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PII: S0040-4039(14)00874-0
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.05.073
Reference: TETL 44664

To appear in: *Tetrahedron Letters*

Received Date: 16 March 2014
Revised Date: 24 April 2014
Accepted Date: 15 May 2014

Please cite this article as: Khalafy, J., Etivand, N., Dilmaghani, S., Ezzati, M., Marjani, A.P., A convenient and mild synthesis of new 2-aryl-3-hydroxy-6,7-dihydro-1*H*-indol-4(5*H*)-ones via a one-pot, three-component reaction in water, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.05.073

Tetrahedron Letters
journal homepage: www.elsevier.com

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Arylglyoxals
1,3-Cyclohexanedione
Three-component reaction
1*H*-indol-4(5*H*)-ones

ABSTRACT

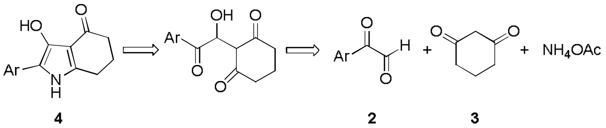
A simple and convenient synthesis of 2-aryl-3-hydroxy-6,7-dihydro-1*H*-indol-4(5*H*)-ones is achieved in high yields via the one-pot, three-component reaction of aryglyoxals, 1,3-cyclohexanedione and ammonium acetate in water under reflux conditions.

Indoles are one of the most widely distributed heterocyclic compounds in Nature. In many natural alkaloids, the indole nucleus is an important structural unit.[1,2] Among the various classes of nitrogen-containing heterocycles, indoles have significant synthetic potential. They are applied in many aspects of pharmaceutical and medicinal chemistry, for example, $GABA_A$ receptor ligands,[3] antipsychotic,[4] and antiproliferative agents,[5] and as soluble guanylate cyclase inhibitors.[6,7]

The use of water as the sole medium for organic reactions contributes to the development of environmentally friendly processes. Carrying out organic reactions in water has become highly desirable to meet environmental considerations.[8-10]

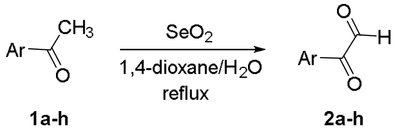
The synthesis of substituted 4-oxo-4,5,6,7-tetrahydroindoles, reported by Stetter and Lauterbach, involved treatment of 1,3-cyclohexanediones and α-haloketones with ammonia or primary amines leading to triones.[11] Heravi et al. have reported that a potassium hydrogen sulfate catalyzed Ugi reaction between cyclohexylisocyanide, an aldehyde, a cyclic 1,3-dicarbonyl compound and ammonium acetate in acetonitrile gave 2,3-disubstituted 6,7-dihydro-1*H*-indol-4(5*H*)-ones.[12] Li's group have reported a microwave-promoted reaction between substituted enamines, phenylglyoxal monohydrate and acetic acid for the preparation of polyfunctionalized indoles via multi-component domino reaction.[13,14]

Herein, we report a convenient and mild one-pot, three-component procedure for the synthesis of 2-aryl-3-hydroxy-6,7-dihydro-1*H*-indol-4(5*H*)-ones **4a-h** via the condensation reaction of arylglyoxals **2** with 1,3-cyclohexanedione (**3**) in the presence of ammonium acetate in water (Scheme 1) Structurally comparable 3-acyl-4-hydroxy-5-arylpyrroles have been prepared by reaction of arylglyoxals with acyclic 1,3-diketones in aqueous ammonium acetate.[15]



Scheme 1. Retrosynthesis of 2-aryl-3-hydroxy-6,7-dihydro-1*H*-indol-4(5*H*)-ones

The arylglyoxals **2a–h** were prepared from commercially available acetophenones **1a–h** by oxidation with selenium dioxide as outlined in Scheme 2.[16]

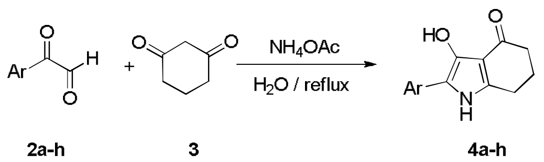


a; Ar = C_6H_5
b; Ar = 4-BrC_6H_4
c; Ar = 3-$MeOC_6H_4$
d; Ar = 4-FC_6H_4
e; Ar = 4-$O_2NC_6H_4$
f; Ar = 4-$MeOC_6H_4$
g; Ar = 3,4-$(MeO)_2C_6H_3$
h; Ar = 4-PhC_6H_4

Scheme 2. Synthesis of arylglyoxals **2a–h**

The reaction of arylglyoxals **2a–h** with 1,3-cyclohexanedione (**3**) in presence of ammonium acetate in water under reflux gave the corresponding 2-aryl-3-hydroxy-6,7-dihydro-1*H*-indol-4(5*H*)-ones **4a–h** (Scheme 3).

The products **4a–h** were obtained in high yields after recrystallization from ethanol.



a; Ar = C_6H_5 **e**; Ar = 4-$O_2NC_6H_4$
b; Ar = 4-BrC_6H_4 **f**; Ar = 4-$MeOC_6H_4$
c; Ar = 3-$MeOC_6H_4$ **g**; Ar = 3,4-$(MeO)_2C_6H_3$
d; Ar = 4-FC_6H_4 **h**; Ar = 4-PhC_6H_4

Scheme 3. Synthesis of 2-aryl-3-hydroxy-6,7-dihydro-1*H*-indol-4(5*H*)-ones

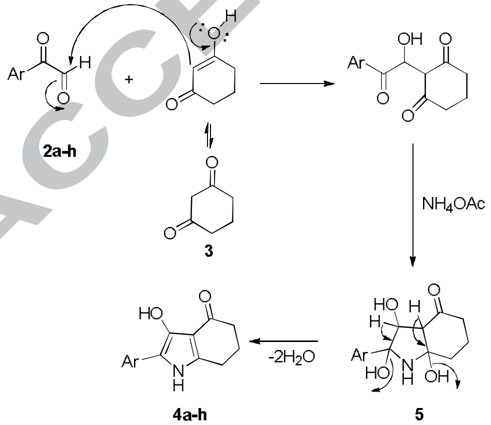
Eight examples of the conversion of arylglyoxals **2a-h** into the corresponding substituted 6,7-dihydro-1*H*-indol-4(5*H*)-ones **4a-h**, along with the reaction conditions are listed in Table 1.

Table 1. Synthesis of 2-aryl-3-hydroxy-6,7-dihydro-1*H*-indol-4(5*H*)-ones **4a-h**

Entry	Substrate	Product	Ar	Time (h)	Mp (°C)	Yield (%)[a]
1	**2a**	**4a**	C_6H_5	2	295-296	87
2	**2b**	**4b**	4-BrC_6H_4	5	210-212	91
3	**2c**	**4c**	3-$MeOC_6H_4$	2.5	248-249	83
4	**2d**	**4d**	4-FC_6H_4	3	288-289	93
5	**2e**	**4e**	4-$O_2NC_6H_4$	2	213-215	80
6	**2f**	**4f**	4-$MeOC_6H_4$	6	268-269	85
7	**2g**	**4g**	3,4-$(MeO)_2C_6H_3$	3	191-193	95
8	**2h**	**4h**	4-PhC_6H_4	5	200-202	94

[a] Isolated yield after recrystallization from ethanol.

The proposed mechanism for this reaction is shown in Scheme 4. The first step involves attack of the enol form of 1,3-cyclohexanedione on the arylglyoxal **2a-h** to form the corresponding intermediate, which is converted into the desired product through intermediate **5**, by loss of two molecules of water.



Scheme 4. The proposed mechanism for the formation of 2-aryl-3-hydroxy-6,7-dihydro-1*H*-indol-4(5*H*)-ones.

The structures of all the products were established from their ^{1}H-NMR, ^{13}C-NMR and FT-IR spectral data and microanalyses.

In summary, we have reported a convenient and simple synthesis of 2-aryl-3-hydroxy-6,7-dihydro-1*H*-indol-4(5*H*)-ones via the reactions of arylglyoxals with 1,3-cyclohexanedione and ammonium acetate in water. The advantageous features of this procedure are mild reaction conditions, high yields, operational simplicity, ready availability of starting materials and the use of water as an environmentally friendly solvent.

General Procedure for the synthesis of 2-aryl-3-hydroxy-6,7-dihydro-1*H*-indol-4(5*H*)-ones (4a-h):

To a mixture of 1,3-cyclohexanedione (1 mmol) and arylglyoxal[16] **2a-h** (1 mmol) in H_2O (10 mL), NH_4OAc (5 mmol) was added. The mixture was stirred and maintained at reflux temperature for the appropriate amount of time (2-6 h). When the reaction was complete, as monitored by TLC, the mixture was left to cool to room temperature. The generated yellow precipitate was filtered, washed with H_2O and dried. The crude product was recrystallized from EtOH to give pure compound **4a-h** in 80-95% yield.

3-Hydroxy-2-phenyl-6,7-dihydro-1*H*-indol-4(5*H*)-one (4a)

Yellow solid. Mp: 295-296 °C. FT-IR (KBr) (ν_{max}, cm^{-1}): 3439, 3243, 2944, 1611, 1470, 1378, 1338, 983, 695. ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 11.46 (1H, s, OH, exchanged on D_2O addition), 9.81 (1H, br s, NH, exchanged on D_2O addition), 7.41 (2H, d, *J* = 7.2 Hz, arom), 7.30 (2H, t, *J* = 7.2 Hz, arom), 7.16 (1H, t, *J* = 7.2 Hz, arom), 2.22 (2H, br t, *J* = 6 Hz, CH_2), 2.02 (2H, br t, *J* = 6 Hz, CH_2), 1.87-1.95 (2H, m, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 192.12, 143.52, 143.36, 133.11, 132.90, 128.65, 125.83, 119.64, 111.06, 23.43, 22.38, 20.43. GC–MS: *m/z* = 227 (M^+). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.81; H, 5.92; N, 6.01.

3-([1,1-Biphenyl-4-yl)-3-hydroxy-2-phenyl-6,7-dihydro-1*H*-indol-4(5*H*)-one (4h)

Yellow solid. Mp 200-202 °C. FT-IR (KBr) (ν_{max}, cm^{-1}): 3411, 3269, 2937, 1602, 1458, 1374, 1214, 1155, 983, 765. ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 11.54 (1H, s, exchanged on D_2O addition, OH), 9.87 (1H, br s, exchanged on D_2O addition, NH), 7.68 (2H, d, *J* = 7.2 Hz, arom), 7.64 (2H, d, *J* = 8.8 Hz, arom), 7.53 (2H, d, *J* = 8.8 Hz, arom), 7.46 (2H, d, *J* = 7.2 Hz, arom), 7.35 (1H, t, *J* = 7.2 Hz, arom), 2.24 (2H, t, *J* = 6 Hz, CH_2), 2.04 (2H, t, *J* = 6 Hz, CH_2), 1.95 (2H, m, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 192.13, 143.73, 143.57, 139.63, 137.28, 132.18, 128.89, 128.28, 127.23, 126.41, 125.63, 119.77, 111.13, 23.43, 22.46, 20.44. GC–MS: *m/z* = 303 (M^+). Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.27; H, 5.79; N, 4.61.

Acknowledgments

The authors gratefully acknowledge the financial assistance from the University of Urmia.

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Graphical Abstract

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