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A novel and facile synthesis of 2-(cyclohexylamino)-6,7-dihydro-3-aryl-1*H*-indole-4(5*H*)-ones via a one-pot multi-component reaction

Majid M. Heravi *, Bita Baghernejad, Hossein A. Oskooie, Rahim. Hekmatshoar

Department of Chemistry, School of Science, Azzahra University, Vanak, Tehran, Iran

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ABSTRACT

A simple and efficient synthesis of 2-(cyclohexylamino)-6,7-dihydro-3-aryl-1*H*-indole-4(5*H*)-ones was achieved via a one-pot multi-component reaction of cyclohexyl isocyanide, an aldehyde, a 1,3-dicarbonyl compound, and ammonium acetate in the presence of a catalytic amount of $KHSO_4$ in acetonitrile.

1. Introduction

There has been tremendous interest in developing highly efficient transformations for the preparation of organic compounds, as well as, biologically active materials, with potential application in the pharmaceutical or agrochemical industries from commercially available compounds. There is also a need for synthetic chemists to find new, efficient, and strategically important processes, which are environmentally benign and lead to greater structural variation in short period of times with high yields and simple work-up procedures. Significant advances have been made to chemical processes to achieve the ultimate goal of hazard-free, waste-free, and energy-efficient syntheses.[1] In this context, multi-component reactions (MCRs)[2] have played an important role in these processes.[3,4] Since the pioneering work by Strecker in 1850 describing the first reported MCR,[5] this well-known concept[6] has been used extensively in both liquid-phase[2e] and solid-phase[7] chemistry for the rapid assembly of complex heterocyclic structures for pharmaceutical development.[8] Isocyanide-based MCRs,[2,9] introduced in 1921 by Passerini,[10] generally predominate for the construction of widely diverse heterocycles.[11]

The indole nucleus is an important substructure found in numerous natural alkaloids.[12,13] The diversity of the structures encountered, as well as their biological and pharmaceutical relevance, has motivated research aimed at the development of new, economical, efficient, and selective synthetic strategies, particularly for the synthesis of substituted indole rings.[14,15] Thus, the development of high-throughput methods for the synthesis of indoles remains an important topic. Therefore, we decided to use a MCR for the synthesis of 2-(cyclohexylamino)-6,7-dihydro-3-aryl-1*H*-indole-4(5*H*)-ones.

Herein, we report a mild, practical, and highly efficient procedure for the preparation of the title compounds using $KHSO_4$ as a catalyst under refluxing conditions (Scheme 1).

2-(Cyclohexylamino)-6,7-dihydro-3-aryl-1*H*-indole-4(5*H*)-ones were obtained by the MCR of cyclohexyl isocyanide, an aldehyde, dimedone or 1,3-cyclohexandione, and ammonium acetate in the presence of a catalytic amount of $KHSO_4$ in acetonitrile (Scheme 1) in good yields (Table 1). To the best of our knowledge, there are no reports on the synthesis of these compounds via MCR using $KHSO_4$ as the catalyst. $KHSO_4$ is one of the components of a triple salt with the formula $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$ which is known as Oxone, and is used as a highly efficient oxidant in many organic reagents.[16] Very recently, we reported the use of $KHSO_4$ as an efficient catalyst for the synthesis of 1,1-diacetates,[17] the aromatization of Hantzsch 1,4-dihydropyridines, and the synthesis of quinoxalines.[18] We evaluated the amount of $KHSO_4$ required for this transformation and found that as little as 10 mol % of $KHSO_4$ catalyzed the reaction to some extent, but a longer reaction time (>3 h) was required. The use of an increased amount of catalyst did not improve the yield significantly. The scope of the reaction with respect to the aldehyde component was examined. As shown in Table 1, aromatic aldehydes containing both electron-donating or -withdrawing groups gave excellent yields of the product. In each reaction, the yield was a function of the reaction time which was optimized at 4 h at reflux.

* Corresponding author. Tel.: +98 2188041344; fax: +98 2188047861.
E-mail address: mmh1331@yahoo.com (M. M. Heravi).

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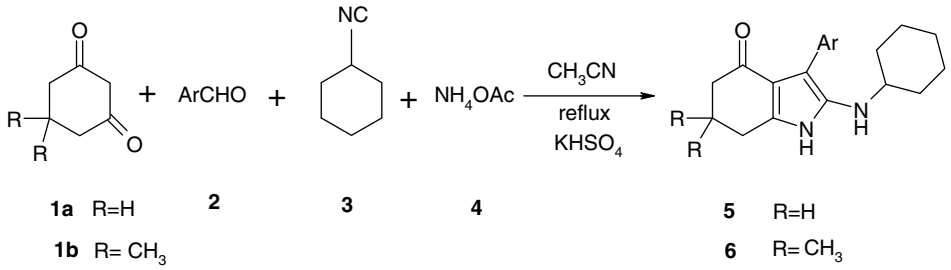
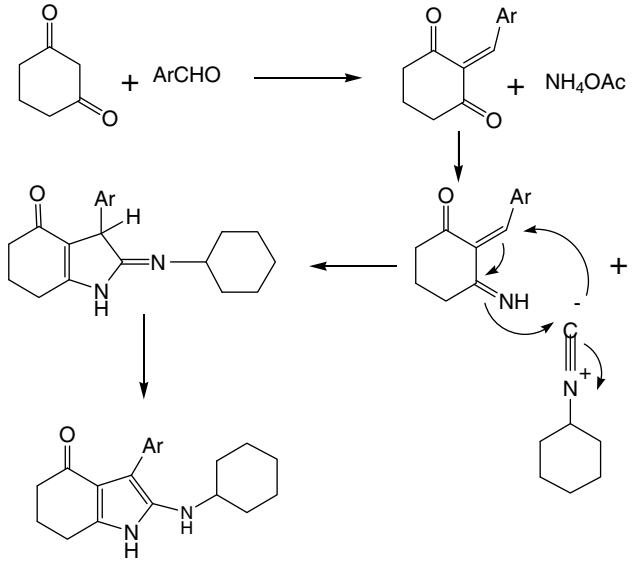


Scheme 1.

Table 1
Synthesis of 2-(cyclohexylamino)-6,7-dihydro-3-aryl-1*H*-indole-4(5*H*)-ones using various aldehydes

Entry	Substrate	Product	Ar	Yield[a] (%)
1	**1a**	**5a**	C_6H_5	90
2	**1a**	**5b**	4-Cl–C_6H_4	85
3	**1a**	**5c**	2-NO_2–C_6H_4	85
4	**1a**	**5d**	4-NO_2–C_6H_4	83
5	**1a**	**5e**	4-CH_3–C_6H_4	90
6	**1a**	**5f**	4-CH_3O–C_6H_4	91
7	**1b**	**6a**	C_6H_5	87
8	**1b**	**6b**	4-Cl–C_6H_4	90
9	**1b**	**6c**	2-NO_2–C_6H_4	84
10	**1b**	**6d**	4-NO_2–C_6H_4	88
11	**1b**	**6e**	4-CH_3–C_6H_4	90
12	**1b**	**6f**	4-CH_3O–C_6H_4	90

[a] Yield of isolated products.



Scheme 2.

A plausible mechanism for this reaction is suggested in Scheme 2. The first step may involve adduct formation by condensation of 1,3-cyclohexanedione with the aromatic aldehyde, followed by attack of ammonium acetate to give the intermediate 2-benzylidiene-3-imino-cyclohexanone. Reaction of cyclohexyl isocyanide with this intermediate then gives the desired product.

In summary, we have reported an efficient process for the synthesis of potentially biologically interesting functionalized 2-(cyclohexylamino)-6,7-dihydro-3-aryl-1*H*-indole-4(5*H*)-ones starting from readily available and inexpensive reagents. The advantages of the present procedure are experimental simplicity, easy work-up, use of an easy to handle and safe catalyst, and high yields of products.

2. Preparation of 2-(cyclohexylamino)-6,7-dihydro–3-aryl-1*H*-indole-4(5*H*)-ones: typical procedure

To a magnetically stirred solution of 1,3-dicarbonyl compound (1 mmol), aldehyde (1 mmol), ammonium acetate (1.5 mmol), and $KHSO_4$ (10 mol %) in acetonitrile (5 mL) was added cyclohexyl isocyanide (1 mmol), and the reaction mixture was refluxed for 4 h. The progress of the reaction was monitored by TLC (ethyl acetate–hexane 1:3). After completion of the reaction, acetonitrile was removed in vacuo and then diethyl ether was added to the solid residue in order to separate the catalyst from the mixture The filtrate was washed twice with 5% $NaHCO_3$ (5 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the product was recrystallized from CH_2Cl_2–EtOH (1:2) to give the pure product.

2.1. 2-(Cyclohexylamino)-6,7-dihydro-3-phenyl-1*H*-indole-4(5*H*)-one (5a)

Mp: 168 °C. IR (KBr) (ν_{max}, cm^{-1}): 1630 (C=N), 1670 (C=O), 3320 (N–H). ^1H NMR ($CDC1_3$, 300 MHz) δ_H (ppm): 1.11–1.99 (10H, m), 2.44 (2H, m), 2.71 (2H, t, J = 5.9), 2.90 (2H, t, J = 6.0), 3.02 (1H, m), 7.45–7.53 (5H, m, arom), 8.22 (1H, s, NH), 9.48 (1H, s, NH). ^{13}C NMR ($CDC1_3$, 125 MHz) δ_C (ppm): 21.91, 24.96, 25.13, 26.67, 27.08, 34.22, 34.09, 42.70, 55.10, 121.25, 128.32 (arom. and 2CH), 129.46 (arom. and 2CH), 131.02, 145.11, 146.98 (C–NO_2), 154.43, 156.92 (C–N), 194.45 (C=O). GC/MS: 308 (M^+). Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 77.88; H, 7.81; N, 9.05.

2.2. 2-(Cyclohexylamino)-6,7-dihydro-3-(2-nitrophenyl)-1*H*-indole-4(5*H*)-one (5c)

Mp: 181 °C. IR (KBr) (ν_{max}, cm^{-1}): 1325 and 1515 (NO_2), 1630 (C=N), 1670 (C=O), 3320 (N–H). ^1H NMR ($CDC1_3$, 300 MHz) δ_H (ppm): 1.11–1.96 (10H, m), 2.38 (2H, m), 2.68 (2H, t, J = 6.1), 2.89 (2H, t, J = 5.9), 3.20 (1H, m), 7.45–7.84 (4H, m, arom), 8.08 (1H, s, NH), 9.32 (1H, s, NH). ^{13}C NMR ($CDC1_3$, 125 MHz) δ_C (ppm): 22.81, 24.92, 25.05, 26.66, 27.10, 34.11, 34.09, 42.65, 65.08, 122.11, 124.33, 125.55, 125.98, 130.12, 139.45, 141.25, 144.32 (C–NO_2), 152.41, 153.97 (C–N), 193.46 (C=O). GC/MS: 353 (M^+). Anal. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 67.89; H, 6.66; N, 11.84.

2.3. 2-(Cyclohexylamino)-6,7-dihydro-3-(4-nitrophenyl)-1*H*-indole-4(5*H*)-one (5d)

Mp: 175 °C. IR (KBr) (ν_{max}, cm^{-1}): 1320 and 1505 (NO_2), 1630 (C=N), 1670 (C=O), 3320 (N–H). ^1H NMR ($CDC1_3$, 300 MHz) δ_H (ppm): 1.15–2.01 (10H, m), 2.42 (2H, m), 2.73 (2H, t, J = 6.1), 2.94

(2H, t, J = 6.2), 3.12 (1H, m), 7.35 (2H, d, J = 8.2), 7.91 (2H, d, J = 8.2), 8.13 (1H, s, NH), 9.50 (1H, s, NH). ^{13}C NMR ($CDC1_3$, 125 MHz) δ_C (ppm): 22.91, 25.12, 25.15, 26.70, 27.12, 34.14, 34.19, 42.61, 55.10, 120.21, 125.92 (arom. and 2CH), 129.33 (arom. and 2CH), 130.05, 145.11, 145.21 (C–NO_2), 153.42, 154.96 (C–N), 193.39 (C=O). GC/MS: 353 (M^+). Anal. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 67.94; H, 6.59; N, 11.81.

2.4. 2-(Cyclohexylamino)-6,7-dihydro-3-(4-methylphenyl)-1*H*-indole-4(5*H*)-one (5e)

Mp: 168 °C. IR (KBr) (ν_{max}, cm^{-1}): 1628 (C=N), 1678 (C=O), 3339 (N–H). ^{1}H NMR ($CDC1_3$, 300 MHz) δ_H (ppm): 1.12–1.97 (10H, m), 2.37 (2H, m), 2.68 (2H, t, J = 6.1), 2.85 (2H, t, J = 6.0), 3.25 (1H, m), 4.01 (3H, s, CH_3), 7.30 (2H, d, J = 8.2), 7.91 (2H, d, J = 8.2), 8.18 (1H, s, NH), 9.45 (1H, s, NH).^{13}C NMR ($CDC1_3$, 125 MHz) δ_C (ppm): 23.41, 25.66, 25.83, 26.72, 27.02, 34.16, 34.29, 42.66, 55.19, 59.12, 120.91, 124.98 (arom. and 2CH), 125.62 (arom. and 2CH), 130.05, 145.15, 144.91 (C-NO_2), 152.94, 153.99 (C–N), 192.25 (C=O). GC/MS: 322 (M^+). Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 78.22; H, 8.12; N, 8.61.

2.5. 2-(Cyclohexylamino)-6,7-dihydro-6,6-dimethyl-3-phenyl-1*H*-indole-4(5*H*)-one (6a)

Mp: 201 °C. IR (KBr) (ν_{max}, cm^{-1}): 1610 (C=N), 1660 (C=O), 3300 (N–H). ^{1}H NMR ($CDC1_3$, 300 MHz) δ_H (ppm): 1.18 (6H, s, $2CH_3$), 1.20–2.12 (10H, m). 2.48 (2H, s), 2.53 (2H, s), 3.31 (1H, m), 7.42–7.63 (5H, m, arom), 8.07 (1H, s, NH), 9.24 (1H, s, NH). ^{13}C NMR ($CDC1_3$, 125 MHz) δ_C (ppm): 25.21, 25.28, 25.51, 27.92, 30.12, 33.96, 33.98, 37.11, 43.16, 53.45, 58.19, 110.91, 123.75 (arom. and 2CH), 125.42, 126.91, 129.56 (arom. and 2CH), 134.79, 150.90, 154.13 (C–N), 190.51 (C=O). GC/MS: 336 (M^+). Anal. Calcd for $C_{22}H_{28}N_2O$: C, 78.53; H, 8.39; N, 8.32. Found: C, 78.42; H, 8.40; N, 8.28.

2.6. 2-(Cyclohexylamino)-6,7-dihydro-6,6-dimethyl-3-(4-nitrophenyl)-1*H*-indole-4(5*H*)-one (6d)

Mp: 221 °C. IR (KBr) (ν_{max}, cm^{-1}): 1328 and 1515 (NO_2), 1610 (C=N), 1665 (C=O), 3300 (N–H). ^{1}H NMR ($CDC1_3$, 300 MHz) δ_H (ppm): 1.17 (6H, s, $2CH_3$), 1.19–1.98 (10H, m), 2.40 (2H, s), 2.63 (2H, s), 3.28 (1H, m), 7.25 (2H, d, J = 8.3), 7.91 (2H, d, J = 8.3), 8.09 (1H, s, NH), 9.44 (1H, s, NH).^{13}C NMR ($CDC1_3$, 125 MHz) δ_C (ppm): 21.91, 25.02, 25.12, 26.66, 27.02, 27.93, 28.15, 34.14, 36.19, 39.61, 58.34, 120.21, 124.82 (arom. and 2CH), 127.36 (arom. and 2CH), 130.06, 145.1, 145 (C–NO_2), 153.4, 154.9 (C–N), 193.3 (C=O). GC/MS: 381 (M^+). Anal. Calcd for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.01. Found: C, 69.15; H, 7.24; N, 10.94.

2.7. 2-(Cyclohexylamino)-6,7-dihydro-6,6-dimethyl-3(4-methoxyphenyl)-1*H*-indole-4(5*H*)-one (6f)

Mp: 198 °C. IR (KBr) (ν_{max}, cm^{-1}): 1622 (C=N), 1669 (C=O), 3324 (N–H). ^{1}H NMR ($CDC1_3$, 300 MHz) δ_H (ppm): 1.17 (6H, s, $2CH_3$), 1.21–1.99 (10H, m), 2.40 (2H, s), 2.63 (2H, s), 3.25 (1H, m), 4.59 (3H, s, CH_3), 7.23 (2H, d, J = 8.2), 7.88 (2H, d, J = 8.2), 8.16 (1H, s, NH), 9.08 (1H, s, NH). ^{13}C NMR ($CDC1_3$, 125 MHz) δ_C (ppm): 21.91, 25.11, 25.22, 26.69, 27.22, 27.98, 28.05, 34.24, 36.39, 39.60, 40.25, 58.34, 120.54, 124.65 (arom. and 2CH), 127.43 (arom. and 2CH), 130.14, 145.12, 145.25 (C–NO_2), 153.42, 154.91 (C–N), 192.22 (C=O). GC/MS: 366 (M^+). Anal. Calcd for $C_{23}H_{30}N_2O_2$: C, 75.38; H, 8.25; N, 7.64. Found: C, 75.35; H, 8.24; N, 7.54.

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