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Convenient and Efficient Synthesis of 1-Oxo-1,2,3,4-tetrahydrocarbazoles via Fischer Indole Synthesis

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Abstract: A convenient synthesis of 1-oxo-1,2,3,4-tetra-hydrocarbazoles has been developed by reaction of 2-aminocyclohexanone hydrochlorides with various phenylhydrazine hydrochlorides via Fischer indole synthesis under mild conditions. The method is more satisfactory in terms of the easy availability of starting materials and the simple one-pot operation.

Keywords: 2-Aminocyclohexanone, Fischer indole synthesis, 1-oxo-1,2,3,4-tetrahydrocarbazole, phenylhydrazine

Although 1-oxo-1,2,3,4-tetrahydrocarbazoles rarely occur in nature, they have been increasingly important intermediates in the synthesis of various biologically active heterocyclic compounds because of their unique structures, such as indo[2,3-a]carbazoles,[1] furo[2,3-a]-carbazoles,[2] pyrimidino[4,5-a]-carbazoles,[3] pyrazolino[3,2,1-j,k]carbazoles,[4] thieno-[2,3-a]carbazoles,[5] and so on. Many methods for the synthesis of 1-oxo-1,2,3,4-tetrahydrocarbazoles have already been developed. These include, for example, cyclization of diphenylhydrazone of cyclohexane-1,2-dione or 2-phenylhydrazono cyclohexanone via Fischer indole synthesis,[6–8] oxidation of 1,2,3,4-tetrahydro-9*H*-carbazole with SeO_2[9] or

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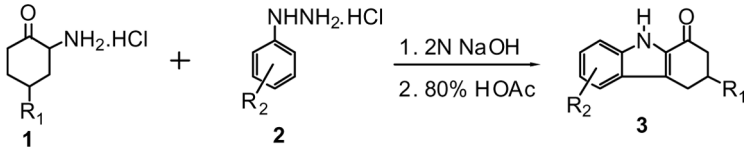


Scheme 1. Synthesis of 1-oxo-1,2,3,4-tetrahydrocarbazoles.

I_2O_5,[10] cyclization of thiohydroxamates with camphorsulfonic acid,[11] and cyclization of indole-3-butanic acid in refluxing xylene with P_2O_5, polyphosphoric acid (PPA), or Lewis acid $Bi(OTf)_3$.[12–14] Some of these methods have modest yields, harsh reaction conditions, or tedious procedures. As part of our growing interest in using phenylhydrazines as heterocyclic building blocks in organic synthesis,[15–17] we describe herein a convenient and efficient one-pot synthetic route for the preparation of 1-oxo-1,2,3,4-tetrahydro-carbazoles via Fischer indole synthesis from 2-aminocyclohexanone hydrochlorides and various phenylhydrazine hydrochlorides. The method is more satisfactory in terms of the easy availability of starting materials and the simple one-pot operation, as shown in Scheme 1.

RESULTS AND DISCUSSION

When an equimolar mixture of 2-aminocyclohexanone hydrochloride **1a** and phenylhydrazine hydrochloride **2a** was refluxed in glacial acetic acid, two products, 1-oxo-1,2,3,4-tetrahydrocarbazole **3a** and indolo[2,3-*a*] carbazole, were yielded in the ratio of 1:2. The reason was that **3a** could proceed in the second Fisher indole synthesis with **2a** to give indolo[2,3-*a*]carbazole. When the amount of **2a** was enhanced to 4 equiv, a single product (indolo[2,3-*a*]carbazole) could be obtained.[16] In opposition, when increasing the amount of compound **1a**, little effect on the yield of 1-oxo-1,2,3,4-tetrahydrocarbazole was exhibited. To seek the general method to get target compound **3a** in high yield, various reaction conditions were scrutinized (see Table 1), but no promising results could be observed.

The mechanism of this reaction probably involves a Fisher indole synthesis, as already reported by our laboratory. (Scheme 2).[16] We believed that the presence of the hydrochloric acid in two reagents would be an important factor to speed up the 1-oxo-1,2,3,4-tetrahydrocarbazole converting to indolo-[2,3-a]-carbazole. For that reason, condensation of free 2-aminocyclohexanone with phenyl hydrazine in weak acid medium would be beneficial to the reaction. Because the 2-aminocyclohexanone and phenyl hydrazine are unstable in air, in this procedure, an equimolar

Table 1. Acid catalysts screening

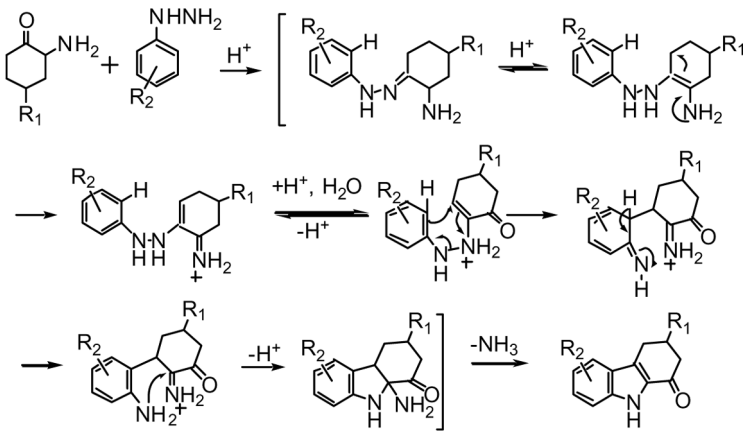
Entry	Acid catalyst	Reaction temp. (°C)	Mole ratio[a]	Yield[b] (%)
1	95% HOAc	100	1:1	32
2	80% HOAc	reflux	1.2:1	40
3	Toluene/33% HOAc	reflux	1.2:1	39
4	$TsOH \cdot H_2O$/EtOH	reflux	1.2:1	29
5	THF/33% HOAc	reflux	1:1	35
6	97% HCOOH	reflux	1:1	15
7	PCl_3/CH_2Cl_2	r.t.	1:1	0[c]

[a]The ratio of 2-aminocyclohexanone hydrochloride **1a** and phenylhydrazine hydrochloride **2a**.

[b]Isolated yield.

[c]No reaction had occurred.

of 2 N sodium hydroxide solution was added to the mixture of **1a** and **2a** to produce 2-aminocyclohexanone and phenyl hydrazine in situ, followed by refluxing in glacial acetic acid for 5 h. A yield of 55% of target compound **3a** was obtained. Encouraged by this result, we studied different reaction parameters. The reaction was performed in different acidic solvents such as HOAc, HCOOH, HOAc–H_2O, HCOOH–H_2O, HOAc–MeOH, and so on. The results disclosed that 80% HOAc was a suitable solvent for the reaction in terms of yield and reaction time. Next, the optimization of the molar ratio of **1a** to **2a** was tested, and it was



Scheme 2. Plausible reaction mechanism for the synthesis of 1-oxo-1,2,3,4-tetrahydrocarbazoles.

found that the ratio of 1.2:1 was sufficient for this reaction with this, the yield of the product **3a** could be improved up to 73%, but the excess **1a** beyond this ratio did not show further increase in conversion and in yield. Having established the optimized reaction conditions, a series of substituted 1-oxo-1,2,3,4-tetrahydrocarbazoles **3a–3s** were synthesized in good to excellent yields, the results are shown in Table 2. However, reacting **1a** with 3-chlorophenylhydrazine hydrochloride **2 m** gave a mixture of 5-chloro-1-oxo-1,2,3,4-tetrahydrocarbazoles **3 m** and 7-chloro-1-oxo-1,2,3,4-tetrahydrocarbazoles **3m′** in a 1.3:1 ratio (entry 13), which could not be separated.

In summary, the present procedure provides an efficient method for the synthesis of 1-oxo-1,2,3,4-tetrahydrocarbazoles via Fischer indole synthesis. The advantages offered by this method are available starting material, simple operation, insensitivity to air and moisture, high yields of products, and cost-effectiveness. The selected products were characterized by ^{1}H NMR, ^{13}C NMR, elemental analysis, and mass spectroscopic (MS) data.

Table 2. Synthesis of 1-oxo-1,2,3,4-tetrahydrocarbazoles

Compound	$\mathbf{R_1}$	$\mathbf{R_2}$	Yield[a] (%)	M.p. (°C)
3a	H	H	73	166–168 (165–168)[10]
3b	H	4-CH_3	90	206–207 (210)[18]
3c	H	4-OCH_3	74	212–214 (210)[18]
3d	H	4-F	91	206–208 (212)[6]
3e	H	4-Cl	94	223–225 (220)[18]
3f	H	4-Br	77	222–223 (230)[18]
3g	H	4-SO_2CH_3	75	239–240
3h	H	2-CH_3	60	156–158 (164)[18]
3i	H	2-OCH_3	65	121–122 (108)[18]
3j	H	2-F	60	132–134 (119)[6]
3k	H	2-Cl	57	158–160 (159)[18]
3l	H	2-Br	50	164–165 (158)[18]
3 m, 3m′	H	3-Cl	78[b]	
3n	4-CH_3	H	83	192–194 (193–195)[19]
3o	4-CH_3	4-Cl	70	181
3p	4-Ph	H	77	167–168
3q	4-Ph	4-Cl	77	187–189
3r	4-$C(CH_3)_3$	H	45	177–179
3s	4-$C(CH_3)_3$	4-Cl	55	260–262

[a]Isolated yield.
[b]A 1.3:1 mixture of **3m** and **3m′**.

EXPERIMENTAL

Melting points were obtained on a B-540 Buchi melting-point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AM 400-MHz spectrometer (at 400 and 100 MHz, respectively) with $SiMe_4$ as the internal standard in $CDCl_3$ or dimethyl sulfoxide (DMSO-d_6). Element analysis were performed on an Eager 300 instrument. Infrared (IR) spectra were recorded on a Brucker Vector-22 spectrophotometer.

General Procedure for the Preparation of 1-Oxo-1,2,3,4-tetrahydrocarbazole (3a)

A solution of 2 N sodium hydroxide (0.48 mL, 0.98 mmol) was added dropwise to the mixture of 2-aminocyclohaxanone hydrochloride (79.3 mg, 0.53 mmol) and phenylhydrazine hydrochloride (63.6 mg, 0.44 mmol) and stirred for 15 min at room temperature. Then, the mixture was refluxed for 5 h followed by addition of 80% HOAc solution (3 mL). After the reaction mixture was cooled to room temperature, it was poured into a saturated $NaHCO_3$ solution (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by a silica-gel column chromatography with petroleum ether and EtOAc (5:1) as eluent to give the desired 1-oxo-1,2,3,4-tetrahydrocarbazole (**3a**).

Previously reported materials were characterized by comparison of their mp, IR, ^{1}H NMR, and MS data with those of authentic samples. All new compounds gave satisfactory spectral data in accordance with their proposed structures.

Data for Selected Compounds

Compound **3g**

IR (KBr, cm^{-1}): 3212, 3028, 2939, 1652, 1566, 1298, 1138, 772; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.17 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 3.02 (m, 2H, CH_2), 3.20 (s, 3H, CH_3), 7.58 (d, $J = 8.8$ Hz, 1H, ArH), 7.79 (dd, $J = 8.8$ Hz, 1H, ArH), 8.32 (s, 1H, ArH), 12.19 (s, 1H, NH); ^{13}C NMR (100 M, DMSO-d_6): 21.0, 24.8, 38.4, 44.6, 114.0, 122.4, 124.1, 124.9, 129.6, 132.5, 133.5, 140.0, 191.2; MS (ESI): $m/z = 263$ [M^+]; Anal. calcd. for $C_{13}H_{13}NO_3S$: C, 59.30, H; 4.98; N, 5.32. Found: C, 59.77; H, 4.69; N, 5.59.

Compound **3o**

IR (KBr, cm^{-1}): 3252, 2957, 2872, 1647, 1541, 1457, 1259, 808; ^1H NMR (400 MHz, DMSO-d_6): δ 1.12 (d, $J = 6.4$ Hz, 3H, CH_3), 2.36 (m, 2H, CH_2), 2.47 (m, 2H, CH_2), 3.02 (dd, $J = 16.0$, 3.2 Hz, 1H, CH), 7.28 (d, $J = 8.8$ Hz, 1H, ArH), 7.41 (d, $J = 8.8$ Hz, 1H, ArH), 7.71 (s, 1H, ArH), 11.82 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 21.4, 29.2, 32.8, 46.6, 114.8, 120.6, 124.6, 126.5, 126.5, 127.1, 132.5, 136.9, 190.7; MS (ESI): $m/z = 235$ [M + 2], 233 [M^+]; (Anal. calcd. for $C_{13}H_{12}ClNO$: C, 66.81, H: 5.18; N, 5.99. Found: C, 66.77; H, 5.39; N, 5.78.

Compound **3p**

IR (KBr, cm^{-1}): 3253, 3060, 2922, 1647, 1538, 1455, 747, 702; ^1H NMR (400 MHz, DMSO-d_6): δ 2.63 (dd, $J = 16.4$, 3.2 Hz, 1H, CH_2), 2.99 (m, 2H, CH_2), 3.25 (dd, $J = 16.0$, 4.4 Hz, 1H, CH_2), 3.56 (m, 1H, CH), 7.06 (t, $J = 7.6$ Hz, 1H, ArH), 7.24 (t, $J = 7.6$ Hz, 1H, ArH), 7.30 (m, 3H, ArH), 7.42 (m, 3H, ArH), 7.67 (d, $J = 8.0$ Hz, 1H, ArH), 11.74 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 29.3, 43.3, 45.4, 113.2, 120.1, 121.6, 125.5, 126.7, 127.0, 127.4, 127.5, 128.8, 131.4, 138.7, 144.5, 189.7; MS (ESI): $m/z = 261$ [M^+]; Anal. Calcd. for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 83.04; H, 5.52; N, 5.08.

Compound **3q**

IR (KBr, cm^{-1}): 3252, 3027, 2919, 1645, 1540, 1467, 809, 729, 698; ^1H NMR (400 MHz, DMSO-d_6): δ 2.64 (d, $J = 16.0$ Hz, 1H, CH_2), 3.01 (m, 2H, CH_2), 3.27 (d, $J = 16.0$ Hz, 1H, CH_2), 3.60 (t, $J = 12.0$ Hz, 1H, CH), 7.24 (t, $J = 8.0$ Hz, 1H, ArH), 7.30 (m, 3H, ArH), 7.41 (t, $J = 7.2$ Hz, Hz, 3H, ArH), 7.79 (s, 1H, ArH), 11.90 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 29.1, 43.0, 45.3, 114.9, 120.8, 124.7, 126.4, 126.7, 126.9, 127.0, 127.4, 128.8, 132.5, 137.0, 144.4, 190.0; MS (ESI): $m/z = 297$ [M + 2], 295 [M^+]; Anal. calcd. for $C_{18}H_{14}ClNO$: C, 73.10; H, 4.77; N, 4.74. Found: C, 73.06; H, 4.55; N, 4.68.

Compound **3r**

IR (KBr, cm^{-1}): 3262, 3078, 2957, 2851, 1643, 1543, 1476, 760; ^1H NMR (400 MHz, DMSO-d_6): δ 1.00 (s, 9H, CH_3), 2.02 (m, 1H, CH_2), 2.38 (m, 2H, CH_2), 2.61 (m, 1H, CH_2), 3.11 (dd, $J = 16.0$, 3.6 Hz, 1H, CH), 7.06 (t, $J = 7.6$ Hz, 1H, ArH), 7.28 (t, $J = 7.6$ Hz, 1H, ArH), 7.38 (d, $J = 8.0$ Hz, 1H, ArH), 7.70 (d, $J = 8.0$ Hz, 1H, ArH), 11.59 (s, 1H, NH); ^{13}C NMR

(100 MHz, DMSO-d_6): 28.4, 29.3, 32.1, 40.5, 47.9, 112.6, 118.9, 120.7, 122.8, 123.2, 129.6, 134.1, 137.5, 190.1; MS (EI): $m/z = 241$ [M^+]; Anal. calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.73; H, 7.62; N, 5.98.

Compound **3s**

IR (KBr, cm^{-1}): 3249, 2962, 2868, 1643, 1542, 1468, 801; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.99 (s, 9H, CH_3), 2.01 (t, $J = 12.0$ Hz, 1H, CH_2), 2.47 (m, 3H, CH_2), 3.13 (dd, $J = 16.0$, 2.0 Hz, 1H, CH), 7.28 (d, $J = 9.2$ Hz, 1H, ArH), 7.39 (d, $J = 9.2$ Hz, 1H, ArH), 7.82 (s, 1H, ArH), 11.80 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 28.2, 29.6, 32.2, 40.3, 47.8, 114.2, 121.0, 124.8, 125.9, 126.7, 127.6, 132.4, 137.2, 190.4; MS (ESI): $m/z = 277$ [M + 2], 275 [M^+]; Anal. calcd. for $C_{16}H_{18}ClNO$: C, 69.69; H, 6.58; N, 5.08. Found: C, 69.94; H, 6.35; N, 5.38.

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