Tetrahedron Letters 52 (2011) 5441–5443

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A novel oxidative decarboxylation—synthesis of 2-amino-1,2-dihydroisoquinoline-3(4*H*)-one and its amide derivatives from tetrahydroisoquinoline-3-carboxylic acid

B. Gopalan [a,*], Mani Umamaheswari [a], P.S. Mohan [b], Sridharan Rajagopal [a]

[a] Department of Medicinal Chemistry, Orchid Research Laboratories Limited, R&D Centre, Plot #476/14, Old Mahabalipuram Road, Sozhanganallur, Chennai 600 119, India
[b] Department of Chemistry, Bharathiar University, Coimbatore, India

ARTICLE INFO

Article history:
Received 8 July 2011
Revised 28 July 2011
Accepted 1 August 2011
Available online 7 August 2011

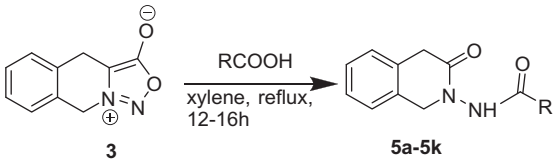
ABSTRACT

A convenient method of synthesizing 2-amino-1,2-dihydroisoquinoline-3(4*H*)-one and its amide derivatives (**4** or **5**) is described through sydnone intermediate (**3**) derived from TIC (**1**) (tetrahydroisoquinoline-3-carboxylic acid) under acidic conditions in good yield.

We are actively engaged in discovery of anti-inflammatory drugs. It is reported that 2-amino-1,2-dihydroisoquinoline-3(4*H*)-one and its amide derivatives have good anti-inflammatory properties and they inhibit metallo aminopeptidase.[1a,b] In the literature[1a,b] the title compounds **4** or **5** have been synthesised from homophthalic acid in five steps. *N*-phenylsydnone has been reported to give phenylhydrazine on treatment with HCl.[2,3] A survey of literature revealed only one isolated report wherein sydnone derived from proline when treated with propiolic acid in refluxing xylene gave the corresponding cyclic hydrazide.[4] These reports combined with their mechanism of formation of the hydrazine and hydrazide product suggested that **4** or **5** could be easily accessed through the sydnone intermediate **3**. We undertook a systematic study on the intramolecular redox reaction of sydnone derived from TIC, expanding the scope of the reaction with various carboxylic acids.

The commercially available TIC (**1**) was treated with $NaNO_2$ in HCl to generate the *N*-nitroso compound[5a–d] (**2**), which on subsequent reaction with trifluoroacetic anhydride gave the corresponding sydnone (**3**). Sydnone **3** was treated with concentrated HCl under reflux condition for 12 h to give the corresponding *N*-amino compound **4** in good yield (Scheme 1).[6] The structure of the compound was confirmed by mass and NMR spectral data.

The reaction of the sydnone **3** with acetic acid under reflux for 13 h gave the corresponding amide **5a** in good yield.[7] We then turned our attention to a few other carboxylic acids. The reaction of **3** with one equivalent of carboxylic acid in refluxing xylene for 12–16 h gave amide derivatives (**5a–k**) of hydrazide **5** in good yield (Scheme 2, Table 1). To confirm the structure of the compound, the reaction of **3** with (*E*)-2-(4-dimethylamino)phenyl-3-phenylacrylic acid was carried out and the resulting the amide's (**5j**), structure was determined using single crystal X-ray diffraction analysis[8] (Fig. 1). Structures of the compounds **5a–k** were determined using NMR and mass spectrum.[9] The pK_a of the carboxylic acid did not change the rate or the yield of the reaction.



Scheme 2.

Scheme 1.

* Corresponding author. Tel. +91 44 24501474; fax: +91 44 24501396.
E-mail address: gopalanb@orchidpharma.com (B. Gopalan).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.08.007

Table 1
Reaction of **3** with carboxylic acids and their yields

Carboxylic acid	**5** (% Yield)
Acetic acid	**5a** (73)
Benzoic acid	**5b** (88)
4-Fluorobenzoic acid	**5c** (75)
E-2,3-Diphenylacrylic aid	**5d** (87)
3,4-Dimethoxybenzoic acid	**5e** (71)
Thiophene 2-carboxylic acid	**5f** (89)
Cinnamic acid	**5g** (69)
Phenylacetic acid	**5h** (78)
4-F-Phenylacetic acid	**5i** (89)
(*E*)-2-(4-Dimethylamino)phenyl-3-phenylacrylic acid	**5j** (91)
4-Fluoro Cinnamic acid	**5k** (78)

Conditions: Reactions were done using 1 mmol of **3** and 1 mmol of carboxylic acid in refluxing xylene for 14–16 h.

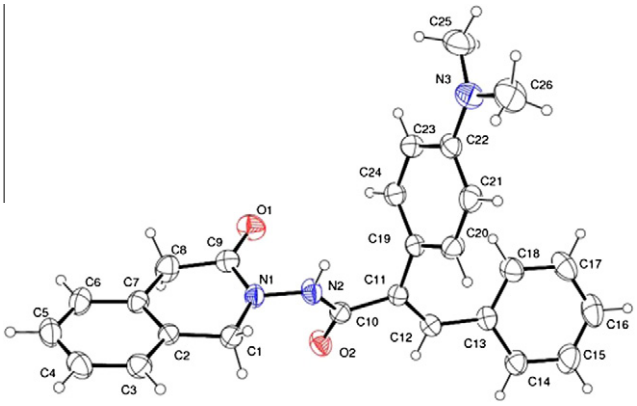


Figure 1. X-ray structure of the compound **5j**.

The proposed mechanism of the reaction is as shown in Scheme 3. The first step of the reaction is protonation of **3** to give **I** which on subsequent addition of water gives **II**. The intermediate **II** on protonation gives **III** which undergoes spontaneous decarboxylation to give **4**.

The formation of **5** can be explained by addition of carboxylate ion to **I** after initial protonation as shown in Scheme 4, followed by decarboxylation and intramolecular acyl transfer to give **VII** which on tautomerism gives **5**.

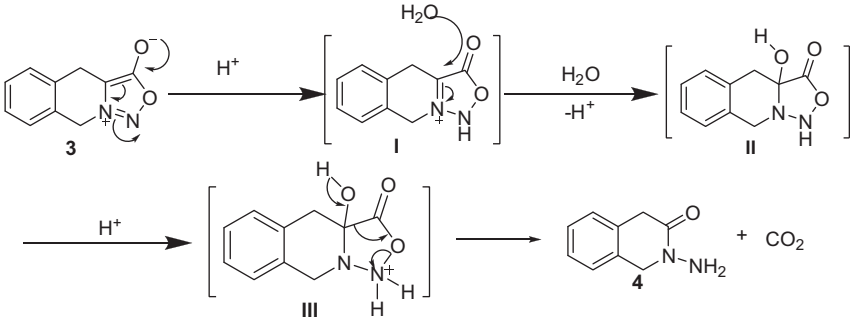
In conclusion we have developed a concise route to the synthesis of the title compounds which are versatile intermediates to diverse condensed heterocycles of biological importance.

Acknowledgments

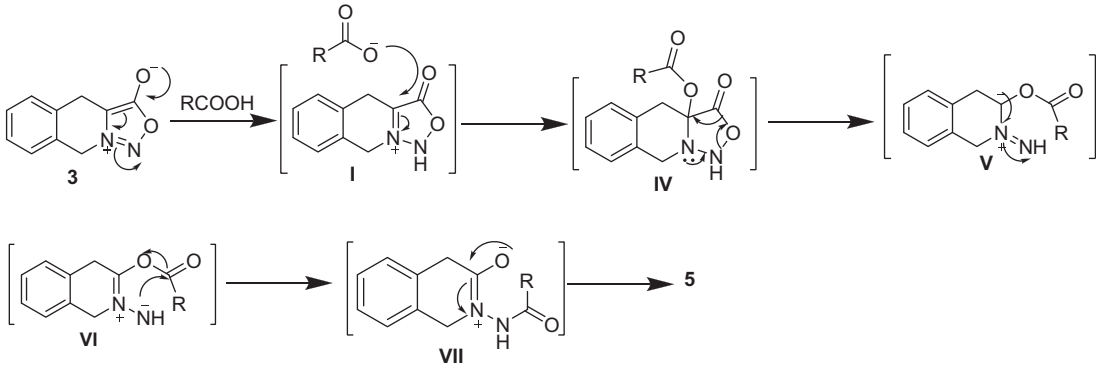
The authors thank RSIC, IIT Madras for the X-ray diffraction analysis, Orchid research laboratories for their support and Professor K. K. Balasubramanian for his technical comments.

References and notes

1. (a) Odasso, G.; Winters, G.; Schiatti, P.; Selva, D. *Farmaco* **1983**, *38*, 199–204; (b) Sebastien, A.; Albert, D.; Emmanuel, S.; Celine, T.; Anders, W.; Jasper, Z. H. *Bioorg. Med. Chem.* **2006**, *14*, 7241–7257.
2. Duncan, L. B.; Joseph, P. A. H. *Tetrahedron* **2010**, *66*, 553–558.
3. Joanne, S.; Donald, D. C. *J. Org. Chem.* **1964**, *29*, 2483–2484.
4. Darshan, R.; Shakti, B. *Tetrahedron Lett.* **1985**, *26*, 5739–5742.
5. (a) Zolfigol, M. A.; Habibi, D.; Mirjalili, F. B.; Bamoniri, A. *Tetrahedron Lett.* **2003**, *44*, 3345–3349; (b) Niknam, K.; Zolfigol, M. A. *Synth. Commun.* **2006**, *36*, 2311–2319; (c) Bamoniri, A.; Zolfigol, M. A.; Mirjalili, B. F.; Fallah, F. *Russian J. Org. Chem.* **2007**, *43*, 1397–1400; (d) Nikitenko, A. A.; Winkley, M. W.; Zeldis, J.; Kremer, K.; Chan, A. W.-Y.; Strong, H.; Jennings, M.; Jirkovsky, I.; Blum, D.; Khafizova, G.; Grosu, G. T.; Venkatesaan, A. M. *Org. Process Res. Dev.* **2006**, *10*, 712–716.
6. Sydnone **3** (0.5 g, 1 mmol) was taken in 20 mL of conc. HCl and stirred overnight under reflux. After completion of the reaction, conc. HCl was evaporated using rotavapour at 50 °C. Resulting crude product was taken in ethylacetate (50 mL) and sonicated for 10 min and filtered to give the product as its HCl salt **4**.



Scheme 3. Proposed mechanism for the formation of **4**.



Scheme 4. Proposed mechanism for the formation of **5**.

Isolated as pale yellow solid. Yield 91%. Mp 94–98 °C; IR ν_{max} (KBr) 1682, 1639, 3382 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 3.79 (s, 2H), 4.81 (s, 2H), 7.23–7.34 (m, 4H); ^{13}C NMR (400 MHz, DMSO) δ_C 35.52, 51.08, 125.75, 126.73, 127.53, 127.73, 129.61, 130.65, 166.94; Mass (M^+ +1) = 163.

7. Sydnone **3** (0.3 g, 1 mmol) was taken in 15 mL of acetic acid and stirred overnight under reflux. After completion of the reaction, acetic acid was evaporated using rotavapour at 50 °C to dryness to give the product **5a** as yellow solid. yield 73%. Mp 184–186 °C; IR ν_{max} (KBr) 1653, 1694, 3552 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.90 (s, 3H), 3.72 (s, 2H), 4.64 (s, 2H), 7.22–7.29 (m, 4H), 10.23 (s, 1H); ^{13}C NMR (400 MHz, DMSO) δ_C 20.52, 36.93, 53.59, 125.44, 126.44, 127.17, 127.36, 131.65, 131.77, 166.87, 168.22; Mass (M^+ +1) = 205.1.
8. X-ray crystal data of compound **5j** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number is CCDC – 829819. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk.
   Crystal data for compound **5j**: $C_{26}H_{25}N_3O_2$, M = 411.49, monoclinic, space group P21/c, a = 14.7503(6) A^0, b = 10.3737(4) A^0, c = 14.1677(5) A^0, β = 96.176(2)°, U = 2155.29(14) A^3, Z = 4, μ = 0.081 mm^{-1}, 16224 reflections collected, 2641 independent reflections, R_{int} = 0.0364, final R indices [$I > 2\sigma(I)$] R_1 = 0.0430, wR_2 = 0.1068, R indices (all data) R_1 = 0.0631, wR_2 = 0.1289. *CCDC – 829819.*
9. *General procedure for the synthesis of* ***5b–k****:* Sydnone **3**, (1 mmol) and xylene (30 mL) were charged to a double necked 100 mL round-bottomed flask, equipped with a water cooled condenser. The stirred solution was purged with nitrogen and heated to 140–145 °C and carboxylic acid (1 mmol) was added slowly over a period of 15 minutes. The reaction was held at 140–145 °C for 16 h. After completion of the reaction, the solvent was removed and the product was purified by column chromatography using hexane–ethylacetate mixture (6:4) as eluent to afford the product. Spectroscopic data for representative 2-amino-1,2-dihydroisoquinoline-3(4H)-one and its amide derivatives are given below.
   N-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)benzamide **5b**: Pale brown solid. Yield 88%. Mp 194–196 °C; IR ν_{max} (KBr) 1654, 1694, 3267 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H 3.76 (s, 2H), 4.78 (s, 2H),7.25–7.33 (m, 4H), 7.51–7.55 (m, 2H), 7.59–7.63 (1H, m), 7.89–7.91 (2H, m), 10.88 (1H, s); ^{13}C NMR (400 MHz, DMSO) δ_C 37.05, 53.67, 125.46, 126.45, 127.19, 127.38, 127.51, 128.54, 131.63, 131.79, 132.10, 165.11, 167.07; Mass (M^+ +1) = 267.1.
   4-fluoro-N-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)benzamide 5c: Pale brown solid. Yield 75%. Mp 220–224 °C; IR ν_{max} (KBr) 1643, 1684, 3435 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H 3.77 (s, 2H), 4.78 (s, 2H), 7.26–7.33 (m, 4H), 7.36–7.40 (m, 2H), 7.96–7.99 (m, 2H), 10.93 (s, 1H); ^{13}C NMR (400 MHz, DMSO) δ_C 37.04, 53.66, 115.50, 115.72, 125.46, 126.46, 127.20, 127.40, 128.55, 128.58, 130.24, 130.33, 131.63, 131.78, 163.10, 164.10, 165.58, 167.10; Mass (M^+ +1) = 285.1.
   (E)-N-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)-2,3-diphenylacrylamide **5d**: Pale brown solid. Yield 87%. Mp 156–158 °C; IR ν_{max} (KBr) 1646, 1682, 1736, 3258 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H 3.77 (s, 2H), 4.85 (s, 2H), 7.03 (m, 2H), 7.14–7.24 (m, 3H), 7.25–7.28 (m, 1H) 7.32–7.33 (m, 2H) 7.37–7.46 (m, 2H), 7.47–7.49 (m, 4H), 7.91 (s, 1H), 10.47 (s, 1H); ^{13}C NMR (400 MHz, DMSO) δ_C 23.29, 37.00, 49.92, 53.55, 125.44, 126.43, 126.57, 127.17, 127.33, 128.06, 128.14, 128.32, 128.60, 128.85, 129.48, 129.56, 129.76, 131.58, 131.76, 134.67, 134.76, 134.97, 135.36, 166.68, 166.84; Mass (M^+ +1) = 369.1.
   3,4-dimethoxy-N-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)benzamide **5e**: Pale brown solid. Yield 71%. Mp 204–206 °C; IR ν_{max} (KBr) 1654, 1682, 3436 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H3.76 (s, 2H), 3.81 (s, 3H), 3.83 (s, 3H), 4.77 (s, 2H), 7.08 (d, 1H, J = 8 Hz), 7.28–7.32 (m, 4H), 7.49 (d, 1H, J = 4 Hz), 7.55 (d, 1H, J = 12 Hz), 10.75 (1H, s); ^{13}C NMR (400 MHz, DMSO) δ_C 37.09, 53.77, 55.55, 55.64, 110.63, 111.01, 121.05, 124.15, 125.45, 126.44, 127.17,127.37, 131.66, 131.88, 148.31, 151.89, 164.62, 167.14; Mass (M^+ +1) = 327.1.
   N-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)thiophene-2-carboxamide **5f**: Pale brown solid. Yield 89%. Mp 202–204 °C; IR ν_{max} (KBr) 1641, 1677, 3436 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H 3.76 (s, 2H), 4.77 (s, 2H), 7.21–7.33 (m, 5H), 7.86–7.89 (m, 2H), 10.93 (1H, s); ^{13}C NMR (400 MHz, DMSO) δ_C 37.04, 53.83, 125.46, 126.47, 127.19,127.41, 128.23, 129.43, 131.59, 131.75, 132.07, 136.76, 160.16, 167.19;; Mass (M^+ +1) = 273.1.
   N-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)cinnamamide **5g**: Pale brown solid. Yield 69%. Mp 154–158 °C; IR ν_{max} (KBr) 1655, 1689, 1638, 3209 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H 3.74 (s, 2H), 4.74 (s, 2H), 6.70 (d, 1H, J = 16 Hz), 7.26–7.28 (m, 4H), 7.44–7.45 (m, 3H), 7.57 (d, 1H, J = 16 Hz), 7.62–7.64 (m, 2H), 10.51 (s, 1H); ^{13}C NMR (400 MHz, DMSO) δ_C 36.95, 53.65, 119.09, 125.50, 126.47, 127.21, 127.40, 127.83, 129.08, 130.03, 131.65, 131.74, 134.49, 164.01, 166.97; Mass (M^+ +1) = 293.1.
   N-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)-2-phenylacetamide **5h**: Pale brown solid. Yield 78%. Mp 144–148 °C; IR ν_{max} (KBr) 1651, 1686, 3436 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H 3.34 (s, 2H), 3.69 (s, 2H), 4.64 (s, 2H), 7.21–7.26 (m, 5H), 7.27–7.33 (m, 4H), 10.57 (s, 1H); ^{13}C NMR (400 MHz, DMSO) δ_C 36.88, 53.46, 125.44, 126.39, 126.54, 127.13, 127.32, 128.28, 129.07, 131.57, 131.65, 135.43, 166.83, 169.03; Mass (M^+ +1) = 281.1.
   2-(4-fluorophenyl)-N-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)acetamide **5i**: Pale brown solid. Yield 89%. Mp 175–177 °C; IR ν_{max} (KBr) 1651, 1686, 3436 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H 3.53 (s, 2H), 3.69 (s, 2H), 4.64 (s, 2H), 7.13–7.18 (m, 2H), 7.22–7.26 (m, 4H), 7.34–7.37 (m, 2H), 10.53 (s, 1H); ^{13}C NMR (400 MHz, DMSO) δ_C 36.87, 53.46, 114.91, 115.12, 125.45, 126.41, 127.14, 127.34, 130.89, 130.97, 131.56, 131.64, 159.93, 162.33, 166.87, 169.00 Mass (M^+ +1) = 299.1.
   (E)-2-(4-(dimethylamino)phenyl)-N-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)-3-phenylacrylamide **5j**:Pale brown solid. Yield 89%. Mp 163–166 °C; IR ν_{max} (KBr) 1678, 1698, 3368 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H 2.93 (s, 6H), 3.70 (s, 2H), 4.69 (s, 2H), 6.71 (d, 2H, J = 12 Hz), 7.05 (d, 2H, J = 8 Hz), 7.13–7.15 (m, 2H), 7.22–7.23 (m, 3H), 7.25–7.28 (m, 5H), 9.87 (1H, s); ^{13}C NMR (400 MHz, DMSO) δ_C 36.96, 53.51, 112.19, 122.02, 125.44, 126.40, 127.16, 127.30, 128.14, 128.27, 129.59, 130.33, 131.68, 131.59, 131.76, 133.12, 134.99, 135.39, 149.92, 166.75, 167.40; Mass (M^+ +1) = 412.2.
   (E)-3-(4-fluorophenyl)-N-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)acrylamide **5k**: Pale brown solid. Yield 89%. Mp 189–192 °C; IR ν_{max} (KBr) 1654, 1682, 1738, 3419 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H 3.74 (s, 2H), 4.74 (s, 2H), 6.64 (d, 1H, J = 16 Hz), 7.24–7.32 (m, 6H), 7.57 (d, 1H, J = 16 Hz), 7.69–7.72 (m, 2H), 10.51 (s, 1H); ^{13}C NMR (400 MHz, DMSO) δ_C 36.92, 53.62, 115.93, 116.14, 118.94, 125.47, 126.44, 127.19, 127.37, 130.02, 130.10, 131.10, 131.13, 131.61, 131.70, 139.65, 161.77, 163.94, 164.23, 166.94; Mass (M^+ +1) = 311.1.