Supporting Information

Base-Catalyzed Tandem Cyclization: Diastereoselective Access to the 3,4-Dihydroisoquinolin-2(1H)-one Core

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1. Experimental Procedures.

1. General Procedure for preparation for synthesis of compounds (4a-4o).

A mixture of aniline 2 (1 mmol, 1.0 equiv), dimethyl acetylenedicarboxylate 3 (1 mmol, 1.0 equiv) and ninhydrine 1 (1 mmol, 1.0 equiv) and NEt₃ (1.0 equiv) was heated at 70 °C in 5 mL of methanol in a round bottom flask for 8 h till almost completed conversion of the substrates by TLC analysis. After completion of reaction methanol was removed through rotary evaporator and concentrated in vacuo. The residue was purified by column chromatography with a hexane–ethyl acetate (9:1) mixture to afford the pure product 4 as a white solid.

2 General Procedure for preparation for synthesis of intermediate.

Dimethyl 2-(phenylamino)maleate (4aa).³ Amine 2 (1 mmol), 3 dialkyl acetylenedicarboxylate (1 mmol) and methanol (3ml) was taken in a dried round bottom flask, is stirred at room temperature for 2 h. At the end of the reaction, the solution is dried (Na₂SO₄), filtered and concentrated under reduced pressure then filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt₃ 97:2:1) The pure product is obtained as a yellow solid.

(Z)-Methyl-3-(phenylamino)but-2-enoate(5aa).² Following a modified procedure of C. A. Brandt, a mixture of methyl acetoacetate 6 (2 mmol), 2 aniline (2 mmol) and acetic acid (0.2 mmol) is stirred at room temperature for 18 h. At the end of the reaction, EtOH (5 mL) is added, the solution is dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt₃ 97:2:1). The pure product is obtained as a yellow solid.
(Z)-methyl 3-(p-tolylamino)but-2-enolate (5bb). Mixtures of 6 (1 mmol), amine 2j (1 mmol), and Yb(OTf)$_3$ (0.02 mmol) were stirred at ambient temperature 9 h. After completion of the reaction, 1 N NaOH (2 mL) was added, the white precipitate filtered, and the resulting solution extracted with Et$_2$O (2 × 2 mL). The organic layers were dried over anhydrous Na$_2$SO$_4$ and the solvent evaporated and subjected to column chromatography to afford the desired product.

(Z)-methyl 3-(4-bromophenylamino)but-2-enolate (5cc). Mixtures of 6 (1 mmol), amine 2c (1 mmol), and Yb(OTf)$_3$ (0.02 mmol) were stirred at ambient temperature for 6 h. After completion of the reaction, 1 N NaOH (2 mL) was added, the white precipitate filtered, and the resulting solution extracted with Et$_2$O (2 × 2 mL). The organic layers were dried over anhydrous Na$_2$SO$_4$ and the solvent evaporated and subjected to column chromatography to afford the desired product.

dimethyl 3a,8b-dihydroxy-4-oxo-1-phenyl-1,3a,4,8b-tetrahydroindenophyrole-2,3-dicarboxylate (5dd): A mixture of aniline 2 (1 mmol, 1.0 equiv), dimethyl acetylenedicarboxylate 3 (1 mmol, 1.0 equiv) and ninhydrine 1 (1 mmol, 1.0 equiv) in 5 mL of DCM in a round bottom flask for 5 h at room temperature till complete conversion of the substrates by TLC analysis. After completion of reaction methanol was removed through rotary evaporator and concentrated in vacuo. The residue was purified by column chromatography with a hexane–ethyl acetate (9:1) mixture to afford the pure product 5dd as a white solid.
2. X-3ray Crystallography:

X-ray data for the compound KA361 was collected at 100 K on a Bruker D8 QUEST instrument with an IμS Mo microsource (λ = 0.7107 Å) and a PHOTON-100 detector. Both the raw data frames were reduced and corrected for absorption effects using the Bruker Apex 3 software suite programs [1]. The structure was solved using intrinsic phasing method [2] and further refined with the SHELXL [2] program and expanded using Fourier techniques. Anisotropic displacement parameters were included for all non-hydrogen atoms. All C bound H atoms were positioned geometrically and treated as riding on their parent C atoms [C-H = 0.93-0.97 Å, and U_{iso}(H) = 1.5U_{eq}(C) for methyl H or 1.2U_{eq}(C) for other H atoms]. O bound H atom was located in difference Fourier maps and their positions and isotropic displacement parameters were refined.

Crystal Data for KA261: C_{22}H_{20}NO_{8}Br (M = 506.31 g/mol): monoclinic, space group P2_1/c (no. 14), a = 7.9534(1) Å, b = 19.5048(3) Å, c = 13.5621(2) Å, β = 103.3434(6)°, V = 2047.09(5) Å^3, Z = 4, T = 100.15 K, μ(Mo Kα) = 2.060 mm^{-1}, D_{calc} = 1.6427 g/cm^3, 30748 reflections measured (5.2° ≤ 2θ ≤ 61.16°), 6239 unique (R_{int} = 0.0482, R_{sigma} = 0.0416) which were used in all calculations. The final R_1 was 0.0366 (I>2σ(I)) and wR_2 was 0.0971 (all data). CCDC 1588852 contains supplementary Crystallographic data for the structure. These data can be

![The relative stereochemistry of 4e based on x-ray crystallography.](image-url)
obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

3. Table 1 Screening of reaction conditions

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4. Spectral Copies of $^1$H and $^{13}$C NMR of Compounds Obtained in this study.
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
\begin{align*}
{^1}H\text{ NMR (400 MHz, CDCl}_3) & \quad \begin{array}{cc}
\text{MeO}_2\text{C} & \text{E} \\
\text{E} & = -\text{CO}_2\text{Me} \\
4d
\end{array} \\
{^{13}}C\text{ NMR (100 MHz, CDCl}_3) &
\end{align*}
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^{1}H$ NMR (500 MHz, CDCl$_{3}$)

$^{13}C$ NMR (125 MHz, CDCl$_{3}$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

13C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

**Compound 4j**

$E$ = CO$_2$Et
$^{1}H$ NMR (400 MHz, CDCl$_3$)

\[
\text{MeO}_2\text{C-OH} \quad \text{E} \quad \text{E} \\
\text{N} \quad \text{F}
\]

$E=-\text{CO}_2\text{Et}$

$^{13}C$ NMR (125 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1\text{H NMR (500 MHz, CDCl}_3\text{)}$

$^1\text{H NMR (100 MHz, CDCl}_3\text{)}$
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl₃)

$^{13}$C NMR (100 MHz, CDCl₃)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^1$H NMR (500 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

Me-\(\text{NH-}CO_2\text{Me}\)

5bb

$^1$H NMR (400 MHz, CDCl$_3$)

Br-\(\text{NH-}CO_2\text{Me}\)

5cc
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)