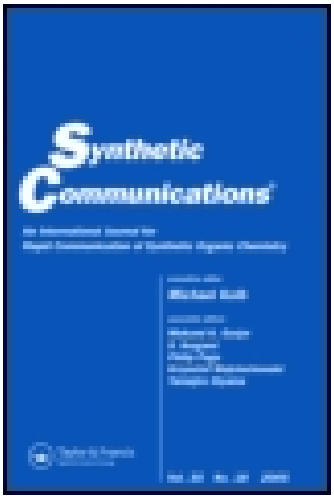

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# Facile Synthesis of Isoquinolines, β-Carbolines, and 3-Deazapurines

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# Facile Synthesis of Isoquinolines, β-Carbolines, and 3-Deazapurines

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**Abstract:** Isoquinoline, β-carbolines, and 3-deazapurines were prepared in 52–81% yields via oxidative decarboxylation of cyclic α-amino acids using ammonium persulfate as an oxidant in the presence of catalytic silver.

**Keywords:** β-carboline, 3-deazapurine, isoquinoline, oxidative decarboxylation, persulfate, silver

Isoquinolines, β-carbolines, and 3-deazapurines are of great interest because of their occurrence in nature and their biological activities.[1–4] One of classical methods of synthesizing these heterocyclic compounds utilizes the Pictet–Spengler reaction[5] to construct a tetrahydropyridine moiety followed by dehydrogenation. Natural β-aryl-α-amino acid **1** can also undergo Pictet–Spengler cyclization to produce tetrahydropyridine derivative **2**, whose oxidative decarboxylation can produce pyridine derivative **3** (Scheme 1). Such oxidative decarboxylation has been widely employed in synthesizing β-carbolines, but uses stoichiometric $K_2Cr_2O_7$ or toxic $SeO_2$ as an oxidant.[6,7] In this article, we report our results on oxidative decarboxylation of tetrahydropyridine derivative **2** using persulfate as an oxidant in the presence of catalytic silver ($Ag^+/S_2O_8^{2-}$).

Induced by $Ag^+/S_2O_8^{2-}$, α-amino acids can undergo smoothly oxidative decarboxylation,[8,9] which has been widely applied in Minisci radical

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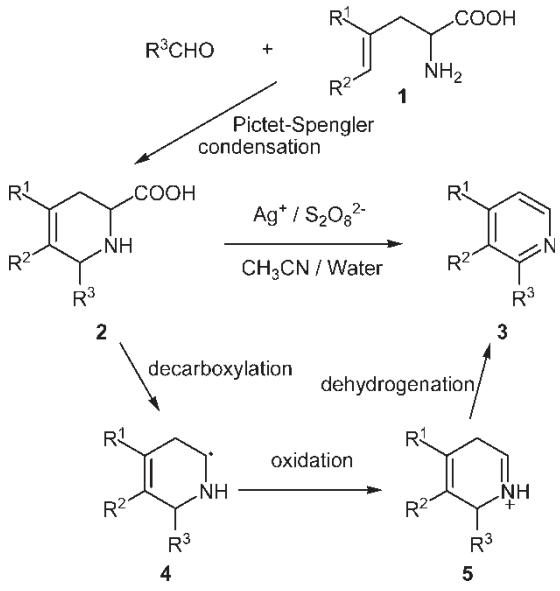


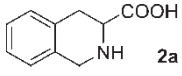
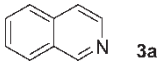
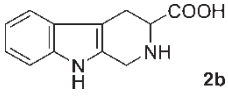
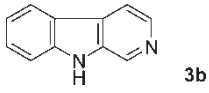
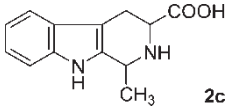
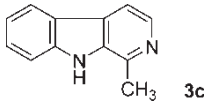
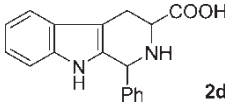
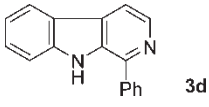
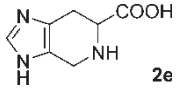
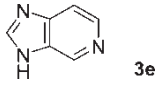
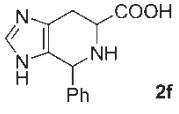
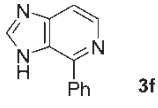

*Scheme 1.*

alkylation.[10,11] To the best of our knowledge, however, little attention has been paid to tetrahydropyridine derivative **2** under similar reaction conditions. As shown in Scheme 1, oxidative decarboxylation of **2** induced by $Ag^{+}/S_2O_8^{2-}$ would lead to the formation of radical **4**. This radical should then be oxidized[12,13] to imine **5**, which would give aromatization product **3** after further oxidation. Starting from phenylalanine, tyrosine, and histidine, this synthetic route would provide a facile entry into isoquinolines, $\beta$-carbolines, and 3-deazapurines, respectively.

Cyclic amino acids **2a–f** were prepared via the Pictet–Spengler cyclization according to the literature procedure.[14–17] Their oxidative decarboxylation was carried out at 80°C using $CH_3CN$/water as solvents in the presence of 10% mol of silver nitrate. Ammonium persulfate was washed dropwise from a small filter-like unit into the reaction mixture by condensing solvents (see the experimental section). Unlike traditional addition methods such as using a syringe, this reduced the risk of introducing air into the reaction mixture and persulfate's decomposition in aqueous solution.

Initially we used tetrahydroisoquinoline **2a** prepared from the condensation of L-phenylalanine and formaldehyde to optimize the usage of persulfate. As shown in Table 1, the best yield (70%) of isoquinoline was obtained by using 2.5 equivalents of persulfate, whereas both 3.0 and 2.0 equivalents of persulfate resulted in lower yield (54%). In the absence of silver nitrate, the reaction gave isoquinoline in only 24% yield, and TLC analysis showed that most of the starting material was not consumed.

***Table 1.*** Synthesis of isoquinoline, $\beta$-carbolines, and 3-deazapurines

| Entry | Substrate **2** | Product **3** | $S_2O_8^{2-}$ (equiv) | Yield[a] of **3** (%) |
|---|---|---|---|---|
| 1 |  **2a** |  **3a** | 3.0 | 54 |
| 2 | **2a** | **3a** | 2.0 | 54 |
| 3 | **2a** | **3a** | 2.5 | 70 |
| 4 | **2a** | **3a** | 2.5 | 24[b] |
| 5 |  **2b** |  **3b** | 2.5 | 52 |
| 6 |  **2c** |  **3c** | 2.5 | 56 |
| 7 |  **2d** |  **3d** | 2.5 | 59 |
| 8 |  **2e** |  **3e** | 2.5 | 79 |
| 9 |  **2f** |  **3f** | 2.5 | 81 |

[a]Isolated yields by preparative TLC.
[b]Without using $AgNO_3$.

Oxidative decarboxylation of tetrahydrocarboline **2b** gave $\beta$-carboline in lower but reasonable yield (52%). Introduction of a methyl or phenyl group at the 1 position afforded harman **3c** or 1-phenyl-$\beta$-carboline **3d** in slightly higher yield (56%, 59%). In sharp contrast, oxidative decarboxylation of spinacines **2e** and **2f** produced 3-deazapurines **3e** and **3f** in 79% and 81% yields, respectively. The lower yields of tetrahydrocarbolines **2b**–**2d** were possibly due to their low solubility in $CH_3CN$/water.

In conclusion, we have demonstrated a general synthetic method for the synthesis of isoquinolines, $\beta$-carbolines, and 3-deazapurines starting from naturally occurring amino acids under mild conditions and using catalytic silver with a greener oxidant.

## EXPERIMENTAL

Ammonium persulfate, silver nitrate, and acetonitrile were purchased from a commercial vendor and were used directly. All melting points were measured on a melting-point apparatus with microscope and hot stage and are uncorrected. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian Inova 500 NMR spectrometer. IR spectra were recorded on a Thermo Nicolet Avatar 360 IR spectrometer. Elemental analyses were performed on a Heraeus Vanio-EL CHN analyzer. All reactions were carried out under nitrogen.

### Typical Procedure for the Synthesis of Isoquinoline

To a reaction tube with a condenser, compound **2a** (1.0 mmol), silver nitrate (0.1 mmol), acetonitrile (8 mL), and deionized water (7.5 mL) were added. Ammonium persulfate (2.5 mmol) was added to a small glass container with pinholes covered with glass wool at the bottom, which was hung on the condenser to allow condensing solvents to wash persulfate dropwise into the reaction mixture. The reaction mixture was degassed by sparging nitrogen, and then the reaction tube was placed in a water bath preheated to 80°C. After persulfate was completely washed out (ca. 30–40 min), the reaction mixture was stirred further for 1 h and then cooled down to room temperature. The reaction mixture was filtered to remove some precipitates after addition of concentrated ammonium hydroxide (2 mL) and then was extracted twice with chloroform (20, 10 mL). Isoquinoline was isolated as an orange oil in 70% yield from the combined organic phase by preparative thin-layer chromatography (TLC) (eluent: EtOAc/petroleum ether 1/3, v/v) after being dried over anhydrous $Na_2SO_4$ and evaporated. The spectral data of the product were in agreement with those reported.[18,19] $^{1}H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.25–7.61 (3H, m, 4,6,7-H), 7.81 (1H, d, $J = 8.0$ Hz, 5-H), 7.94–7.97 (1H, m, 4-H), 8.52 (1H, d, $J = 6.0$ Hz, 3-H), 9.25 (1H, s, 1-H); IR (KBr) 1627, 1588, 1497 $cm^{-1}$.

### Data

**β-Carboline (3b).** A yellow solid: mp 194–196°C (lit.[20] 196°C); $^{1}H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.26–7.34 (1H, m), 7.58–7.60 (2H, m), 8.02–8.04 (1H, m, 4-H), 8.15–8.17 (1H, m), 8.46 (1H, d, $J = 5.5$ Hz, 3-H), 9.05 (1H, s, 1-H), 9.51 (1H, br, NH); IR (KBr) 1623, 1557, 1495 $cm^{-1}$; eluent: $CHCl_3$/MeOH 10/1, v/v.

**Harman (3c).** A yellow solid: mp 214–216°C (lit.[21] 235–236°C); $^{1}H$ NMR (500 Hz, $CDCl_3$) $\delta$ 2.92 (3H, s, $CH_3$), 7.29–7.33 (1H, m, 6-H), 7.55–7.62 (2H,

m, 7,8-H2), 7.87–7.89 (1H, m, 4-H), 8.12–8.14 (1H, m, 5-H), 8.35 (1H, d, $J = 5.5$ Hz, 3-H), 9.23 (1H, br, NH); IR (KBr) 1625, 1605, 1564, 1506 $cm^{-1}$; eluent: $CHCl_3$/MeOH 10/1, v/v.

**1-Phenyl-β-carboline (3d).** A pale yellow solid: mp 234–236°C (lit.[21] 245–246°C); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.31–7.35 (1H, m, 6-H), 7.50–7.62 (5H, m, ArH), 7.95–7.99 (3H, m, 7,8, 4-H), 8.16–8.19 (1H, m, 5-H), 8.58–8.60 (2H, m); IR (KBr) 1624, 1594, 1560, 1496 $cm^{-1}$; eluent: $CHCl_3$/MeOH 10/1, v/v.

**3-Deazapurine (3e).** A pale yellow solid: mp 164–166°C (lit.[22] 165–168°C); $^1H$ NMR (500 MHz, $D_2O$) $\delta$ 7.55 (1H, dd, $J = 1.0$, 6.0 Hz, NCH═C*H*), 8.17 (1H, d, $J = 5.5$ Hz, NC*H*═CH), 8.24 (1H, s, N═CHC), 8.77 (1H, d, $J = 1.0$ Hz, NCHN); IR (KBr) 3382, 1633, 1471, 1462, 1434 $cm^{-1}$. Because of its solubility in water, the workup procedure was modified: the reaction mixture was evaporated to remove all solvents after reaction, and the product was isolated by preparative TLC (eluent: $CHCl_3$/MeOH 5/1, v/v) from the extracts of the resulting residue with MeOH (2 × 20 mL).

**6-Phenyl-3-deazapurine (3f).** A pale yellow solid: mp 166–169°C; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.26–7.50 (4H, m, ArH + NCH═C*H*), 8.03 (1H, s, NCHN), 8.28–8.30 (2H, m, ArH), 8.43 (1H, d, $J = 5.5$ Hz, NC*H*═CH); $^{13}C$ NMR (125.7 MHz, DMSO-$d_6$) $\delta$ 107.4, 128.8, 129.5, 129.6, 138.3, 138.7, 140.0, 141.7, 144.1, 147.9; IR (KBr) 1611, 1586, 1493, 1463 $cm^{-1}$. Anal. calcd. for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.85; H, 4.46; N, 21.40.

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