 diabetes.[24,25]

The first formation of an α-amino nitrile molecule was documented in the year 1850 by Adolph Strecker, who mixed available acetaldehyde, an aqueous solution of ammonia, and hydrogen cyanide and obtained amino nitrile adduct (2-aminopropane nitrile) in good yield. Subsequent acid hydrolysis of the obtained adduct (Strecker intermediate) afforded racemic alanine.[26] During the past decades, this simple transformation has been recognized as a three-component reaction,[27] one of the oldest known multi-component condensation reactions, and the most straightforward route for the synthesis of α-amino acids on both laboratory and industrial scale (Scheme 1). Nowadays, the Strecker reaction is the most practical and efficient tool for the preparation of α-amino acids via the formation of α-amino nitriles.

Even today after more than 160 years, the three-component Strecker synthesis as well as the direct hydrocyanation of imines (a modified version of the Strecker reaction) remains as a very popular and significant tool in the synthesis of diverse synthetic drugs such as anti-platelet agent clopidogrel (Plavix),[28] opoid analgesic 4-anilidopiperidine-based drugs (carfentanil, remifentanil and alfentanil)[29–31] or the anti-HIV agent DPC 083.[32] Strecker intermediates are successfully used also in the synthesis of numerous pharmaceutically important indole alkaloids like reserpine,[33] hirsutine[34] or eburnamonine,[35] which can act as potent antihypertensive agents (Fig. 2).

The above examples show that α-amino nitriles are important, versatile building blocks in heterocyclic chemistry, pharmaceuticals, and agrochemicals, and suitable prototypes for modern drug

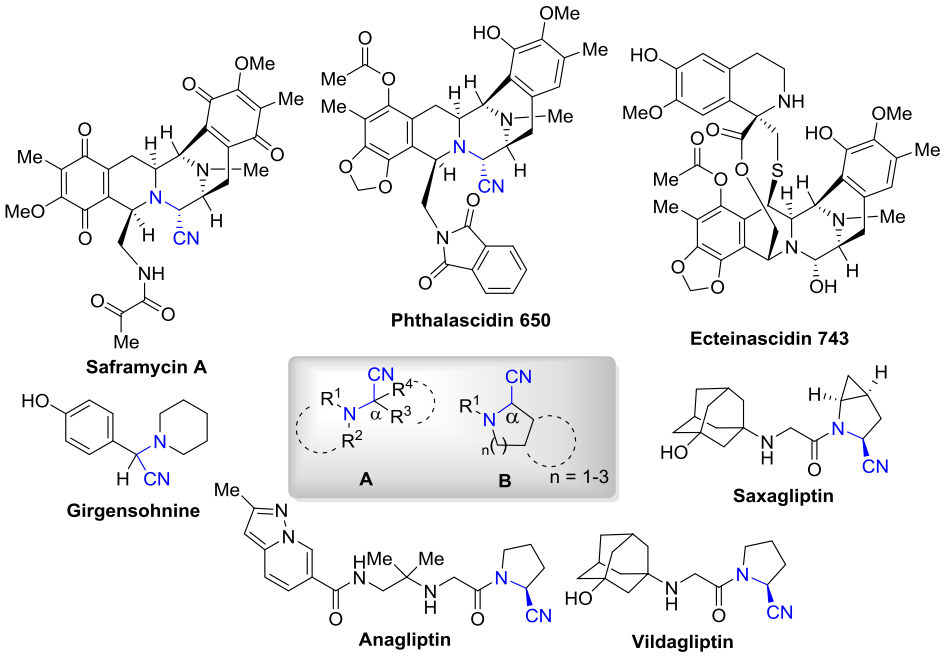

Fig. 1. General structural types of α-amino nitriles. Representative biologically active α-amino nitrile-containing natural products and synthetic drugs.