Synthesis and Antitumor Evaluation of a Novel Class of 4-Substituted-1,4-Dihydroisoquinolin-3-ones

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An efficient method for the solution-phase parallel synthesis of 4-substituted-1,4-dihydroisoquinolin-3-ones is developed. The isoquinolinones were constructed employing an intramolecular Heck reaction, providing full regio- and stereoselectivity. Most of the synthesized compounds showed potent antiproliferative activities against tumor cell lines.

1. Introduction

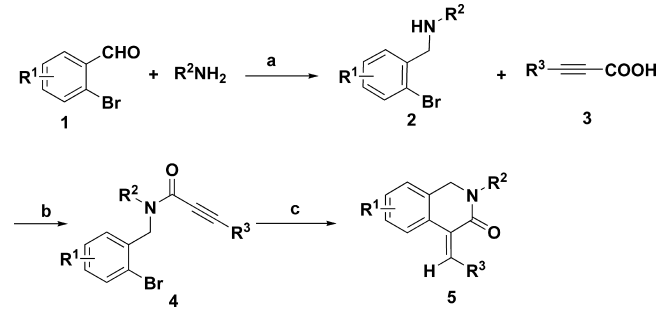
The isoquinoline is an important heterocyclic scaffold widely found in many natural alkaloids[1] and pharmaceuticals[2] that exhibit antitumor,[3] antimicrobial,[4] antiplasmodial activity,[5] and noncompetitive inhibition to AMPA receptor.[6] The wide range of biological and pharmacological importance of isoquinolinones promoted us to prepare new derivatives of these compounds utilizing a simple and efficient method. Although many syntheses of isoquinolinones have been reported, they require troublesome processes. Most of these methods involve the use of either a preformed isoquinoline or homophthalic acid, which are in turn obtained from a multistep synthesis.[7] To the best of our knowledge, very few such heterocyclic derivatives with a multisubstituted exo double bond were reported.[8] Palladium-catalyzed reductive reactions have successfully been utilized for the preparation of various heterocyclic compounds in a one-step procedure.[9] Thus, we wish to report a palladium-catalyzed process for the synthesis of isoquinolinone applying the intramolecular Heck-carbocyclization. Additionally, we report the antitumor activities of these products, most of which exhibited potent inhibition of tumor growth.

2. Result and Discussion

2.1. Synthesis and Optimization of 4-Substituted-1,4-Dihydroisoquinolin-3-ones. 2-Bromophenylethylamines **2** were synthesized from commercially available 2-bromobenzaldehydes **1** and primary amines. After compounds **2** were coupled with various 3-substituted 2-propynoic acids **3**, amides **4a**−**r** (Scheme 1) were obtained in excellent yields, which were ready for follow-up intramolecular cyclization. Following intramolecular cyclization, the products **5** with Z-configuration of the exocyclic double bond were obtained exclusively. Moreover, because insertion to the triple bond follows the cis addition, the regioselectivity was determined and the ring size of the generated product was fixed as six members.

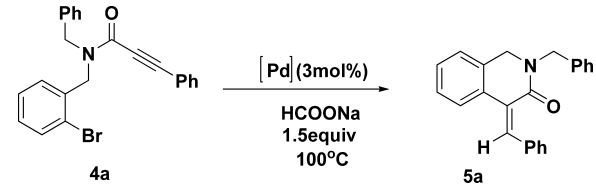
The optimal conditions for the intramolecular Heck reaction (Table 1) were determined by utilizing the amide **4a** as starting material. The reaction was performed under heat in the presence of 3 mol % of Pd $(PPh_3)_4$ as the catalyst and sodium formate as a reducing agent. Switching to other Pd catalysts (Table 1, entries 2 and 3), such

Scheme 1. Synthesis of 1,4-Dihydroisoquinolin-3-ones[a]



[a] Reagents and conditions: (a) $NaBH_4$, CH_3OH; (b) 1-hydroxypyrrolidine-2,5-dione (1.1 equiv), DCC (2 equiv), 4-DMAP (1 equiv), dioxane; (c) $Pd(PPh_3)_4$ (3 mol %), HCOONa, DMF/H_2O

Table 1. Optimization of the Reaction Conditions[a]



entry	time (h)	solvent (v/v)	catalyst	dilution (nM)	yield (%)
1	3	DMF/H_2O(3:1)	$Pd(PPh_3)_4$	70	79
2	3	DMF/H_2O(3:1)	$Pd(OAc)_2$ + $2PPh_3$	70	75
3	3	DMF/H_2O(3:1)	$PdCl_2$ + $2PPh_3$	70	65
4	3	DMF/H_2O(4:1)	$Pd(PPh_3)_4$	70	68
5	6	DMF/H_2O(3:1)	$Pd(PPh_3)_4$	140	65
6	12	DMF/H_2O(3:1)	$Pd(PPh_3)_4$	140	61

[a] Reactions were run on a 0.4 mmol scale; the mixture was heated at 100 °C (oil bath temperature).

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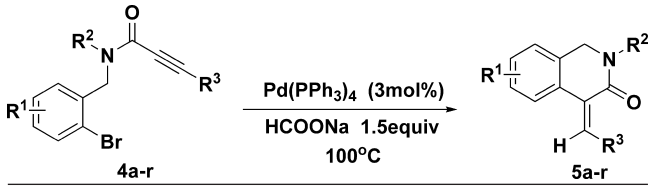
Table 2. Heck Reductive Cyclization of the Amides **4a−r**



entry	product	R^1	R^2	R^3	yield (%)
1	**5a**	H	benzyl	Ph	79
2	**5b**	5-Cl	Me	Ph	75
3	**5c**	5-Cl	benzyl	Ph	79
4	**5d**	5-F	Me	Ph	73
5	**5e**	5-F	benzyl	Ph	78
6	**5f**	3,4,5-MeO	benzyl	Ph	76
7	**5g**	H	benzyl	Me	85
8	**5h**	5-Cl	Me	Me	82
9	**5i**	5-Cl	benzyl	Me	88
10	**5j**	5-F	Me	Me	83
11	**5k**	5-F	benzyl	Me	85
12	**5l**	3,4,5-MeO	Me	Me	81
13	**5m**	3,4,5-MeO	benzyl	Me	86
14	**5n**	H	Me	*p*-toly	69
15	**5o**	H	benzyl	*p*-toly	73
16	**5p**	5-Cl	Me	*p*-toly	72
17	**5q**	5-Cl	benzyl	*p*-toly	74
18	**5r**	3,4,5-MeO	benzyl	*p*-toly	70

as $Pd(OAc)_2$-Ph_3P or $PdCl_2$-Ph_3P, did not have a significant effect on the rate or the yield of the reaction. The best reaction system was shown in Table 1 (entry 1). Water was essential to activate the reducing agent in this reaction.[9c] The higher yields for cyclization were generated when high dilution conditions (70 nM) were employed.

With the optimized conditions in hand, the analogs of 4-substituted-1, 4-dihydroisoquinolin-3-ones **5a** were synthesized in good yields using the same reaction conditions mentioned above (entry 1). Different substitutions including electron-withdrawing or electron-donating groups on the R^1 position had little effect on the speed of generating the desired product. When compound **4** possessed a CH_3 group at the R^3 position, the cyclization progressed smoothly and the corresponding products **5g−m** generated the best yields (Table 2, entries 7−13); while a substitution of aryl on the R^3 position resulted in products with decreased yields relative to the other products in this study.

2.2. Biological Evaluation. The synthesized 1,4-dihydroisoquinolin-3-ones were evaluated for their cytotoxic activity in vitro against five human cancer cell lines (human colon cancer cell line HCT-116, human gastric cancer cell line SGC-7901, human lung carcinoma cell line A549, human acute myeloid leukemia cell line HL-60, and human hepatocellular liver carcinoma cell line HepG2) using Taxol as the reference drug. As shown in Table 3, most of the synthesized compounds exhibited inhibitions against the selected tumor cell lines, especially the HL-60 and HCT-116 cell lines. The products **5a**, **5b**, **5i**, and **5p** showed the highest level of anticancer activity in the series. Most compounds from **5g−m** exhibited less cytotoxicity, suggesting that a CH_3 at the R^3 position is not favorable for this class of compounds. When an electron-withdrawing substituent F was present on the R^1 position, the compounds containing a benzyl group at the R^2 position showed better antiproliferative activities, for example **5d** compared to **5e** and **5j** compared to **5k**. The data in Table 3 showed that compound **5b** was the most potent inhibitor of HL-60 cells, having an IC_{50} of 1.76 μM.

3. Conclusion

In summary, we have developed an efficient method for the solution-phase parallel synthesis of 4-substituted-1,4-dihydroisoquinolin-3-ones. The six-member ring was constructed employing a reductive intramolecular Heck reaction, providing full regio- and stereoselectivity. Meanwhile, the effects of the 4-substituted-1,4-dihydroisoquinolin-3-ones on inhibition activities against tumor cell lines (HCT-116, SGC-7901, A549, HL-60, and HepG2) were examined. Most of the synthesized compounds showed potent antiproliferative activities against these cell lines. Further study on the mechanism of these compounds in suppression of tumor cells growth is currently underway in our laboratory.

Table 3. Cytotoxicity of the 4-Substituted-1, 4-Dihydroisoquinolin-3-ones against Five Human Cancer Lines in Vitro[a]

test article	HCT-116 IC_{50} (μM)	SGC-7901 IC_{50} (μM)	A549 IC_{50} (μM)	HL-60 IC_{50} (μM)	HepG2 IC_{50} (μM)
5a	17.33 (8.30−36.14)	23.02 (11.46−46.22)	36.45 (20.74−64.01)	3.38 (1.71−6.96)	21.51 (8.95−52.15)
5b	31.47 (21.74−45.49)	31.54 (8.77−113.35)	25.02 (16.88−37.10)	1.76 (1.08−2.62)	25.37 (13.43−48.27)
5c	>50	16.42 (8.03−33.56)	30.09 (10.61−85.30)	5.00 (2.68−9.26)	>50
5d	>50	>50	>50	11.22 (5.54−21.72)	>50
5e	>50	47.03 (41.85−52.85)	>50	5.82 (2.15−15.23)	>50
5f	32.25 (18.65−64.81)	42.60 (21.97−82.57)	37.93 (19.16−75.02)	2.89 (1.52−5.98)	>50
5g	26.32 (7.71−89.93)	>50	>50	2.28 (0.89−6.34)	17.47 (6.48−47.63)
5h	23.68 (9.11−61.43)	>50	>50	4.96 (3.43−6.77)	>50
5i	24.71 (24.28−25.18)	29.28 (14.71−58.23)	22.90 (8.13−64.51)	2.35 (1.46−3.79)	23.84 (11.71−49.01)
5j	>50	>50	>50	4.39 (2.44−8.70)	>50
5k	13.79 (1.85−103.66)	>50	46.68 (23.43−93.10)	7.11 (2.44−19.04)	25.60 (17.57−37.71)
5l	>50	>50	>50	14.06 (8.82−22.97)	>50
5m	48.78 (29.32−81.13)	>50	>50	4.81 (4.55−4.90)	>50
5n	>50	>50	>50	2.28 (2.33−2.35)	>50
5o	>50	31.79 (24.16−41.84)	30.67 (29.14−32.29)	3.54 (2.05−6.10)	>50
5p	23.57 (14.24−39.05)	17.29 (12.83−23.27)	8.33 (5.37−12.93)	2.01 (2.05−6.10)	7.05 (4.94−10.33)
5q	>50	>50	>50	5.35 (3.28−8.86)	>50
5r	38.00 (20.91−69.13)	36.23 (17.60−74.60)	11.27 (5.36−23.75)	2.33 (1.03−3.33)	>50
taxol	0.0087 (0.0037−0.020)	0.54 (0.06−5.02)	0.10 (0.02−0.64)	0.00035 (0.00019−0.00061)	0.068 (0.021−0.220)

[a] Values are means of three experiments; standard deviation is given in parentheses.

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Supporting Information Available. Experimental procedures, characterization data for all products, and copies of ^{1}H spectra for **5a**−**5r**. This material is available free of charge via the Internet at http://pubs.acs.org.

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