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Organometallic reagent-mediated one-pot synthesis of 3,5,6-trisubstituted naphthostyrils

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Abstract—A one-pot synthesis of 3,5,6-trisubstituted naphthostyrils is described. Addition of organometallic reagents to β-iodovinyl ketone **1** followed by elimination gave the *Z*-form β-alkyl vinyl ketone **15**. Intramolecular cyclization of **15** under the reaction conditions afforded 3,5,6-trisubstituted naphthostyrils **4**.

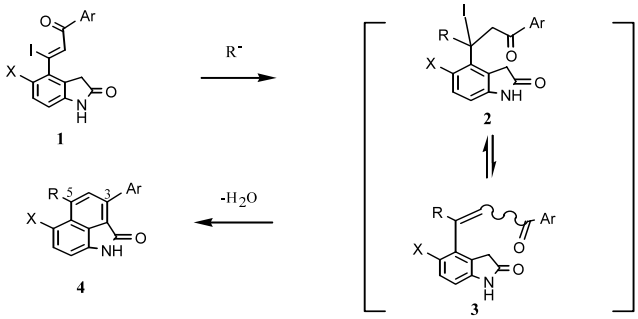
Recently we have developed a novel and convenient method[1] for the synthesis of 3,5,6-trisubstituted naphthostyrils which showed potent activity against CDKs.[2] The process involves the generation of a β-iodovinyl ketone, Michael addition of nucleophiles to the β-iodovinyl ketone and a subsequent base-catalyzed intramolecular Dieckman type cyclization.

Michael addition reaction in our process was a key step in which substituent groups were introduced into the 5-position of the final naphthostyril ring system. In our previous work, amines and alcohols were used as nucleophiles in the key step. In order to expand the scope of the method, we decided to examine the use of organometallic reagents as carbon nucleophiles which would form a new C–C bond at the β-position of the β-iodovinyl ketone to give intermediates **2** or **3**. Under suitable conditions, the excess amount of the reagent could also serve as a base to catalyze the subsequent intramolecular cyclization of **2** or **3** to form naphthostyril **4** (Scheme 1).

From the literature it is known that organometallic reagents, such as Grignard reagents,[3] organocopper,[4] alkylzinc[5] and alkylaluminum compounds,[6] could serve as effective nucleophiles toward Michael acceptors. To our knowledge, there are only a few examples in which simple Grignard reagents[7] and organocuprates[8] were successfully used as nucleophiles for addition to a β-iodovinyl ketone, although substitution reactions of some organometallic reagents with 3-iodo-2-cyclohexenone have been studied by a number of groups.[9] In this paper we show that organocuprates and organozinc–copper reagents can be used to introduce alkyl substituents at the 5-position of naphthostyrils via a nucleophilic addition to a β-iodovinyl ketone followed by elimination and an intramolecular Dieckman type cyclization.

In the first series of experiments, we studied the reaction between our model compound **8** and simple organometallic reagents (Scheme 2).

Compound **8** was prepared easily from ethynyl alcohol **5**, derived from benzaldehyde and ethynylmagnesium chloride, and *N*,*O*-di-protected-5-fluoro-4-iodo-oxindole **6** (Scheme 2). Thus, the cross-coupling reaction between **5** and **6** in the presence of catalytic amount of tetrakis-(triphenylphosphine)-palladium(0) and copper(I) iodide in tetrahydrofuran followed by oxidation with manganese dioxide gave compound **7**. Treatment of **7** with NaI in TFA led to β-iodovinyl ketone **8** in



Scheme 1.

Keywords: trisubstituted naphthostyril; intramolecular cyclization; C–C bond formation; organometallic reagents.

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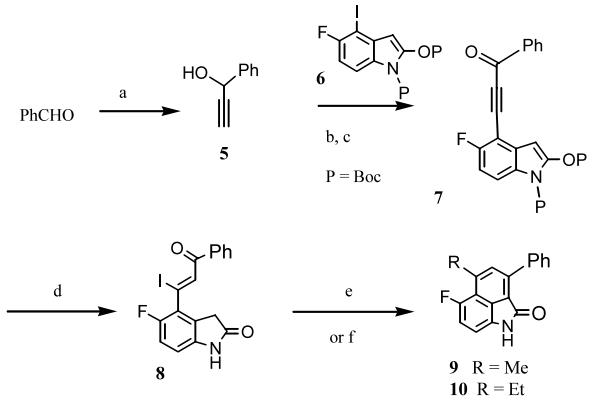


Scheme 2. *Reagents and conditions*: (a) ethynylmagnesium chloride (0.5 M in THF, 1.25 equiv.), THF, −65°C to rt, 1.5 h, 98%; (b) **5** (1.3 equiv.), $(Ph_3P)_4Pd$ (0.08 equiv.), CuI (0.16 equiv.) THF, TEA, rt, 2 h, 65%; (c) MnO_2 (10.0 equiv.), CH_2Cl_2, rt, overnight, 88%; (d) NaI, TFA, rt, 78%; (e) MeLi (20.0 equiv.), CuI (10.0 equiv.), THF, 0°C, 1.5 h, 96%; (f) $Zn(Et)_2$ (7.5 equiv.), CuCN (7.5 equiv.), LiCl (15 equiv.), −78°C, 1 h, then rt, 15 h, 99%.

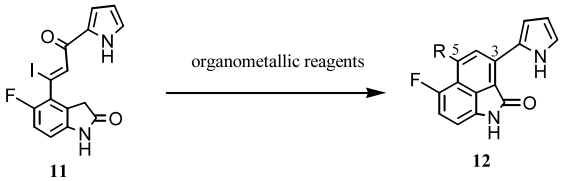
good yield. The reactions to synthesize naphthostyrils were run by slow addition of a THF solution of **8** to a dry, stirred THF solution of the appropriate organometallic reagents under argon. The reaction was then stirred at the same or higher temperature for several hours. As shown in Scheme 2, the expected 1,4 addition occurred when **8** was treated with Me_2CuLi–LiI or $Zn(Et)_2$–CuCN–LiCl complex. The final product isolated in almost quantitative yield was the 5-alkyl-naphthostyril **9** or **10**. Thus, the desired intramolecular cyclization catalyzed by the excess amount of the organic base did occur under the reaction conditions. On the other hand, no stable product was identified from the reaction in which Grignard reagent EtMgBr was used (EtMgBr, THF, −15°C to reflux).

Encouraged by the results from the model studies, we then checked the reaction of compound **11** with various organometallic reagents under similar conditions (Table 1). While Grignard reagents such as CH_2=$CHCH_2MgBr$ did not work with **11** as expected (Table 1, **12c**), the reaction of alkylcuprates can be extended to **11** to give the desired 5-alkyl naphthostyrils as the final products (Table 1, **12a** and **12d**). The yield of the final product decreased dramatically as the size of the alkyl group increased (**12a** versus **12d**).

A typical procedure using an alkylcuprate is as follows. Preparation of 6-fluoro-5-methyl-3-(1*H*-pyrrol-2-yl)-1*H*-benzo[*cd*]indol-2-one (**12a**): To a suspension of copper(I) iodide (190 mg, 1.0 mmol) in dry THF (2 mL) was added MeLi (1.4 M solution in ether, 1.42 mL, 2.0 mmol) by injection, under argon, at 0°C and the reaction mixture was allowed to stir for 15 min. To the colorless solution obtained was added a solution of (*Z*)-5-fluoro-4-[1-iodo-3-oxo-3-(1*H*-pyrro-2-yl)-propenyl]-1,3-dihydro-indol-2-one (39.6 mg, 0.1 mmol) in THF (2 mL). After stirring at 0°C for another 45 min, the reaction mixture was quenched with a saturated aqueous ammonium chloride solution (10 mL) and extracted with ethyl acetate (3×20 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 to give a crude product (28.5 mg) which was further purified by preparative TLC (SiO_2, 20% AcOEt in hexanes) to afford 6-fluoro-5-methyl-3-(1*H*-pyrrol-2-yl)-1*H*-benzo[*cd*]indol-2-one (12.6 mg, 47.4%) as a yellow solid.[10]

Dialkylzinc cuprate complex also worked in this case but gave a rather poor yield. Remarkably, the functionalized organozinc-copper reagent derived by the activation of $NCCH_2CH_2ZnBr$ with CuCN/LiCl[11] reacted with **11** to afford the corresponding 5-alkyl naphthostyril in 16% yield (Table 1, **12e**). Interestingly, in a

Table 1. One-pot reaction of organometallic reagents to β-iodovinyl ketone **11**

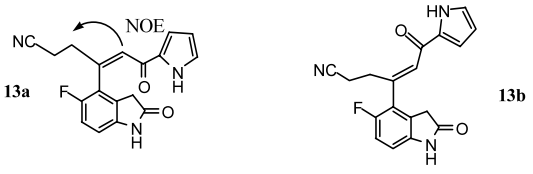


11 **12**

Entry	Nucleophile/conditions[a]	**12** (R =)	Yield (%)
a	MeLi (20.0 equiv.), CuI (10.0 equiv.), THF, 0°C, 45 min	Me	47
b	Et_2Zn (15.0 equiv.), CuCN (1.5 equiv.), LiCl (3.0 equiv.), THF/−78°C, 1.5 h, then rt, 12 h and reflux for 3 h	Et	19
c	CH_2=$CHCH_2MgBr$, THF/0°C, 1 h then reflux for 2 h	CH_2=$CHCH_2$	0
d	sBuLi (20.0 equiv.), CuI (10.0 equiv.), THF, 0°C, 45 min, then rt, 2 h	*s*-Bu	12
e	$NCCH_2CH_2ZnBr$ (15.0 equiv.), CuCN (1.5 equiv.), LiCl (3.0 equiv.), THF/−5°C, 0.5 h, then rt, 2 h and reflux for 12 h	$NCCH_2CH_2$	16
f[b]	1) $NCCH_2CH_2ZnBr$ (10.0 equiv.), CuCN (10.0 equiv.), LiCl (20.0 equiv.), THF, −5°C, 20 min, then rt, 3 h 2) NaOH aq. rt overnight	$NCCH_2CH_2$	41

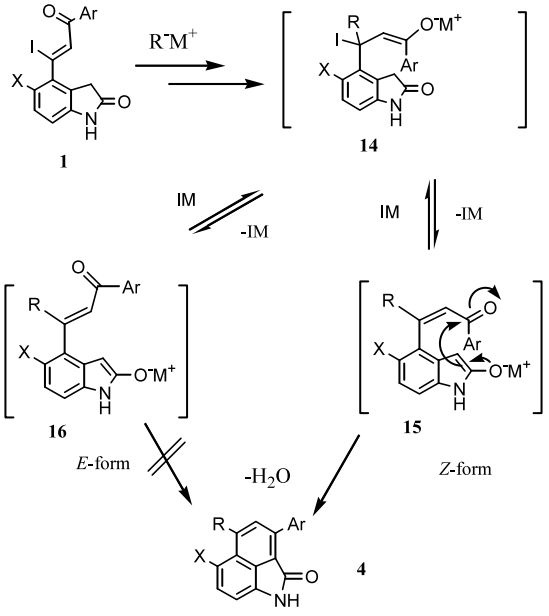
[a] Conditions are not optimized.
[b] The intermediate was isolated by flash column.[12]

separate experiment, the intermediate 1,4-addition product **13a**, was isolated for the first time from the reaction in 41% yield.[12] The *Z* stereochemistry was suggested by NOE studies.[13] Compound **13a** readily underwent intramolecular cyclization upon treatment with aqueous NaOH solution at room temperature to form the corresponding naphthostyril quantitatively. That is consistent with the result from our earlier study of the *cis* olefin.[14] Thus the 2-step reaction actually gave a better yield than the one-pot reaction in this case. The *E* isomer **13b** was not detected from the reaction.



Although the exact mechanism of the stereoselective formation of the inversion product **13a** is not clear,[15] its isolation provided useful information and strong evidence for the mechanism of this one-pot reaction that involves addition–elimination–cyclization sequence. In this process, the iodovinyl ketone **1** reacted with a nucleophilic species (or an electron-transfer reagent[16]) to provide initially the 1,4-addition intermediate **14**. The following elimination reaction should form vinyl ketones **15** and/or **16**. By geometric consideration,[11] only the *Z*-form, vinyl ketone intermediate **15**, could go through the intramolecular cyclization in the presence of excess base to afford the final product, naphthostyril **4**, as shown in Scheme 3.

As 1,4-addition and the subsequent elimination to the desired *Z*-form α,β-enone were the key steps of the one-pot reaction for the synthesis of substituted naphthostyril, nucleophiles such as a Grignard reagent which favors 1,2-addition, might not be suitable to trigger the reaction.[17]



Scheme 3. Mechanisms of intramolecular cyclization of β-iodovinyl ketone **1** to naphthostyrils **4**.

In conclusion, we have found a novel organometallic reagent mediated one-pot synthesis of 3,5,6-trisubstituted naphthostyrils. The present findings provide a useful method for the introduction of a rich variety of alkyl side chains including functionalized alkyl groups, into the 5-position of naphthostyrils. Further investigations using other organometallic reagents are in progress.

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10. Spectroscopic data for selected compounds are provided. **9**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.76 (s, 1H), 7.82 (m, 2H), 7.66 (s, 1H), 7.50 (m, 3H), 7.22 (dd, 1H, $J_1=12.7$ Hz, $J_2=7.8$ Hz), 6.88 (dd, 1H, $J_1=7.8$ Hz, $J_2=2.9$ Hz), 3.22 (q, 2H, $J=7.8$ Hz), 1.34 (t, 3H, $J=7.8$ Hz). IR (thin film) $\nu=3415$, 1703, 1644, 1466. HRMS m/z calcd for $C_{19}H_{14}FNO$ [M$^+$]: 291.1059. Found: 291.1061. **12a**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.38 (s, 1H), 11.26 (s, 1H), 8.05 (s, 1H), 7.27 (br.s, 2H), 7.16 (dd, 1H, $J_1=13.7$ Hz, $J_2=7.8$ Hz), 6.99 (dd, 1H, $J_1=7.8$ Hz, $J_2=2.9$ Hz), 6.34 (m, 1H), 2.83 (s, 3H). IR (thin film) $\nu=3145$, 3064, 2927, 1672, 1642. HRMS for $C_{16}H_{11}FN_2O$ (M$^+$) calcd: 266.0855, found: 266.0859. **12e**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.36 (br.s, 1H), 11.34 (s, 1H), 8.16 (s, 1H), 7.28 (m, 2H), 7.21 (dd, 1H, $J_1=13.7$ Hz, $J_2=7.8$ Hz), 7.02 (dd, 1H, $J_1=7.8$ Hz, $J_2=2.9$ Hz), 6.36 (m, 1H), 3.47 (t, 1H, $J=6.8$ Hz), 3.00 (t, 1H, $J=6.84$ Hz). IR (thin film) $\nu=3419$, 3171, 2247, 1675, 1643, 1575. HRMS for $C_{18}H_{12}FN_3O$ (M$^+$) calcd: 305.0964, found: 305.0968.
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12. Isolation of compound **13a**: The suspension of copper(I) cyanide (1.51 g, 16.9 mmol) and lithium chloride (1.44 g, 34.3 mmol) in dry THF (20 mL) was stirred at rt for 15 min to give a light green solution. To this solution was added $NCCH_2CH_2ZnBr$ (0.5 M solution in THF, 34 mL, 16 mmol) by injection, under argon, at −5°C and the reaction mixture was allowed to stir for 15 min at the same temperature. To the reaction mixture at −5 to 0°C was added the solution of (*Z*)-5-fluoro-4-[1-iodo-3-oxo-3-(1*H*-pyrro-2-yl)-propenyl]-1,3-dihydro-indol-2-one (0.64 g, 1.6 mmol) in dry THF (20 mL). After stirring at the same temperature for 20 min, the reaction mixture was allowed to warm up slowly to room temperature and stirred for 3 h. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (20 mL) and extracted with ethyl acetate (3×30 mL). The combined organic extracts were successively washed with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a crude product which was purified by flash column (SiO_2, 20% AcOEt in hexanes) to give 4-(5-fluoro-2-oxo-2,3-dihydro-1*H*-indol-4-yl)-6-oxo-6-(1*H*-pyrrol-2-yl)-hex-4-enenitrile (0.212 g, 40.8%) as a yellow solid. **13a**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.48 (br.s, 1H), 10.40 (s, 1H), 7.16–7.12 (m, 3H), 7.00 (dd, 1H, $J_1=9.8$ Hz, $J_2=8.8$ Hz), 6.72 (dd, 1H, $J_1=8.8$ Hz, $J_2=3.9$ Hz), 6.24 (m, 1H), 3.47 (d, 1H, $J=22.5$ Hz), 3.00 (d, 1H, $J=22.5$ Hz), 2.77–2.50 (m, 4H). IR (thin film) $\nu=3409$, 2246, 1706, 1683, 1649. HRMS for $C_{18}H_{14}FN_3O_2$ (M$^+$+Na) calcd: 346.0962, found: 346.0966.
13. 5 and 10% NOEs between the vinyl proton and the two protons of the side chain were observed, respectively.
14. See: Liu, J. J.; Konzelmann, F.; Luk, K. C. *Tetrahedron Lett.* **2003**, *44*, 2545–2548, Ref. 10.
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17. There was no change on TLC after **8** or **11** was added to the THF solution of a Grignard reagent such as EtMgBr at −15°C and when the reaction mixture was finally heated up to reflux for 2 h the starting material decomposed.