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Free-Radical Addition to Ketimines Generated In Situ. New One-Pot Synthesis of Quaternary α-Aminoamides Promoted by a $H_2O_2/TiCl_4-Zn/HCONH_2$ System

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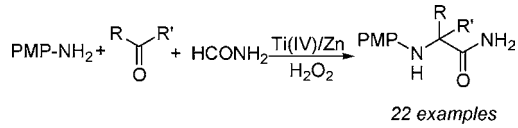
ABSTRACT



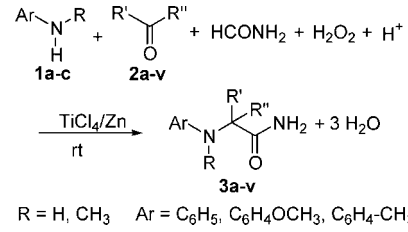
A free radical multicomponent reaction mediated by an acidic $TiCl_4-Zn/H_2O_2$ system allows the assembly of an amine, a ketone, and formamide in one pot, affording instant access to quaternary α-amino acid derivatives.

The use of free radical reactions in organic synthesis has continued to increase in the past years, providing multiple advantages over classical ionic chemistry, which often requires expensive reagents and hazardous operating conditions.[1] In particular, nucleophilic radical addition to the carbon atom of imine derivatives has attracted much attention in the past decade as a versatile route to the synthesis of a wide range of polyfunctional molecules,[2] and many procedures based on this convenient approach[3] have been developed.

Herein we present a new one-pot multicomponent free-radical synthesis of quaternary α-aminoamides promoted by an acidic $TiCl_4/Zn/H_2O_2$ system (Scheme 1).

Until now studies involving the reductive radical addition to ketimines are scant in comparison with those conducted on aldimines.[4] Among the few examples reported, in all cases the preformation of the ketimines is required. The reason of

Scheme 1. Synthesis of Quaternary α-Aminoamides Mediated by a $TiCl_4/Zn/H_2O_2$ System



† Deceased May 3, 2008.

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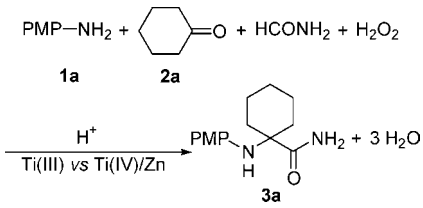
Table 1. Radical Addition of Formamide to Ketimines Generated in Situ from PMP-NH_2 **1a** and Cyclohexanone **2a**[a]



entry	$TiCl_3$, mmol	$TiCl_4$, mmol	Zn, mmol	HCl 37%, mL	**3a** yield, %[b]
1	8				23
2	2		5		47
3		2.5	5		74
4		2.5			
5			5		
6		1.5	5		33
7		1.5	5	1	72
8		1.5	8	1	71
9		1.5	8	2	60

[a] 2 mmol of **1a** was reacted with 12 mmol of **2a** in 10 mL of formamide. [b] Yield determined by ^1H NMR with 2-methyl-benzylalcohol added as an internal standard to the crude reaction mixture.

this lack in the literature can be ascribed to the lower reactivity (due to the poor electrophilicity of the C═N bond) combined with the lower stability of ketimines (anhydrous conditions are usually required because they easily undergo hydrolysis). However, free-radical addition to ketone-derived imino compounds is particularly intriguing as it could provide an unique route to the synthesis of *tert*-alkyl-amino-derivatives not conventionally prepared via ionic chemistry.

We have recently reported that a novel system, based on $TiCl_3$ and hydroperoxides (*t*-BuOOH or H_2O_2), promotes one-pot bond-forming transformations via the radical addition of ethers,[5] formamide,[6] and alcohols[7] to aldimines, generated in situ under aqueous conditions.[8] As a part of our ongoing interest in this field, we wanted to verify whether the free-radical addition to aldimines, promoted by our system in formamide[6] as a pivotal subtrate, could be also applied to ketimines generated in situ for the one-pot synthesis of α,α-disubstituted-α-aminoamides. This procedure would represent a convenient route to quaternary α-amino acids, which are considered important building blocks in the design of bioactive peptides with enhanced properties, as they are able to introduce conformational constraints and consequent structure stabilization.[9]

Initial experiments, devoted to the optimization of the protocol, were conducted under different operating conditions by reacting *p*-methoxyaniline (PMP-NH_2) **1a** in the presence of cyclohexanone **2a**. Disappointingly, preliminary attempts to extend the free radical addition to ketimines by using our classic $TiCl_3/H_2O_2$ system and $HCONH_2$ gave poor results, affording only 23% of the desired product **3a** (Table 1, entry 1). We ascribed this behavior to the high amount of water present in the reaction medium (8 mmol of $TiCl_3$ corresponds to ca. 8 mL of a 15% aqueous acidic solution), which could negatively affect the formation and the stability of the ketimine.

To verify this hypothesis and improve progressively the efficiency of the protocol, we added Zn metal (powder) to a lower amount of $TiCl_3$ solution (entry 2) and then completely replaced $TiCl_3$ with stoichiometric amounts of an anhydrous $TiCl_4$ solution in CH_2Cl_2. In doing so we succeeded in increasing the yield up to 74% (entry 3), whereas in the absence of Zn metal no reaction occurred (entry 4).

In a generic procedure, a homogeneous solution of formamide (10 mL) containing **1a**−**c** (2 mmol), **2a**−**v** (12 mmol), and $TiCl_4$ (2.5 mL of a 1 M CH_2Cl_2 solution, 2.5 mmol) was stirred at 0 °C under N_2 atmosphere. After 30 min, Zn powder (300 mg, ca. 5 mmol) was suspended in the reaction medium, and an aqueous 35 wt % H_2O_2 solution (ca. 0.5 mL, 5 mmol), diluted in 4.5 mL of formamide, was added dropwise over 3 h. Analogous results were observed by reducing the amount of $TiCl_4$ (1.5 mmol) in favor of the cheaper Zn metal (8 mmol), after addition of a 37% HCl aqueous solution (Table 1, entries 6−9). The reaction proceeds like a titration, with periodic changes of color from orange to violet, until a pale orange is barely maintained also upon further addition of Zn. On the basis of these observations we suggest the possible mechanism depicted in Scheme 2.

While the changes of color prove the periodic variation of the oxidation state of titanium ion in solution, the lack of conversion in the desired products in the absence of titanium salts (Table 1, entry 5) makes it obvious that zerovalent Zn metal has the sole role to continuously convert Ti(IV) (orange) to Ti(III) (violet) (paths *i* and *iii*). Instead, titanium species play a multiple key role. Ti(III) acts both as radical initiator, generating the hydroxyl radical (path *ii*), which is in turn responsible for the hydrogen abstraction from formamide (path *iv*), and as radical terminator, causing the reduction of the aminium radical intermediate (path *vii*). In both cases, Ti(III) is reoxidized to Ti(IV), thus prolonging the redox cycle and justifying the color oscillation. At the same time, Ti(IV), as a Lewis acid, increases the electro-

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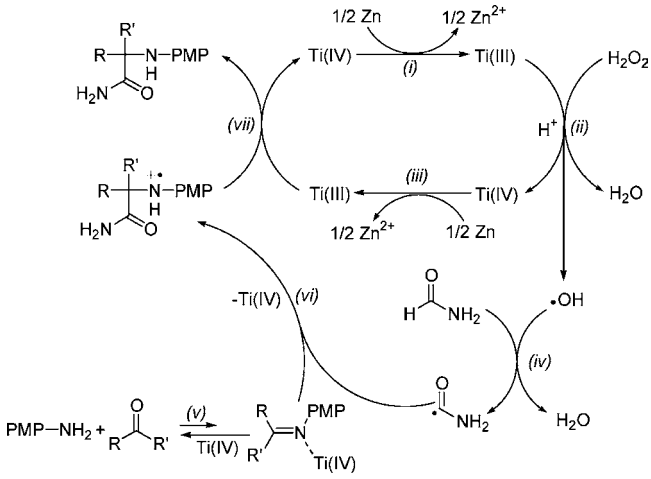
Scheme 2. Reaction Mechanism



philicity of the C═N carbon atom (path *vi*), thus promoting both the formation of the ketimine (path *v*) and its activation toward the carbamoyl radical addition.

This is a further example of highly selective radical reaction due to dominant polar effects: it occurs when charged species are involved. The nucleophilic carbamoyl radical is much more reactive and selective with protonated or coordinated than with the simple imines.[10,2e] It is probably because of the same ketimine stabilization, due to the Ti(IV) coordinating effect, that the ketone is not free to directly afford the classical addition product with formamide under our acidic conditions.[11]

With the optimized conditions in hand, we set out to examine the scope of the reaction. Both cyclic (Table 2) and acyclic (Table 3) ketones resulted suitable for this new procedure, thus confirming its general applicability. In particular, the synthesis of rigidified cyclic amino acid precursors is intriguing as they play an important role in drug design and development.[12]

PMP-NH_2 **1a** was chosen as a representative primary arylamine, since the protective PMP group can be further removed according to the methodologies reported in the literature.[13] However we also proved that the reaction might be extended to other substituted anilines, by reacting *p*-toluidine **1b** and *N*-methyl-aniline **1c** both with cyclohexanone (Table 2, entries 13 and 14) and acetone (Table 3, entries 7 and 8). In analogy with what is observed for aldimines,[5−7] steric hindrance around the C═N bond negatively affects the reaction. As for ketimines deriving from cyclic ketones, the best results were achieved in the presence of strained rings (Table 2, entries 1, 3, 4, 10, and 11), while cycloheptanone afforded the desired product in poor yields (entry 12). Because of similar steric effects, relatively lower yields were observed with cyclic ketones bearing an alkyl or aryl substituent in the α position to the carbonyl (Table 2, entries 2 and 7), while no product was observed with 2,2,6-trimethyl-cyclohexanone (entry 8). Moreover, the steric effect was also confirmed by difference NOE experiments carried out to detect the isomer distribution for compounds **3b**, **3c**, **3d**, **3e**, **3f**, **3g**, and **3i** (see Supporting Information for details).

Table 2. Radical Addition of Formamide to Ketimines Generated in Situ from Aryl Amines **1a** and Cyclic Ketones **2a**−**n**[a]

2a−**n** $\xrightarrow[0\ ^\circ C,\ N_2]{\mathbf{1a}/TiCl_4/Zn/H_2O_2/HCONH_2}$ **3**−**n** (1)

entry	**2**	**3** yield, %[b] (yield, %)[c]
1	**2a**: cyclohexanone	**3a**: 70 (74)
2	**2b**: 2-methyl-cyclohexanone	**3b**: 33 (36)
3	**2c**: 3-methyl-cyclohexanone	**3c**: 68 (73)
4	**2d**: 4-methyl-cyclohexanone	**3d**: 72 (78)
5[d]	**2e**: 4-*tert*-butyl-cyclohexanone	**3e**: 45 (51)
6	**2f**: 3,3,5-trimethyl-cyclohexanone	**3f**: 36 (40)
7	**2g**: 2-methoxy-cyclohexanone	**3g**: 25 (28)
8[d]	**2h**: 2,2,6-trimethyl-cyclohexanone	**3h**:
9	**2i**: 4-phenyl-cyclohexanone	**3i**: 51 (55)
10	**2j**: cyclopentanone	**3j**: 84 (90)
11	**2k**: cyclobutanone	**3k**: 60 (65)
12	**2l**: cycloheptanone	**3l**: 24 (30)
13[e]	**2m**: cyclohexanone	**3m**: 70 (75)
14[f]	**2n**: cyclohexanone	**3n**: 40 (51)

[a] The molar ratio of **1**/**2**/$TiCl_4$/Zn was 2:12:2.5:5. [b] Yield of isolated products is based on the starting amine; yields based on converted amines were always ≥90%. [c] Yield determined by ^1H NMR with 2-methyl-benzylalcohol added as an internal standard to the crude reaction mixture. [d] 10 mL of acetic acid was added to the reaction mixture. [e] **1b** was used instead of **1a**. [f] **1c** was used instead of **1a**.

Table 3. Radical Addition of Formamide to Ketimines Generated in Situ from PMP-NH_2 **1a** and Acyclic Ketones **2o**−**v**[a]

2o−**v** $\xrightarrow[0\ ^\circ C,\ N_2]{\mathbf{1a}/TiCl_4/Zn/H_2O_2/HCONH_2}$ **3o**−**v** (2)

entry	**2**	**3** yield, %[b] (yield, %)[c]
1[d]	**2o**: acetone	**3o**: 72 (76)
2	**2p**: butan-2-one	**3p**: 54 (60)
3	**2q**: pentan-2-one	**3q**: 33 (37)
4	**2r**: hexan-2-one	**3r**: 25 (30)
5	**2s**: 1-methoxy-propan-2-one	**3s**: 26 (32)
6	**2t**: 4-phenyl-butan-2-one	**3t**: 14 (18)
7[d,e]	**2u**: acetone	**3u**: 72 (77)
8[d,f]	**2v**: acetone	**3v**: 58 (62)

[a] The molar ratio of **1**/**2**/$TiCl_4$/Zn was 2:24:2.5:5. [b] See footnote b of Table 2. [c] See footnote c of Table 2. [d] 5 mL of acetone (68 mmol) was added. [e] **1b** was used instead of **1a**. [f] **1c** was used instead of **1a**.

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In all of these cases, the geometry of the major isomers resulted in a chair conformation with the alkyl substituent in equatorial position and the amino group in the axial position, the carbamoyl addition occurring in the less hindered equatorial position.[14] For the same reasons, the reactivity of imines deriving from acyclic ketones was also variable: whereas in the presence of acetone the corresponding products were achieved in good yields (Table 3, entries 1, 7, and 8), the efficiency of the reaction progressively decreased by increasing the length of the ketone side chains and with the introduction of ramifications (entries 2−6).

In conclusion, the protocol shown herein describes the first application of a Ti(IV)/Zn mediated free-radical addition leading to the selective carbamoylation of ketimino acceptors. This reaction leads to a novel synthesis of quaternary α-amino acid precursors and may be conducted under nonanhydrous conditions, requiring neither the preformation of the ketimine nor the protection of the amino group. Owing to its versatility, this protocol offers an expeditious access to a wider range of *tert*-alkyl-amino-derivatives, and future studies will be devoted to the extension to other families of nucleophilic radicals (i.e., alcohols and ethers).

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Supporting Information Available: General experimental procedures and chracterization and spectral data for products **3a**−**v**. This material is available free of charge via the Internet at http://pubs.acs.org.

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