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Tetrahedron Letters 44 (2003) 2545–2548

TETRAHEDRON LETTERS

A novel and convenient method for the synthesis of substituted naphthostyrils

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Received 11 November 2002; revised 28 January 2003; accepted 31 January 2003

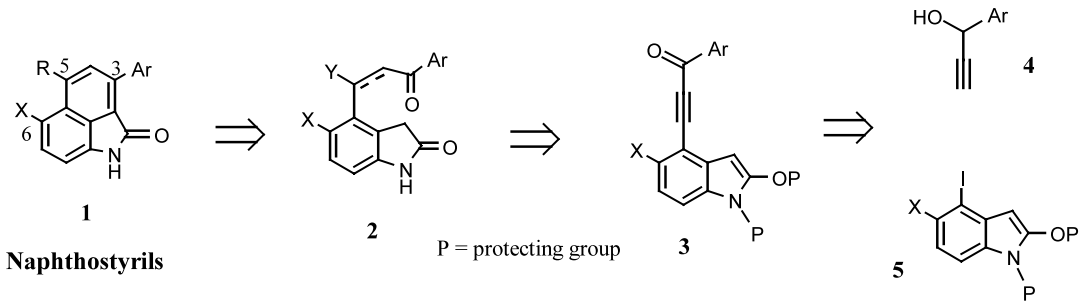
Abstract—3-Pyrrolyl-6-fluoro-naphthostyril **13** was synthesized via a base-catalyzed intramolecular cyclization of oxindole precursor **2** (Y = H). Derivatization of **2** (Y = I) through a one-pot reaction give 5-substituted naphthostyrils. This method allows convenient access to 3,5,6-trisubstituted naphthostyrils which may serve as a new template for CDK2 inhibition.

In an effort to discover novel cyclin-dependent kinase (CDK) inhibitors[1] we set out to design a series of small molecular weight compounds[2] which would be more stable and have better potency than oxindole derivatives reported in the literature.[3] To this end conformationally restricted naphthostyril **1** was designed, which possessed, at the 5-position, a side chain bearing a terminal proton donor substituent as a potential new template for kinase inhibition.

We were particularly interested in a series of 5-substituted 3-pyrrolyl-6-fluoro-naphthostyrils. Conventional preparation of naphthostyrils[4a–d] normally requires naphthalimides, naphtholactones or 1-naphthyl isocyanates as starting materials. These intermediates are often difficult to prepare and thus limit the usefulness of these approaches for the introduction of substituents[4e,f] at the 3- and 5-positions. In this paper we report a novel approach for the synthesis of 3-aryl-naphthostyrils, via an intramolecular cyclization of oxindole precursor **2** (Y = H). Furthermore, derivatization of **2** (Y = I) allows for the introduction of diverse substitution at the 5-position of the naphthostyril ring system.

Scheme 1 illustrates our retrosynthetic analysis using 4-iodoindole **5** and ethynyl alcohol **4** as starting materials. Cross-coupling of **4** and **5** followed by oxidation would afford ethynyl ketone **3**. Sequential reduction of the triple bond or a Michael addition reaction would give the precursors **2**, which then would undergo a base-catalyzed intramolecular Claisen-type condensation to form the 3,5,6-trisubstituted naphthostyrils.

The first example, 3-pyrrolyl-6-fluoro-naphthostyril **13** was prepared as shown in Scheme 2. Thus, protection of 4-iodo-5-fluoro-oxindole **6**[5] with di-*tert*-butyl-dicarbonate in the presence of DMAP gave the *N*,*O*-di-pro-



Scheme 1. Retrosynthesis of 3,5,6-trisubstituted naphthostyrils.

Keywords: naphthostyril; intramolecular cyclization; cross-coupling; CDK2 inhibition.

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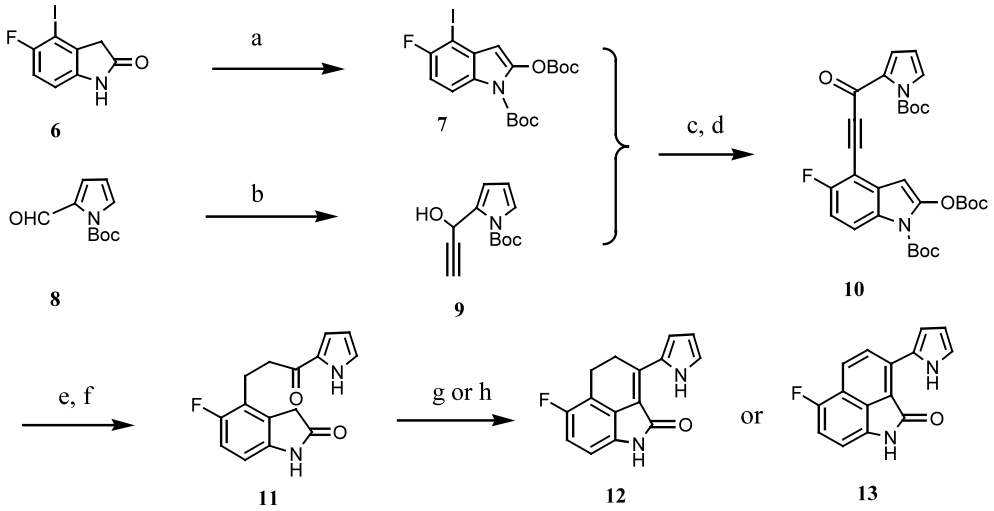
0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00292-2



Scheme 2. *Reagents and conditions*: (a) di-*tert*-butyl dicarbonate (3.0 equiv.), DMAP (0.1 equiv.), MeCN, rt 6 h, 52%; (b) ethynylmagnesium chloride (0.5 M in THF, 2.0 equiv.), THF, −65°C 30 min then rt 1 h, 94%; (c) **9** (1.8 equiv.), $(Ph_3P)_4Pd$ (0.08 equiv.), CuI (0.16 equiv.) THF, TEA, rt 3.5 h, 83%; (d) MnO_2 (10.0 equiv.), CH_2Cl_2, rt, overnight, 93%; (e) H_2/Lindlar cat./THF/45°C, 3 h; (f) TFA/CH_2Cl_2 (87% in two steps); (g) 1.0N NaOH aq. reflux overnight, **12**, 90%; (h) 1.0N NaOH aq. reflux 2.5 days, **13**, 89%.

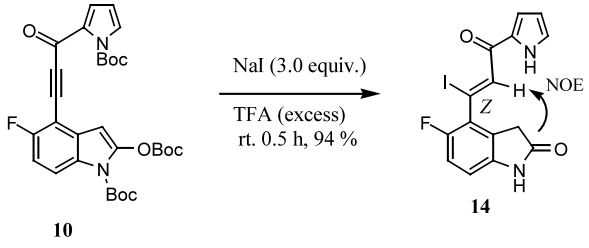
tected indole **7**[6] in moderate yield. The *N*-Boc-ethynyl alcohol **9** was obtained in very high yield by adding ethynylmagnesium chloride to a solution of the aldehyde **8**[7] in tetrahydrofuran. The cross-coupling reaction[8] of **7** and **9** using a catalytic amount of tetrakis(triphenylphosphine)palladium(0) and copper(I) iodide in tetrahydrofuran at room temperature, followed by oxidation with manganese dioxide afforded the corresponding ethynyl ketone **10** in high yield.

Hydrogenation of **10** in the presence of Lindlar catalyst in tetrahydrofuran at 45°C for 3 h provided, after treatment with 50% trifluoroacetic acid solution in dichloromethane, the saturated ketone precursor **11** in 87% yield. The base-catalyzed intramolecular Claisen-type condensation was carried out by suspending the precursor **11** in 1.0N sodium hydroxide and heating the mixture at reflux overnight to give the desired dihydronaphthostyril compound **12** in 90% yield. Under similar conditions, 3-pyrrolyl-6-fluoro-naphthostyril compound **13** was obtained in high yield after refluxing for 2.5 days, presumably by air-oxidation.

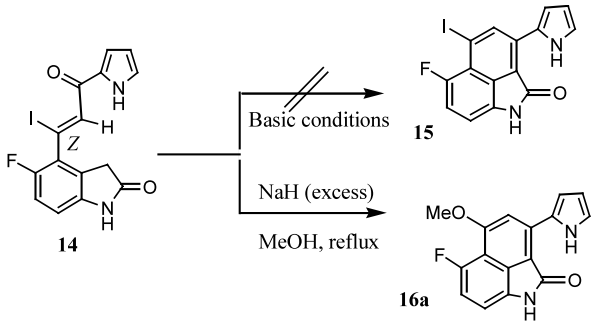
We then checked the conversion of ethynyl ketone **10** to functionalized intermediates suitable for the introduction of substituents at the 5-position of naphthostyrils. After several attempts, we found that the iodination can be easily achieved by reacting **10** with sodium iodide under acidic conditions as shown in Scheme 3.[9] Thus, treatment of ethynyl ketone **10** with 3 equiv. of sodium iodide in trifluoroacetic acid at room temperature for 30 min gave 94% of vinyl iodide **14** as a single isomer.

Key observations that support the assignment of the *Z*-form of the vinyl iodide **14** are as follows: (i) in a NOE study of compound **14**, 7% NOE between the vinyl proton and the two protons of the oxindole ring was observed; (ii) the attempted cyclization of **14** when treated with bases did not provide the desired cyclized compound **15** (Scheme 4), as expected for an *E*-isomer.[10]

Further manipulation of vinyl iodide **14** provides the opportunity to introduce a variety of substitution groups into the 5-position of the naphthostyril ring system. When **14** was treated with sodium hydride in MeOH under refluxing conditions, to our surprise and delight, the product isolated was the 3-pyrrolyl-naphthostyril with a methoxy group at the 5-position (**16a**, Scheme 4).



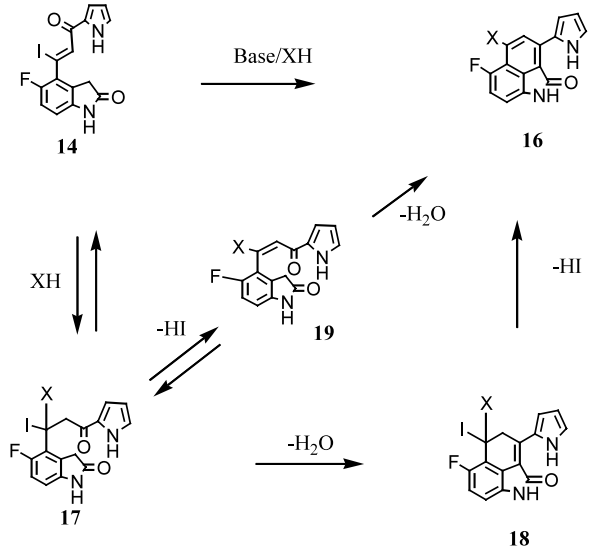
Scheme 3. Preparation of vinyl iodide **14**.



Scheme 4. Preparation of naphthostyrils via vinyl iodide **14**.

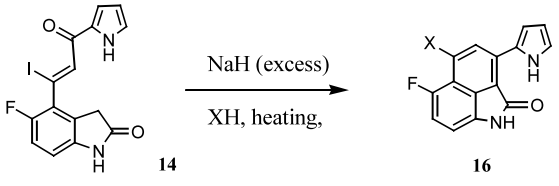
Possible mechanisms for this transformation are as follows: Michael addition of the nucleophile (XH) to the vinyl iodide **14** affords ketone **17**, which could form the 5-substituted naphthostyril derivative **16** either by an intramolecular cyclization to give **18** followed by elimination of HI, or via an elimination reaction to the *E*-olefin **19** followed by a conformationally favorable intramolecular cyclization in the presence of base (Scheme 5).

Table 1 shows the results of the one-pot cyclization reaction when vinyl iodide **14** was treated with a variety of alcohols and amines in the presence of NaH.[11] The reaction appears to work well with most of the amines and alcohols that were used in our experiments to give 5-substituted naphthostyrils in 20–89% yield. Application of these approaches to examples where the pyrrole group is replaced by a phenyl ring affords the corresponding 3-phenyl naphthostyrils.[12]



Scheme 5. Possible mechanisms of intramolecular cyclization of vinyl iodide **14** to naphthostyril **16**.

Table 1. Preparation of naphthostyrils **16** via vinyl iodide **14**



Entry	XH	Condition	Yield of **16** (%)
a	MeOH	NaH/reflux/1.5 h	52
b	EtOH	NaH/reflux/2.0 h	20
c	PrOH	NaH/130°C /3.0 h	24
d	$HOCH_2CH_2OH$	NaH/reflux/1.5 h	41
e	$HO(CH_2)_3OH$	NaH/110°C /2.5 h	32
f	$BocNH(CH_2)_2OH$	NaH/120°C/3.0 h	22
g	$NH_2(CH_2)_2NH_2$	NaH/120°C/1.5 h	89
h	$NH_2(CH_2)_3NH_2$	NaH/120°C/2.5 h	26

A typical procedure is as follows. Preparation of **16a**: To a suspension of (*Z*)-5-fluoro-4-[1-iodo-3-oxo-3-(1*H*-pyrro-2-yl)-propenyl]-1,3-dihydro-indol-2-one (**14**, 200 mg, 0.5 mmol) in methanol (20 mL) was added NaH (60%, 0.6 g, 15 mmol) in portions at room temperature. After stirring at room temperature for 30 min, the reaction mixture was then heated at reflux for 1.5 h. The reaction was quenched by pouring the reaction mixture into an ice-cold saturated aqueous ammonium chloride solution (20 mL) and extracted with ethyl acetate (3×50 mL). The combined organic extracts were successively washed with water (10 mL) and brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by a flash column (SiO_2, 25% AcOEt in hexanes) to give 6-fluoro-5-methoxy-3-(1*H*-pyrrol-2-yl)-1*H*-benzo-[*cd*]indol-2-one **16a** (73.2 mg, 51.9%) as a yellow solid.

In summary, we have developed a novel and convenient method for the synthesis of 3-aryl naphthostyrils.[13] By utilizing the vinyl iodide intermediate **14**, 3,5,6-trisubstituted naphthostyrils can be easily prepared in a one-pot reaction. The method is very general and useful for the preparation of a wide range of substituted naphthostyrils. Naphthostyrils **16** bearing side chains at the 5-position showed moderate to strong CDK2 inhibition.[14] Details of the kinase inhibition activities will be disclosed elsewhere.

Acknowledgements

We thank Mr. Gino Sasso for ^{1}H NMR spectral analysis and NOE studies, Mr. Vance Bell, Mr. Richard Szypula, Ms. Theresa Burchfield, and Mr. Michael Lanyi for mass and IR spectral analysis.

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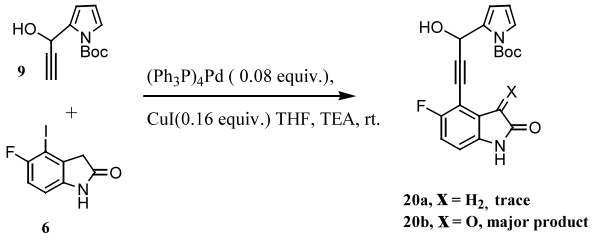
5. 5-Fluoro-4-iodo-1,3-dihydro-indole-2-one **6** was prepared according to a patent procedure: Chen, Y.; Corbett, W. L.; Dermatakis, A.; Liu, J. J.; Luk, K. C.; Mahaney, P. E.; Mischke, S. G. WO 0035908 2000.
6. Protection of the oxindole is necessary for the subsequent cross-coupling reaction. Coupling of the unprotected oxindole **6** with **9** under the same conditions gave only a trace of the desired product **20a**. The major product was the oxidized diketone **20b**.



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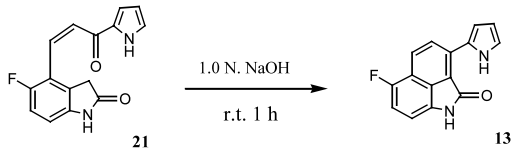
10. In our early study, the *cis*-olefin **21**, obtained by partial hydrogenation of **10** using Lindlar catalyst followed by deprotection with TFA, readily cyclized to form **13** when treated with base as expected.



11. NaH gave the best result of the bases tried in the reaction including KH, KOH, and organic bases.
12. Liu, J. J.; Luk, K. C.; Konzelmann, F. unpublished data.
13. Spectroscopic data for selected compounds are provided. **12**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.71 (br.s, 1H), 10.83 (s, 1H), 7.40 (m, 1H), 7.01 (m, 1H), 6.86 (dd, 1H, $J_1=10.8$ Hz, $J_2=7.8$ Hz), 6.68 (dd, 1H, $J_1=7.8$ Hz, $J_2=2.9$ Hz), 6.37 (m, 1H), 3.20 (t, 1H, $J=7.8$ Hz), 2.97 (t, 1H, $J=7.8$ Hz). IR (thin film) $\nu=3131$, 1669, 1567. HRMS for $C_{15}H_{11}FN_2O$ (M^+) calcd: 254.0855, found: 254.0851. **13**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.31 (br.s, 1H), 11.34 (s, 1H), 8.26 (d, 1H, $J=8.8$ Hz), 8.15 (d, 1H, $J=8.8$ Hz), 7.29 (m, 1H), 7.25 (m, 1H), 7.20 (dd, 1H, $J_1=12.7$ Hz, $J_2=7.8$ Hz), 7.00 (dd, 1H, $J_1=7.8$ Hz, $J_2=2.9$ Hz), 6.36 (m, 1H). IR (thin film) $\nu=3148$, 2925, 1676, 1643. HRMS for $C_{15}H_9FN_2O$ (M^+) calcd: 252.0699, found: 252.0696. **14**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (s, 1H), 10.53 (s, 1H), 7.63 (s, 1H), 7.21 (br.s, 1H), 7.16 (br.s, 1H), 7.11 (dd, 1H, $J_1=10.7$ Hz, $J_2=8.8$ Hz), 6.79 (dd, 1H, $J_1=7.8$ Hz, $J_2=3.9$ Hz), 6.25 (m, 1H), 3.52 (s, 2H). IR (thin film) $\nu=3264$, 1731, 1704, 1642. HRMS for $C_{15}H_{10}FIN_2O_2$ (M^+) calcd: 395.9711, found: 395.9764. **16a**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.55 (s, 1H), 11.19 (s, 1H), 7.49 (s, 1H), 7.35 (br.s, 1H), 7.28 (br.s, 1H), 7.10 (dd, 1H, $J_1=12.7$ Hz, $J_2=7.8$ Hz), 6.99 (dd, 1H, $J_1=7.8$ Hz, $J_2=2.9$ Hz), 6.35 (m, 1H), 4.13 (s, 3H). IR (thin film) $\nu=3166$, 1664, 1644. HRMS for $C_{16}H_{11}FN_2O_2$ (M^+) calcd: 282.0804, found: 282.0803. **16d**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.55 (s, 1H), 11.17 (s, 1H), 7.50 (s, 1H), 7.34 (br.s, 1H), 7.27 (br.s, 1H), 7.08 (dd, 1H, $J_1=12.7$ Hz, $J_2=7.8$ Hz), 6.99 (dd, 1H, $J_1=7.8$ Hz, $J_2=2.9$ Hz), 6.35 (m, 1H), 4.98 (dd, 1H, $J_1=5.9$ Hz, $J_2=4.9$ Hz), 4.41 (dd, 1H, $J_1=9.8$ Hz, $J_2=5.9$ Hz), 3.87 (dd, 1H, $J_1=9.8$ Hz, $J_2=4.9$ Hz). IR (thin film) $\nu=3154$, 1698, 1672, 1644. HRMS for $C_{17}H_{13}FN_2O_3$ (M^+) calcd: 312.0910, found: 312.0909.
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