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CAN mediated decarboxylative hydroxylation/alkoxylation of *N*-aryl-γ-lactam-carboxylic acids at room temperature: an easy access to *N*-aryl-α-hydroxy/alkoxy-γ-lactams

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Abstract

An efficient and mild protocol for one-pot decarboxylative hydroxylation/alkoxylation of 1,3-diaryl-5-oxo-pyrrolidine-2-carboxylic acids to *trans*-5-hydroxy-1,4-diarylpyrrolidin-2-ones and 5-alkoxy-1,4-diaryl-1,5-dihydropyrrol-2-ones at room temperature using CAN in organo-aqueous solvent has been developed.

Keywords: Decarboxylative hydroxylation; γ-Lactam-carboxylic acid; Ceric ammonium nitrate; 1,5-Dihydropyrrol-2-one

1. Introduction

The carboxylic acid functionality is present in many classes of synthetic as well as natural bioactive aza-heterocycles. The possibility of manipulating this ubiquitous functional group under mild conditions should open up new vistas in terms of partial syntheses and improved biological activity profiles. A number of high valent metals,[1] for examples, Pb(IV), Mn(III) and Tl(III) have been used as oxidative decarboxylating agents, but all of these reagents suffer from the disadvantages of toxicity. Due to the lack of a convenient oxidizing agent, the room temperature decarboxylative hydroxylation/alkoxylation of γ-lactam-carboxylic acids in a single-step is a complex problem in synthetic organic chemistry. This one-pot transformation would be very useful for the synthesis of a variety of bioactive hydroxy/alkoxy-γ-lactam derivatives which constitute attractive synthetic targets for promising biological applications including antimicrobial,[2a] α-glucosidase inhibiting[2b] and as neuritogenic agents.[2c,d]

α-Hydroxy-γ-lactams are of particular interest to chemists due to their versatile applications, for example, as the core structure of the neuritogenic agent epolactaene,[3a] in the synthesis of a number of heterocyclic compounds[3b,c] and also as precursors for the highly reactive cyclic α-acyliminium ion.[3d] *N*-Methyl-α-hydroxy-γ-lactam is an important intermediate for the synthesis of (−)ecgoninic acid,[3e] whereas the alkaloid isolongistrobine contains an *N*-aryl-α-hydroxy-γ-lactam unit as a key structural feature.[3f] *N*-Alkyl-α-hydroxy-γ-lactams are usually prepared as the major product by anodic oxidation of *N*-alkyl-γ-lactams,[4a] $NaBH_4$/HCl mediated regioselective reduction of substituted succinimides,[4b] osmium tetroxide–sodium metaperiodate (Lemieux–Johnson reagent)[4c] mediated oxidation of *cis*- or *trans*-4-octen-1,8-dicarboxamides[4d] or via an electrochemical method.[4e]

Although radical-induced decarboxylation of amino acids[5] is of great significance for biological systems considering the many well-established enzymatic or metabolic pathways for radical generation in vivo,[6] to date there are no reports on the one-pot decarboxylative hydroxylation/alkoxylation of γ-lactam-carboxylic acids at room temperature. In continuation of our ongoing interest to develop simple methodologies[7] for various functional

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group transformations of *N*-aryl-γ-lactam derivatives, herein we report our study on a reagent system that provides a simple, one-step method for the conversion of 1,3-diaryl-5-oxo-pyrrolidine-2-carboxylic acids (1,3-diaryl-γ-lactam-2-carboxylic acids) to *trans*-5-hydroxy-1,4-diaryl-pyrrolidin-2-ones (*trans*-1,4-diaryl-α-hydroxy-γ-lactams) and 5-alkoxy/azido-1,4-diaryl-1,5-dihydropyrrol-2-ones at room temperature.

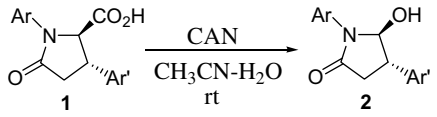
The advantages of good solubility in water (1.41 g/mL at 25 °C and 2.27 g/mL at 80 °C), low cost, low toxicity, commercial availability, ease of handling and the profound reactivity endowed in the reduction potential of +1.6 V compared to NHE (normal hydrogen electrode) have contributed to the general acceptance of ceric ammonium nitrate (CAN) as a versatile one-electron oxidant for carbon–heteroatom bond formation reactions[8] and give rise to the possibility of the development of more practical reactions in organo-aqueous medium at room temperature.

In view of the above usefulness of CAN as a single electron oxidant, we became interested in exploring its reactivity towards the decarboxylative hydroxylation/alkoxylation of 1,3-diaryl-5-oxo-pyrrolidin-2-carboxylic acids (1,3-diaryl-γ-lactam-2-carboxylic acids) at room temperature in organo-aqueous solvent.

The starting materials for this study, 1,3-diaryl-5-oxo-pyrrolidin-2-carboxylic acids **1**, were synthesized following the general method[7,9] developed in our laboratory. Decarboxylative hydroxylation[10] of **1** with CAN in acetonitrile–water (1:1, v/v) at room temperature furnished exclusively *trans*-5-hydroxy-1,4-diarylpyrrolidin-2-ones **2** (Scheme 1) in high yields (Table 1).

The trans arrangement of the C-4 and C-5 substituents of **2** was confirmed from the coupling constant values between C-4H and C-5H (~2–2.4 Hz).[11]

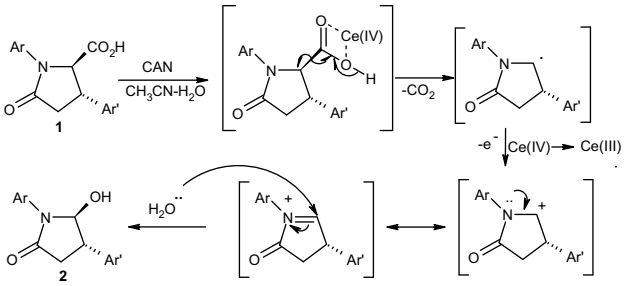
Although the mechanism of the reaction is uncertain, as might be expected of a very powerful one-electron oxidant, the chemistry of Ce(IV) oxidation of organic molecules is dominated by radical cation chemistry and by analogy[12]



Scheme 1.

Table 1
Synthesis of *trans*-5-hydroxy-1,4-diarylpyrrolidin-2-ones **2** from 1,3-diaryl-5-oxo-pyrrolidin-2-carboxylic acids **1**

Substrate	Ar	Ar′	Product	Yield (%)
1a	Ph	Ph	**2a**	90
1b	4-ClC_6H_4	Ph	**2b**	88
1c	3,4-$Cl_2C_6H_3$	Ph	**2c**	87
1d	3-Cl,4-FC_6H_3	Ph	**2d**	88
1e	3-Cl,4-FC_6H_3	2-Thienyl	**2e**	82
1f	4-FC_6H_4	Ph	**2f**	91



Scheme 2.

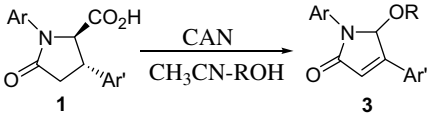
it can be speculated that the reaction proceeds (Scheme 2) through an *N*-acyliminium intermediate. The mechanism involving a complex intermediate as evidence for a complex in the Ce(IV) oxidation of acetic acid has been obtained.[13] This complex is generated through loss of CO_2 leading to an alkyl radical α to nitrogen, which is easily oxidized by excess CAN to a cation, and the resulting iminium ion is converted to the α-hydroxy-γ-lactam (*trans*-5-hydroxy-1,4-diarylpyrrolidin-2-one) via nucleophilic attack of water.

The pleasing outcome of the above reaction prompted us to extend this method to include other nucleophilic solvents. Instead of water, we performed the same reaction using alcohols with acetonitrile (1:1, v/v). However, in this case, dehydrogenation[14] along with decarboxylative alkoxylation (Scheme 3) occurred to give 5-alkoxy-1,4-diaryl-1,5-dihydropyrrol-2-ones **3** in good yields (Table 2).

To further test the generality of this reaction we next investigated the reaction of *trans*-1-(3,4-dichlorophenyl)-3-phenyl-5-oxo-pyrrolidin-2-carboxylic acid **1c** (1 mmol) with sodium azide (1.1 mmol) as the nucleophilic agent in acetonitrile (15 mL) at room temperature. After stirring for 5 h, we obtained 5-azido-1-(3,4-dichlorophenyl)-4-phenyl-1,5-dihydropyrrol-2-one **4** in 77% yield (Scheme 4).

Though we are able to speculate a possible mechanistic pathway for the decarboxylative hydroxylation (Scheme 2), we are unable to put forward a plausible mechanism for the dehydrogenation to give compounds **3** and **4**.

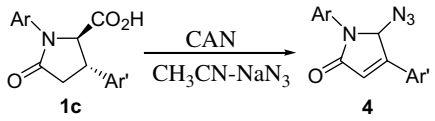
In summary, we have developed a mild and efficient method for the synthesis of α-hydroxy/alkoxy/azido-γ-



Scheme 3.

Table 2
Synthesis of 5-alkoxy-1,4-diaryl-1,5-dihydropyrrol-2-ones **3** from 1,3-diaryl-5-oxo-pyrrolidine-2-carboxylic acids **1**

Substrate	Ar	Ar′	R	Product	Yield (%)
1a	Ph	Ph	Et	**3a**	84
1f	4-FC_6H_4	Ph	Me	**3b**	93



Scheme 4.

lactam derivatives via CAN mediated one-pot decarboxylative hydroxylation/alkoxylation/azidination of 1,3-diaryl-5-oxo-pyrrolidin-2-carboxylic acids at room temperature. The 5-alkoxy/azido-dihydropyrrol-2-one derivatives may serve as dienophiles in Diels–Alder reactions.[15] The lactam carbonyl could be further reduced[7a,d,e] using sodium borohydride–iodine in dry THF to synthesize differently substituted hydroxy-pyrrolidine derivatives, which have often been found to show versatile biological activities.[16a–c] The operational simplicity and the mild conditions of this one-pot process open up new prospects in this area and it is anticipated that this method will lead to broader applications in the synthesis of bioactive hydroxy-pyrrolidine derivatives.

2. General procedure for the synthesis of *trans*-5-hydroxy-1,4-diarylpyrrolidin-2-ones (2) from 1,3-diaryl-5-oxo-pyrrolidine-2-carboxylic acids (1)

To a stirred solution of 1,3-diaryl-5-oxo-pyrrolidine-2-carboxylic acid **1** (1 mmol) in acetonitrile (10 mL) in an open-necked round bottom flask, an aqueous solution of ceric ammonium nitrate (2.2 mmol in 10 mL of water) was added and stirring was continued at room temperature (25–30 °C) for 3–4 h. After completion of the reaction (monitored by TLC), acetonitrile was removed under vacuum and the residue was dissolved in ether. The solution was washed with saturated sodium bicarbonate solution and then with brine solution and dried over anhydrous Na_2SO_4. Removal of the solvent furnished the crude product, which was purified by crystallization from ether–petroleum ether (6:1) mixture.

3. Spectral data of representative compounds

3.1. 1-(3,4-Dichlorophenyl)-5-hydroxy-4-phenylpyrrolidin-2-one (**2c**)

White solid; mp 164–166 °C; ^{1}H NMR (200 MHz; $CDCl_3$): δ 2.67 (dd, 1H, $J \sim 4.3$ Hz and 17.5 Hz), 3.22 (dd, 1H, $J \sim 8.9$ Hz and 17.5 Hz), 3.41–3.47 (m, 1H), 5.49 (d, 1H, $J \sim 2.1$ Hz), 7.19–7.24 (m, 3H), 7.29–7.37 (m, 3H), 7.41–7.44 (m, 1H), 7.70 (d, 1H, $J \sim 2.8$ Hz). ^{13}C NMR (50 MHz; $CDCl_3$ + DMSO-d_6): δ 36.9, 45.0, 89.6, 121.1, 123.3, 126.0, 127.5, 128.2, 129.5, 131.4, 136.7, 140.5, 172.4. ESI-MS: for $C_{16}H_{13}Cl_2NO_2$ [M], $[M+H]^+ = 322.03$ (^{35}Cl), 324.03 (^{35}Cl and ^{37}Cl). Anal. Calcd for $C_{16}H_{13}Cl_2NO_2$: C, 59.65; H, 4.07; N, 4.35. Found: C, 59.57; H, 4.04; N, 4.30.

3.2. 1-(4-Fluorophenyl)-5-methoxy-4-phenyl-1,5-dihydropyrrol-2-one (**3b**)

Colourless solid; mp 136–139 °C; IR (KBr) ν_{max} 1688, 1509 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$): δ 2.99 (s, 3H), 6.40 (s, 1H), 6.61 (s, 1H), 7.06–7.15 (m, 2H), 7.45–7.49 (m, 3H), 7.70–7.78 (m, 4H). ^{13}C NMR (50 MHz; $CDCl_3$): δ 48.7, 88.4, 115.8 (d, $J \sim 22.4$ Hz), 122.3, 122.4, 122.6, 126.9, 129.1, 130.1, 130.9, 133.2, 152.9, 159.8 (d, $J \sim 242.7$ Hz), 168.7. Anal. Calcd for $C_{17}H_{14}FNO_2$: C, 72.07; H, 4.98; N, 4.94. Found: C, 71.98; H, 5.01; N, 4.92. ESI-MS: for $C_{17}H_{14}FNO_2$ [M], $[M+H]^+ = 284.09$.

3.3. 5-Azido-1-(3,4-dichlorophenyl)-4-phenylpyrrolidin-2-one (**4**)

Off-white solid; yield 77%; mp 224–226 °C; ^{1}H NMR (200 MHz; $CDCl_3$ + DMSO-d_6): δ 6.13 (s, 1H), 6.24 (s, 1H), 7.20–7.26 (m, 4H), 7.54–7.61 (m, 3H), 7.88 (d, 1H, $J \sim 2.5$ Hz). ^{13}C NMR (50 MHz; $CDCl_3$ + DMSO-d_6): δ 82.6, 118.9, 119.2, 120.9, 125.8, 127.1, 128.4, 129.7, 130.0, 130.1, 131.5, 137.1, 156.4, 167.7. Anal. Calcd for $C_{16}H_{10}Cl_2N_4O$: C, 55.67; H, 2.92; N, 16.23. Found: C, 55.78; H, 2.90; N, 16.19.

Acknowledgements

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