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Protocol

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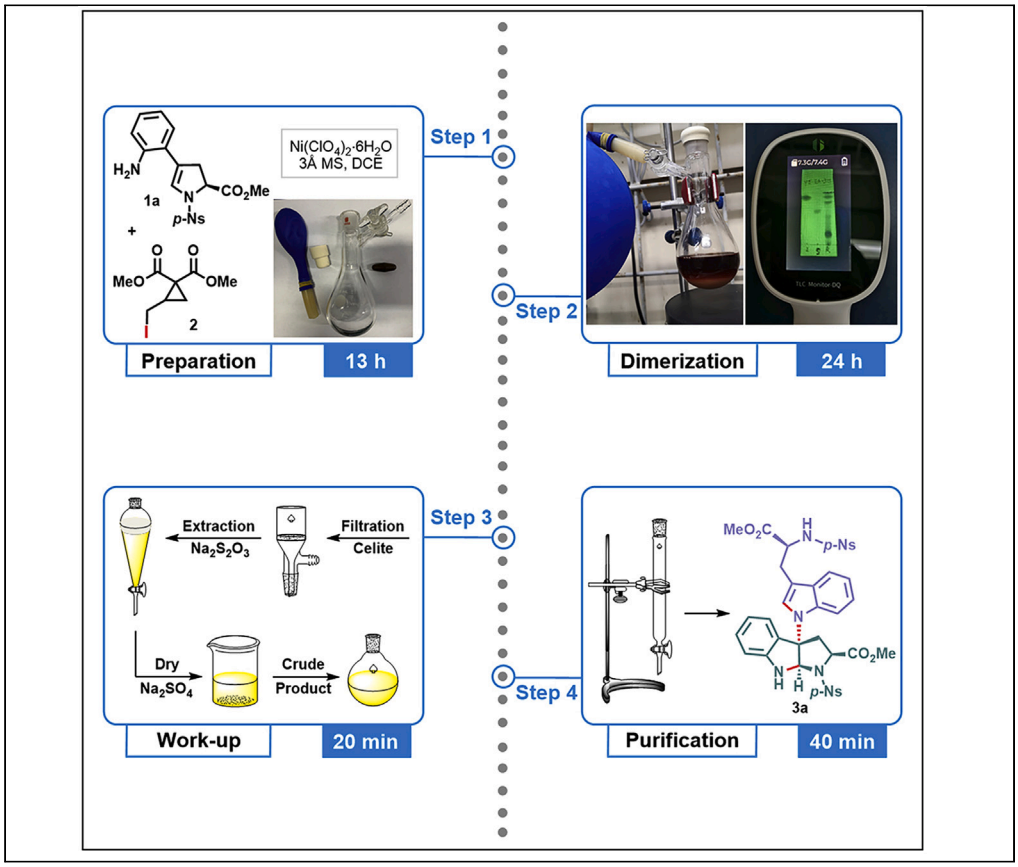

Here, we present an efficient protocol for stereoselective 4*N*-based domino dimerization in one single step, establishing a 22-membered library of asperazine A analogs. We describe steps for performing a gram-scale 2*N*-monomer to access the unsymmetrical 4*N*-dimer. We detail the synthesis of the desired dimer **3a** as a yellow solid in 78% yield. This process demonstrates the 2-(iodomethyl)cyclopropane-1,1-dicarboxylate to be an iodine cation source. The protocol is limited to unprotected aniline of 2*N*-monomer.

Publisher's note: Undertaking any experimental protocol requires adherence to local institutional guidelines for laboratory safety and ethics.

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Highlights

Masked iodine effect of 2-(iodomethyl) cyclopropane-1,1-dicarboxylate

Ni-catalyzed sustained-release iodine cation

Stereoselective 4*N*-based domino unsymmetrical dimerization

A 22-membered library of asperazine A analogs

Bai et al., STAR Protocols 4, 102114
March 17, 2023
https://doi.org/10.1016/j.xpro.2023.102114

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A one-step gram-scale protocol for stereoselective domino dimerization to asperazine A analogs

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https://doi.org/10.1016/j.xpro.2023.102114

SUMMARY

Here, we present an efficient protocol for stereoselective 4*N*-based domino dimerization in one single step, establishing a 22-membered library of asperazine A analogs. We describe steps for performing a gram-scale 2*N*-monomer to access the unsymmetrical 4*N*-dimer. We detail the synthesis of the desired dimer 3a as a yellow solid in 78% yield. This process demonstrates the 2-(iodomethyl) cyclopropane-1,1-dicarboxylate to be an iodine cation source. The protocol is limited to unprotected aniline of 2*N*-monomer.

For complete details on the use and execution of this protocol, please refer to Bai et al. (2022).[1]

BEFORE YOU BEGIN

Dimeric indole alkaloid exhibiting an unusual C3−N1′ linkage are remarkably attractive targets owing to the unique challenge of assembling the C3−N bond and their anticancer and antibiotic properties (Staab et al.[2]; Schallenberger et al.[3]). In contrast to the more common C3−C type dimer (Steven et al.[4]; Schmidt et al.[5]; Trost et al.[6]; Shen et al.[7]; Mei et al.[8]), C3−N1′ type dimer have witnessed significantly less endeavors from the synthetic community. The inherent preference for tryptamine, tryptophan or oxindole derivatives dimerization to favor C−C bond construction, rather than C−N bond formation, makes the reversal of this chemoselectivity remarkably challenging. Challenges in the controlling of chemoselectivity in organic synthesis have historically been overcome either by utilizing reactants/reagents/catalysts that adjustably interact with the substrate or employing protecting groups to block the undesired reactivity (Shenvi et al.[9]; Kawamata et al.[10]). In the terms of manipulating the chemoselectivity and stereoselectivity of C3−C and C3−N1′ dimerization, pioneering contributions have been made elegantly by Kawasaki via tryptamine−tryptamine/indoline cross coupling (Tayu et al.[11]; Tayu et al.[12]), by Movassaghi through diverse arylative dimerization (Kim et al.[13]; Movassaghi et al.[14]; Kim et al.[15]; Loach et al.[16]; Nelson et al.[17]; D'Angelo et al.[18]) and by Knowles' photo-iridium driven capture of pyrroloindoline carbocation (Gentry et al.[19]). Though the biological origins of dimeric indole alkaloids linked at carbon are assumed to proceed via oxidative (radical) dimerization process (Kirby et al.[20]), the genesis of nitrogen-linked dimers is not clear (García-Domínguez et al.[21]; Sun et al.[22]). From our point of view, the controllable diverse dimerization could even be regarded as "yardsticks" to measure progress in the art and science of controlling chemoselectivity, which nature has practiced deftly for billions of years but man has yet to master (Shenvi et al.[9]).

Figure 1. Activate 3 Å molecular sieves

To explore how nature might create this extraordinary connectivity, our designed 2*N*-featured monomer was considered as the cornerstone to achieve the fascinating chemoselectivity of 4*N*-dimer in one step. Persevering with our efforts on the total syntheses of alkaloids (Wang et al.[23]; Wang et al.[24]), the oxidant was found to be the key switch to reverse the symmetrical C3a−C3a′ dimerization (Bai et al.[25]) to unsymmetrical C3−N1′ dimerization (Bai et al.[1]). The former relied on a single electron oxidation catalyzed by Fe(III), the latter depended on a two-electron oxidation mediated via sustained-release iodine cation catalyzed by Ni(II).

Domino reaction is an elegant tool applied to achieve step economy in organic synthesis. This protocol describes a domino dimerization process to directly construct the intriguing C3−N1′ bond in one single operation, which was further applied to establish a 22-membered library of asperazine A analogues and fulfill the total synthesis of (+)-asperazine A. For details of the cascade transformation and synthetic technology, please refer to (Bai et al.[1]).

Preparation of the reagents and equipment

A complete list of reagents and equipment can be found in the ''key resources table'' and ''materials and equipment.'.

Preparation of the 3 Å molecular sieves

Timing: 13 h

1. Activate 3 Å molecular sieves (MS) as mentioned below (Figure 1):
   a. Place 100 g 3 Å MS (powder) in a crucible.
   b. Heat the MS in a 550°C muffle furnace for 12 h.
   c. Cool down the muffle furnace to 30°C–40°C.
   d. Dry the vials in the oven at 80°C for 5 h before their use.
   e. Cool down the oven to 30°C–40°C.
   f. Transfer the MS to the vials.
   g. Seal the vials and move them into a vacuum desiccator with $CaCl_2$ as the desiccant.
   h. Use a vacuum pump to keep the vials under vacuum before use.

Note: Gloves and crucible tongs would be needed since the crucible will be hot.

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, peptides, and recombinant proteins		
$Ni(ClO_4)_2 \cdot 6H_2O$, 99%	Strem Chemicals	CAS: 13520-61-1
3 Å MS (powder)	Energy Chemical	CAS: 308080-99-1
1,2-Dichloroethane, 99.5%, Extra Dry, with molecular sieves, Water ≤ 50ppm (byK.F.), Energyseal	Energy Chemical	CAS: 107-06-2
Argon, ≥99.999%	Pu Jiang	GB/T 4842-2017

(*Continued on next page*)

Continued

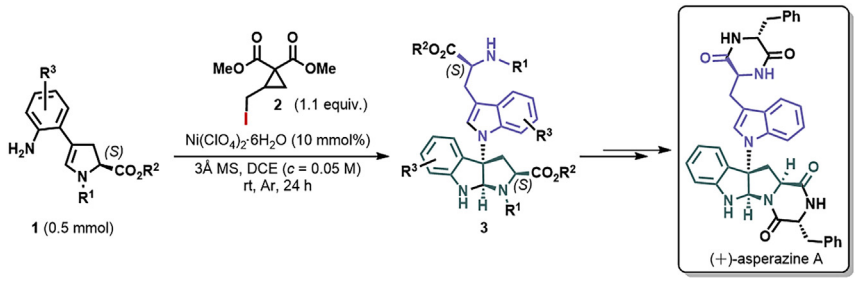
REAGENT or RESOURCE	SOURCE	IDENTIFIER
Celite 535	Adamas	CAS: 68855-54-9
Dichloromethane (AR)	Greagent	CAS: 75-09-2
$Na_2S_2O_3 \cdot 5H_2O$ (AR)	Greagent	CAS: 10102-17-7
NaCl (AR)	Greagent	CAS: 7647-14-5
Na_2SO_4 (AR)	Greagent	CAS: 7757-82-6
Silica gel for chromatography (100–200 mesh, AR)	Greagent	CAS: 63231-67-4
Silica gel for chromatography (300–400 mesh, AR)	Greagent	CAS: 63231-67-4
Quartz sand (AR)	Sinopharm	CAS: 14808-60-7
Petroleum ether (AR)	Greagent	CAS: 8032-32-4
Ethyl acetate (AR)	Greagent	CAS: 141-78-6
Hexane (RG)	Adamas	CAS: 92112-69-1
Deuterated chloroform, 99.8 atom%D	J&K Scientific	CAS: 865-49-6
Other		
Electronic balance	Sartorius	Cat# BSA124S
Rubber septum	Tansoole	Cat# 02026477
Glass syringe (10 mL)	Tansoole	Cat# 02041725
Glass syringe (100 mL)	Tansoole	Cat# 02037339
Syringe needle	Jiaqicheng Dianzi	Cat# 9#/20G-150 mm
Crucible	Bkmam	Cat# 120701005
Gloves	3 M	Cat# WX300953410
Crucible tongs	Thermo Fisher	Cat# 02-620
Muffle furnace	Shanghai Y-feng	Cat# SX2-5-12
Organic microporous membrane	Tianjin Navigator	Cat# NMF10
Vial (4 mL)	ALWSCI	Cat# C0000025
Vial (40 mL)	LH Labware	Cat# LH-333-205
Oven	Shanghai Yi Heng	Cat# DHG-9015A
Vacuum desiccator	Synthware	Cat# B135424
Vacuum pump	VRLUE	Cat# VRD-8
High vacuum pump oil	Shell	Cat# S3 RX100
Schlenk bottle (100 mL)	Synthware	Cat# F909100G
Magnetic stirrer	Heidolph	Cat# MR Hei-Tc
Thin-layer chromatography (TLC-Plates 0.25 mm)	Leyan	Cat# C100053
TLC Monitor-DQ	ECNU Green Lab	Cat# DQA1601
Filter funnel (150 mL)	LH Labware	Cat# LH-239-108
Separating funnel (250 mL)	LH Labware	Cat# LH-218-250
Chromatography column	LH Labware	Cat# LH-263-895
Low-temperature pump	Shanghai Xiangya	Cat# LC-310
Water Circulating Multi-purpose Vacuum Pump	Shanghai Xiangya	Cat# SHB-III
Rotary evaporator	Heidolph	Cat# Hei-Vap Value
Splash-proof ball	LH Labware	Cat# LH-163-202
Absorbent cotton	Tansoole	Cat# 02025831
500 MHz NMR spectrometer	Bruker	Cat# Avance III
X-ray single crystal diffractometer	Rigaku	Cat# XtaLAB

MATERIALS AND EQUIPMENT

Reagents

Reagents	Storage	Maximum time for storage
1a[a]	2°C–8°C	more than two years
2[b]	−20°C to −10°C	two years
$Ni(ClO_4)_2 \cdot 6H_2O$	room temperature in desiccator	more than two years
3 Å MS	room temperature in desiccator	more than two years

[a]Prepared following Bai et al.[1]
[b]Prepared following Kitagawa et al.[26]



Scheme 1. General domino dimerization reaction

STEP-BY-STEP METHOD DETAILS

Part 1: Synthesis of C–N dimer (3a)

Timing: 24 h

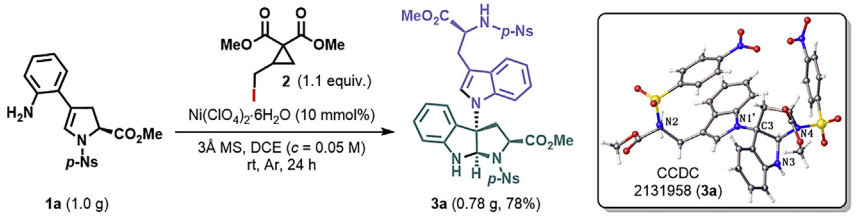
In this part, the C–N dimers **3** are prepared by a one-step domino dimerization procedure from monomers **1** following Bai et al.[1] (Scheme 1). The monomers **1** are obtained following Bai et al.[25] and Bai et al.[1] The oxidant 2-(iodomethyl)cyclopropane-1,1-dicarboxylate **2** is acquired following Kitagawa et al.[26] Twenty-two asperazine A scaffolds have been established via this straightforward conversion (Scheme 1), and subsequent total synthesis of (+)-asperazine A was advantageously achieved. The full scope of the transformation is described in Bai et al.[1]

1. Set up the reaction (Scheme 2, Table 1, Figure 2).
   a. Add the monomer **1a** (1.0 g, 2.50 mmol, 1.0 equiv.), iodocyclopropane **2** (819 mg, 2.75 mmol, 1.1 equiv.), molecular sieve 3Å (10.0 g), and $Ni(ClO_4)_2 \cdot 6H_2O$ (91 mg, 0.25 mmol, 10 mmol%) to a flame-dried 100 mL Schlenk bottle, successively (troubleshooting 1, 2, and 5).

   Note: It is **danger** to heat $Ni(ClO_4)_2 \cdot 6H_2O$ (melting point: 140°C) to remove its crystal water, avoiding the potential explosion. Since its innate hygroscopicity, this Ni(II) hydrate salt is used directly without prior dried.

   Note: It was demonstrated that the addition of water (10 equiv.) completely suppressed the transformation. Underperforming conversions (40% yield and 55%, respectively) were afforded when the reaction was launched in the absence of 3 Å MS or conducted with unactivated 3 Å MS (more details see Bai et al.[1]).

   b. Add an argon balloon to the bottle, back-flush the bottle with argon and repeat this vacuum-argon cycle 3 times.
   c. Seal the bottle with a rubber septum under the argon gas flow.
   d. Add anhydrous 1,2-dichloroethane (50 mL, 0.05 M) to the bottle with a 100 mL glass syringe.
   e. Stir the reaction at room temperature for 24 h (troubleshooting 3).



Scheme 2. Dimerization of 1a to yield 3a

Table 1. Quantification of reagents, solvent, and product

Reagent	Mw (g/mol)	m (g)	n (mmol)	Equiv.	V (mL)	Conc (M)	Yield (%)
1a	403	1	2.5	1			
2	298	0.82	2.75	1.1			
$Ni(ClO_4)_2 \cdot 6H_2O$	365	0.091	0.25	0.1			
3 Å MS		10					
1,2-Dichloroethane					50	0.05	
3a[a]		0.78					78

[a]The product is benchtop stable. Can be stored at 20°C–25°C without any precautions to avoid moist and/or air.

Note: The reaction should not be conducted more than 24 h, avoiding the de-Ns byproduct.

f. Use TLC (petroleum ether/EtOAc = 3/1) with UV-light detection (254 nm) to monitor the reaction after 24 h (Figure 2D).
g. Witness a color change from pale yellow (start, Figure 2A) to pale red (after 10 h, Figure 2B), and finally to the dark red (24 h, Figure 2C).

Part 2: Purification of the crude material

Timing: 1 h; step 2: 20 min; step 3: 40 min

This section completes the purification of the dimer **3a**.

2. Work-up (20 min).
   a. Pour the reaction mixture to a filter funnel (150 mL, height of Celite: 2 cm, Figure 2E).
   b. Rinse with dichloromethane (3 × 30 mL).
   c. Transfer the filtrate to separatory funnel (250 mL).
   d. Add 30 mL saturated $Na_2S_2O_3$ (Figure 2F), then shake it vigorously (Figure 2G).
   e. Add 30 mL saturated brine, then shake it vigorously and let the aqueous phase separate from the organic one (troubleshooting 4 and 5).

   Note: The brine is used to dilute the $Na_2S_2O_3$ phase, ensuring the aqueous phase suspend on the top layer and the organic phase stay the bottom layer.

   f. Dry the organic phase with Na_2SO_4 until floating is observed and filter (Figures 2H and 2I).
   g. Remove the solvent by rotatory evaporation (35°C, 80 rpm, 0.080–0.095 MPa) to give the crude product (Figures 2J and 2K).
3. Purification via column chromatography (40 min).
   a. Dilute the concentrated crude mixture with 100 mL dichloromethane.
   b. Add 8 g of silica gel (100–200 mesh).
   c. Swirl the flask and evaporate the solvent under vacuum (35°C, 80 rpm, 0.080–0.095 MPa, Figure 2L).

   Note: The absorbent cotton is stuffed into the splash-proof ball to avoid the eruption of silica gel during vacuum evaporate.

   d. Use petroleum ether to wet the silica gel (15 cm, 300–400 mesh) and quartz sand (2 cm) in a column (Ø of the column = 4.6 cm).
   e. Load the free-flowing silica gel and quartz sand (2 cm) to the column (Figure 2M).
   f. Elute the product with a 3:1 (by volume) mixture of petroleum ether (PE) /ethyl acetate (EA) (approximate 3 L).

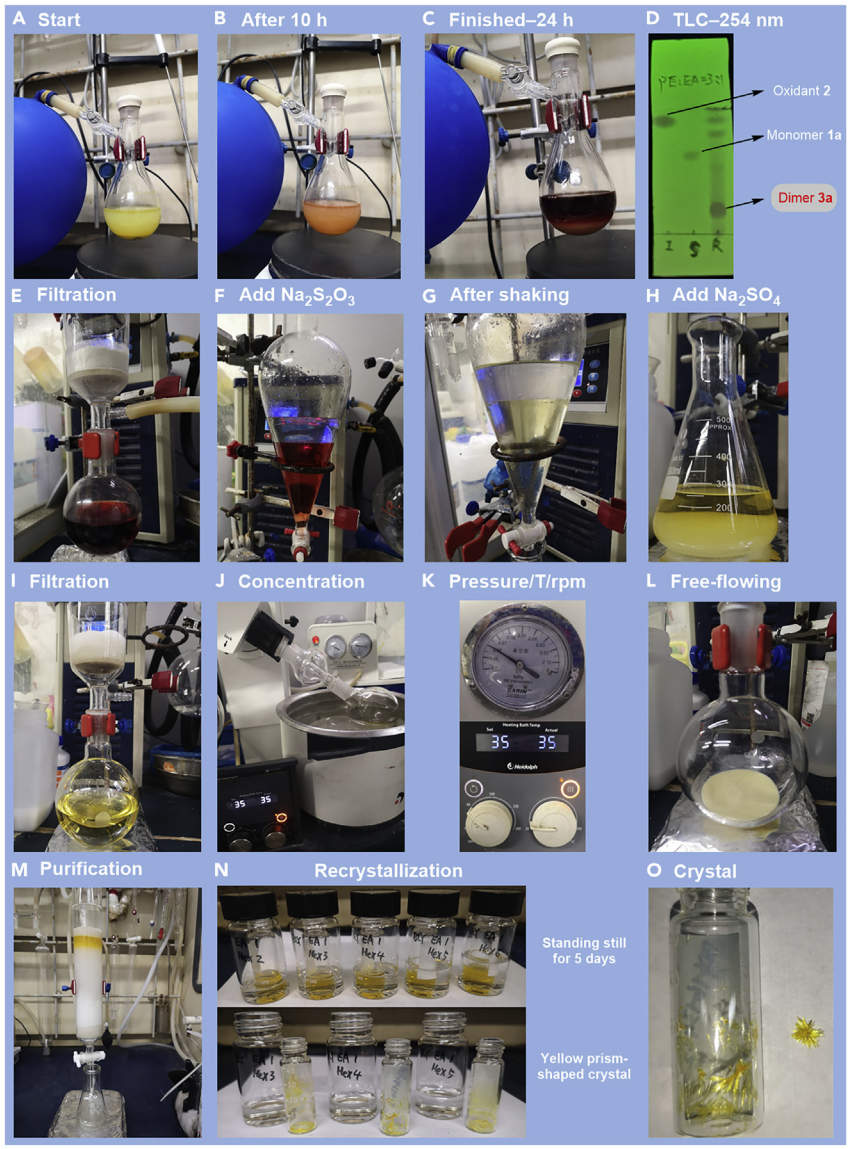


Figure 2. Reaction and appearance of dimer 3a at different stages of the reaction

g. Use TLC (petroleum ether/EtOAc = 3/1) with UV-light detection (254 nm) to analyze the fractions.
h. Collect the fractions containing product (R_f = 0.1).
i. Remove the solvent under rotary evaporation (35°C, 80 rpm, 0.080–0.095 MPa) to give the pure product.
j. Identify and characterize the product by ^{1}H-NMR,^{13}C-NMR and HRMS.

Part 3: Recrystallization

Timing: 5 days

This section obtains the crystal of the dimer **3a**.

4. Set-up for Recrystallization.

a. Weigh 30 mg dimer **3a** on the electronic balance.
b. Dissolve the dimer with 6 mL ethyl acetate in a 40 mL vial.
c. Filter the solvent through an organic microporous membrane using a 10 mL glass syringe.

Note: The filtration is essential to remove insoluble impurities, delivering a clear filtrate.

d. Divide the filtrate equally into five 4 mL vials.
e. Fill five 40 mL vials with hexane: 2 mL, 3 mL, 4 mL, 5 mL, and 6 mL respectively.
f. Transfer the five 4 mL vials into the five 40 mL vials.
g. Seal the five 40 mL vials and keep them standing still at room temperature (Figure 2N).

Note: Put the vials on a flat and quiet place! Do not move the sample!

h. After slow evaporation for 5 days, the yellow prism-shaped crystals are obtained (Figure 2O).

EXPECTED OUTCOMES

The dimer **3a** is obtained as a yellow solid in 78% yield (780 mg, purity >99.0%). The yellow prism-shaped crystal is recrystallized from EtOAc/hexane (purity >99.9%, Figure 2O).

QUANTIFICATION AND STATISTICAL ANALYSIS

Analytical data

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.7 Hz, 2H), 8.11 (d, *J* = 8.7 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.83 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.74 (s, 1H, $H^{2'}$), 6.70 (t, *J* = 7.7 Hz, 1H), 6.42 (d, *J* = 8.3 Hz, 1H), 5.79 (s, 1H, H^{2}), 5.77 (d, *J* = 9.0 Hz, 1H, $NH^{12'}$), 5.18 (s, 1H, NH^{1}), 4.85 (d, *J* = 8.7 Hz, 1H, H^{11}), 4.22–4.10 (m, 1H, $H^{11'}$), 3.56 (s, 3H), 3.36 (dd, *J* = 13.2, 8.9 Hz, 1H, $H^{10\alpha}$), 3.30 (s, 3H), 3.08 (dd, *J* = 14.8, 4.5 Hz, 1H, $H^{10'}$), 2.99 (d, *J* = 13.0 Hz, 1H, $H^{10'}$), 2.91 (dd, *J* = 14.8, 8.2 Hz, 1H, $H^{10\beta}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 170.3, 150.4, 149.5, 145.2, 144.4, 134.3, 131.7, 129.5, 128.6, 127.7, 125.6, 125.4, 124.8, 124.8, 123.8, 122.0, 120.3, 120.1, 119.4, 111.5, 110.8, 108.5, 81.4 (C^{2}), 75.2 (C^{3}), 61.5 (C^{11}), 56.3 ($C^{11'}$), 52.85, 52.82, 39.6 (C^{10}), 28.5 ($C^{10'}$).

HRMS (ESI) $[M+H]^+$ Calcd for $C_{36}H_{33}N_6O_{12}S_2$ 805.1592, Found 805.1585.

LIMITATIONS

The protocol is limited to unprotected aniline of 2*N*-monomer.

TROUBLESHOOTING

Problem 1

Step 1a: The activated 3 Å MS and $Ni(ClO_4)_2 \cdot 6H_2O$ are sensitive to water.

Potential solution

The activated 3 Å MS and $Ni(ClO_4)_2 \cdot 6H_2O$ are stored in a vacuum desiccator with $CaCl_2$ as the desiccant, a vacuum pump is used to keep the desiccator under vacuum before use. They are added to the Schlenk bottle as quickly as possible in the open air or through the glove box.

Problem 2

Step 1a: The dimerization process is sensitive to water, which will cause no reaction.

Potential solution

The Schlenk bottle is flame-dried and cooled down before use. Check whether the branch of bottle is residual with a few drops of water, since sometimes it is not totally dried via the oven. Ensure enough quantity of activated 3 Å MS is added.

Problem 3

Step 1e: The isolation of de-Ns byproduct.

Potential solution

The reaction should not be performed more than 24 h.

Problem 4

Step 2e: The emulsification is observed under extraction.

Potential solution

Add brine and dichloromethane to dilute the $Na_2S_2O_3$ phase, ensuring the aqueous phase suspend on the top layer and the organic phase stay the bottom layer.

Problem 5

Steps 1a and 2e: Yield is lower than expected.

Potential solution

This protocol is water-sensitive, therefore, ensure the solvent is extra dry (Water $\leq$ 50ppm). The domino dimerization process is also oxidation-sensitive, hence, do not add excess nickel catalyst or oxidant, which will lead to over-oxidation and byproduct. Additionally, product may be lost during extraction caused by emulsification, dilute the $Na_2S_2O_3$ phase with brine and dichloromethane is recommended.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Xuefeng Jiang (xfjiang@chem.ecnu.edu.cn).

Materials availability

This study did not generate new unique reagents, all compounds have been described in the original article; see Bai et al.[1]

Data and code availability

All data reported in this paper will be shared by the lead contact upon request.

This paper does not report the original code.

Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

The published article includes all [datasets/code] generated or analyzed during this study, see Bai et al.[1]

ACKNOWLEDGMENTS

The authors are grateful for financial support provided by the NSFC (22125103 and 21971065) and the STCSM (22JC1401000 and 20XD1421500).

AUTHOR CONTRIBUTIONS

L.B. and X.J. designed and wrote the protocol with inputs from all the authors. L.B. and B.F. performed the experimental data. X.J. supervised the project. All authors approved the final version of the manuscript for submission.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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