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Three-Component Synthesis of Ninhydrin Derived α-Acyloxycarboxamides

Ali R. Karimi[1,*], **Afshin Rajabi-Khorrami**[1], **Zahra Alimohammadi**[1], **Ali A. Mohammadi**[2], and **Mohammad R. Mohammadizadeh**[3]

[1] Department of Chemistry, Faculty of Science, Islamic Azad University-Karaj Branch, Karaj, Iran
[2] Department of Chemistry, Faculty of Science, Islamic Azad University-Sabzevar Branch, Sabzevar, Iran
[3] Chemistry Department, Shahid Beheshti University, Tehran, Iran

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Summary. A series of ninhydrin derived α-acyloxycarboxamide derivatives were synthesized in good yields in a *Passerini* three-component reaction by condensation of ninhydrin, carboxylic acids, and isocyanides.

Keywords. α-Acyloxycarboxamides; Three-component synthesis; Ninhydrin.

Introduction

The α-acyloxycarboxamide group is a frequently recurring motif in many natural products, as *e.g.* in the pharmacologically interesting depsipeptides [1]. Peptidyl and peptidomimetic α-ketoamide scaffolds are useful in small molecule drug discovery programs as transition-state analog protease inhibitors [2]. Such covalent inhibitors generally exhibit potent *in vitro* enzyme inhibitory activity, with subnanomolar equilibrium inhibitor constants. Accordingly, they are finding increasing applications as potential therapeutics for important diseases [3].

Ninhydrin is a unique tricarbonyl compound which is widely used in biochemical settings for the analysis of amino acids [4]. In context of our general interest in multiple component reactions [5] and due to the pharmacological interest in compounds which belong to the α-acyloxycarboxamides and ninhydrin, we report herein the three-component synthesis of some new α-acyloxycarboxamide derivatives *via* condensation of ninhydrin, carboxylic acids, and isocyanids under mild conditions.

* Corresponding author. E-mail: ar_karimi55@yahoo.com

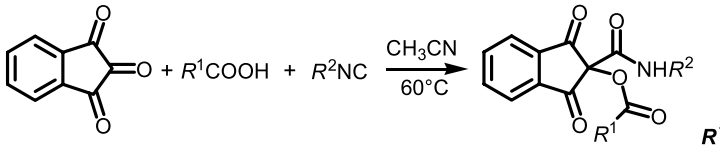
Results and Discussion

Although the reaction of ninhydrin and isocyanides in the absence of carboxylic acids gave dispiro(iminodioxolane) derivatives **5** (Scheme 2) [6], completely different results were obtained from the reaction of ninhydrin and isocyanides in the presence of carboxylic acids (Scheme 1).

It has been shown that isocyanide adds to carbonyl compounds to generate an intermediate **A** in the *Passerini* reaction and it has been trapped by carboxylic acid to give α-acyloxycarboxamide derivatives after a *Mumm* rearrangement (Scheme 3) [7].

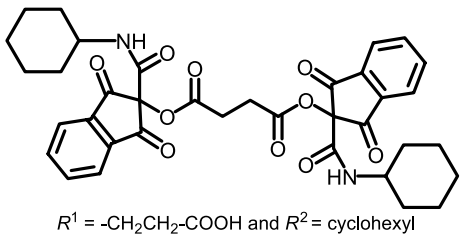
When a mixture of ninhydrin (**1**), carboxylic acids **2**, and isocyanides **3** in a ratio of 1:1:1 in acetonitrile was refluxed at 60°C for 2 h, α-acyloxycarboxamides **4** were obtained in excellent yields.

The structures of **4a**–**4h** were deduced from their elemental analyses and their IR, ^{1}H, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values. The ^{1}H NMR spectrum of **4a** exhibited one single sharp line at $\delta = 6.21$ ppm readily recognized as CH_3 along with multiplets at



1 2 3

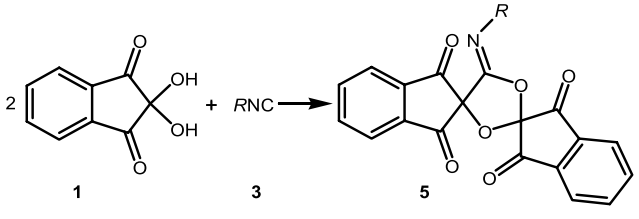
	R^1	R^2
4a	CH_3-	cyclohexyl
4b	CH_3CH_2-	cyclohexyl
4c	CH_3-	*t-Bu*-
4d	$ClCH_2$-	cyclohexyl
4e	1-naphthyl	cyclohexyl
4f	benzophenone-1-yl	cyclohexyl
4g	styryl-	cyclohexyl



R^1 = -CH_2CH_2-COOH and R^2 = cyclohexyl

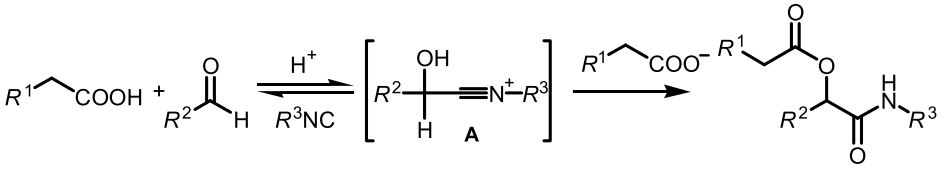
4h

Scheme 1



1 3 5

Scheme 2



Scheme 3

$\delta = 1.23–1.94$ ppm for the cyclohexyl protons. The multiplet and broad singlet at $\delta = 3.70$ and 6.46 ppm is related to methine and NH. The multiplet at $\delta = 7.89–8.03$ ppm is characteristic of aromatic protons. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 12 distinct resonances in agreement with the proposed structure.

In conclusion, the multicomponent reaction described provides a simple and direct entry into a number of interesting novel α-acyloxycarboxamide derivatives derived from ninhydrin that may be of value in medicinal chemistry.

Experimental

Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were measured on a Shimadzu IR-470 Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker 300 DRX AVANCE instrument at 300 and 75 MHz.

2-(Cyclohexylcarbamoyl)-2,3-dihydro-1,3-dioxo-1H-inden-2-yl acetate (**4a**, $C_{18}H_{19}NO_5$)
To a mixture of 0.178 g ninhydrin (1 mmol) and 0.63 cm^3 acetic acid (1.2 mmol) in 30 cm^3 CH_3CN, 0.122 cm^3 cyclohexyl isocyanide (1 mmol) were added *via* a syringe and refluxing was continued for a further 1 h. The solvent was removed under vacuum and the product was crystallised from acetone: H_2O (15:1, *v*:*v*) to give a white crystalline solid. Mp 219–220°C; IR (KBr): $\bar{\nu} = 3255$ (NH), 1661, 1720–1750 (3C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.23–1.71$ (m, 10cyclohexyl), 2.26 (s, CH_3), 3.70 (m, N–CH), 6.46 (bs, NH), 7.89–8.03 (m, $4H_{arom}$) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 19.84$ (CH_3), 24.72, 25.34, 32.64, 49.08 (cyclohexyl) 84.01 (C_q), 123.96, 135.96, 141.56 (C_{arom}), 161.27, 167.87, 191.72 (3C=O) ppm; MS: m/z (%) = 330 (M^++1, 25), 287 (100), 205 (60), 162 (70), 132 (45), 104 (30), 76 (25), 43 (100).

2-(Cyclohexylcarbamoyl)-2,3-dihydro-1,3-dioxo-1H-inden-2-yl propionate (**4b**, $C_{19}H_{21}NO_5$)
Prepared as described for **4a**. White crystalline solid, mp 179–180°C; IR (KBr): $\bar{\nu} = 3255$ (NH), 1661, 1720, 1738 (3C=O) cm^{-1}; ^{1}H NMR (*DMSO-d*$_6$, 300 MHz): $\delta = 0.96$ (t, $J = 7.30$ Hz, CH_3), 1.01–1.69 (m, 10cyclohexyl), 2.60 (q, $^{3}J = 7.30$ Hz, CH_2), 3.49 (m, N–CH), 8.05 (m, $4H_{arom}$), 8.45 (bs, NH) ppm; ^{13}C NMR (*DMSO-d*$_6$, 75 MHz): $\delta = 7.98$ (CH_3), 24.29 (CH_2), 24.43, 24.94, 31.31, 48.05 (cyclohexyl), 82.55 (C_q), 123.08, 136.31, 140.29 (C_{arom}), 160.62, 171.89, 191.78 (3C=O) ppm; MS: m/z (%) = 344 (M^++1, 25), 287 (100), 205 (35), 162 (50), 132 (30), 104 (30), 76 (25), 57 (80).

2-(tert-Butylcarbamoyl)-2,3-dihydro-1,3-dioxo-1H-inden-2-yl acetate (**4c**, $C_{16}H_{17}NO_5$)
Prepared as described for **4a**. White crystalline solid, mp 200–203°C; IR (KBr): $\bar{\nu} = 3340$ (NH), 1665, 1715, 1746 (3C=O) cm^{-1}; ^{1}H NMR (*DMSO-d*$_6$, 300 MHz): $\delta = 1.26$ (s, *t*-Bu), 2.27 (s, CH_3), 7.77 (s, NH), 8.06 (s, $4H_{arom}$) ppm; ^{13}C NMR (*DMSO-d*$_6$, 75 MHz): $\delta = 19.89$ (CH_3), 28.61 (CH_3), 52.50 (C), 83.72 (C_q), 124.07, 137.28, 141.47 (C_{arom}), 162.07, 169.44, 192.87 (3C=O) ppm; MS: m/z (%) = 304 (M^++1, 15), 261 (90), 205 (100), 162 (90), 132 (50), 104 (30), 76 (25), 43 (70).

2-(Cyclohexylcarbamoyl)-2,3-dihydro-1,3-dioxo-1H-inden-2-yl 2-chloroacetate (**4d**, $C_{18}H_{18}NO_5$)
Prepared as described for **4a**. White crystalline solid, mp 223–225°C; IR (KBr): $\bar{\nu} = 3295$ (NH), 1661, 1719, 1750 (3C=O) cm^{-1}; ^{1}H NMR (*DMSO-d*$_6$, 300 MHz): $\delta = 1.09–1.67$ (m, 10cyclohexyl), 3.51 (m, N–CH), 4.77 (s, CH_2), 8.09 (s, $4H_{arom}$), 8.49 (bs, NH) ppm; ^{13}C NMR (*DMSO-d*$_6$, 75 MHz): $\delta = 25.21$, 25.44, 32.40, 49.16 (cyclohexyl), 58.00 (CH_2), 84.16 (C_q), 124.33, 137.69, 141.29 (C_{arom}), 161.10, 166.53, 191.76 (3C=O) ppm; MS: m/z (%) = 364 (M^++1, 20), 287 (100), 205 (40), 162 (65), 132 (30), 104 (40), 77 (35), 55 (45).

2-(Cyclohexylcarbamoyl)-2,3-dihydro-1,3-dioxo-1H-inden-2-yl 1-naphthoate (**4e**, $C_{27}H_{23}NO_5$)
Prepared as described for **4a**. White crystalline solid, mp 231–232°C; IR (KBr): $\bar{\nu} = 3315$ (NH), 1661, 1721, 1755 (3C=O) cm^{-1}; ^{1}H NMR (*DMSO-d*$_6$, 300 MHz): $\delta = 1.07–1.66$ (m, 10cyclohexyl), 3.57 (s,

N–CH), 7.61–8.70 (m, 11H_{arom}), 8.47 (bs, NH) ppm; ^{13}C NMR (*DMSO-d_6*, 75 MHz): $\delta = 25.33$, 25.43, 32.20, 49.36 (cyclohexyl), 84.68 (C_q), 122.63, 124.30, 124.86, 125.38, 127.18, 129.18, 129.53, 131.06, 133.24, 133.80, 135.99, 137.41, 141.32 (C_{arom}), 161.65, 165.26, 192.69 (3C=O) ppm; MS: m/z (%) = 442 (M^++1, 4), 316 (4), 281 (5), 189 (6), 155 (100).

2-(Cyclohexylcarbamoyl)-2,3-dihydro-1,3-dioxo-1H-inden-2-yl 1-benzophenoate (**4f**, $C_{30}H_{25}NO_6$)
Prepared as described for **4a**. White crystalline solid, mp 190–191°C; IR (KBr): $\bar{\nu} = 3320$ (NH), 1660, 1720, 1754 (3C=O) cm^{-1}; ^{1}H NMR (*DMSO-d_6*, 300 MHz): $\delta = 1.02$–1.67 (m, 10cyclohexyl), 3.52 (m, N–CH), 7.43–8.49 (m, 13H_{arom}), 8.47 (d, $J = 7.55$ Hz, NH) ppm; ^{13}C NMR (*DMSO-d_6*, 75 MHz): $\delta = 25.29$, 25.42, 32.18, 49.36 (cyclohexyl), 84.67 (C_q), 124.21, 125.25, 128.27, 129.25, 129.68, 130.51, 132.24, 134.22, 134.92, 136.20, 137.38, 141.06, 142.71 (C_{arom}), 161.30, 163.80, 191.62, 196.22 (4C=O) ppm; MS: m/z (%) = 496 (M^++1, 1), 271 (4), 209 (100), 152 (30), 105 (30).

(E)-2-(Cyclohexylcarbamoyl)-2,3-dihydro-1,3-dioxo-1H-inden-2-yl cinnamate (**4g**, $C_{25}H_{23}NO_5$)
Prepared as described for **4a**. White crystalline solid, mp 226–228°C; IR (KBr): $\bar{\nu} = 3275$ (NH), 1661, 1722, 1756 (3C=O) cm^{-1}; ^{1}H NMR (*DMSO-d_6*, 300 MHz): $\delta = 1.03$–1.70 (m, 10cyclohexyl), 6.86 (d, $J = 16.15$ Hz, CH_{alkene}), 7.49 (m, 3H_{arom}), 7.74 (m, 2H_{arom}), 7.86 (d, $J = 16.15$ Hz, CH_{alkene}), 8.08 (s, 4H_{arom}), 8.51 (d, $J = 7.94$ Hz, NH) ppm; ^{13}C NMR (*DMSO-d_6*, 75 MHz): $\delta = 25.32$, 25.47, 32.40, 49.18 (cyclohexyl), 83.77 (C_q), 115.22, 124.15, 129.20, 129.59, 131.86, 133.97, 137.35, 141.41, 149.03 (C_{arom} and C_{alkene}), 161.69, 164.67, 192.72 (3C=O) ppm; MS: m/z (%) = 418 (M^++1, 10), 287 (100), 205 (30), 162 (40), 132 (20), 104 (35), 76 (15), 57 (60).

Bis(2-(cyclohexylcarbamoyl)-2,3-dihydro-1,3-dioxo-1H-inden-2-yl) succinate (**4h**, $C_{36}H_{36}N_2O_{10}$)
Prepared as described for **4a**. White crystalline solid, mp 237–238°C; IR (KBr): $\bar{\nu} = 3365$ (NH), 1666, 1716, 1743 (3C=O) cm^{-1}; ^{1}H NMR (*DMSO-d_6*, 300 MHz): $\delta = 1.03$–1.65 (m, 20cyclohexyl), 2.90 (s, 2CH_2), 3.48 (m, 2N–CH), 8.05 (s, 8H_{arom}), 8.44 (d, $J = 7.43$ Hz, 2NH) ppm; ^{13}C NMR (*DMSO-d_6*, 75 MHz): $\delta = 22.73$ (CH_2), 22.89, 25.01, 29.80, 46.54 (cyclohexyl), 81.10 (C_q), 121.59, 134.82, 138.75 (C_{arom}), 158.93, 167.97, 189.77 (3C=O) ppm; MS: m/z (%) = 657 (M^++1, 1), 575 (1), 532 (15), 287 (80), 245 (20), 205 (25), 162 (30), 104 (80), 55 (100).

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