Supplementary Information

Chemical Labelling of 5-Iodo-2'-Deoxyuridine with 4-Ethynyl-N-Ethyl-1,8-Naphthalimide Using Copper-Free Sonogashira Cross-Coupling in Aqueous Medium

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EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on Varian Mercury 300 (Varian, USA) or Bruker Avance 500 (Bruker, Switzerland). Chemical shifts were reported as δ values relative to the internal standard tetramethylsilane. MS was carried out on Agilent 6120 Quadrupole LC/MS (Agilent Technologies, USA). HRMS spectra were collected with IonSpec 4.7 Tesla FTMS (IonSpec, USA). Fluorescence excitation and emission spectra were recorded with a PerkinElmer LS55 (PerkinElmer, USA) fluorescence spectrometer.

4-Bromo-1,8-naphthalic anhydride was purchased from Sigma-Aldrich, 5-iodo-2'-deoxyuridine and $\text{Pd}(\text{OAc})_2$ were purchased from Alfa Aesar, 2-(dimethylamino)-4,6-pyrimidinediol was purchased from Matrix Scientific.

Synthesis of 4-trimethylsilylethynyl-N-ethyl-1,8-naphthalimide (compound 3)

Compound **3** was synthesized according to literature.^[1,2] Briefly, 4-bromo-1,8-naphthalic anhydride (1.00 g, 3.6 mmol) and ethylamine (70% soln in water)(0.35 ml, 4.3 mmol) were refluxed in 1,4-dioxane (50 ml) for 7 h. The crude mixture was then poured onto ice-water. The precipitate was washed with water and dried under vacuum to yield 4-bromo-N-ethyl-1,8-naphthalimide (compound **2**) as a yellow solid without further purification. For the acetylation, 4-bromo-N-ethyl-1,8-naphthalimide (234 mg, 0.77 mmol) was stirred overnight with tetrakis(triphenylphosphine)palladium (90 mg, 0.078 mmol), CuI (30 mg, 0.16 mmol),

trimethylsilylacetylene (0.54 ml, 3.82 mmol) and *N,N*-diisopropylethylamine (0.5 ml, 2.87 mmol) in THF (10 ml) under nitrogen atmosphere at room temperature (25-30°C) for 10h. Then 10-15 ml EtOAc was added, the crude mixture was washed with saturated NH₄Cl solution, dried over Mg₂SO₄ and concentrated under vacuum. The solid was then purified with flash column chromatography on silica gel (AcOEt/hexane 1:9) to yield the corresponding trimethylsilyl compound (yield 90%).
¹H (300 MHz, CDCl₃): δ=8.65 (dd, *J*₁=6 Hz, *J*₂=1.8 Hz, 2H), 8.54 (d, *J*=7.8 Hz, 1H), 7.92 (d, *J*=7.8 Hz, 1H), 7.90 (t, *J*=6 Hz, 1H), 4.26 (q, 2H), 1.35 (t, *J*=5.7 Hz, 3H), 0.38 (s, 9H). The spectra of this compound corresponded to the literature.^[1,3]

Synthesis of 4-ethynyl-*N*-ethyl-1,8-naphthalimide (compound 4) For synthesis of compound **4**, K₂CO₃ was used for deprotection instead of tetrabutylammonium fluoride which used in the literature 2, and 4-ethynyl-*N*-ethyl-1,8-naphthalimide (compound **4**) was obtained in a yield nearly 100%. Compound **3** was dissolved in 25 ml MeOH. K₂CO₃ (138mg, 1mmol) dissolved in a small amount of water and was added into the MeOH solution. The mixture was stirred at 25°C for 3h and then filtrated. The precipitates were then desiccated to give 4-ethynyl-*N*-ethyl-1,8-naphthalimide as a yellow-brown solid (yield 100%).
¹H (300 MHz, CDCl₃): δ=8.65 (t, *J*=6.6Hz, 2H), 8.53 (d, *J*=7.8Hz, 1H), 7.93 (d, *J*=7.8Hz, 1H), 7.83 (t, *J*=8.1Hz, 1H), 4.25 (q, 2H), 3.74 (s, 1H), 1.34 (t, *J*=6.6Hz, 3H).
¹³C-NMR (75 MHz, CDCl₃,) δ=163.97, 132.38, 131.86, 130.32, 127.91, 126.40, 123.24, 86.75, 80.57, 35.86, 13.60. MS (ESI) calcd for C₁₆H₁₀NO₂⁻¹: 248.3, found: 247.9. The spectra of compound **4** corresponded to the literature values.^[1,3]

Palladium Catalyst Preparation^[4] 2-Dimethylamino-4,6-dihydroxypyrimidine (31.86mg, 0.2mmol) and 4 ml of a 0.10 M NaOH stock solution were added to a 10.00 ml volumetric flask. The pyrimidine ligand was dissolved completely by stirring for 2 minutes in a water bath preheated to 65 °C. Pd(OAc)₂ (22.0 mg, 0.1 mmol) was added to the resulting solution. The mixture was stirred vigorously at 65 °C for 30 minutes (open air) to give a homogenous yellow-orange solution. After cooling to room temperature, the stir bar was removed and the solution diluted to 10.00 ml with distilled water to give a catalyst solution 0.01 M in Pd(II).

¹H spectrum of compound 2

¹H spectrum of compound 3

¹H spectrum of compound 4

¹³C spectrum of compound 4

^1H spectrum of compound **5**

MS spectrum of compound 5

IonSpec HiResMALDI
File: W1130775_DHB_MALDI.trans
ZZG

Shanghai Institute of Organic Chemistry

Mode: Positive
Scans: 1

Date: 03-APR-2013
Time: 11:34:14
Scale: 93.6126

HRMS spectrum of compound 5

Shanghai Mass Spectrometry Center
Shanghai Institute of Organic Chemistry
Chinese Academic of Sciences
High Resolution MS DATA REPORT

Instrument: IonSpec 4.7 Tesla FTMS

Card Serial Number : WI13 0776

Sample Serial Number: ZZG

Operator : HuaQin Date: 2013/04/03

Operation Mode: MALDI/DHB

Elemental Composition Search Report:

Target Mass:

Target m/z = 476.1457 $\pm$ 0.002
Charge = +1

Possible Elements:

Element:	Exact Mass:	Min:	Max:
C	12.000000	0	100
H	1.007825	0	100
N	14.003074	0	10
O	15.994915	0	10

Additional Search Restrictions:

DBE Limit Mode = Both Integer and Half-Integer
Minimum DBE = 0

Search Results:

Number of Hits = 5

m/z	Delta m/z	DBE	Formula
476.14523	0.00047	16.5	$C_{25}H_{22}N_3O_7^{+1}$
476.14522	0.00048	22.0	$C_{24}H_{16}N_{10}O_2^{+1}$
476.14656	-0.00086	21.5	$C_{26}H_{18}N_7O_3^{+1}$
476.14657	-0.00087	16.0	$C_{27}H_{24}O_8^{+1}$
476.14389	0.00181	17.0	$C_{23}H_{20}N_6O_6^{+1}$

References

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