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LETTERS

Synthesis of 1,2,3-Trisubstituted Pyrrolo[3,2-*c*]quinolines *via* Palladium-Catalyzed Heteroannulation with Internal Alkynes

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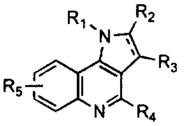
Abstract: Various 1,2,3-trisubstituted pyrrolo[3,2-*c*]quinolines were synthesized by palladium-catalyzed heteroannulation of 4-amino-3-iodoquinoline derivatives and internal alkynes. The 1,2,3-trisubstituted pyrrolo[3,2-*c*]quinolines could be further transformed by desilylation, debenzylation, or substitution.

Pyrrolo[3,2-*c*]quinolines (I) are very important skeleton due to their diverse biological activities such as gastric (H^+/K^+)-ATPase inhibitor,[1] antitumor,[2] bradykinin receptor antagonist,[3] anti-inflammary activity,[4] *etc.*[5] Thus many synthetic pathways for pyrrolo[3,2-*c*]quinolines were reported including thermal cyclizations,[6] intramolecular 1,3-dipolar cycloaddition,[7] Diels-Alder reactions,[8] free radical cyclization,[9] electrocyclization,[10] and transition metal cyclizations.[11] However, only Fisher-indole synthesis which required high reaction temperature (250 °C), provided completely aromatized pyrrolo[3,2-*c*]quinolines.



I

In the course of our study on gastric (H^+/K^+)-ATPase inhibitors, it was desired to prepare 3-substituted 1-arylpyrrolo[3,2-*c*]quinoline derivatives. To our knowledge, none of the synthetic methods provided 3-substituted 1-arylpyrrolo[3,2-*c*]quinolines in reasonable yields. We examined intramolecular palladium-catalyzed Heck reaction of 4-arylallylamino-3-iodoquinolines. However, the reaction provided low yields of desired products with limited functional groups. Also, the preparation of starting materials which required selective allylation of 4-arylaminoquinolines with allyl halide was very difficult due to quaternarization. To overcome these limitations, we now report a simple and convenient synthetic approach to 1,2,3-trisubstituted pyrrolo[3,2-*c*]quinolines under palladium-catalyzed heteroannulation of internal alkynes.[12] Initial studies were performed with various 4-arylamino-3-iodoquinoline derivatives and 1-(trimethylsilyl)-1-propyne to

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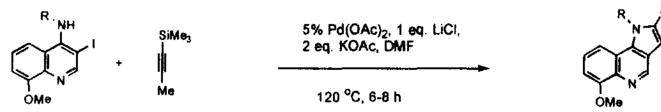
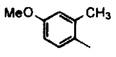
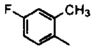
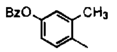
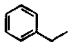
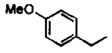
afford various 1-aryl-3-alkylpyrrolo[3,2-*c*]quinolines which were prepared by desilylation of corresponding 2-trimethylsilylpyrrolo[3,2-*c*]quinolines. The results are summarized in Table 1. The reactions using 4-arylamino-3-iodoquinoline derivatives provided high yields of 1-arylpyrrolo[3,2-*c*]quinlines (entries 1-3). This synthetic method showed possibility of introducing diverse substituents to 1-arylpyrrolo[3,2-*c*]quinolines. Another reaction of 4-alkylamino-3-iodoquinolines with 1-(trimethylsilyl)-1-propyne provided high yields of 1-alkylpyrrolo[3,2-*c*]quinolines which were not easily prepared by alkylation of 1*H*-pyrrolo[3,2-*c*]quinolines with alkyl halide due to quaternarization (entries 4-5). The reaction of 4-amino-8-methoxy-3-iodoquinoline was performed to obtain 2,3-disubstituted 1*H*-pyrrolo[3,2-*c*]quinoline, but 4-amino-8-methoxy-3-(1-propynyl)-quinoline was obtained as a major product with trace amount of desired product (entry 6). Finally, the reactions of 4-benzylamino-3-iodoquinolines were also examined to obtain 1*H*-pyrrolo[3,2-*c*]quinoline after debenzylation of 1-benzylpyrrolo[3,2-*c*]quinolines (entries 7-8).

Table 1. Palladium-catalyzed heteroannulation of 4-amino-3-iodoquinolines with 1-(trimethylsilyl)-1-propyne.



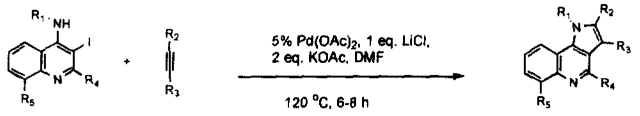
Entry[a]	R	Isolated yield (%)	Entry[a]	R	Isolated yield (%)
1		82	5	*n*-Butyl	81
2		70	6[b]	H	-
3		75	7		61
4	CH_3	75	8		58

[a] All reactions were run on a 0.5 mmol scale.

[b] 4-Amino-8-methoxy-3-(1-propynyl)quinoline was obtained as a major product.

In order to synthesize diverse pyrrolo[3,2-*c*]quinolines, the reactions using variety of 4-amino-3-iodoquinoline derivatives and internal alkynes were examined. The results were summarized in Table 2. The reactions provided 6-trifluoromethoxy and 6-methoxypyrrolo[3,2-*c*]quinolines in high yields (entries 1-4). The reactions showed the substituents on quinolines are not very important in this process. It was also reported that derivatization of 5-membered ring in pyrrolo[3,2-*c*]quinoline by electrophilic substitution was not easy compared with indole derivatives.[1b] However, our heteroannulation provided pyrrolo[3,2-*c*]quinolines with alcoholic substituents at 3 position which could be further transformed to various functional groups. The reaction using 4-octyne gave trialkylpyrrolo[3,2-*c*]quinoline in 80% yield, but the reactions using phenyl substituted internal alkynes provided regioisomeric pyrrolo[3,2-*c*]quinolines. The isomers were isolated and identified with ^1H NMR spectroscopy.

Table 2. Synthesis of trisubstituted pyrrolo[3,2-*c*]quinolines with alkynes.

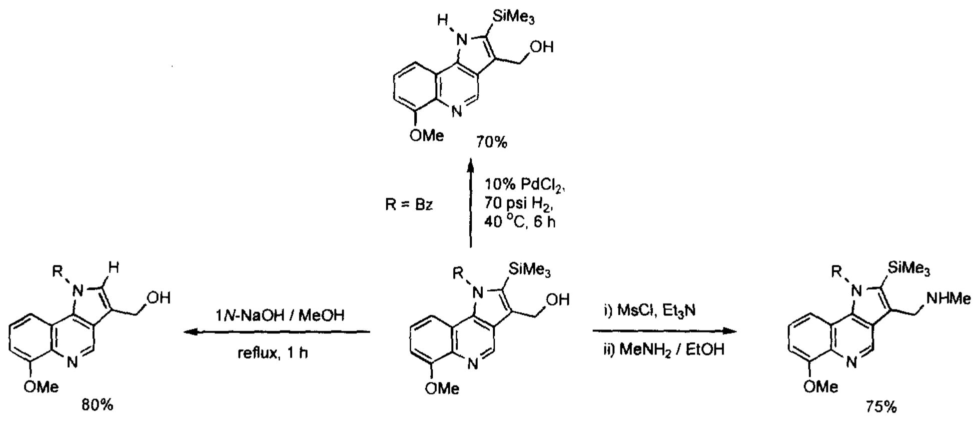


Entry[a]	R_1	R_2	R_3	R_4	R_5	Isolated yield (%)
1	2-Methylphenyl	$Si(CH_3)_3$	CH_3	H	OCF_3	85
2	"	"	CH_3	CH_3	OCH_3	82
3	"	"	CH_2OH	H	OCF_3	78
4	"	"	CH_2OH	CH_3	OCH_3	60
5	"	"	CH_2CH_2OH	H	"	65
6	4-Methoxy-2-methylphenyl	"	CH_2OH	H	"	82
7	Benzyl	"	CH_2OH	H	"	68
8	*n*-Butyl	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	H	"	80
9[b]	"	Ph	CH_3	H	"	75 (2:1)
10[b]	"	Ph	CH_2OH	H	"	60 (1:1)

[a] All reactions were run on a 0.5 mmol scale.

[b] The reaction provided two regioisomers in the ratio of given in parenthesis.

The prepared pyrrolo[3,2-*c*]quinoline derivatives could be further transformed to various pyrroloquinoline derivatives by desilylation, debenzylation, or substitution.



In summary, the palladium-catalyzed heteroannulation of 4-amino-3-iodoquinolines with internal alkynes provided 1,2,3-trisubstituted pyrrolo[3,2-*c*]quinolines with high regioselectivity. The facile elaboration of trisubstituted pyrrolo[3,2-*c*]quinolines could afford various pyrrolo[3,2-*c*]quinolines. The applications of this synthetic method to other heterocycles are in progress.

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***Typical Procedure**: Synthesis of 3-Hydroxymethyl-6-methoxy-1-(4-methoxy-2-methylphenyl)-2-trimethylsilyl-1H-pyrrolo[3,2-c]quinoline.*

Palladium acetate (6 mg, 0.025 mmol), LiCl (22 mg, 0.5 mmol), KOAc (98 mg, 1.0 mmol), 3-iodo-8-methoxy-4-(4-methoxy-2-methylphenylamino)quinoline (210 mg, 0.5 mmol), and 3-trimethylsilyl-2-propyn-1-ol (193 mg, 1.5 mmol) in DMF (10 mL) were added to a pressure tube with a stirring bar. After heating for 6-8 h at 120 °C, the reaction mixture was diluted with ethyl acetate and washed with saturated aqueous ammonium chloride solution. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography using hexane–ethyl acetate (1:3) as an eluent. 3-Hydroxymethyl-6-methoxy-1-(4-methoxy-2-methylphenyl)-2-trimethylsilyl-1*H*-pyrrolo[3,2-*c*]quinoline (172 mg, 0.41 mmol, 82%) was obtained as a yellow solid: mp 102-104 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 9.35 (s, 1H, ArH), 7.26 (d, 1H, J = 8.4 Hz, ArH), 7.05 (t, 1H, J = 8.4 Hz, ArH), 6.90 (m, 4H, ArH), 6.47 (d, 1H, J = 8.4 Hz, ArH), 5.04 (s, 2H, CH_2O), 4.04 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 2.23 (br, 1H, OH), 1.76 (s, 3H, CH_3), 0.1 (s, 9H, $SiCH_3$); ^{13}C NMR($CDCl_3$, 52 MHz) δ 160.32, 155.85, 143.36, 139.75, 139.14, 137.33, 135.96, 133.22, 130.38, 126.66, 125.67, 121.57, 119.19, 116.11, 111.98, 111.87, 105.71, 56.00, 55.83, 55.47, 17.55, 0.75; HRMS calcd for $C_{24}H_{28}N_2O_3Si$ 420.1869, found 420.1868.