Supporting Information

Zinc (II)-Mediated Selective O-Benzylation of 2-Oxo-1,2-dihydropyridines Systems

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1. General procedures

All of the starting materials, reagents, and solvents are commercially available and used without further purification. The microwave-assisted reactions were performed using a CEM Discover System 908010 microwave apparatus (Matthews, NC, USA). Melting points were determined with a X-4 apparatus and were uncorrected. The nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 600 MHz spectrometer in CDCl$_3$ or DMSO-$d_6$ using tetramethylsilane (TMS) as an internal standard. Electrospray ionization mass spectrometry (ESI-MS) analyses were recorded in an Agilent 1100 Series MSD Trap SL (Santa Clara, CA, USA). The reactions were monitored by thin-layer chromatography (TLC: HG/T2354-92, GF254), and compounds were visualized on TLC with UV light.

2. Microwave-assisted synthesis of 3a

To a solution of 1a (0.20 g, 1.35 mmol), zinc oxide (0.12 g, 1.48 mmol), zinc chloride (0.20 g, 1.48 mmol), $N,N$-diisopropylethylamine (0.19 g, 1.48 mmol), 1,4-dioxane (3 mL) was added benzyl chloride (0.2 g, 1.61 mmol). The mixture was irradiated at 110 °C for 60 min in a dedicated CEM-Discover system, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W. After completion of the reaction, the insoluble residue was filtered off through celite, and the cake was wash with ethyl acetate (30 mL). The filtrate was washed with water (10 mL×2), once with brine (10 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo to afford crude product. The product was purified by column chromatography on silica gel (ethyl acetate: petroleum ether=1:20) to afford $O$-benzylation in 65% yield and $N$-benzylation in 21% yield.

3. General procedures for the synthesis of substituted aromatic lactam of 1a-1k

A substituted alkyl methyl ketone or cyclic ketone (1 equiv) and ethyl formate or
ethyl acetic (1 equiv) was added dropwise to absolute ether solution of sodium metal (1 equiv) for 1 hour while maintained below 20 °C. After the addition, the reaction was allowed to stir at ice bath until the sodium metal was disappeared. The precipitate was filtered, washed with absolute ether and dried to give the corresponding compound which was directly used next step without purification.

To a solution of previous product (1 equiv), and cyanoacetamide (1.05 equiv) in water was stirred 6 minutes at room temperature. The mixture was added dropwise piperidine acetate solution (0.3 equiv), which was prepared from piperidine (1 equiv), acetic acid (1 equiv) and water (5 equiv). The solution was heated to reflux for 2 hours. Then, the reactor was cooled to room temperature, and adjusted to pH 4 by 4 N hydrochloric acid. The resulting solid was filtered, respectively washed with water and ether, and dried to give the corresponding compound which was purified by recrystallizing using menthol as solvent.

4. General procedures for the synthesis of 3a-3m

To a solution of substituted aromatic lactam (3.36 mmol), zinc oxide (0.30 g, 3.70 mmol), zinc chloride (0.50 g, 3.70 mmol), N,N-diisopropylethylamine (0.48 g, 3.70 mmol), 1,4-dioxane (15 mL) was added benzyl chloride (0.58 g, 4.04 mmol) under argon atmosphere. The mixture was heated in 110°C oil bath with rapid stirring for the indicated time. The reactor was cooled to room temperature, and the insoluble residue was filtered off through celite, and the cake was wash with ethyl acetate (30 mL). The filtrate was washed with water (10 mL×2), once with brine (10 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo to afford crude product. The product was purified by column chromatography on silica gel (ethyl acetate: petroleum ether=1:20) to yield the corresponding compounds.

5. General procedures for the synthesis of 4a-4k

To a solution of 1a (0.5 g, 3.36 mmol), zinc oxide (0.30 g, 3.70 mmol), zinc chloride (0.50 g, 3.70 mmol), N,N-diisopropylethylamine (0.48 g, 3.70 mmol),
1,4-dioxane (15 mL) was added substituted benzyl halides (4.04 mmol) under argon atmosphere. The mixture was heated in 110 °C oil bath with rapid stirring for the indicated time. The reactor was cooled to room temperature, and the insoluble residue was filtered off through celite, and the cake was wash with ethyl acetate (30 mL). The filtrate was washed with water (10 mL×2), once with brine (10 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The product was purified by column chromatography on silica gel (ethyl acetate: petroleum ether=1:20) to yield the corresponding compounds.

6. **¹H NMR spectra of 1a-1k**

![¹H NMR spectra of 1a](image)
\[^1\text{H} \text{NMR} \text{ spectra of } 1\text{b} \]

\[^1\text{H} \text{NMR} \text{ spectra of } 1\text{c} \]
$^1$H NMR spectra of 1d

$^1$H NMR spectra of 1e
$^1$H NMR spectra of 1f

$^1$H NMR spectra of 1g
$^1$H NMR spectra of 1h

$^1$H NMR spectra of 1i
$^1$H NMR spectra of 1j

$^1$H NMR spectra of 1k
7.  $^1$H and $^{13}$C NMR spectra and HRMS spectra of 3a-3m

$^1$H NMR spectra of 3a

$^{13}$C NMR spectra of 3a
HRMS spectra of 3a

\[\text{NMR spectra of 3b}\]
$^{13}$C NMR spectra of 3b

HRMS spectra of 3b
$\text{H NMR spectra of 3c}$

$\text{C NMR spectra of 3c}$
HRMS spectra of 3c

$^1$H NMR spectra of 3d
$^{13}$C NMR spectra of 3d

HRMS spectra of 3d
$^1$H NMR spectra of 3e

$^{13}$C NMR spectra of 3e
HRMS spectra of 3e

^1^H NMR spectra of 3f
\(^{13}\text{C}\) NMR spectra of 3f

HRMS spectra of 3f
$^1$H NMR spectra of 3g

$^{13}$C NMR spectra of 3g
HRMS spectra of 3g

$^1$H NMR spectra of 3h
C NMR spectra of 3h

HRMS spectra of 3h
**1H NMR spectra of 3i**

**13C NMR spectra of 3i**
HRMS spectra of 3i

$^{1}$H NMR spectra of 3j
$^{13}$C NMR spectra of 3j

HRMS spectra of 3j
$^{1}$H NMR spectra of 3k

$^{13}$C NMR spectra of 3k
HRMS spectra of 3k

$^1$H NMR spectra of 3l
$^{13}$C NMR spectra of 3l
MS spectra of 3l
$^1$H NMR spectra of 3m

$^{13}$C NMR spectra of 3m
MS spectra of 31
8. $^1$H and $^{13}$C NMR spectra and HRMS spectra of 4a-4k

$^1$H NMR spectra of 4a

$^{13}$C NMR spectra of 4a
HRMS spectra of 4a

$^{1}H$ NMR spectra of 4b
$^{13}$C NMR spectra of 4b

HRMS spectra of 4b
$^{1}H$ NMR spectra of 4c

$^{13}C$ NMR spectra of 4c
HRMS spectra of $4c$

$^1H$ NMR spectra of $4d$
$^{13}$C NMR spectra of 4d

User Spectra

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| Fragmentor Voltage | Collision Energy | Ionization Mode |
|--------------------|------------------|-----------------|
| 200                | 0                | ESI             |
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HRMS spectra of 4d
$^1$H NMR spectra of 4e

$^{13}$C NMR spectra of 4e
HRMS spectra of 4e

\[ ^1H \text{ NMR spectra of } 4f \]
$^{13}$C NMR spectra of 4f

HRMS spectra of 4f
$^1$H NMR spectra of 4g

$^{13}$C NMR spectra of 4g
HRMS spectra of 4g

$^1$H NMR spectra of 4h
13C NMR spectra of 4h

User Spectra

HRMS spectra of 4h
$^1$H NMR spectra of 4i

$^{13}$C NMR spectra of 4i
HRMS spectra of 4i

^1^H NMR spectra of 4j
$^{13}$C NMR spectra of $4j$

User Spectra

HRMS spectra of $4j$
$^1$H NMR spectra of 4k

$^{13}$C NMR spectra of 4k
HRMS spectra of 4k

9. $^1$H NMR spectra of $N$-benzylation product 5