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Solvent-Free Synthesis of α-Amino Nitrile-Derived Ureas

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ABSTRACT

An efficient and environmentally friendly methodology for the solvent-free synthesis of α-amino nitrile derived ureas from α-amino acid based amino nitriles has been developed. At room temperature no epimerization was observed in the resulting ureas, but under microwave heating, epimerization occurred at the chiral center bearing the cyano group.

α-Amino nitriles are versatile intermediates for the synthesis of multiple building blocks.[1] In particular, α-amino acid derived amino nitriles have shown high potential for molecular diversity generation.[2] Thus, we have shown their utility in the synthesis of pseudopeptides[3] and diverse chiral heterocyclic compounds.[4]

Among α-amino nitrile derivatives, *N*-acyl-amino-nitriles have proven to be important molecules for the search of inhibitors of therapeutically important peptidases,[5] such as dipeptidyl peptidase IV,[6] prolyl oligopeptidases,[7] and cysteine cathepsins.[8] More concretely, several α-amino nitrile derived ureas have been patented as inhibitors of cholesteryl ester transfer protein[9] and diverse enzymes,[10] agents for neurological disorders,[11] pesticides,[12] or fungicides.[13] On the other hand, α-amino nitrile derived ureas are intermediates in the synthesis of diverse pharmacologically active hydantoin derivatives from α-amino nitriles,[14] although these intermediates have not been isolated and characterized. Therefore, the development of simple and versatile methods for the synthesis and identification of *N*-(cyanomethyl)ureas is an important goal in synthetic organic chemistry, in particular, environmentally friendly solvent-free procedures.

In the context of a medicinal chemistry project focused on the search for modulators of protein−protein interactions,

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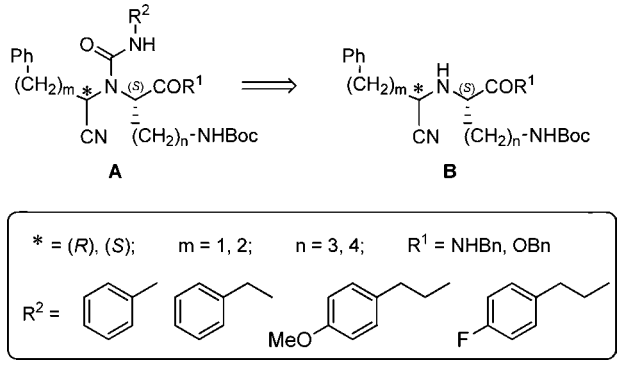
we required the basic amino acid derived *N*-(cyanomethyl)-ureas of general formula **A** (Scheme 1), which were expected to be easily accessible from the corresponding α-amino nitriles **B**, by reaction with isocyanates. These α-amino nitriles **B** were previously obtained by a modified Strecker synthesis as epimeric mixtures in the carbon bearing the cyano group, which were chromatographically resolved.[15]

Scheme 1



The reaction of the α-amino nitrile **(*S*)-1a** (Scheme 2) with 2 equiv of phenyl isocyanate was used for setting up the methodology. Initially, the synthesis of the *N*-(cyanomethyl)urea **(*S*)-2a** was explored in parallel in two different solvents, in CH_2Cl_2 at room temperature and in THF at 0 °C, under described reaction conditions.[14a,16] When the reaction was carried out in THF, 86% of urea **(*S*)-2a** was isolated after 3 days of reaction. However, in the case of the reaction in CH_2Cl_2, after 5 days, the starting amino nitrile **(*S*)-1a** remained unaltered, but after 3 additional days, when the solvent had accidentally evaporated, the TLC and HPLC analysis of the crude reaction mixture showed the presence of 60% of **(*S*)-2a**. This result induced us to study the reaction under solvent-free conditions. These involved the mixture and homogenization of reagents with a minimum amount of dry CH_2Cl_2, followed by evaporation of the solvent under argon. As shown in Table 1, under these conditions, a 98% yield of the desired urea **(*S*)-2a** was obtained after 48 h.

Scheme 2. Synthesis of the *N*-(Cyanomethyl)ureas **2a** from the α-Amino nitrile **(*S*)-1a** as Indicated in Table *1*

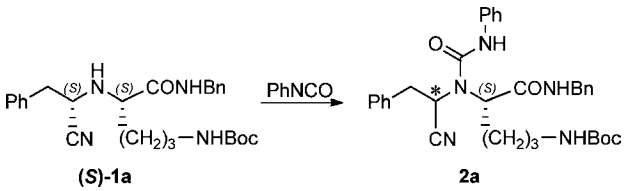


Table 1. Influence of Reaction Conditions on the Synthesis of the *N*-(Cyanomethyl)ureas **2a**

	amino nitrile				(cyanomethyl)urea	
entry	no.	solvent	*t* (°C)	*t*	no	(%)[a]
1	**(*S*)-1a**	THF	0	3 d	**(*S*)-2a**	86
2	**(*S*)-1a**	CH_2Cl_2	rt	5 d	**(*S*)-2a**	0
3	**(*S*)-1a**	–	rt	48 h	**(*S*)-2a**	98
4[b]	**(*S*)-1a**	CH_2Cl_2	80	2 h	**(*S*)-2a**	0
5[b]	**(*S*)-1a**	–	80	2 h	**(*RS*)-2a**	98[c]
6[b]	**(*R*)-1a**	–	80	2 h	**(*RS*)-2a**	98[c]

[a] Isolated yield. [b] Microwave irradiation. [c] [(*R*)/(*S*)] epimer ratio ≈ 1:1.

Next, with the aim of decreasing the reaction time, the reaction was carried out under heating at 80 °C by microwave irradiation. When this heating was applied using CH_2Cl_2 as solvent, the starting amino nitrile **(*S*)-1a** was recovered unaltered after 2 h (Table 1, entry 4). However, when microwave (MW) heating was applied to the solvent-free reaction mixture, a 98% yield of the epimeric mixture of ureas **(*RS*)-2a** was obtained. A similar result was obtained when the starting amino nitrile was the epimer **(*R*)-1a** (Table 1, entry 6). In both cases, the HPLC analysis of the crude reaction mixture showed the presence of the two epimeric ureas **(*R*)-** and **(*S*)-2a** with t_R = 27.7 and 27.5 min, respectively, in an ~1:1 ratio and traces of the corresponding starting amino nitrile **(*R*)-** or **(*S*)-1a** at 23.28 or 23.89 min. These data indicated epimerization in the (cyanomethyl)urea at the carbon bearing the cyano group, which had not occurred in the starting amino nitriles **(*R*)-** and **(*S*)-1a**. These results were confirmed in the ^{1}H NMR analysis of the crude reaction products. As shown in Scheme 3, the higher propensity of *N*-(cyanomethyl)ureas to epimerize, with respect to the corresponding α-amino nitrile, could be explained by the electron attracting effect of the ureido group, which would increase the acidity of the proton in the position α to the cyano group, facilitating the formation of the tautomeric ketimine species **3a**, which would revert to give the epimeric mixture of *N*-(cyanomethyl)ureas **(*RS*)-2a**. Both pure isolated epimers **(*R*)-** and **(*S*)-2a** epimerized by heating at 80 °C under MW irradiation, although this epimerization was slower in **(*S*)-2a** than in **(*R*)-2a** (180 vs 120 min for complete epimerization). However, under similar

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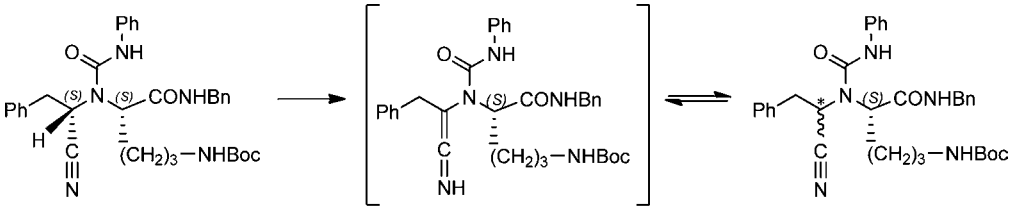
Scheme 3. Proposed Mechanism of Epimerization of *N*-(Cyanomethyl)ureas

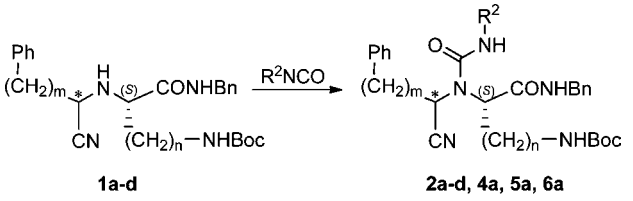


conditions, the starting amino nitriles **(*R*)-** and **(*S*)-1a** were recovered without epimerization. In relation to these results, two recent reports, on the enzymatic resolution of α-amino nitriles, reported the complete racemization of α-acylamino nitriles at 40 °C, while no racemization at all was observed in their respective α-amino nitriles.[17] After chromatographic resolution of the epimeric mixtures **(*RS*)-2a**, each of the resulting epimers showed the same optical rotation as **(*R*)-2a** and **(*S*)-2a** obtained under epimerization-free conditions. This result indicated that epimerization had taken place at the carbon bearing the cyano group and not at the carbon bearing the *N*-benzyl carboxamide group, as in that case the epimerization compounds would be enantiomers of **(*R*)-2a** and **(*S*)-2a** with the same optical rotation value, but opposite sign.

In view of the results shown in Table 1, we considered that the best conditions for the epimerization-free synthesis of *N*-(cyanomethyl)ureas from α-amino nitriles would include the solvent-free reaction with 2 equiv of isocyanate at room temperature. These conditions were applied for the synthesis of ureas **2a**–**d** and **4**–**6a** as shown in Scheme 4 and Table 2. When, due to problems of resolution, the starting α-amino nitrile was an epimeric mixture, to optimize the reaction time, the synthesis was carried out under MW irradiation.

The methodology was also applied to the methyl ester α-amino nitriles **(*R*)-** and **(*S*)-7a,b**, derived from ornithine (**a**) and lysine (**b**) (Scheme 5). In these cases, the HPLC-MS analyses of the crude reaction mixtures indicated that the

Scheme 4



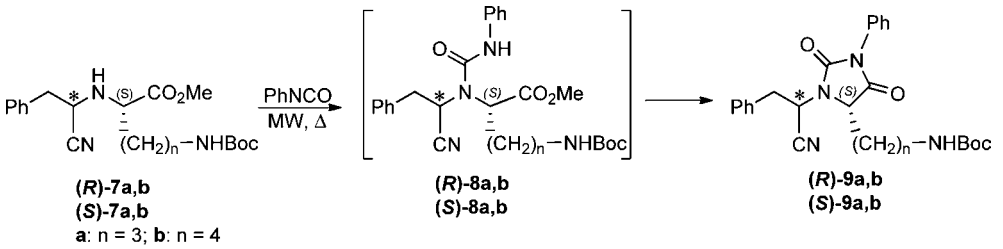
a: m = 1, n = 3; **b**: m = 1, n = 4; **c**: m = 2, n = 3; **d**: m = 2, n = 4

Table 2. Synthesis of *N*-(Cyanomethyl)ureas **2a**–**d** from α-Amino Nitriles **1a**–**d**

α-amino nitrile			(cyanomethyl)urea		
entry	no.	method[a]	no.	R^2	(%)[b]
1	**(*R*)-1a**	B	**(*R*)-2a**	Ph	96
2	**(*S*)-1a**	B	**(*S*)-2a**	Ph	86
3	**(*RS*)-1a**[c]	C	**(*RS*)-2a**	Ph	95
4	**(*R*)-1a**	B	**(*R*)-4a**	Bn	95
5	**(*S*)-1a**	B	**(*S*)-4a**	Bn	93
6	**(*RS*)-1a**[c]	C	**(*RS*)-4a**	Bn	97
7	**(*R*)-1a**	B	**(*R*)-5a**	4-MeO-Ph-$(CH_2)_2$	94
8	**(*S*)-1a**	B	**(*S*)-5a**	4-MeO-Ph-$(CH_2)_2$	93
9	**(*RS*)-1a**[c]	C	**(*RS*)-5a**	4-MeO-Ph-$(CH_2)_2$	90
10	**(*S*)-1a**	B	**(*S*)-6a**	4-F-Ph-$(CH_2)_2$	91
11	**(*RS*)-1a**[c]	C	**(*RS*)-6a**	4-F-Ph-$(CH_2)_2$	96
12	**(*RS*)-1b**[d]	C	**(*RS*)-2b**	Ph	95
13	**(*RS*)-1c**[c]	C	**(*RS*)-2c**	Ph	92
14	**(*RS*)-1d**[c]	C	**(*RS*)-2d**	Ph	97

[a] Method B: Solvent-free, rt, 2–3 days. Method C: MW 80 °C, 2–3 h. [b] Isolated yield. [c] [(*R*)/(*S*)] epimer ratio = 1:1. [d] [(*R*)/(*S*)] epimer ratio = 1:3.

Scheme 5



reactions were significantly slower and, after 7 days, they showed 75% conversion to give 43% of the respective *N*-(cyanomethyl)urea **(*R*)-** and **(*S*)-8a,b** along with 33% of the corresponding hydantoin derivative **(*R*)-** and **(*S*)-9a,b**. However, when the reactions were carried out under MW irradiation at 80 °C, after 2 h, the HPLC-MS analyses of the crude reaction mixtures showed the formation of a 90% yield of ureas **(*R*)-** and **(*S*)-8a,b** and traces of the corresponding hydantoin. After silica gel column chromatography, the ureas cyclized completely to the respective hydantoin derivatives **(*R*)-** and **(*S*)-9a,b**, which were isolated free of epimerization in 70−78% yield.

In conclusion, we have developed an environmentally friendly solvent-free methodology for the synthesis of amino acid based chiral highly functionalized *N*-(cyanomethyl)ureas with a high potential for the generation of molecular diversity in drug discovery. Although the synthesis can be activated by MW heating, precautions must be taken as it can induce epimerization at the chiral center bearing the cyano group.

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Supporting Information Available. Detailed experimental procedures and full characterization for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.