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Free-Radical Version of the Strecker Synthesis of α-Aminoamides Promoted by Aqueous $H_2O_2/TiCl_3/HCONH_2$ System

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The development of new methods for the synthesis of natural and unnatural α-amino acid derivatives is an area of current interest both in synthetic[1,2] and medicinal[3] chemistry. Although many valuable multistep routes to α-amino acid precursors are available,[1] syntheses of these compounds by one-pot multicomponent reactions (MCRs)[4] are particularly fascinating since they facilitate rapid construction of very large compound libraries which can, then, be used for drug discovery.[3]

Classical examples of such a reaction are the evergreen Strecker synthesis and the Ugi condensation,[4,5] according to which α-amino acid precursors are efficiently assembled by adding a nucleophilic carboxylate synthon (cyanide or isocyanides) to an imine generated in situ.[6] In recent years, glyoxylate imine derivatives, either preformed or generated in situ, have been used as versatile electrophilic glycine equivalents to provide rapid access to a wide range of natural and unnatural α-amino acid derivatives through radical alkylation[7] or nucleophilic addition of organometallic reagents.[8]

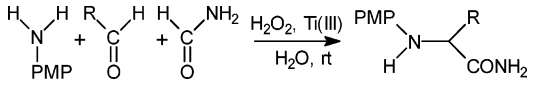
In the course of our studies,[9] we have disclosed the manifold roles simultaneously played by Ti(III) and Ti(IV) ions in promoting radical Mannich-type MCRs. As a part of our ongoing interest in this area, we now report that the aqueous acidic Ti(III)/H_2O_2 system readily assembles an amine **1**, an aldehyde **2**, and formamide in a one-pot reaction leading to a wide range of α-aminoamides **3** in fair to good yields (Table 1).

The reaction smoothly proceeds at 20 °C by adding dropwise (20 min) H_2O_2 (5 mmol of a 35% aqueous solution) to a homogeneous solution of **1** (4 mmol), **2** (2 mmol), and $TiCl_3$ (8 mmol, ca. 8 mL of a 15% aqueous acidic solution) in formamide (10 mL). The reaction is like a titration and its end is clearly shown by a sharp change of the color from blue to orange; furthermore, after work up, most of the α-aminoamides **3** crystallize out in pure form from the crude reaction mixtures dissolved in a suitable solvent.

In planning the synthesis, we started first with *p*-methoxyaniline (PMP−NH_2) **1a**, as a representative amine, since the protective PMP group can be further removed by CAN oxidation.[6,10] As shown in Table 1, several types of aldehydes can participate in this process: these include primary (entries 2 and 3), secondary (entries 4−7), tertiary (entry 8), α,*β*-unsaturated (entry 9), aromatic (entries 10−20), and heteroaromatic (entry 21) ones. Only formaldehyde gave an abnormal result: N-aminomethylation[11] of formamide occurred (entry 1, 60% yield) instead of the expected C-aminomethylation.

We next proved that the reaction may be extended to other substituted anilines, allowing structural variety.[12] For example, *p*-toluidine **1b** and *p*-bromoaniline **1c** reacted with benzaldehyde and formamide (entries 22 and 23) affording the corresponding *N*-arylphenylglycinamides **3v** and **3z** in 78 and 60% yields, respectively.

Table 1. Addition of Formamide to an Equilibrium Mixture of PMP−NH_2 and Aldehydes **2a**−**u**



1a **2a-u** **3a-u**

entry	R–CHO R–	**3** yield (%)[a]
1	H−	*b*
2	CH_3−	**3a**: 60
3	$(CH_3)_2CHCH_2$−	**3b**: 75
4	$(CH_3)_2CH$−	**3c**: 62
5	$(C_2H_5)(CH_3)CH$−	**3d**: 65
6	$Ph(CH_3)CH$−	**3e**: 40
7	cyclohex−	**3f**: 50
8	$(CH_3)_3C$−	**3g**: 45
9	$PhCH{=}CH_2$−	**3h**: 55
10	Ph−	**3i**: 79 (85)
11	*p*-HO−C_6H_4−	**3j**: 66 (75)
12	piperonyl−	**3k**: 70
13	*o*-HO−C_6H_4−	**3l**: 30
14	*o*-CH_3O−C_6H_4−	**3m**: 60
15	*m*-CH_3O−C_6H_4−	**3n**: 59
16	*p*-CH_3O−C_6H_4−	**3p**: 66
17	*p*-Br−C_6H_4−	**3q**: 64
18	*p*-F−C_6H_4−	**3r**: 60
19	1-naphthyl−	**3s**: 37
20	2-naphthyl−	**3t**: 60
21	2-furyl−	**3u**: 85
22[c]	Ph−	**3v**: 78
23[d]	Ph−	**3z**: 60

[a] Isolated yields based on the starting aldehyde RCHO (2 mmol); yields in parentheses were determined by ^{1}H NMR with an internal standard added to the crude reaction mixture; yields based on the converted aldehydes are always >90%. [b] *N*-[(*p*-Methoxyphenylamino)methyl]formamide was obtained. [c] **1b** was used instead of **1a**. [d] **1c** was used instead of **1a**.

From the mechanistic point of view (Scheme 1), the initial step is the Ti(III) one-electron reduction of H_2O_2 (step *i*) leading to a hydroxy radical and Ti(IV) ion, which both participate in the subsequent steps leading to **3**: (a) hydroxy radical abstracts a H atom from the C−H bond of formamide forming a carbamoyl radical (step *ii*); (b) Ti(IV) ion, owing to its oxophilicity, coordinates the carbonyl oxygen of the aldehyde favoring imine formation and, as a strong Lewis acid, increases the imine electrophilicity by N-complexation (step *iii*);[13] (c) addition of the nucleophilic carbamoyl radical[14] proceeds at the C atom of **A** to generate an aminium radical **B** (step *iv*), which is readily reduced to the final product **3** by a second equiv of Ti(III) ion (step *v*).

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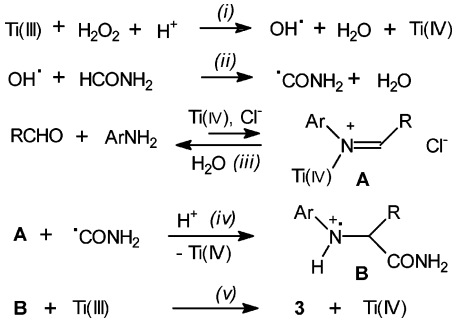
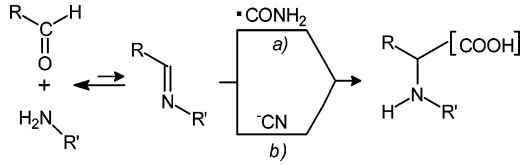
Scheme 1. Mechanistic Rationale



Scheme 2. Radical Version (path *a*) of the Strecker Synthesis (path *b*) of α-Amino Acid Derivatives



The H atom abstraction from the C−H bond of formamide (BDE ≈ 94 kcal mol^{-1}) by a hydroxy radical is a fast process due to favorable enthalpy balance ($\Delta H \approx -24$ kcal) and polar effects,[14] but the equilibria involved in the formation of **A** under aqueous conditions[13] lie by far on the left side.

However, the irreversible addition step *iv* shifts the whole reaction sequence on the product side, rendering the process preparatively advantageous. This approach to α-amino acid derivatives, in which a carbamoyl radical is used as a carboxylate synthon, may be regarded as a radical version of the Strecker synthesis (Scheme 2).

After examining the results of Table 1, the characteristic features of the reaction are as follows: (a) only a very bulky substituent at the C atom of the intermediate imine depresses the yield of **3** (entries 6−8, 13, and 19); (b) the reaction is relatively insensitive to the polar nature of the substituents on the aromatic ring of either benzaldehyde or aniline, indicating that the polarization of the C=N bond induced by N−Ti(IV) complexation overcomes the substituent effect and/or that the equilibrium concentration of **A** does not affect the yield of **3**, since the driving force of the global reaction sequence is the two last irreversible steps. The low yield of **3l** (30%) may well be ascribed to steric congestion around the imine C atom, due to the formation of a chelated Ti(IV)−salicylaldimine complex.[15] In fact, the parent *o*-methoxy-substituted amide **3m** was obtained in 60% yield; (c) interestingly, the reaction can be used for the synthesis of *o*-, *m*-, and *p*-hydroxy- and methoxy-substituted arylglycine precursors (entries 11−16), which constitute key components of some of the most widely used antibiotics, such as Amoxicillin, Nocardicin, Vancomicin, and Chloropeptins;[8b,16] (d) in addition, biocatalytic kinetic resolution of α-aminoamides, catalyzed by amidase, does not require the previous nitrile hydratase-catalyzed hydration of a nitrile to an amide.[17]

In conclusion, we have developed a new general and convenient one-pot radical multicomponent reaction for the synthesis of aliphatic, aromatic, heteroaromatic, and β,γ-unsaturated α-aminoamides, utilizing cheap and commercially available starting materials. An aqueous cosolvent and the ultimately nontoxic TiO_2 metal residue contribute to render the reaction significant also from an ecological point of view.

Future efforts will focus on combinatorial application of the method in the preparation of new structural types of α-aminoamides.

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Supporting Information Available: Experimental procedures and characterization of products **3a**−**z** (NMR data, ^{1}H and ^{13}C NMR spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

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