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A novel synthetic approach towards *N*-phenylsuccinimides from γ-lactam-2-carboxylic acid derivatives by reaction with CAN–$NaBrO_3$

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Abstract

N-Arylsuccinimides have been synthesized by decarboxylative oxidation of *N*-aryl-γ-lactam-2-carboxylic acids with the dual oxidant CAN/$NaBrO_3$ in refluxing acetonitrile–water.

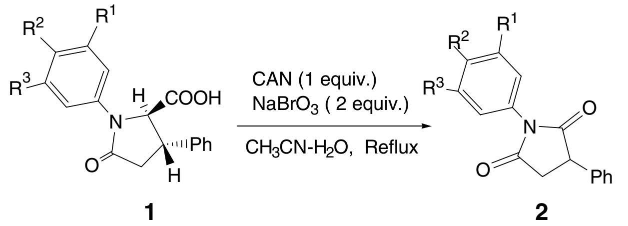
Keywords: Dual oxidant; Decarboxylative oxidation; *N*-Arylsuccinimides; Radical cation

1. Introduction

Imide derivatives have numerous applications in biology, synthetic and polymer chemistry.[1,2] Cyclic *N*-arylimides have high antifungal activity, especially against *Sclerotinia sclerotiorum* and *Botrytis cinerea*.[3] However, the availability of simple routes for their synthesis is limited.

We herein report the synthesis of *N*-aryl-substituted succinimides by decarboxylative oxidation of γ-lactam carboxylic acids. Many of the oxidants used for the decarboxylation of carboxylic acids are metal derivatives, such as lead(IV), cobalt(III), silver(II), manganese(III) and thallium(III) salts; chromic acid and non-metallic oxidants have also been reported.[4]

Cerium(IV) compounds, particularly ceric ammonium nitrate [$(NH_4)_2Ce(NO_3)_6$, CAN], are notable oxidants. Cerium(IV)-promoted oxidations were originally carried out under strongly acidic conditions but recent studies have focused on the development of much milder and more convenient procedures with wider applications.[5] Ho have found that the dual oxidant system Ce^{4+}/BrO_3^- allows the use of cerium(IV) as a catalyst as it is continuously replenished by the action of the bromate. Using this system, hydroquinones are oxidized to quinones, sulfides to sulfoxides and arylmethanols are transformed into the corresponding carbonyl compounds in good yields.[6,7] Loudon et al. reported that oxidative decarboxylation of amino acids with [bis(trifluoroacetoxy)iodo]benzene in the presence of pyridine gives the corresponding aldehyde in about 45% yield.[8] In 1988, Ochiai and Moriaty et al. found that oxidation of L-proline with iodosobenzene (ISB) gave 2-pyrrolidinone under neutral conditions.[9] The reaction of the γ-lactam-carboxylic acids **1** with CAN–$NaBrO_3$ in acetonitrile–water (1:1; v/v) at 80 °C furnished exclusively the 1,3-diaryl succinimides **2** in high yields (Scheme 1, Table 1). The starting materials for this study, γ-lactam-2-carboxylic acids **1**, were synthesized by a general method.[10–13]



Scheme 1. Decarboxylative oxidation of γ-lactam-2-carboxylic acids.

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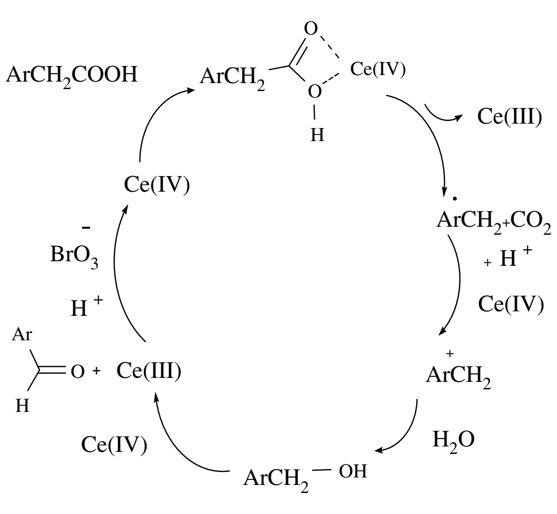
Table 1
Synthesis of *N*-arylsuccinimides **2** from γ-lactam-2-carboxylic acids **1**[a]

Substrate *N*-aryl-γ-lactam-2-carboxylic acid	Product *N*-arylsuccinimide	Yield (%)
1a $R^1 = R^3 = H$, $R^2 = Cl$	**2a**	87
1b $R^1 = R^3 = H$, $R^2 = F$	**2b**	76
1c $R^1 = R^3 = H$, $R^2 = Br$	**2c**	70
1d $R^1 = R^3 = H$, $R^2 = CH_3$	**2d**	80
1e $R^1 = R^3 = R^2 = H$	**2e**	90
1f $R^1 = Cl$, $R^2 = F$, $R^3 = H$	**2f**	76

[a] Reagents and conditions: All the reactions were carried out with 1 equiv of CAN, and 2 equiv of $NaBrO_3$ in $CH_3CN–H_2O$ (1:1, v/v) at 80 °C for 5–8 h.

Except for oxalic, malonic and α-hydroxycarboxylic acids, carboxylic acids are resistant to oxidation with cerium(IV). In our case CAN–$NaBrO_3$ acts as a dual oxidant although the cerium(IV) ion is the actual reagent. Cerium(IV) has a high oxidation potential of +1.61 V compared to the NHE (normal hydrogen electrode),[14] and acts as a single electron oxidant. The oxidation by Ce(IV)/BrO_3^- occurred via a radical cation in the above reaction. In 1974, Trahanovsky et al. proposed a mechanism for the CAN mediated decarboxylative oxidation of substituted phenyl acetic acids.[4] However, the mechanism of the reaction is uncertain, and we were unable to isolate any intermediates, although a plausible mechanism may be written as depicted in Scheme 2.[15]

The standard electrode potential, $E^0(Ce^{IV}/Ce^{III})$ is unknown. The formal potential for equal concentrations of cerium(IV) and cerium(III) varies considerably with the nature and concentration of the acidic medium. Cerium(III) is converted to cerium(IV) by the BrO_3^- ion in the reaction medium, also the BrO_3^- ion can oxidize the alcohol formed during the course of the reaction.[15] The electronic configurations of Ce^{III} and Ce^{IV} are $[Xe]4f^1$ and $[Xe]4f^0$ where Xe represents the xenon configuration. The stability of the vacant f shell accounts for the ability of cerium to exist in the Ce^{IV} oxidation state.[14]



Scheme 2. Mechanistic pathway.

In conclusion, we have developed a novel and simple method for the decarboxylative oxidation of γ-lactam-carboxylic acids to *N*-arylsuccinimides in one step and in good yields. This procedure demonstrates the potential of the CAN–$NaBrO_3$ reagent system as a decarboxylative oxidating agent in refluxing acetonitrile–water as solvent. The synthesis allows oxidation under mild conditions using low cost reagents. The experimental simplicity of the reaction opens new opportunities for the use of this reaction in synthetic and industrial processes.

2. Typical experimental procedure

*2.1. General procedure for the synthesis of 1,3-diarylsuccinimides **2** from N-aryl γ-lactam-2-carboxylic acid* **1**

To a flask containing the γ-lactam-2-carboxylic acid **1** (1 mmol) in acetonitrile (10 mL) was added a mixture of ceric ammonium nitrate (1 mmol) and $NaBrO_3$ (2 mmol) in water (15 mL) and the mixture was stirred for 15 min at room temperature. The reaction mixture was refluxed for 6–8 h (monitored by TLC) and then cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was extracted with CH_2Cl_2. The combined organic layer was washed successively with H_2O, 10% $NaHCO_3$ solution and then again with more H_2O. After drying the organic layer with Na_2SO_4, the solvent was evaporated under reduced pressure. The product thus obtained was crystallized from an ethyl acetate–petroleum ether mixture.

3. Physical properties and spectral data of representative compounds

3.1. Compound **2a***, 1-(4-chlorophenyl)-3-phenylpyrrolidine-2,5-dione*

Light yellow solid; mp 158–162 °C, ^1H NMR ($CDCl_3$, 200 MHz) δ 2.96 (dd, $J = 4.9$, 18.5 Hz, 1H), 3.32 (dd, $J = 4.5$, 8.8 Hz, 1H), 4.16 (dd, $J = 4.9$, 9.6 Hz, 1H), 7.13–7.54 (m, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 36.96, 45.76, 127.24, 127.56, 127.98, 129.15, 129.21, 130.24, 134.26, 134.76, 174.75, 176.33, IR ($CHCl_3$): ν_{max} 1718, 1685, 1560 cm^{-1}, ESI-MS for $C_{16}H_{12}NO_2Cl$ [M], $[M+H^+] = 286.071$ (100%). HRMS (ESI) calcd for $C_{16}H_{12}NO_2Cl$ $[M+H^+]$: 286.063, found: 286.060.

3.2. Compound **2b***, 1-(4-fluorophenyl)-3-phenylpyrrolidine-2,5-dione*

Light yellow solid, mp 136–140 °C, ^1H NMR ($CDCl_3$, 200 MHz) δ 3.00 (dd, $J = 4.9$, 18.6 Hz, 1H), 3.38 (dd, $J = 9.5$ Hz, 18.7 Hz, 1H), 4.19 (dd, $J = 4.9$, 9.5 Hz, 1H), 7.12–7.51 (m, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.12, 45.91, 115.98, 116.44, 127.33, 128.14, 128.20, 129.15, 129.31, 132.43, 136.93, 175.04, 176.5, IR ($CHCl_3$): ν_{max} 1717, 1655, 1509 cm^{-1}, ESI-MS for $C_{16}H_{12}NO_2F$ [M],

$[M+H^+] = 270.088$ (100%). HRMS (ESI) calcd for $C_{16}H_{12}NO_2F$ $[M+H^+]$: 270.085, found: 270.089.

3.3. Compound **2c**, 1-(4-bromophenyl)-3-phenylpyrrolidine-2,5-dione

Light yellow solid, mp 155–158 °C, ^1H NMR ($CDCl_3$, 200 MHz) δ 3.01 (dd, $J = 4.9$, 18.6 Hz, 1H), 3.39 (dd, $J = 9.6$, 18.6 Hz, 1H), 4.20 (dd, $J = 4.9$, 9.6 Hz, 1H), 7.22–7.45 (m, 7H), 7.59–7.65 (m, 2H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.07, 45.87, 122.45, 127.30, 127.87, 128.10, 129.79, 130.81, 133.75, 136.78, 174.69, 176.25, IR ($CHCl_3$): ν_{max} 1718, 1655, 1508 cm^{-1}, ESI-MS for $C_{16}H_{12}NO_2Br$ [M], $[M+H^+] = 330.020$ (^{79}Br), 332.020 (^{81}Br).

3.4. Compound **2d**, 1-(p-tolyl)-3-phenyl-pyrrolidine-2,5-dione

Light yellow solid, mp 145–147 °C (lit. mp 142 °C).[16]

3.5. Compound **2e**, 1,3-diphenyl-pyrrolidine-2,5-dione

Light yellow solid, mp 135–138 °C (lit. mp 140 °C).[16]

3.6. Compound **2f**, 1-(3-chloro-4-fluorophenyl)-3-phenyl-pyrrolidine-2,5-dione

Yellow viscous dense liquid ^1H NMR ($CDCl_3$, 200 MHz) δ: 3.00 (dd, $J = 4.9$, 18.7 Hz, 1H), 3.35 (dd, $J = 9.6$, 18.6 Hz, 1H), 4.20 (dd, $J = 4.8$, 9.5 Hz, 1H), 7.20–7.47 (m, 8H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 37.02, 45.87, 116.75, 117.20, 121.53, 121.90, 126.29, 126.43, 127.30, 127.74, 128.23, 128.82, 129.04, 129.92, 136.62, 155.26, 160.26, 174.64, 176.20, IR ($CHCl_3$): ν_{max} 1718, 1654, 1500 cm^{-1}, ESI-MS for $C_{16}H_{11}NO_2FCl$ [M], $[M+H^+] = 304.055$.

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